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Features

PEER REVIEWED

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Dear Clinical Research Professional,

Clinical Researcher is your journal. Those of us on ACRP's Marketing & Communications staff work with the members of our Editorial Advisory Board to brainstorm and shape the journal. We edit it. We design it. But you are the content. You are the heart of the publication. Your writing is what makes people pick up *Clinical Researcher* every other month. They are looking to learn. To earn certification credits. To understand new trends, and to benefit from new ideas and best practices.

Simply put, this journal would not exist without your contributions. We look to you to provide insightful articles drawn from your own experiences and observations. What's working for you? What mistakes or problems have you encountered and solved? Where do you think the clinical research enterprise is going?

You have questions. But you also have answers. We need to share our collective lessons learned. You, and your colleagues, can often solve each other's challenges—or at least highlight your concerns—by contributing articles to *Clinical Researcher.*

We need to share our collective lessons learned.

I won't sugar coat this: We don't publish everything we receive. We adhere to a peer-review process and the bar is high. It's part of our commitment to bring you the best possible publication. That said, our Editorial Advisory Board members, serving as our reviewers, are quite willing to work with you if needed. Some articles are accepted with relatively few changes; others require more revisions. When you submit an article to *Clinical Researcher*, you can count on feedback on the highest level. You'll be forced to think long and hard about your subject before you start banging at the keyboard—and benefit from insights that might surprise. You'll learn how to be a better writer. Finally, you might be featured in our pages. Your work might inspire others to step forward and add to the conversation.

As we head into 2016, we hope you'll consider submitting an article to *Clinical Researcher.* Sharing information with your colleagues is a way to give back. And who knows, you might learn a little something along the way, too.

All the best,
James Michael Causey
Editor-in-Chief
Clinical Researcher

GUEST EDITOR'S MESSAGE

Erika J. Stevens, MA

[DOI: 10.14524/CR-15-4092]

Clinical Research Revenue Cycle: *Understanding Research Finance*

Research organizations that concentrate on the back-end processes alone find limited improvement in cash flow. More importantly, the effectiveness of a healthcare organization's efforts to collect cash is tied to how well the organization monitors and manages the requirements and performance of third-party payers, such as study sponsors.

The clinical research revenue cycle includes front-end, middle, and back-end process for managing clinical research finance. The ability to accurately capture financial information and research-related activities mitigates financial risk.

Functional areas throughout the research management process act sequentially on a research participant visit, adding critical information required for procuring payment from sponsors and third-party payers. If one area in this process performs poorly, the ultimate goal of cash collections will decline.

The Revenue Cycle

The clinical research revenue cycle includes front-end, middle, and back-end process for managing clinical research finance (see Figure 1). The ability to accurately capture financial information and research-related activities mitigates financial risk.

In four of this issue's articles, specially selected authors illustrate various perspectives on clinical research finance and highlight leading practices for management. These subject matter thought leaders provide insight into the many complex finance processes involved in managing clinical research finance, and offer applied solutions to challenges throughout the clinical research revenue cycle.

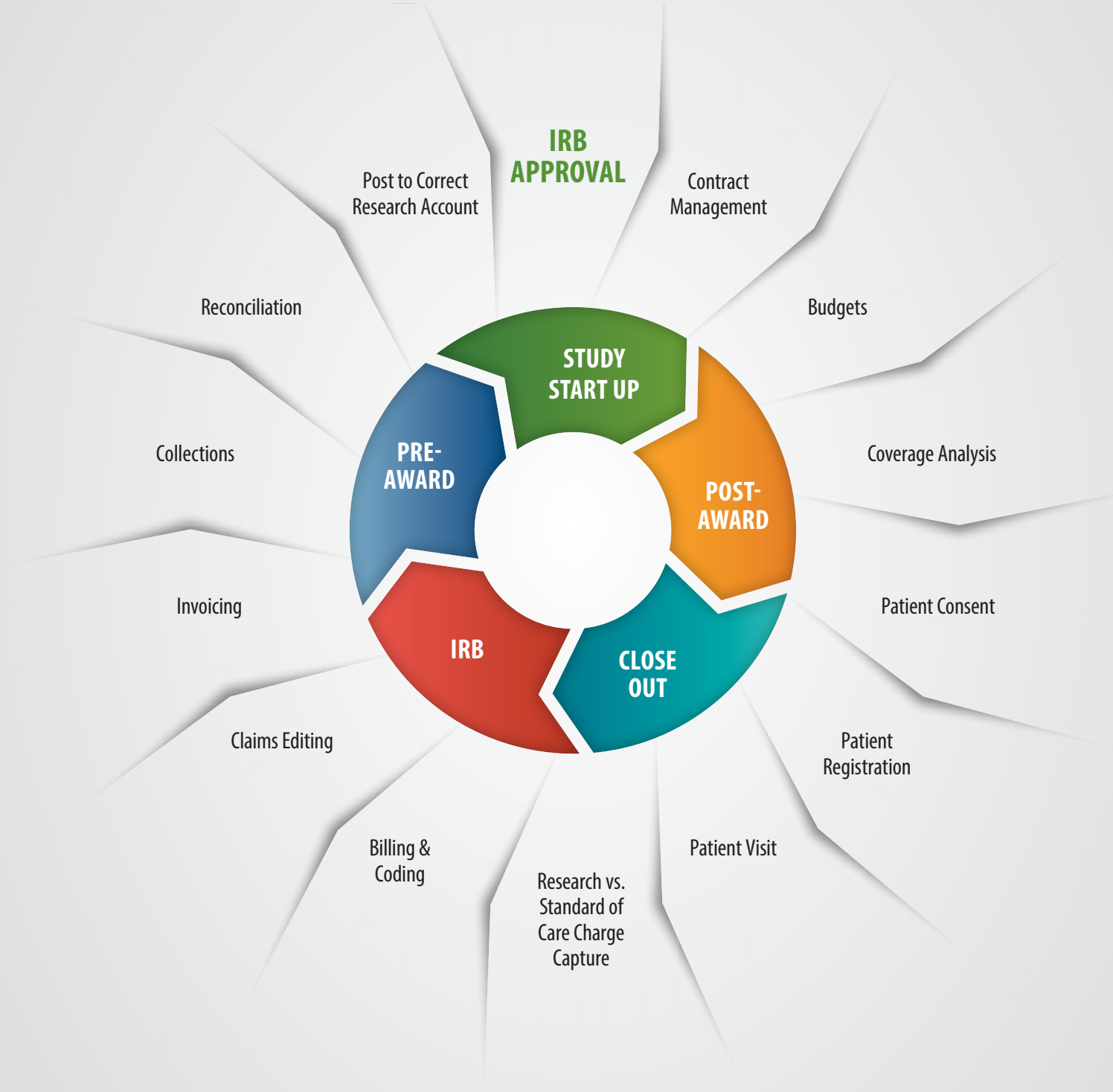
Mitchell Appleson from Children's Hospital of Philadelphia leads this issue by providing solutions to the complex issue of clinical trial billing. Developing a system to track research patients throughout the life cycle of the trial is a necessary step in managing the billing process. The ability to capture patient research activity helps to mitigate research compliance risks.

Understanding the compliance risks associated with clinical research is a complex process for many research organizations. Opportunities for financial errors exist throughout the clinical research revenue cycle. Emmelyn Kim from North Shore Long Island Jewish Health System recommends a gap analysis approach for managing financial noncompliance. Understanding the potential risks from budgeting, patient identification, and charge capture will enable better compliance oversight.

Lisa Murtha and Nicole Visyak from FTI Consulting provide insight into the complex process of Medicare coverage analysis in clinical trials. The careful review and front-end analysis of study-related and nonstudy-related charges limits billing errors.

Finally, Tina Noonan from St. Vincent Hospital provides insight for improving financial performance in clinical trials from the site perspective. Assessing financial feasibility, developing processes to improve negotiation turnaround, and implementing standard institutional fees are simple tips. Managing research finance remains a complex issue, but developing a systematic approach throughout the clinical research revenue cycle enables improved financial outcome.

FIGURE 1: Clinical Research Revenue Cycle Processes



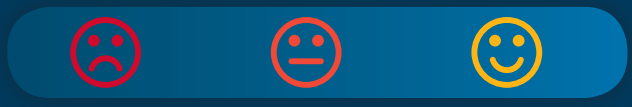
Erika J. Stevens, MA, (erika.stevens@ey.com) is senior manager for advisory service-healthcare at Ernst & Young and a member of the ACRP Board of Trustees.

BY THE NUMBERS

Taking a look at trends you may not have noticed are having an influence on the finances of clinical research.

Data from a study that examined contracts processing for 2010 Clinical and Translational Science Awards revealed that an average clinical study contract negotiation time of **55 days**, exclusive of budget and safety board approvals, could be **reduced to 22 days** if standardized research and confidentiality agreements were used.

Source: Stanford Medicine, http://med.stanford.edu/news/all-news/2015/08/new-clinical-trial-agreements-expedite-contract-negotiations.html



New data show that **68%** of clinical trials at Top 10 pharmaceutical companies, **45%** at Top 50 companies, and **90%** at small companies now implement patient-reported outcome measures to add to product value propositions during regulatory approval discussions and pricing and reimbursement negotiations.

Source: Cutting Edge Information, www.marketwired.com/press-release/-2036131.htm

In surveys of institutional review board (IRB) members at U.S. academic health centers, the percentage of respondents who felt another IRB member had presented a protocol in a biased manner because of his or her industry relationship decreased from **13.5%** in 2005 to **8.4%** in 2014.

Source: Massachusetts General Hospital, www.eurekalert.org/pub_releases/2015-07/tjnj-ssp070915.php

ACRP
ASSOCIATION OF CLINICAL RESEARCH PROFESSIONALS

DEPUTY EXECUTIVE DIRECTOR'S MESSAGE

Terri Hinkley, RN, BScN, MBA, CCRC

[DOI: 10.14524/CR-15-4086]

Let's Make Competency About Talent—Not Tenure

The clinical research enterprise is evolving at the speed of innovation and technology. New tools, new best practices, and new ways of raising the performance bar make this an exciting time to be a clinical researcher.

However, we need to do more. If we want to continue to grow, we must go back to the beginning and take a good, hard look at some of our most basic assumptions.

I'm thinking of the arbitrary requirement that individuals must have two years of monitoring experience before being able to secure a position as a clinical research associate (CRA). Competency should not be about turning calendar pages. It's far more than that. Competency should be about possessing a basic skill set along with a demonstrable core of knowledge.

Where did the two-year threshold come from? No one seems certain. I argue that if it ever made sense in the past, it certainly doesn't make sense today. Instead of encouraging a higher caliber of professional, it may well be discouraging some very talented younger people from sticking with our industry.

Avoiding the Brain Drain

This brain drain is avoidable—and unacceptable. There are more than 10,000 open CRA positions being recruited right now, according to data presented at the June 2015 DIA meeting in Washington, D.C.

However, on a daily basis, we are approached by individuals who want to move into a CRA role, but don't have the two years of experience as a CRA. They ask how they can get the experience if no one will hire them to allow them to gain the experience. It seems a bit "chicken and egg" to me.

We're challenging ourselves and everyone else who wants to better serve trial subjects to join us by taking a step back. Together, let's examine what we've done in the past—and what we continue to do today—and put it to a stress test. Are we being served as an industry by a barrier based solely on time and tenure?

Common sense certainly suggests the answer is no.

There is a real opportunity here. It's time to ask ourselves some tough questions. It's time for us challenge ourselves and find new ways to work together to identify the core skill sets and competencies a job-seeker needs to attain before they advance to the next level. How do we define entry-level competencies? Or mid-level ones? Or overall research experience? Such determinations cannot be contingent on merely working at the same job for 730 days!

Let's explore what's working in other comparable industries. Let's consider a wide array of potential best practices that can better inform what could be a groundbreaking leap forward for all of us.

ACRP aims to be part of an industry-wide team shift toward basing required competencies on extensive job analysis surveys of individuals working on the front lines of clinical research. What activities do these research team members perform on a daily basis? What skills are truly needed to do their jobs well? Is simply working at the same job for 24 months the metric we should be looking at? We can't know until we to collect objective, real-world data, analyze the findings, and then roll up our sleeves to create solutions based on the findings together.

Analyzing the Situation

New initiatives cannot be adequately developed in a silo of silence. If this is going to work—if we're going to respect clinical trial subjects and earn their trust—our joint efforts toward rethinking and reforming how we approach job competencies and their related repercussions on hiring trends for CRAs must be as public and transparent as possible. Methods and goals simply must be harmonious. It's not about agendas. It's about getting it right.

From where I sit, I'd like to see increased involvement from stakeholders across the wide spectrum of clinical research professionals in this initiative, and in future efforts aimed at other job specialties in our industry.

Work already done by the Joint Taskforce for Clinical Trial Competency (see "Moving from Compliance to Competency: A Harmonized Core Competency Framework for the Clinical Research Professional" by Sonstein, et al. in the June 2014 *Clinical Researcher*) could become the foundation of our shared effort to create professional development standards based on the attainment of recognized skill levels. No longer would something this important be based on time served. Instead, individuals who have made the effort to reach or exceed a set of standards will be justifiably rewarded with new professional opportunities.

Who Stands to Gain, and Next Steps

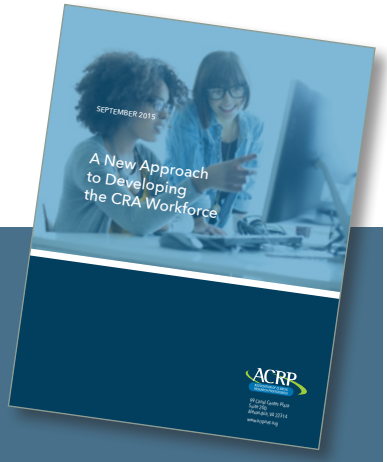
The industry at large will benefit. The professionals in the trenches will benefit. Most importantly, subjects will benefit when served by researchers who have the right training and the proven skills to offer them the highest possible level of care. A more robust work force will take pressure off everyone.

Let's explore what's working in other comparable industries. Let's consider a wide array of potential best practices that can better inform what could be a groundbreaking leap forward for all of us.

It's time to get the discussion started. In September, ACRP published a position paper officially calling for an end to arbitrary requirements that limit the CRA workforce. We will continue the discussion through a just-announced task force charged with defining CRA-specific competencies. I invite you to take a look at our position paper and send us your feedback. To view the paper, please visit http://www.acrpnet.org/positions.

Working together, we can advance our shared vision of better serving our subject populations. We can expand trials, recruit the most appropriate participants, and embrace the future with new ideas.

Terri Hinkley, RN, BScN, MBA, CCRC, (thinkley@acrpnet.org) is the deputy executive director of the Association of Clinical Research Professionals (ACRP), based in Alexandria, Va.



It's time to get the discussion started. ACRP just published a position paper officially calling for an end to arbitrary requirements that limit the CRA workforce.

www.acrpnet.org/positions

Making a Difference in Recruitment and Accrual by Taking a Closer Look at Your Site's Policies and Procedures

RECRUITMENT & RETENTION

Margo Michaels, MPH

[DOI: 10.14524/CR-15-4091]

As we seek ways to increase participation in our trials, it's important that we take a look in the mirror.

Four areas to reflect on are:

1. How well research is integrated into our care delivery.[1]
2. How well we systematically identify, screen, and approach potential participants: *Systematic patient screening has been shown to increase overall*[2] *and minority participation*[3] *in trials and reduce the opportunity for bias in offering trials.*[4–9] *About one-third of accrual sites have no systematic approach to screening patient charts for eligibility, and about one-third of physicians affiliated with a research site do not actively participate in studies.*[10]
3. How well we select new trials: *Sites seldom use a systemized process for trial selection, often relying on individual physician interest. This "process" results in poor potential participant/trial match; inconsistent site commitment to a study; and low(er) accrual rates.*[11]
4. How well we ensure comprehension during the consent process: *Poor communication around consent has been proven as a challenge to research participation.*[6, 12–17]

This column will help you think about the first and second areas of reflection as noted above. In the next issue of *Clinical Researcher,* we will discuss the third and fourth areas.

POLICIES AND PROCEDURES REFLECTION CHECKLIST

Share this with your colleagues to see what they think about these issues.

Question	Very Well	OK	Not Very Well
1. How well do we collaborate with other departments (e.g., nursing, imaging, labs) to make accrual and participation more efficient?	☐	☐	☐
2. How well is clinical research integrated into the mission of the larger organization (and how well do administrators promote a culture supportive of research)?	☐	☐	☐
3. How well can other medical, clinical, or administrative staff appropriately provide messages about clinical trials?	☐	☐	☐
4. How well do staff members (other than research staff) understand clinical trials?	☐	☐	☐
5. How well are clinical trials integrated into the outreach and community relations efforts at our site?	☐	☐	☐
6. How well do we collaborate with other departments (e.g., nursing, imaging, labs) to make accrual and participation more efficient?	☐	☐	☐
7. How well do we screen all eligible patients for clinical trials?	☐	☐	☐
8. How effective is our site in offering trial participation for those flagged for possible recruitment?	☐	☐	☐
9. How well do we educate patients about clinical trials, before the consent process or the initial offer?	☐	☐	☐
10. How well do we understand and reflect upon the reasons patients have for declining participation?	☐	☐	☐
11. How well do we understand and reflect upon the reasons physicians have for declining to offer a trial to a patient, even though the person's chart was flagged?	☐	☐	☐

If you answered, "OK" or "Not Very Well" to more than two of these questions, your site may need to implement changes in this area. Read on for some tips to consider implementing.

TIPS FOR IMPROVING POLICIES AND PROCEDURES

Principle	How to do it
Develop and Implement Ongoing Educational Programs for Staff Who are Outside the Research Department(s)	• Provide training **for all staff** who provide care to patients about the importance and availability of trials » We All Have a Role in Clinical Trials[18–20] Staff Training » 5 Messages any Staff Member Can Use to Encourage Inquiry About Clinical Trials • Use communication strategies to keep staff aware of clinical trials (e.g., "Ask Me" buttons, posters, newsletters, cafeteria information tables, employee pay stubs, or newsletters) • Make sure every staff member knows where to find clinical trials information
Use Promotional Materials	• Keep potential participants aware of clinical trials (e.g., "Ask Me" buttons, posters, newsletters, cafeteria information tables) • Hang "Ask Me" posters inside every exam room • Play videos in waiting room • Play research-related messages on computer screens in rooms where patients are waiting for examinations
Change Internal Systems and Procedures	• Integrate clinical trials messages in all support groups • "Normalize" clinical trials in context of quality care to complement prior information received; "what we do here" • Integrate clinical trial messaging with social workers, navigators, and support groups • Develop procedures to enhance communication between research staff and clinical staff, imaging, and labs
Implement Standard Operating Procedures	• Develop prompts and reminders to ensure systematic prescreening for trials[21] • Differentiate the key roles/handoffs of the physician presenting the trial vs. research staff • Utilize screening log
Improve Internal Systems and Procedures: Research Staff Action	• Standardize prescreening and flagging processes involving staff responsibilities so that all staff and the physicians with whom they work follow the same routines • Assign prescreening task to particular staff person(s)[22] or through rotating assignments to improve efficiency and reduce redundancy[23] • Link open trials/trial management systems to electronic health records (EHRs)[24] and ensure their use for prescreening and screening » Build and flag relevant fields in EHRs; set alerts as applicable • Have research staff strengthen prescreening by: » Reviewing targeted pathology reports and positive diagnostic scans » Flagging all eligible patients, listing potential trials and additional tests needed » Attending multidisciplinary meetings to suggest relevant trials • Have other staff (e.g., medical assistants) strengthen prescreening by alerting the research department about new and potentially eligible patients • Provide research staff nurse time to visit external referring providers to review charts and discuss trials with patients[25]
Improve Internal Systems and Procedures: Focus on Physician Action	• Standardize prescreening and flagging processes involving physician responsibilities so that all physicians and the staff with whom they work follow the same routines • Ensure flags are acted upon and reported in EHR or other tracking (may be subject to institutional review board (IRB)/legal approval) • Assist physicians in practical ways with recalling open studies and strengthening offers to patients » Provide "cheat sheet" protocol listing that fits into a lab coat pocket and is updated monthly; listing should include current trials and contact information » Prominently display a usable and practical open trials list in every exam room • Ensure staff and physicians are up to date on details and availability of trials through scheduled meetings • Consider the advantages of using a clinical trial management system
Provide "Incentives" to Physicians and Staff	• Use internal, visible "scoreboard" or "thermometer" on prescreening and related activities » Send monthly accrual reports to all members of research team and all treating physicians[26] » Highlight leaders in a monthly newsletter/e-mail[26] » Establish a quarterly competition and award "prizes" to teams with the highest total accrual and highest increases from previous quarters[23] • Institute clear expectations for minimal levels of clinical trial activities in annual performance plans for staff and physicians • Require participating physicians to be accountable for responding to prescreen notifications and enrolling patients to clinical trials as part of their contract or performance plan[27] » *If not possible, share comparison accrual data among physicians to stimulate self-awareness* • Implement incentive system to demonstrate commitment to clinical trials accrual (with IRB approval)

How well is clinical research integrated into the mission of the larger organization (and how well do administrators promote a culture supportive of research)?

Poor communication around consent has been proven as a challenge to research participation.

References

1. Research must be incorporated into clinical care
   - Patients eligible to participate in trials are educated about the option to participate
   - Patients not eligible for open trials are educated about research participation
   – asked if wish to be informed of future research opportunities
   – flagged for future consideration

   American Society of Clinical Oncology Community Research Forum. ASCO Research Program Quality Assessment Tool: Basics for a Quality Community-Based Research Site. Version 1.0. Alexandria, Va.; American Society of Clinical Oncology; 2014.
2. Chen L, Grant J, Cheung WY, Kennecke HF. *JOP* March 2013.
3. Wujcik D, Wolff SN. *J Health Care Poor Underserved* 2010;21:38–50.
4. Simon MS, Du W. Factors associated with breast cancer clinical trials participation and enrollment at a large academic medical center. *J Clin Oncol.* 2004;22(11):2046–52.
5. Kemeny MM, et al. Barriers to clinical trial participation by older women with breast cancer. *J Clin Oncol.* 2003;21(12):2268–75.
6. Albrecht TL, et al. Influence of clinical communication on patient's decision making on participation in clinical trials. *J Clin Oncol.* 2008, June 1;26(16):2666–73.
7. Joseph G, Dohan D. Diversity of participants in clinical trials in an academic medical center: the role of the 'good study patient?' *Cancer.* 2009;1:115(3):608–15.
8. Ford, JG, et al. Barriers to recruiting underrepresented populations to cancer clinical trials: A systematic review. *Cancer.* 2008;112:228–42.
9. Wendler D, Kington R, Madans J, et al. Are racial and ethnic minorities less willing to participate in health research? *PLoS Med.* 2006;3(2):e19.Epub 2005.
10. Klabunde CN, Keating NL, Potosky AL, Ambs A, He Y, Hornbrook MC, Ganz PA. A population-based assessment of specialty physician involvement in cancer clinical trials. *J Natl Cancer Inst.* 2011;103(5):384–97.
11. Dilts DM, Sandler AB. The 'Invisible' Barriers to Clinical Trials: The impact of Structural, Infrastructural, and Procedural Barriers to Opening Oncology Clinical Trials. *J Clin Oncol.* 2006;24(28):4545–52.
12. Michaels M, Blakeney N, Britton L, et al. Enhancing Cancer Clinical Trials access: impact and outcomes of a community centered pilot education and advocacy program. *J Clin Oncol.* 2010. ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 28, No 15_suppl (May 20 Supplement).
13. Albrecht TL, Blanchard C, Ruckdeschel JC, Coovert M, Strongbow R. Strategic physician communication and oncology clinical trials. *J Clin Oncol.* 1999;17(10):3324–32.
14. ENACCT Policy Webinar: "What Does Informed Consent Look like in a Health Literate Organization," Cindy Brach, MPP, AHRQ, May 2013.
15. The health literacy of America's adults: Results from the 2003 National Assessment of Adult Literacy. U.S. Department of Education (2006) http://nces.ed.gov/pubs2006/2006483.pdf
16. U.S. Department of Education, Institute of Education Sciences, National Center for Education Statistics, 2003 National Assessment of Adult Literacy.
17. Brown RF, et al. *Patient Educ Couns.* 2012.
18. Paula Fracasso, UVA Cancer Center Clinical Trials: A Culture Change. ENACCT National Clinical Trials Breakthrough Collaborative Learning Session 1 October 4, 2011.
19. Sherwood PR, Given BA, Scholnik A, Given CW. To Refer or Not to Refer: Factors that Affect Primary Care Provider Referral of Patients with Cancer to Clinical Treatment Trials. *J Cancer Educ.* 2004;19(1): 58–65.
20. Michaels M, et al. The Promise of Community-Based Advocacy and Education Efforts for Increasing Cancer Clinical Trials Accrual. *J Cancer Educ.* 2012;27(1):67–74.
21. Irwin ML, et al. Recruiting and retaining breast cancer survivors into a randomized controlled exercise trial: the Yale exercise and survivorship study. *Cancer,* Supplement – cancer survivorship: embracing the future. 2008;112(S11):2593–606.
22. ENACCT Policy Webinar Series: How can "Pre-Screening" Patients for Eligibility Make a Difference in Cancer Trials Accrual, Debra Wujcik, Speaker. November 2012. www.enacct.org/node/271
23. ENACCT. A Quality Improvement Program to Improve Cancer Clinical Trial Recruitment, Accrual and Retention. Lessons Learned from the National Cancer Clinical Trials Pilot Breakthrough Collaborative. Final Report; 2012.
24. Nass SJ, Moses HL, Mendelsohn J. A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program. Washington, D.C.: The National Academies Press; 2010.
25. McKinney MM, Weiner BJ, Carpenter WR. Building community capacity to participate in cancer prevention research. *Cancer Control.* 2006;13(4):295–302.
26. Fracasso P. UVA Cancer Center Clinical Trials: A Culture Change. NCCTBC Learning Session 1 October 4, 2011.
27. Petrelli NJ, Grubbs S, Price K. Clinical Trial Investigator Status: You Need to Earn It. *J Clin Oncol.* 2008;26(15):2440–1.

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This test expires on October 31, 2016

(original release date: 10/1/2015)

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

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

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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.

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

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The Association of Clinical Research Professionals (ACRP) provides 3.0 contact hours for the completion of this educational activity. These contact hours can be used to meet the certifications maintenance requirement. (ACRP-2015-HMS-010)

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The California Board of Registered Nursing (Provider Number 11147) approves the Association of Clinical Research Professionals (ACRP) as a provider of continuing nursing education. This activity provides 3.0 nursing education credits. (Program Number 11147-2015-HMS-010)

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Clinical Trial Billing: *Solutions to a Complex Problem*

PEER REVIEWED | Mitchell Appleson, CPA, MBA

[DOI: 10.14524/CR-15-0025]

Managing a clinical trial used to be much easier. Years ago, when a research patient came in for a visit, a study team recorded basic information, kept it in a binder on a desk, and sent data to a sponsor as needed.

Today, we have multiple systems, numerous processes, and a myriad of rules and regulations. There are multiple individuals and departments that must be contacted before, during, and after a clinical trial is conducted. Within this environment, accurate billing has become both more challenging and more vital.

LEARNING OBJECTIVE
After reading this article, the learner should be able to analyze key resources and tools available to address the challenges in clinical trial billing.

DISCLOSURES
Mitchell Appleson, CPA, MBA:
Nothing to disclose

Facing the Challenge (or Not)

As medicine and research have become more complex, the billing processes to support that complexity have not kept pace. Historically, the focus for most institutions has been on the actual research taking place, with little thought placed on the billing associated with the research.

Until recently, many institutions did not have centralized offices to handle budgeting, billing, and other administrative functions for clinical research. Therefore, many responsibilities were handled by the study team, or not at all.

The state of research billing was often a reactive one. If a bill was sent out incorrectly, it only became known when a patient called to question the bill.

Once a problem was identified, there was not always a clear process for how to fix it. If a patient's insurance was billed incorrectly, the insurance needed to be refunded and the research grant had to be charged. However, unless a patient called multiple times to follow up on the erroneous bill, it was often difficult to know whether the problem had been fixed. Not all patients check their explanation of benefits, and they would not be aware if their insurance had been billed incorrectly.

We therefore lived in a very reactive state, in which a problem was only known if someone outside the billing function raised it as a problem. Due to this lack of transparency, it was difficult to identify the problem to begin with, and it was just as difficult to identify whether the problem had been resolved.

This lack of transparency became more glaring as audits became a regular part of institutional processes. Federal regulations mandate that Medicare, Medicaid, and other payers may not be billed for services that are not considered standard of care. Standard of care procedures are those that the patient would receive regardless of study participation. In addition, if a service is paid by a clinical trial sponsor, it may not also be billed to a third-party payer.[1]

Whether through a federal audit, sponsor audit, or internal audit, the pieces of the billing process must all come together to create an audit trail. That can be difficult enough for a simple study with only two procedures and visits; it is much more complicated when the study has 50 visits, each visit has 35 procedures, and some are considered research and some standard of care.

An Example of What's at Stake

One of the audits that raised awareness of research billing problems came in 2003 at Rush University Medical Center in Chicago. Rush internally reviewed the Division of Hematology and Oncology, and identified certain services performed in research that had incorrectly been billed to Medicare. Rush took immediate action by instituting a bill hold for all clinical trial services within the

division, while expanding its investigation. Rush also disclosed these billing issues to the federal government. This self-disclosure resulted in a $1 million fine.[2]

Many hospitals and academic medical centers, concerned with the fines levied against Rush and other large institutions over the past decade, have looked at Rush's self-disclosure and the government's response for lessons on how to approach clinical trial billing properly and effectively. The root cause of Rush's billing issues was a lack of coordination between its research and billing operations, and its corrective action focused on the centralization of clinical trial billing processes within the medical center.[2]

One result of the situation at Rush was the creation of a centralized clinical trials office, which conducts coverage analyses of all clinical trials using the protocol, informed consent, and sponsor budget. The office is also a liaison between the medical center's research and billing arms.

Getting a Grip on the Issues

To understand research billing and how to properly address it, we need to start by understanding budgeting, which is the first step toward correct billing.

The purpose of creating a clinical trial budget is two-fold: 1) To determine the total costs incurred as part of the study; and 2) to determine which procedures are to be billed to a research grant and which are to be billed to a patient's account.

When preparing a clinical trial budget, some people prepare a "funding-based" budget. Using the funding provided by the sponsor, individual line items are determined as a proportion of those funds to prepare the itemized budget. For example, if 10% of a budget is allocated to startup costs, and the total funding for the study is $20,000, a total of $2,000 would be allocated for startup costs.

A problem with a funding-based budget is that it does not consider the actual startup costs incurred. It may cost more than $2,000 to get the study up and running, which will cause the study to be in a deficit or not to run properly—and the same problem can occur with other study activities. Rather than backing into a budget, best practice is to prepare a total internal budget.

Preparing a total internal budget begins with reviewing the protocol and using actual internal costs to develop a detailed budget. To determine the internal costs of a study, the study protocol must be thoroughly reviewed to identify all procedures and visits to be performed as part of the study.

Each procedure is then assigned a corresponding charge, which should be pulled from the institution's charge master—a comprehensive list of institutional charges billable to a patient or his or her insurance. The charge master should be the sole source of identifying individual charges when creating the budget, to ensure that all pricing information comes from the same source.

KEY QUESTIONS FOR SITES TO CONSIDER WHEN PREPARING A BUDGET

Does the budget include:

- ? Resources required by other departments or vendors?
- ? An appropriate estimate for startup costs?
- ? Screening costs?
- ? Coverage for unscheduled visits?
- ? Costs associated with the purchase or lease of required equipment not provided by the sponsor?
- ? The cost of phone queries from the sponsor as part of a remote monitoring system?

Other Questions:

- ? Does the informed consent form clearly address participant financial responsibilities?
- ? Will the sponsor pay for additional tests and procedures if they are requested during the course of the trial?
- ? Under what conditions are additional payments made?
- ? What are the expectations for timely payment?
- ? How will the accounts receivable from the sponsor be tracked?
- ? Who is responsible for billing sponsors of clinical trials?
- ? How is the information included in the budget communicated to the billing office to ensure billing accuracy?

LESSONS LEARNED

- Prepare an internal budget to assess the costs of a study
- Identify a sole source of pricing data
- Communicate with key stakeholders involved with the study
- Know which charges are research and which are standard of care
- Perform a root cause analysis when a billing error occurs
- Ensure that study participants understand their potential financial obligations
- Engage your institution's billing office when deviating from institutional processes
- Create an environment of transparency and crossfunctional coordination
- Consider the use of a CTMS
- Review the payment terms in each study agreement

The internal budget should establish the cost to perform the trial. Upon completing the internal budget, the total budget amount should be compared to the sponsor offer and any shortfalls should be addressed, either with more aggressive sponsor negotiations or identifying supplemental sources of funding.

Any departments that will participate in the clinical trials should be given an opportunity to review and approve the budget for coding accuracy and feasibility. For example, if a study involves an MRI during each visit and the intention is to enroll 100 participants over the next six months, radiology should know of the expected volume and confirm that the proper codes have been added to the budget. Finally, ensure accurate costs in the budget via one institutional source for pricing.

And...Who's Paying for All This?

Knowing the costs of a study is not sufficient; the budget must delineate who is paying for which costs. If a visit has 10 procedures, and five procedures will be paid by Sponsor X, three by Sponsor Y, and two are standard of care, the budget should reflect this. Using this method, a billing office will have an easier time determining which charges must be billed to which sponsor, and which charges must be billed to a research participant.

There are several purposes in creating a clinical trial budget, besides documenting all procedures and costs. The budget should contain the approvals of the investigator, study coordinator, and any ancillary departments. These approvals document the signatories' ability to provide technical and professional services, as required by the study.

The budget also:

- Clarifies which procedures in the protocol are considered research and which are standard of care
- Assists study coordinators with registration and scheduling of research patients
- Supports charge auditors as they review and adjudicate charges

Finally, when billing errors do occur, the budget should be reviewed during the root cause analysis to understand what went wrong.

Once the budget is complete, the informed consent form must articulate which procedures are standard of care. This will mitigate confusion when a patient receives a bill for what he or she thought was a study-related visit, but was approved to be billed as standard of care. An institutional review board (IRB) should review the informed consent form's financial language for clarity.[3]

Taking the Next Steps

Now, we should get a better understanding of why an accurate budget is critical to getting correct billing. Let's take a look at two key issues.

CONFUSIONS AND COMPLICATIONS

First of all, a billing office can follow the budget when determining how to post charges from a research visit. When a patient, or his or her insurance, is billed incorrectly, a root cause analysis should be performed. Starting with a review of the budget, it should be readily apparent whether the process was followed correctly. Research procedures may not be listed correctly, or a research procedure may be listed as standard of care.

An alternate cause of confusion may be that the participant was not correctly identified as a research participant at the time of registration. The participant may have been registered for procedures not included on the budget, and therefore the participant was charged for study-related procedures. Another option is that the bill is correct, and the participant was not provided with a clear sense of his or her potential financial obligations. Having an accurate budget is central to the root cause analysis.

Yet another possible complication may be that a clinical department created a workaround outside the billing system to handle financial interactions with hospital ancillary departments. Dr. X has limited funding and has asked Dr. Y to perform a test for free. Although Dr. Y agrees, neither Dr. X nor Dr. Y realizes that a charge may be automatically generated in an electronic medical system. If clinical activity is not entered into systems, productivity and utilization data may be skewed. Therefore, include the billing office when deviating from institutional processes to handle financial interactions.

Some additional causes of improper billing relate to a lack of training to properly identify and bill research participants, use of paper processes that do not provide transparency, and a lack of coordination across functional areas. Creating an

Whether through a federal audit, sponsor audit, or internal audit, the pieces of the billing process must all come together to create an audit trail.

internal budget and implementing robust financial processes while tracking participant visits can mitigate these issues.

HAVING A SYSTEM

To successfully manage the finances of a clinical trial, there must be a system in place to track participant visits and procedures throughout the trial. The system must be easy to use for both research and finance staff, as research staff should enter all visits that would cause billable activity. Further, finance staff should invoice the sponsor of the study and follow up on outstanding receivables. The total outstanding balance should be clear for any study, as well as which procedures specifically make up that outstanding balance.

Consider utilizing a clinical trial management system (CTMS) to track individual studies, participants, and visits. In many systems, once a budget is entered for a study, the registration process entails entering a participant's medical record number and date of visit, and specifying which visit is being scheduled (screening, visit 1, etc.). Once the visit has been chosen, the individual procedures for that visit should automatically populate on the registration form. This eliminates the possibility of procedures being scheduled that were not initially budgeted, which can cause a patient to erroneously receive a bill.

The processes for invoicing, cash receipts, and accounts receivable tracking should be clear to all stakeholders. A CTMS can be helpful with this, as many systems allow an invoice to be generated from the visit, and cash receipts and accounts receivable can be tracked using the system.

When using a CTMS is not an option, the need for communication is even more critical. Whose responsibility is it to do the invoicing? Often, a central office in an institution receives the cash and posts the funds to an account. Do staff in this office know what invoices have been sent? Do the people who sent the invoices find out the detail of what was paid? If not, it will be very difficult to establish how much money is outstanding for clinical trials.

REVIEWS AND REPORTS

It is important to review the payment terms associated with each clinical trial to understand when sponsor payment will be made and what needs to be done to receive payment. These terms should be reviewed carefully when negotiating the Clinical Trial Agreement, prior to executing the agreement.

Many payment terms indicate quarterly site payments. According to a recent CenterWatch survey, 60% of investigative sites have less than three months of operating cash on hand.[4] When employees are paid biweekly, vendor terms are monthly, and utilities and rent must be paid monthly, sites end up funding the study until payment arrives.

If a site does not have significant cash on hand, quarterly payments from the sponsor are not sustainable and must be negotiated to a term that a site can manage. Ideally, this would be monthly payments from the sponsor.

Whatever payment terms are agreed to, review them carefully and make sure they are feasible for your site before agreeing to them.

Finally, consider establishing a reporting process in which study teams are sent a detailed report of all charges posted to their account during a particular time period. Encourage study teams to review their reports and respond if the information on the report is accurate.

The report should also include total funds received and balance outstanding. This proactive approach will serve as a final check to ensure that charges have been captured correctly in a timely manner, while also providing a strong level of transparency into the study's finances.

Wrapping it Up

In conclusion, managing the finances of a clinical trial is challenging and requires significant collaboration across different functional areas. While it may seem to be a daunting task, take incremental steps and create a realistic timeframe for each milestone.

Consider ways to make your processes more transparent, such as via the use of a CTMS to create an integrated, transparent system that serves as a single portal for all clinical research studies. Allow for the ability to track the status of budget negotiations, contract execution, and IRB approval for any study, and institute reporting processes that incentivize study teams to regularly review their account.

Finally, build long-lasting relationships with your institution's billing office, and partner with its staff to ensure that the billing is done correctly.

References

1. Moran J, Stevens E, Statzel J. Navigating clinical trials billing: are you compliant? *App Clin Trials* 2013. www.appliedclinicaltrialsonline.com/navigating-clinical-trials-billing-are-you-compliant
2. Pfadenhauer J. Navigating the clinical trial billing maze. *J Oncol Prac* 2006;2(6):280. http://jop.ascopubs.org/content/2/6/280.full.pdf
3. Meade R. IRB members should know more about the reimbursement rules for clinical trial services, medical research law and policy. *BNA* 2006;18:65.
4. Rosenfeld C. Site solutions survey: lack of operating capital, cash flow plague investigative sites. *CenterWatch News Online,* November 2010. www.centerwatch.com/news-online/article/1010/site-solutions-survey-lack-of-operating-capital--cash-flow-plague-investigative-sites#sthash.SEAC70T6.dpuf

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Key Financial Audit Strategies and Considerations: A Research Compliance Officer's Perspective

PEER REVIEWED | Emmelyn Kim, MA, MPH, CCRA, CHRC

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Clinical research is a constant source of excitement, evolving regulatory changes, and challenges—all at the same time. As a research compliance officer, I can honestly say that financials have been the most challenging aspect of research to manage and audit.

LEARNING OBJECTIVE
After reading this article, the learner should be able to use strategies to effectively evaluate financial compliance in research.

DISCLOSURES
Emmelyn Kim, MA, MPH, CCRA, CHRC:
Nothing to disclose

The issues that arise are broad, always different, and sometimes interconnected. Among many other issues, a research compliance officer's day-to-day duties may include ensuring compliance in coverage analysis and in billing, coding, and charging of accounts tied to grants or contracts. Other issues that may crop up along the way can run the gamut from ensuring appropriate research sponsor contract language to handling financial issues affecting research participants.

When I attend research compliance conferences, financial compliance is often a "hot topic," which is understandable, because ensuring compliance requires a smooth-running and well-equipped machine involving multiple players. This means that operational processes have to be aligned with trained personnel, adequate resources, and ongoing checks and balances.

However, creating and maintaining a smooth-running operation may be challenging for institutions that are constantly balancing growing business and regulatory demands against limited resources. This rings true for me, as I am based out of a large, decentralized, and expanding health system. In my experience, most financial compliance sessions I've attended during conferences have been well attended, leading me to believe that this area is one that many institutions are struggling with today.

Regardless of the types of challenges your institution may have, using the right strategies and allocating resources wisely are key elements to the success of your audit or quality improvement programs. In this article, I'll share practical research compliance audit strategies and considerations from a research compliance officer perspective.

Planning Reviews by Performing Risk Assessments

After working in research compliance for many years, I have come to realize that there are different ways to identify and resolve issues; some are easy to detect and fix, while others are hard to uncover and need fixing "upstream," which may take months to ultimately close the loop.

As the central point of contact for all research compliance issues, I sometimes found it challenging to tease out audit priorities amongst all of the noise from urgent and ongoing issues. One thing I learned was that I could not identify (let alone fix) financial compliance issues by myself, and needed to partner with or rely on other departments to identify and resolve problems. The habits that I have grown accustomed to over time are planning, preparation, and communication, which are important skill sets for any auditor.

These concepts are incorporated into the annual research compliance work plan development process where I work. The work plan provides

an overview of audits and reviews of various areas scheduled for evaluation in the coming year, and is presented to and vetted by executive audit and compliance committees and institutional research committees.

The priority areas of the work plan are based on a risk assessment that occurs during the last quarter of every year, involving the following:

- interviews with key stakeholders (e.g., research teams, administrative and financial department staff, research support offices, compliance and research leadership) about what they believe are the top risk areas;
- an assessment of the current regulatory environment and focus (e.g., work plans, reviews and regulatory notices from the Office of the Inspector General, Centers for Medicare and Medicaid Services [CMS], Office of Management and Budget, etc.); and
- evaluation of past compliance or internal review findings.

Other factors are taken into consideration, such as new acquisitions and mergers, and an evaluation of the facilities or departments that will be conducting research studies involving grants or contracts and billing.

Taking the time to prioritize and plot out reviews using a workable timeframe (e.g., monthly or quarterly), based on regulatory compliance deadlines or institutional priorities will allow you to strategically perform reviews throughout the year. Building in enough space between reviews always helps, as there may be incidental reviews that pop up along the way, or ongoing reviews may take longer than anticipated.

Knowing Your Strengths and Weaknesses

Employing an effective audit strategy requires having a high level of self-awareness, a keen understanding of the environment in which you operate, and knowing your limitations. Questions to ask yourself include:

- Are clinical research financial processes at your institution handled manually or facilitated through mostly electronic systems (e.g., an electronic medical record, a billing registration system, a clinical trial management system, etc.)?
- What are the environments in which research billing may occur (e.g., inpatient, outpatient, and ancillary services)?
- Is the billing process centralized or spread out among many departments?
- What are the key departments that touch this process?

It is also important to know what processes people are handling well and where there are gaps. In order to identify areas of concern you have to investigate further and understand the root causes.

Are there areas with weak internal controls or a high potential for human error? For example, if your financial activity is driven by paper processes and multiple players, you may want to audit upstream manual processes that have a high impact on overall compliance. If your activity is largely automated through electronic systems, you may want to run reports that can detect problem areas throughout the process.

Focusing on high-risk areas where there are likely to be gaps may bring attention to operational kinks that have to be worked out, or additional education that may be needed. For example, are research participants and research-specific services flagged up front so that correct billing occurs on the backend?

If processes are in place, it's a matter of testing the system to ensure that it's working effectively. Conversely, if you know that you have a fundamental issue—for example, an up-front financial evaluation of research is not done (e.g., a coverage analysis and billing grid does not exist)—you may want to take a different approach, as it may be difficult to perform a financial audit without this step.

You may want to initially evaluate clinical trials billing more holistically and provide leadership with an idea of where operational resources need

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to be allocated. You should also be aware of what people are doing well, and which departments have strong leadership to leverage change.

The same concepts apply to departmental resources needed to perform financial research audits or reviews. Do you have personnel with the appropriate qualifications and enough resources to conduct compliance reviews? If so, are they properly equipped with the right tools, training, and support to perform the audit?

If you don't have internal staff, you may want to consider outsourcing and working with consultants who can provide the appropriate level of expertise and assist you in developing a strong program.

Evaluating the Financial Life Cycle

There are many components that make up the financial life cycle, and you can choose to break them down and prioritize reviews based on risk and the overall maturity of your program. Reviews can be of a study-specific nature or broad, in the sense that programmatic processes from different departments are evaluated.

The following are examples of financial areas to consider for review:

- Budgeting and contracts process (initial and modifications)
- Harmonization of research documents (e.g., contract, protocol, and consent)
- Coverage analysis process and billing grid development
- Front-end registration, charge capture, and segregation processes
- Evaluation of services at various entry points, such as inpatient, outpatient, and specialized ancillary services
- Insurance-based reviews, such as Medicare Advantage Plan billing
- Investigational device studies and CMS review process
- Back-end billing, scrubbing, and coding (e.g., professional, technical, and National Clinical Trial number) processes
- Capturing and posting of correct charges to research accounts
- Research account deficits or residual balances
- Sponsor invoicing process
- Cost allocation on federal grants (e.g., allowable costs and time and effort)
- Research and medical record documentation to support billing
- Participant issues (e.g., billing at external institutions and indigent populations, insurance denials, or study-related injury)

Looping Back from Findings to Improvements and Evaluation

Information gleaned from reviews should be used to inform institutional leadership and the stakeholders of key findings. For example, significant issues can be discussed at executive audit and compliance committees or operational level committees. Identified gap areas can subsequently be used to improve operational processes and inform policy creation or revisions to standardize processes and set expectations.

Financial hotspots should be included in ongoing education, training, and communication to raise awareness and prevent continued issues. A comprehensive training program or event that brings together all the players that touch the process is ideal. Training can be facilitated by key individuals within operational or compliance departments and supplemented by experts in the field, whether it be through consultants or individuals from other institutions.

Lastly, findings and processes developed as a result of the reviews should be used to inform future reviews. For example, if a new policy was created or revised or an operational issue resolved, a follow-up review should be performed at the right time to ensure that processes were fixed and operating smoothly.

The timing of reviews is crucial; reviewing a process that you know is lacking or still undergoing changes too soon may not provide meaningful

FIGURE 1: Research Financial Audit Strategy

information. The key factor is understanding that change is inevitable—departmental staff will turnover, electronic systems will change, institutions may acquire facilities or undergo mergers/acquisitions, and rules and regulations will change. Applying a loop back through well-planned and regular reviews, training, and education will ensure continued effectiveness of your program (see Figure 1).

Standing on Solid Ground

In today's complex and ever-changing business and regulatory environment, it is more important than ever to have solid strategy built into your financial audit program. This involves planning and prioritization, which should be developed and shared with stakeholders. It also involves being grounded and understanding strengths and weaknesses of your program to effectively target reviews and leverage leadership to effect change.

Ensure that your audits cover the full spectrum of risk and priority areas, and that they continually evaluate both internal and external environments to determine the scope of future reviews. Finally, ensure that you have a process to close the loop and continue the cycle through effective policy development, training, and communication.

Taking the time to prioritize and plot out reviews using a workable timeframe (e.g., monthly or quarterly), based on regulatory compliance deadlines or institutional priorities will allow you to strategically perform reviews throughout the year.

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Medicare Coverage in Clinical Trials: *Are Your Clinical Research Billing Practices Compliant?*

PEER REVIEWED | Lisa Murtha, JD, CHC, CHRC | Nicole Visyak, MS, MA, CCRC

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Clinical research billing remains a source of discontent for most research centers around the United States, due to its inherently complex operational and regulatory challenges. The U.S. federal regulations surrounding clinical research billing are arguably ambiguous and difficult to interpret, presenting significant compliance challenges for sites conducting clinical research.

LEARNING OBJECTIVE
After reading this article, the learner should be able to define what a Medicare coverage analysis (MCA) is and demonstrate an understanding of how an MCA is used to mitigate research billing compliance risks.

DISCLOSURES
Lisa Murtha, JD, CHC, CHRC, and Nicole Visyak, MS, MA, CCRC:
Nothing to disclose

The Centers for Medicare and Medicaid Services (CMS) published the National Coverage Determination (NCD) for Routine Costs in Clinical Trials (310.1) (sometimes referred to as the "Clinical Trial Policy") in 2000, and a second version in 2007, which remains in effect today. NCD (310.1) states that only "routine costs" in "qualifying clinical trials" are billable to the Medicare program.

The formalized process of determining what is considered a "qualifying clinical trial" (QCT) and "routine cost" has been cultivated over the past 10 years, and today is known as a Medicare coverage analysis (MCA) or a coverage analysis. The outcome of an MCA is a coverage memorandum, which outlines whether the study meets Medicare's qualifying criteria, and a coverage grid/billing grid, which stipulates what items and services performed in a clinical trial can and cannot be billed to Medicare and Medicaid.

Addressing research billing compliance is often not a glamorous subject, but its implications for research centers are tremendous, and cannot be avoided. Rush University Medical Center was the first institution to reach a public settlement with the government in 2005 for research billing irregularities under the False Claims Act, which subsequently cost Rush more $1 million dollars in fines and penalties. Rush was obligated to implement a process to analyze research protocols and CMS billing rules to document which items and services are billable and which should be invoiced to a research sponsor. It was this process that lead to the inception of the MCA.

MCAs are now not only expected by CMS, but it is widely accepted that they are the safest way to mitigate research compliance billing risks. The coordination and communication of information entailed in the MCA is equally imperative in building a robust compliance program.

Why Perform a Coverage Analysis?

The concept seems relatively simple: Do not bill Medicare for services that do not meet the requirements in NCD (310.1), and do not bill Medicare for items and services that are paid for by the sponsor. However, those familiar with performing an MCA often agree that the process is not always so straightforward, and can be incredibly arduous; yet the billing compliance risk that sites face when this procedure is not implemented can result in a myriad of unfavorable outcomes.

In addition to stiff financial penalties—as was seen in the Rush case—sites and individuals can be charged with civil and criminal penalties under the False Claims Act, with ramifications potentially as severe as termination of all research activity. Several other institutions have entered into public settlements with the government since 2005, but the Rush case was the first to heighten awareness of the confusion surrounding NCD (310.1), and forced institutions to take a more serious look at clinical research billing compliance.

Beyond the purposes of billing compliance, the MCA can provide several benefits to clinical research operations. For example:

- MCAs become a very useful tool in negotiations for payments from sponsors during study start-up processes;
- Revenue recovery can be improved when sites preemptively determine which items/services are not billable to Medicare, by ensuring that the study sponsor is providing payment for those items; and
- The MCA can be a useful tool in the institutional review board (IRB) review process.

In terms of the last item mentioned above, the IRB is charged with approving the final informed consent form, and part of this process includes informing research subjects of any financial burdens they may accrue as part of their participation in the clinical trial. The informed consent form must clearly state which items/services in the clinical trial are subject to payment from the patient and/or his/her insurance.

Research coordinators may also find the MCA to be a helpful resource for scheduling and registration. Furthermore, in the event of an audit or investigation, the presence of an MCA demonstrates a good faith effort by your site to maintain compliance in clinical research billing practices.

Routine Costs in a Qualifying Trial

NCD (310.1) from CMS stipulates that Medicare will cover the routine costs of QCTs, as well as reasonable and necessary items and services used to diagnose and treat complications arising from participation in these qualified trials. Routine costs, as defined by CMS, include[1]:

- Items or services that are typically provided absent a clinical trial (e.g., conventional care);
- Items or services required solely for the provision of the investigational item or service (e.g., administration of a noncovered chemotherapeutic agent), the clinically appropriate monitoring of the effects of the item or service, or the prevention of complications; and
- Items or services needed for reasonable and necessary care arising from the provision of an investigational item or service in particular, for the diagnosis or treatment of complications.

NCD (310.1) identifies the following items as being excluded from coverage[1]:

- The investigational item or service itself, unless otherwise covered outside the clinical trial;
- Items and services provided solely to satisfy data collection and analysis needs, and that are not used in the direct clinical management of the patient (e.g., monthly CT scans for a condition usually requiring only a single scan); and
- Items and services customarily provided by the research sponsors on a free-of-charge basis for any enrollee in the trial.

A study must meet QCT criteria as part of the MCA process and be documented accordingly in a billing grid. Generally, a study is considered a QCT if it meets the following criteria[1]:

1. The subject or purpose of the trial must be the evaluation of an item or service that falls within a Medicare benefit category (e.g., physicians' service, durable medical equipment, diagnostic test) and is not statutorily excluded from coverage (e.g., cosmetic surgery, hearing aids).
2. The trial must not be designed exclusively to test toxicity or disease pathophysiology (i.e., it must have therapeutic intent).
3. Trials of therapeutic interventions must enroll patients with diagnosed disease rather than healthy volunteers; however, trials of diagnostic interventions may enroll healthy patients in order to have a proper control group.
4. The clinical trial must be "deemed" to qualify (see below).

NCD (310.1) defines seven desirable characteristics a clinical trial must possess to be considered "deemed." The Agency for Healthcare Research and Quality (AHRQ) is an agency within the U.S. Department of Health and Human Services that has identified the following types of trials to be considered "automatically qualified" to receive Medicare coverage for routine costs[1]:

- Trials funded by the National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), AHRQ, CMS, Department of Defense (DOD), and Department of Veterans Affairs (VA);
- Trials supported by centers or cooperative groups that are funded by the NIH, CDC, AHRQ, CMS, DOD, and VA;
- Trials conducted under an Investigational New Drug application (IND) reviewed by the U.S. Food and Drug Administration (FDA); and
- Drug trials that are exempt from having an IND under 21 CFR 312.2(b)(1) in the *Code of Federal Regulations* will be deemed automatically qualified until the qualifying criteria are developed and the certification process is in place. At that

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time, the principal investigators of these trials must certify that the trials meet the qualifying criteria in order to maintain Medicare coverage of routine costs. This certification process will only affect the future status of the trial, and will not be used to retroactively change the earlier deemed status.

Local and National Coverage Determinations

In addition to the national coverage determinations detailed in NCD (310.1), coverage limitations may be determined by state governments. These are known as local coverage determinations (LCDs), and must also be considered when billing clinical research items to Medicare. The coverage analysis must reflect any relevant LCD or NCD for each item and service evaluated.

LCDs are determined by each state's Medicare Administrative Contractor, formerly known as the Fiscal Intermediary. These contractors make the majority of coverage determinations, so it is imperative that LCDs are researched, analyzed, and interpreted appropriately to determine if an item is billable to Medicare. This can be a major pitfall in clinical research billing compliance if not done properly.

NCD (310.1) and Medical Devices

Generally, NCD (310.1) does not apply to research billing for medical device studies. Through an interagency agreement, CMS and the FDA have developed a process to categorize all FDA-approved Investigational Device Exemptions (IDEs) for Medicare coverage and payment purposes.

There are two categories for devices for payment purposes:

- **Category A** devices are considered experimental and/or innovative devices, and are not covered by Medicare. However, the regulations do allow for the coverage of routine care services related to Category A devices furnished in conjunction with an FDA-approved clinical trial.
- **Category B** devices are nonexperimental and/or investigational devices, and may be submitted to Medicare for reimbursement in conjunction with routine care services related to the device.

Effective for Category A and B IDE studies approved by the FDA on or after January 1, 2015, study sponsors must submit a request to CMS for review and approval for Medicare coverage. Further details regarding this process and device coverage can be found in *The Medicare Benefit Policy Manual* (Chapter 14 is devoted to medical devices).[2]

How to Perform an MCA

As explained further in this section, the six-step process for completing an MCA consists of:

1. Gather essential documents
2. Conduct QCT analysis
3. Document patient care costs
4. Document which patient care costs are promised free of charge
5. Assess routine care items
6. Assign appropriate codes and modifiers as necessary

STEP 1: GATHER ESSENTIAL DOCUMENTS

The essential documents include the study protocol, clinical trial agreement, budget, and informed consent form. If FDA IND/IDE approval letters or Medicare Administrative Contractor approval letters are available, they should also be collected and referenced in the MCA.

The coverage memo should list which documents were used in the process and reference their version numbers/dates. The coverage memo will also contain all of the study identifying information (i.e., protocol name, number, principal investigator/coordinator name and contact info, etc.). The National Clinical Trial number listed at ClinicalTrials.gov should be referenced in the MCA.

STEP 2: CONDUCT QUALIFYING CLINICAL TRIAL ANALYSIS

The study must be reviewed to determine if it meets QCT status using the criteria mentioned above. This information should be clearly documented in the coverage memo.

The first criterion asks if the study is an investigation of a product or service that is covered by Medicare (e.g., drugs and biologics, lab services, etc.). The protocol title should often answer this question.

The second criterion is whether the study has therapeutic intent. This can be answered by referencing the study objectives or the study endpoints. For example, a statement indicating that the study intends to assess "progression-free survival rates" in a chemotherapy trial implies that the study drug or treatment regimen is intended to slow or

halt tumor progression, suggesting anticipated therapeutic intent.

The third criterion asks if the study enrolls patients with a diagnosed disease. This information is often identified in the protocol title or study eligibility criteria.

Finally, the study must be deemed, as described earlier. If the study does not meet one of the automatically "deeming" criteria, it must demonstrate that it meets the seven desirable characteristics. Identifying the study as "deemed" is not the same as meeting the QCT criteria; deemed trials meet one of the four criteria for QCT, but the other three criteria also must be met.

STEP 3: DOCUMENT PATIENT CARE COSTS

Patient care costs include all the items and services that are performed in the trial. This information is most often easily found in the protocol's Schedule of Activities grid. This information should be replicated in the Coverage Grid of the MCA.

A thorough review of the protocol should be conducted to ensure that required items/procedures were not left out of the Schedule of Activities. An "X" should be placed in the grid for each item required on its corresponding study day.

STEP 4: DOCUMENT PATIENT CARE COSTS PROMISED FREE OF CHARGE

The Clinical Trial Agreement and study budget provided by the sponsor should clearly detail what is provided to research subjects free of charge. For these items, any "X" in the coverage grid should be replaced by an "S" to indicate that the item is being paid for by the study sponsor.

It is helpful to include a "Comments" box for each line item in the coverage grid for making notes of where payment obligations reside (i.e., Clinical Trial Agreement, sponsor budget, etc.).

STEP 5: ASSESS ROUTINE CARE ITEMS

The remaining items must be assessed to determine if they meet CMS's description of a routine cost in a clinical trial, as listed above. In determining "routine/conventional care," a rigorous review of relevant medical literature must be performed to obtain objective support for what is typical care for patients absent a clinical trial.

For cancer trials, the National Comprehensive Cancer Network Guidelines are often consulted. The *New England Journal of Medicine,* Medline, and publications from professional societies, such as the American Academy of Cardiology, are also good resources that may be utilized.

Input from the principal investigator may be necessary in determining what is considered conventional care, if it is not always clear from published treatment guidelines. The source used in making a routine care determination should be referenced in the Comments section of the coverage grid. These items should have any "X" replaced with an "M" to indicate that the item can be billed to Medicare.

All items marked as billable to Medicare need to be evaluated for potential LCDs or NCDs. Details of any relevant LCDs/NCDs must be documented in the Comments section, as well.

STEP 6: ASSIGN APPROPRIATE CODES AND MODIFIERS AS NECESSARY

Finally, for all items marked as billable to Medicare, appropriate medical billing codes should be assigned. Coding professionals should be consulted to ensure that the proper codes are identified for the required protocol items/services. Online coding resources may be utilized, as well.

Effective January 1, 2015, the study's aforementioned National Clinical Trial number must also be included on a Medicare Claim. The V70.7 Code designated by Medicare should also be placed in the secondary diagnosis position on a Medicare Claim to note that this is a research participant. In some cases, Condition Code 30 (for nonresearch services provided to all patients, including managed care enrollees, enrolled in a QCT) will also be applicable.

What are known as Q0 and Q1 modifiers must be used to differentiate between routine and investigational items and/or services on outpatient claims submitted to CMS. Investigational items or services provided during, or as part of, an approved clinical research study should have a Q0 modifier. Q1 modifiers should be used for a routine item or service provided during, or as part of, an approved clinical research study.

Conclusion: A Solo Mission Impossible?

It is nearly impossible to find one individual qualified in all aspects of completing an MCA, so the best approach is generally to make it a team effort.

For the best results, the process should be centralized to ensure that all clinical trials are being analyzed with the same rigor on an institutional level. Operationalizing the information in the MCA within the revenue cycle is another challenge that most sites face, but the simplest solution starts with effective and ongoing communication.

Without proper controls in place and clear lines of communication identified among all parties involved in the clinical research enterprise, the MCA will not serve its purpose in avoiding billing risks. A commitment from leadership and concerted effort from all research professionals are necessary to implement these steps involved in building and maintaining a successful and compliant clinical research program.

A thorough review of the protocol should be conducted to ensure that required items/procedures were not left out of the Schedule of Activities.

References

1. Center for Medicare and Medicaid Services, National Coverage Determination for Routine Costs in Clinical Trials, July 2007, https://www.cms.gov/Medicare/Coverage/ClinicalTrialPolicies/index.html?redirect=/clinicaltrialpolicies/
2. *The Medicare Benefit Policy Manual,* Chapter 14 Medical Devices, November 2014, Centers for Medicare and Medicaid Services, www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/bp102c14.pdf

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HOME STUDY HS

Clinical Trial Billing

OPEN BOOK TEST

This test expires on October 31, 2016

(original release date: 10/1/2015)

Clinical Trial Billing: Solutions to a Complex Problem

1. What has prompted the recent increased attention on clinical trial billing?

A. Medicaid regulations
B. Audits
C. Whistleblowers
D. Budget constraints

2. Some institutions have implemented the following office to address billing challenges:

A. Centralized clinical trials office
B. Research compliance office
C. Technology transfer office
D. Sponsored projects office

3. Which of the following most accurately describes the purpose of creating a clinical trial budget?

1. To estimate how much will be left over at the end of the project
2. To determine the total costs that will be incurred as part of the study
3. To determine which procedures are to be billed to a research grant and which are to be billed to a patient's account
4. To compare costs at one site with costs incurred at other sites

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

4. What is the best way to prepare a budget?

A. Take your best guess
B. Take the sponsor's offer and make it work
C. Identify all costs that will be incurred during the study
D. Double the best estimate

5. Which document is needed to begin the first step of creating the budget?

A. Protocol
B. Sponsor budget
C. CMS regulations
D. Institutional code of conduct

6. At what point during budget development should the sponsor's offer be considered?

A. As soon as the sponsor's offer is received
B. Once the IRB has approved the study
C. Once the study is open to enrollment
D. Only after an internal budget has been completed

7. What role does the informed consent form have in clinical trial billing?

A. It must articulate which procedures are standard of care
B. It assures participants that they will never have a financial obligation when involved in the study
C. It must state that any bills received while participating in the study should be sent to the study team
D. It lets the reader know that the IRB approves all bills received by a participant

8. Which of the following resources can be helpful in tracking critical information related to clinical trial budgeting and billing?

A. Institutional compliance office
B. IRB submission
C. Study protocol
D. Clinical trial management system (CTMS)

9. Reviewing a contract's payment terms allows a reader to:

A. Prepare for sponsor negotiations
B. Submit full information to the IRB
C. Understand when and how a sponsor payment will be made
D. Determine whether a conflict of interest exists

10. Which of these is a good example of a proactive approach to managing clinical trial billing?

A. Distributing a monthly report that allows study teams to review current charges that have not yet been paid
B. Implementing a closeout process that requires a review of all past charges billed to a study
C. Calling all participants in a study and inquiring whether they received a bill
D. Requesting an audit to review past billing

Key Financial Audit Strategies and Considerations: A Research Compliance Officer's Perspective

11. Research financials are often difficult to manage and audit because issues arise that are:

1. Broad
2. Different
3. Interconnected
4. Costly

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

12. What are important skill sets for any auditor?

A. Planning, preparation, and communication
B. Coding, presentation skills, and planning
C. Report writing, communication style, and preparation
D. Problem solving, organization, and flexibility

13. What are priority areas of compliance that work plans are typically developed from?

A. Recent news articles, legal cases, and internal review findings
B. Recent internal audit findings, budget data, and regulatory notices
C. Stakeholder interviews, current regulatory environment, and past internal review findings
D. Hospital patient satisfaction surveys, review of top risk areas, and new acquisitions

14. What does OIG stand for?

A. Office of Inspections Guidance
B. Office of the Inspector General
C. Organization for International Guidance
D. Organization for the Inspector General

15. Which quality is important when employing an effective audit strategy?

A. Being diplomatic with all parties involved in the process
B. Including enough charts and figures in the work plan
C. Knowing how to use the electronic medical record system
D. Understanding the environment and knowing limitations

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

16. **What are important types of up front financial processes one can evaluate?**
- **A.** Flagging of research services or subjects
- **B.** Application of billing modifiers
- **C.** Transfer of charges to research fund accounts
- **D.** Time and effort certification

17. **What is a key financial area to consider for review in research?**
- **A.** Tax return forms for research subjects
- **B.** Coverage analysis for a study
- **C.** Hospital patient billing system security
- **D.** Research review committee turnaround time

18. **Which group of people should information from reviews be used to inform?**
- **A.** Patients and patient advocates
- **B.** Registrars, billers, and coders only
- **C.** Research investigators and coordinators only
- **D.** Institutional leadership and stakeholders

19. **What should review findings and processes developed as a result of the reviews be used for?**
- **A.** To review processes that are still undergoing changes
- **B.** To develop manuals for appropriately registering research subjects
- **C.** To prevent turnover of staff who are involved in billing
- **D.** To inform future reviews to ensure past issues were resolved

20. **What are the three elements of an effective loop back?**
- **A.** Planning, educating, and communication
- **B.** Evaluating, strategizing, and auditing
- **C.** Planning, executing, and improving
- **D.** Risk assessment, committee review, and policy creation

Medicare Coverage in Clinical Trials: Are Your Clinical Research Billing Practices Compliant?

21. **The federal policy that states only "routine costs" in "qualifying clinical trials" are billable to the Medicare program is known as:**
- **A.** NCD 310.1: National Coverage Decision for Clinical Trials
- **B.** NCD 310.1: Local Coverage Decision for Clinical Trials
- **C.** 45 CFR part 46
- **D.** 21 CFR 812

22. **Which of the following are examples of routine costs as defined by the Centers for Medicare and Medicaid Services?**
- **1.** Items or services required solely for the provision of the investigational item or service (e.g., administration of a noncovered chemotherapeutic agent), the clinically appropriate monitoring of the effects of the item or service, or the prevention of complications
- **2.** Items or services needed for reasonable and necessary care arising from the provision of an investigational item or service in particular, for the diagnosis or treatment of complications
- **3.** Items and services customarily provided by the research sponsors free-of-charge for any enrollee in the trial
- **4.** Items or services that are typically provided absent a clinical trial (e.g., conventional care)
  - **A.** 1, 2, and 3 only
  - **B.** 1, 2, and 4 only
  - **C.** 1, 3, and 4 only
  - **D.** 2, 3, and 4 only

23. **Which one of the following criteria must be met for a study to be considered a Qualifying Clinical Trial as stated in the Clinical Trial Policy?**
- **A.** Trial must evaluate drug safety and tolerability
- **B.** Trial must be funded by the NIH
- **C.** Trial must enroll healthy subjects
- **D.** Trial must have therapeutic intent

24. **Which category of medical devices may be submitted to Medicare for reimbursement?**
- **A.** Category A devices
- **B.** Category B devices
- **C.** Category C devices
- **D.** Category D devices

25. **Which of the following are essential documents required to perform a Medicare coverage analysis?**
- **1.** Research charge master
- **2.** Study protocol
- **3.** Informed consent form
- **4.** Study budget
  - **A.** 1, 2, and 3 only
  - **B.** 1, 2, and 4 only
  - **C.** 1, 3, and 4 only
  - **D.** 2, 3, and 4 only

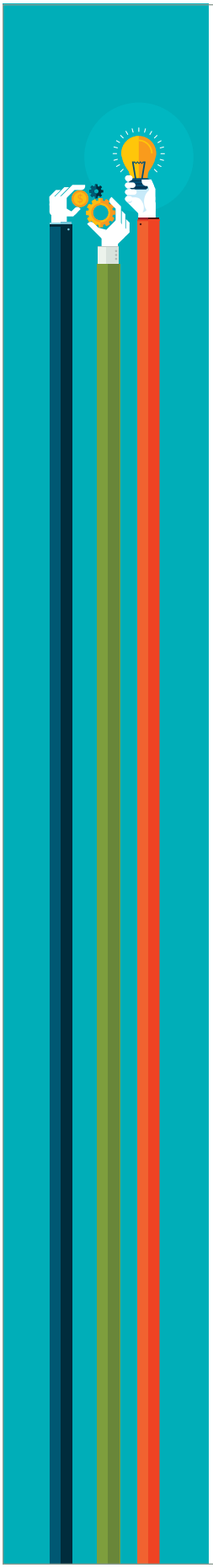
26. **Qualifying Clinical Trial analysis requires a review of:**
- **1.** Medicare benefit category
- **2.** Progression-free survival
- **3.** Therapeutic intent
- **4.** Diagnosed disease
  - **A.** 1, 2, and 3 only
  - **B.** 1, 2, and 4 only
  - **C.** 1, 3, and 4 only
  - **D.** 2, 3, and 4 only

27. **Which essential document provided by the sponsor details which items and services are provided to subjects free of charge?**
- **A.** Clinical Trial Agreement
- **B.** Study protocol
- **C.** FDA IND letter
- **D.** Schedule of activities

28. **Routine care items determined to be billable to Medicare are indicated in the coverage grid with which letter?**
- **A.** B
- **B.** S
- **C.** M
- **D.** X

29. **Which of the following are required to be affixed to Medicare claims for items/services performed in a clinical trial?**
- **1.** Patient study ID number
- **2.** V70.0 code
- **3.** Condition code 30
- **4.** NCT number
  - **A.** 1, 2, and 3 only
  - **B.** 1, 2, and 4 only
  - **C.** 1, 3, and 4 only
  - **D.** 2, 3, and 4 only

30. **Investigational items or services provided during or as part of an approved clinical research study should have which modifier?**
- **A.** V70.0
- **B.** Condition code 30
- **C.** Q0
- **D.** Q1



Feeding the Hunger for New Ideas

Curiosity is wired into our DNA. We want to always be moving forward. To learn. To understand. To crane our necks in an effort to see what's coming around the next bend.

Today's clinical researchers are hungry for new ideas, and they devote time and energy to locating those rewarding professional environments that actively encourage them to lean forward. It's about finding the best new courses, seeking new certifications, and culling the strongest ideas from a wide assortment of tools, including management reports, conference presentations, webinars, and onsite training opportunities.

Across the board, clinical researcher employers appear to be getting the message. To learn more, we asked employees at medical device, pharmaceutical, and contract research organization (CRO) firms about their shops' policies on education and training (see chart below).

Within a few wrinkles here and there, the overarching message was clear: More than half offered in-house training and/or allowed employees to participate in educational opportunities. CROs tended to lead the way with in-house programs; medical device and pharmaceutical shops more often encouraged personnel to explore educational opportunities at other venues.

Companies also kicked in financially: More than 70% of medical device firms paid for employee meeting, training, and development events. More than half of pharma companies and more than one-third of CROs did the same. These companies understand that a well-trained workforce is also a productive, motivated work force.

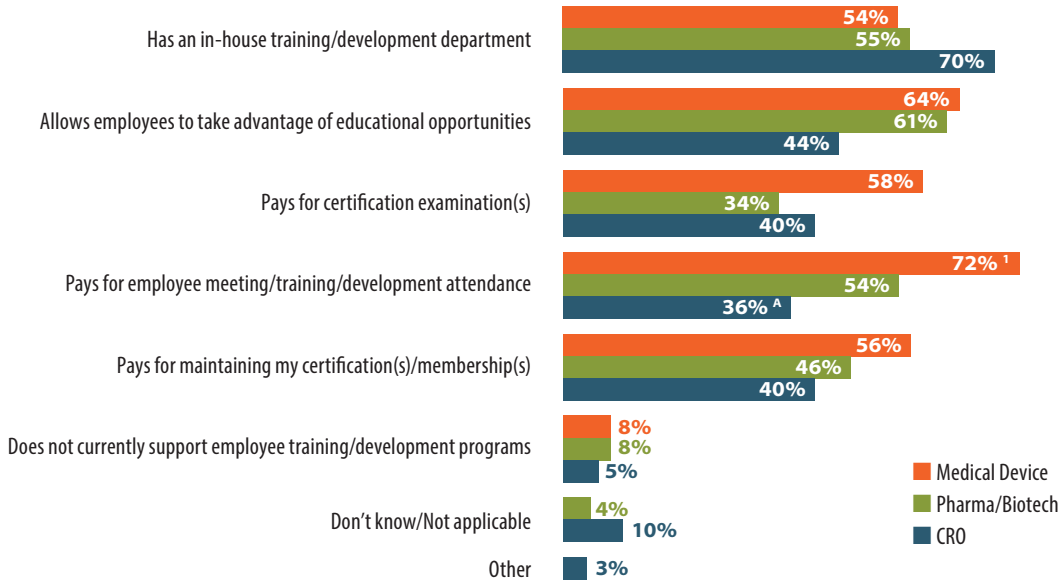
It's more than a hunch: In our CRC Perspective column, guest author Nancy A. Needler, BS, CCRC, and frequent columnists Claudia G. Christy, RN, MSN, CCRC, and Laura B. Cowan, MA, reference an important 2008 survey that found job satisfaction was tied directly to job training programs. You'll find more on that on page 31.

At ACRP, we obviously recognize the importance of training and certification. Few would argue that these are not valuable pursuits for clinical researchers and the industry as a whole.

In this special report, a handful of leading training practitioners make the best case for their own philosophy and resources. We hope the information contained here, and throughout *Clinical Researcher*, informs future training decisions and inspires clinical researchers everywhere to continue their quest to be their best.

James Michael Causey
Editor-in-Chief
Clinical Researcher

COMPANY POLICIES ON EDUCATIONAL MEETING ATTENDANCE AND EXTERNAL TRAINING/DEVELOPMENT OF EMPLOYEES



% mentioning
Base: Total (n=270), CRO (n=149), Pharma/Biotech (n=71), Medical Device (n=50), Sample Size = 270. ***Statistically significant at 95%: 1 > A***

The Rutgers University Biopharma Educational Initiative Offers a Unique Curriculum Design for Online Graduate Programs in Clinical Research

Drug development is a costly and timely process, requiring highly knowledgeable and skillful research professionals. This was the impetus for a collaboration between Merck and the Rutgers School of Health Related Professions, and the subsequent development of a unique online Masters Degree in Clinical Trial Sciences. This program began as a post-baccalaureate Certificate in Recruitment Sciences in 2006. Merck recognized that one of the bottlenecks to bringing a drug to the marketplace was subject recruitment. New methodologies and metrics were being collected to document recruitment but there was a shortage of individuals who understood the science and psychology involved. With the help of high-level individuals at the company, and Rutgers faculty, this 15-credit certificate was created. After reviewing the needs of the pharmaceutical companies within New Jersey, Rutgers developed two additional certificates, Regulatory Affairs and Informatics. In 2009 the certificates were converted to tracks and a Masters Degree was created to further meet the work-force needs of the industry.

The Biopharma program has grown from 11 students to over a 100, and now offers specialization tracks in four areas including; Regulatory Affairs, Drug Safety & Pharmacovigilance, Clinical Trial Management, and Informatics. The program has a unique curriculum design in that students take three core courses including a capstone course or field-work experience and then specialize in one of the four areas. Students take electives from the alternate tracks so they fully understand the breadth and depth of the enterprise. This design enhances their marketability and avoids forcing them to apply to only one job type. Additionally, students have been placed at the FDA, Merck, Novartis, and other companies for fieldwork experiences as well as CROs and academic medical centers.

> The MS in Clinical Trial Sciences program has been a tremendous asset to my career. Not just in terms of a competitive advantage but also in my understanding and execution of learned skills from my curriculum.

Faculty support and advisement is a big component of this program. Faculties from pharmaceutical companies bring real-life experiences. Faculty are also heavily involved in professional societies including ACRP, DIA, SOCRA, and RAPS. Additionally, the program is a member of the Consortium of Academic Programs in Clinical Research, and faculty are involved in writing accreditation standards for academic programs.

While academic programs in clinical research are fairly new, employers and graduates already recognize their value. As noted by some of the graduates: "The MS in Clinical Trial Sciences program has been a tremendous asset to my career. Not just in terms of a competitive advantage, but also in my understanding and execution of learned skills from my curriculum. The online program was easy to balance with my demanding job. My acquired skill-set and knowledge has proven invaluable in my career in this dynamic regulated industry," says Michael P.

Anna B. shares that joining the Biopharma Educational Initiative was one of her best life choices. "Besides excellent education and mentorship, I was exposed to a whole new world of potential opportunities to pursue."

Applications are accepted in the fall and spring. GREs are not necessary but a goal statement, resume, transcripts, and references are required. Many of the students are adult learners who have full-time jobs and families to support. They find the online mode of administration and flexibility extremely helpful.

Given the complexities of bringing products to market, specialists in drug development are needed in a variety of positions and job roles, and Rutgers is poised to meet these needs.

For more information please call 973 972-6482 or visit http://shrp.rutgers.edu/dept/biopharma/

Barbara Gladson PhD, Director of the Biopharma Educational Initiative, MS in Clinical Trial Sciences

Rutgers, The State University of New Jersey

1766-2016 RUTGERS 250 *Revolutionary for 250 Years*

Things move fast in the pharmaceutical industry.

The MS in Clinical Research Organization and Management program offered both flexibility and a rigorous curriculum, and eventually piqued Dean's interest in entrepreneurship.

For professionals like Brian Dean—a former clinical research manager for Auxilium Pharmaceuticals (now Endo International) whose career in the pharmaceutical industry has taken him all over the world doing pharmaceutical trials—mastering the latest industry trends is imperative.

"In clinical and pharmaceutical research, you can always learn more with how often and quickly things change," said Dean.

Dean knew that a graduate degree would be the best way to gain the skills needed to be successful in the pharmaceutical industry. But with a hectic travel schedule, he knew he would need a program that allowed the flexibility to attend online.

As an employee of a Drexel Online partner organization, Dean was able to receive significant tuition savings to participate in the Drexel University College of Medicine's Master's in Clinical Research Organization and Management program.

The MS in Clinical Research Organization and Management program offered both flexibility and a rigorous curriculum, and eventually piqued Dean's interest in entrepreneurship. Shortly after he graduated from the program in 2014, he decided to leave his position at Auxilium to launch his own clinical research consulting firm, Dean Clinical Consulting.

"While I was at Auxilium I was already putting what I learned each day into practice. And now, as a consultant, having that degree on my CV is absolutely essential," said Dean.

In the future, Dean plans to launch his own Contract Research Organization (CRO), CliniTx International, with a partner in Texas; a venture he says Drexel helped prepare him for.

"Drexel's program offered courses that are essential to both my consulting work and new CRO—classes such as Pharmaceutical Law and Pharmacovigilance cover issues that come up every day," said Dean. "What I learned has helped me immensely."

Drexel University's College of Medicine offers online clinical research programs that train students to administer and manage critical medical investigations in a variety of settings. Designed to meet your specific career goals, these degrees and certificates utilize research practicum supplemented by coursework focused on contemporary business, legal, and ethical issues pertinent to the clinical research, pharmaceutical, and healthcare industries.

To learn more about Drexel University's online clinical research programs, please visit: Drexel.edu/OnlineCR

Queen Muse,
Communications Manager

Drexel UNIVERSITY ONLINE

Nancy A. Needler, BS, CCRC; Claudia G. Christy, RN, MSN, CCRC; Laura B. Cowan, MA

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CTSA Program and Other Training Resources for CRCs

Have you ever found someone who appears to be a promising new clinical research coordinator (CRC) for your research team but, because he or she is brand new to the position's duties, you wondered where to begin with explaining how study sites are managed and what the job expectations are? For new hires and existing staff alike, orientation and continued training development opportunities are essential components of even the most basic of clinical research offices.

While training may initially appear as a complex and potentially costly program to implement, some great resources exist to ease the burden. In fact, the Clinical and Translational Science Award (CTSA) program's Research Coordinator Taskforce has focused on this very topic. Based within the National Institutes of Health (NIH), the CTSA program addresses the development and implementation of national standards and best practices for translation of research from bench to bedside. The program supports a national network of medical research institutions collaborating to transform how clinical and translational science is conducted nationwide.[1]

Membership and Methodology of the Research Coordinator Taskforce

For new hires and existing staff alike, orientation and continued training development opportunities are essential components of even the most basic of clinical research offices.

The Research Coordinator Taskforce began in 2006, and included as its members colleagues from the initial 16 academic medical centers that had received CTSA program funding. The taskforce averaged 43 people, and included institutional trainers, CRCs, and institutional review board members who worked together via web conferences, e-mails, and phone conversations to fulfill the group's mission to support the professional development of CRCs and to help guide institutional leaders on how to organize and network their CRC workforce.

The taskforce sought to understand the needs of coordinators, and in 2008 a survey of CRCs was fielded and analyzed. The critical need for academic health centers to assess the training, support, and career development requirements of CRCs emerged in a published report.[2]

One of the survey's findings demonstrated that job satisfaction is tied directly to job training, therefore the taskforce recommended retention of CRCs through recognized training programs at the local, institutional, or national levels. The taskforce also emphasized that training topics covered must be adequate to arm CRCs with the tools to be successful in the execution of their job responsibilities.

Tools from the Taskforce

To address these training recommendations, the taskforce developed an extensive document on "Training Elements of Human Subject Research Coordination." This comprehensive list maps to the life cycle of study management and provides a categorical listing that serves as a lesson plan for educators and trainers to begin developing training programs that provide content areas typically relevant for CRCs. An accompanying document on professional resources lists books, organizations, and websites of use to CRCs and trainers.[3]

Other Sources of Note

During the same time period as the taskforce's work, other academic offices, individual principal investigator teams, research industry agencies, and local and national groups identified standards for training the CRC workforce. Enhanced standardization of training has also occurred through fruitful discussions advanced through collaborative groups such as, but not limited to:

- Oncology Nursing Society (core competencies) at https://www.ons.org/practice-resources/competencies
- The Consortium of Academic Programs in Clinical Research at www.coapcr.org/
- Joint Task Force for Clinical Trial Competency at http://mrctcenter.org/files/mrct/files/jointtaskforceforclinicaltrialcompetency.pdf[4]

- TransCelerate Biopharma Inc., Site Qualification and Training project at www.transceleratebiopharmainc.com/initiatives/site-qualification-and-training-sqt/
- Association of Clinical Research Professionals: Competency Domains for the Clinical Research Professional at www.acrpnet.org/MainMenuCategory/Education/Building-Competencies.aspx
- Collaborative Institutional Training Initiative at the University of Miami, Clinical Research Coordinator course at https://www.citiprogram.org/index.cfm?pageID=834

Furthermore, the National Center for Advancing Translational Science (NCATS), which is home to the CTSA program (see https://ncats.nih.gov/), awards funds for projects with special attention to developing the research workforce. A project on "Enhancing Clinical Research Professionals Training & Qualifications" was funded at the CTSA program at University of Michigan, with its first goal being to establish standardized training for good clinical practice for clinical trial personnel. Having accomplished that, the development of a competency-based education curriculum for training principal investigators and CRCs is the next phase of the grant's activities (see www.ctsa-gcp.org/news).

Conclusion

As training standards are further developed and available, the future is looking bright for research coordinators and investigators at academic health institutions and other sites at the institutional and national levels.

We hope that you find these resources to be valuable both to yourself and other current and future research processionals. The Research Coordinator Taskforce worked diligently to compile a list of quality resources to help guide your training practices. We invite you to share what was developed and join the conversation to continue the advancement of clinical research training opportunities.

Disclosure

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References

1. www.ncats.nih.gov/ctsa
2. Speicher LA, Fromell G, Avery S, et al. The critical need for academic health centers to assess the training, support and career development requirements of clinical research coordinators: recommendations from the Clinical and Translational Science Award Research Coordinator Taskforce, *CTS Journal,* 5(6): December 2012, pp 470–5. www.ctsjournal.com
3. University of North Carolina. Carolina Digital Repository. Training Elements of Human Subjects Research Coordination CTSA Research Coordinator Taskforce https://cdr.lib.unc.edu/record/uuid:87328561-9e23-472c-83f6-5e78ac18f4d3
4. For more information, see: Sonstein SA, Seltzer J, Li R, Silva H, Jones CT, Daemen E. Moving from compliance to competency: A harmonized core competency framework for the clinical research professional. *Clinical Researcher,* June 2014, pp 17–23.

Clinical Research That Takes You to a New Level of Proficiency

Many clinical research associates spend as much as **75%** of their time on the road

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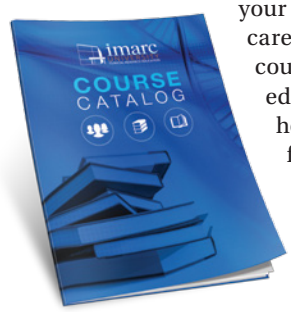

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THE OHIO STATE UNIVERSITY

MISSION IMPOSSIBLE:
Research Billing Compliance

Learning to differentiate between what is considered routine care or research related services in a qualifying trial is daunting. Getting this process correct is tricky. New regulations, updates, and the latest information sharing has placed clinical trial billing on the top of everyone's mind. Pharmaceutical sponsors and device companies are also developing expertise, as well as sites in this area. Are you aware of the recent regulations from the Medicare Advantage Plans and the drug trials? What is the latest with revenue code 53 and the device approvals from Medicare? Budgets, billing grids, contracts and workflows are complex and with many teams in an organizational "silo" structure, no one group is accountable for the entire process.

This process includes the clinical teams, as well as the finance and coding teams. Claims for clinical trial services to third party payer misdirection come about because hospital billing systems do not always have the infrastructure build to help in this process. In order to aid in the standardization, consistency, transparency and accountability of clinical trial services, as well as assist Principal Investigators to focus on accrual, setting up a centralized clinical trial support office is recommended. In order to develop a sustainable and scalable program in billing compliance, EMR and hospital billing systems must be involved. A clinical trial management system (CTMS) complete with a calendar and tools will empower your billing compliance team to develop a process flow. These processes involve the IT department, the EMR, and the facility/professional billing areas as well.

Gaining a return on investment for this centralized process is challenging for both sites and pharmaceutical sponsors. In order to be successful, it is necessary to prepare a coverage analysis with a solid budget, and establishing a bill hold on all claims in order to process them accordingly and determine the proper codes and modifiers. Then it takes widespread collaboration. Taking on payer challenges, appeals, timely filing, and Medicare Advantage with an understanding of what will work and what will not work should be a part of the process flow. How do you accomplish all of this with cuts in staffing?

In hospital, physician practices, and clinic settings, these topics still remain a challenge. By attending the 10th Clinical Trial Billing and Research Compliance Conference February 28 – March 2 in New Orleans, those responsible for billing and research compliance will benefit from two workshops, a master class session, and multiple case study and panel discussions from thought leaders in the field.

For more information please visit our website at exlevents.com/CBRC.

Kelly Willenberg, MBA, BSN, CCRP, CHRC, CHC

Kelly Willenberg is the owner of Kelly Willenberg, LLC. Kelly has extensive knowledge in clinical trials management and research compliance, including all aspects of clinical trial billing compliance. She has nearly 30 years of clinical research experience and billing compliance.

Increasing Fiscal Return and Mitigating Financial Risk in Clinical Trials

PEER REVIEWED | Tina Noonan, MBA, CHRC, CIP | Erika J. Stevens, MA

[DOI: 10.14524/CR-15-0033]

Developing robust clinical trial budgets is a challenge for many sites, as is maintaining adherence to Centers for Medicare and Medicaid Services regulations for research billing. Poor clinical research fiscal forecasting and undefined clinical research billing compliance practices increase the risk of deficits and of federal regulatory investigations.

This article identifies pre-award processes and institutional approaches for increasing fiscal return and mitigating fiscal compliance risk for clinical trials. Strategies for covering the full true costs to sites of clinical trial research are described, and techniques for avoiding false claims and other related research billing problems are illustrated.

The Clinical Research Billing Compliance Process

In today's highly competitive clinical research environment, it is vital for sites to establish and maintain processes for increasing fiscal return from clinical trials while simultaneously mitigating financial regulatory compliance risks. The backbone to accomplishing both goals is a strong research billing compliance program, and this begins with the coverage analysis process.

The regulatory impetus for the coverage analysis process arose in 2000, when the federal government issued the National Coverage Determination (NCD). The NCD authorized Medicare to pay for routine patient care and costs of medical complications associated with a patient's participation in a clinical trial. To qualify for such coverage, a study must meet certain criteria, as detailed in the NCD.[1]

The term "coverage analysis" is just one of several interchangeable terms (e.g., Medicare coverage analysis, prospective reimbursement analysis) used to describe a uniform method of analyzing the items and services provided in a clinical study to determine if the item or service can be appropriately billed to Medicare under the terms of the NCD. It is also important to understand that coverage analysis can refer to the overall process, or to the document underlying the process.[2]

Attributes of the Analysis

A strong coverage analysis process allows for routine care services to be routed to the appropriate payer, and appropriately coded for that payer. As such, a thorough and complete coverage analysis is crucial for several reasons, not the least of which is to protect the clinical research site from noncompliance with the False Claims Act and other similar regulations. Complete coverage analyses, when used in conjunction with clinical trial budgeting, can also support a detailed assessment of the costs to the site of participating in the study.

Coverage analysis may provide potential study participants with an estimate of their financial liability before they enroll. For many sites, this simply means that the coverage analysis document can help the person who consents the patient to answer questions about the cost of participating in the study. Some sites, however, include a simplified billing grid in the informed consent document itself to aid the patient in understanding his or her potential financial liability.

A thorough coverage analysis coordinates relevant study information (protocol, consent, contract, budget, etc.), facilitates and strengthens the budgeting process, provides a standardized billing tool to all parties involved in the billing process, and establishes a financial and compliance auditing platform. In short, it serves as a centralized repository for documentation of all relevant research billing decisions.

Variations On a Theme

Each clinical research study is unique in its scope and complexity, so the coverage analysis process and document will likely vary from study to study, and from site to site. The critical unifying thread, however, is that the coverage analysis process should result in strong documentation of the reasoning process behind the research billing decisions.

Figure 1 shows excerpts from a coverage analysis template used at some sites. This template highlights two important components for all coverage analysis: 1) a mechanism to document the site's assessment of the qualifying status of the study itself, and 2) a grid noting which specific protocol-required items and services are considered billable to Medicare (or

Before beginning budget negotiations, it is very helpful to pull together the full study team (including the person who will be doing the actual budget negotiation) to review the budget.

other third-party billers) and which must be paid through the study budget. One further component not shown in this example, but which is equally important, is a signature page, including a place for the principal investigator (PI) to indicate agreement with the determinations made during the coverage analysis process. The PI signature provides documentation of investigator accountability in the coverage analysis process.

A strong clinical research billing compliance program incorporates oversight of the research billing activities before a study begins, as well as during and after the study. It is important to establish the "front-end" and "back-end" safeguards that facilitate the process of achieving total compliance. On the front end, the coverage analysis process synchronizes study information and documents billing determinations for a study as a whole. On the back end, site processes should use those tools developed for the front end to direct the actual charges to the appropriate payer.

Maintaining clinical research billing compliance is crucial, and can become highly problematic if conducted improperly. There is no single correct way to develop and implement research billing compliance controls to meet federal clinical trials billing regulations, but standardization of the entire billing process is a key step.

A comprehensive clinical trial billing compliance program can help organizations establish standards to meet regulatory requirements and provide sustainable organizational consistency. Failure to comply with federal clinical trial billing regulations can lead to research suspension, fines, the imposition of Corporate Integrity Agreements, and damage to the organization's and/or PI's reputation. Establishing standards is essential for mitigating the risks associated with billing noncompliance.

Techniques and Leading Practices for Clinical Research Fiscal Activities

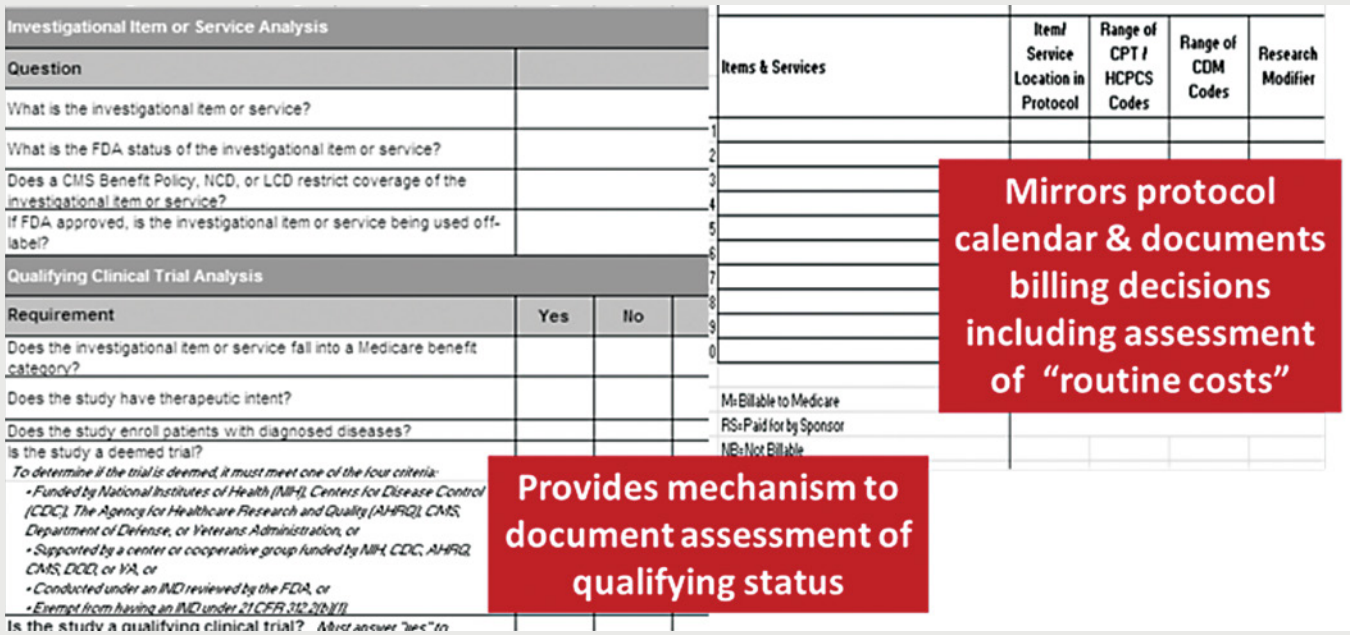
In the previous section of this article, we reviewed the overall clinical research billing compliance process. In this section, we present several real-world techniques and leading practices for managing the financial aspects of clinical research. The focus will be primarily on the front end of the site's research billing compliance process.

When a new study is presented to a site by a sponsor, there is generally a budget offer accompanying the protocol and other study documentation. The question is whether the sponsor's budget is truly adequate to cover the site's costs of performing the study.

If the sponsor provided a detailed budget to the site, this can make a good starting point; however, sponsor-prepared budgets do not always include all the costs associated with the study. Developing a coverage analysis as described above, and determining the site costs for each of the items and services that will be billed to the study, is an important next step.

However, an additional leading practice for the site is to thoroughly review the study protocol to

FIGURE 1: Example of Coverage Analysis Document



ascertain the difficulty and/or complexity of the study; study preparation and training requirements; participant acuity and age; and overall length of the study. Each of these factors may affect actual costs of study performance. For example, acuity of a study participant's medical condition could complicate or lengthen the time required for obtaining informed consent or for performing certain study procedures.

Nonpatient costs are important to consider as well. For example, if the sponsor offered a lump sum to cover study start-up costs, is the amount sufficient to pay for the site's time and effort in terms of contract and/or budget preparation and negotiation? How about the time spent preparing and maintaining regulatory documents?

Also keep in mind the costs of all staff duties related to data management (both while the study is active and during close-out), case report form completion, time spent with the monitors, any advertising expenditures, and archiving. Screening, including the costs of prescreening before any subject is enrolled, pharmacy storage and preparation costs, and shipping costs also factor into the equation.

In addition, the payment schedule should take into account front-loaded screening or dose-escalation visits that may be more intensive than later visits. Furthermore, failure to manage the timeline for when the study site is initiated often presents problems, especially if payments are based on milestones.

Laying the Groundwork

Before beginning budget negotiations, it is very helpful to pull together the full study team (including the person who will be doing the actual budget negotiation) to review the budget. Questions to think about during this review should include:

- Is the study financially feasible? If not, is there departmental/organizational support for doing the study (i.e., is there a compelling reason the study should be done even if an overall financial loss has been projected)?
- Does the budget reflect the coverage analysis? Have all potential cost elements been incorporated?
- Has a budget negotiation strategy been discussed and agreed to by the study team?
- How will stalled budget negotiations be handled? Consider if the PI is willing and able to assist, and is an organizational official at a higher level willing to step in, as needed?

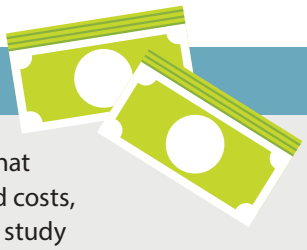
Why is the budget development and review process so important? For one thing, a thorough cost analysis, when done as part of budget development, allows the investigators, departments, and other site stakeholders to understand the study's true cost, thus allowing for more robust financial planning. Furthermore, the process links coverage analysis results with the study budget, thereby providing an opportunity to resolve any outstanding questions of standard-of-care vs. research categorization before budget negotiations begin.

As such, full budgetary review should be done for all clinical research studies, irrespective of funding source. Even in the case of unfunded studies, the process aids in the clarification of the actual financial investment needed to do the study, thus promoting an informed decision to move forward. Finally, the budget development and review process provides leverage to the site's budget negotiator by having a full understanding of the rationale for how the budget was set.

Along with the development and review process, it is important to develop practical and effective budget negotiation strategies. For instance, it is prudent to open negotiations with a sufficient cushion to enable concessions, as necessary. Consider setting the opening quote for procedure costs at the site's "full charge" level, with an extra percentage added for price increases in future years.

As an example, if the MRI institutional full charge is $3,500, and the study is expected to last two years with an inflation rate of 3% per year, the price for the MRI used at the opening of budget negotiations would be set at $3,605 ($3,500 plus 3% to cover potential price increase in year two). When setting full-time equivalent and salary opening quotes (whether as part of the per-patient fee or as a separate budget line item), add a buffer to each so that there is room to negotiate. No matter how the opening quote is established, the site's budget negotiator should always keep the actual costs in mind to prevent dropping too low during the negotiations.

TABLE 1: Dos and Don'ts of Clinical Research Budget Development



- **DO** create a project-specific, detailed budget that includes all protocol procedures and associated costs, even if it's not required by the sponsor or if the study is not yet funded. This should be done before the site agrees to take on a study.
- **DO** make sure the site's budget appropriately includes all the procedures that were determined to be study-related in the study's coverage analysis.
- **DON'T** enter into final budget negotiations and execute an agreement until a final budget has been created and all study costs have been identified.
- **DON'T** give final approval to the budget without reviewing the final protocol.

Before concluding budget and contract negotiations, be sure to review the study documents to provide harmonization of terms between the informed consent document, contract, and budget. Pay particular attention to terms related to any of the sponsor's promises to pay for specific items or services, the timing of and/or restrictions on a sponsor's payments to the site, and any subject injury clauses.

Finally, keep in mind time limitations that often accompany budget and contract negotiation; this mandates careful adherence to well-planned timelines for the process. To employ the oft-quoted maxim, "Time is of the essence." This holds true for most clinical research, so having standard timelines for completion of the various pre-award steps is helpful.

An example of such standard timelines is presented in Table 2. While specific timelines may not fit for every site or every study, establishing and utilizing such standards are highly effective for many sites, and can ensure that both the site and the sponsor maintain the momentum necessary to open a new study.

Study Start-Up

An important key to maintaining compliant billing once the study begins is to implement a reliable method of identifying and tracking participants in the institution's billing system. One option is to "register" all study participants in the institution's electronic medical record (EMR) system and flag them under a "research" category. This assumes that the EMR and the billing system are linked, and that the research flag carries through from one system to the next.

Another option is to use a clinical trial management system (CTMS) to register and track all studies and study participants. This also assumes that the CTMS and the billing system are linked, and that research information flows from one system to the next.

Finally, one might utilize a special research procedure order form, or a special research code on regular clinical order forms. This assumes that the appropriately marked form is matched up with any resulting bill *before* that bill is released. This part of the process can be especially challenging for an organization whose primary mission is clinical patient care rather than research. In those cases, billing or revenue management units may not have experience with the regulatory complexities of research, so their systems and processes may not be set up in a way that will readily accommodate what is required to produce appropriate billings to research participants.

Conclusion

Balancing fiscal responsibility in clinical research with regulatory billing compliance demands is challenging for most sites. This article addressed the clinical research billing compliance process, with emphasis on those processes done by the site on the front end of initiating a new clinical trial. Tips and leading practices that are effective at some sites were shared as examples that may prove useful for adaptation to the reader's own site.

TABLE 2: Example of Standard Timelines for Pre-Award Processing of Industry-Sponsored Clinical Research

COVERAGE ANALYSIS AND INITIAL BUDGET:

- Drafted and sent to the research team for review and approval within five business days of receipt of all study-related documents.
- Research team is asked to respond with revisions, issues, or concerns within two business days.

LEGAL REVIEW OF CLINICAL TRIAL AGREEMENT:

- Initial redline drafted and sent to sponsor within five business days of receipt of all study-related documents.

FOLLOW-UP:

- Weekly follow-up with sponsors who have not responded within one week of documents/query being sent to them.

THREE STRIKES POLICY:

- If sponsor does not respond after two weekly follow-up attempts, the PI is asked to contact the sponsor to inquire as to status. Further escalation to higher level institutional officials may also be useful.

References

1. Centers for Medicare & Medicaid Services. *National Coverage Determination (NCD) for Routine Costs in Clinical Trials* (310.1). July 9, 2007. www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=1&ncdver=2&bc=BAABAAAAAAAA& (accessed June 1, 2015).
2. Moran M, Stevens E, Statzel J, "Navigating Clinical Billing: Are You Compliant?" *Applied Clinical Trials*, 2013 January; 22.

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Ronald S. Waife

Erase RACI

One of the operating assumptions widely used in biopharmaceutical process analysis is the "RACI" model. RACI stands for Responsible, Accountable, Consulted, and Informed, referring to what role any particular person, job, or department has in a particular project or process.

RACI has met the common fate of other time-worn jargon: It is now misused, misunderstood, and misleading.

The point of RACI is to provide a handy structure for teams or complex organizations to sort out, and document clearly, who is going to do what. However, RACI has met the common fate of other time-worn jargon: It is now misused, misunderstood, and misleading.

WHAT WENT WRONG?

Unless you are a sapphire-belt Six Sigma facilitator, the RACI model has long outlived its usefulness. Flawed at birth, its failings are ever more manifest, and yet the RACI model lives on like Tang on the International Space Station.

Perhaps you have never heard of the RACI model, in which case you have been spared. Each component of the model, *in actual use* today (not as it was originally conceived) is problematic. It is not enough to say, "well, people just aren't using it correctly." If the original definitions are forgotten or are no longer intuitive, then it's the model, or more precisely the language in it, that has to change.

This is important for two reasons: The purpose of the RACI model is still a compelling notion—not everyone involved in a process has the same responsibilities (lower case "r"!). Further, the misuse of the individual R, A, C, I words contribute to people actually misunderstanding their responsibilities, not least because the labels are made somehow holy by the jargon.

The cost of this mistake is that reams of standard operating procedures and other control documentation are created using the RACI model, which are then auditable, and more importantly, add complexity and time to the very processes we are trying to make more efficient.

DISSECTING THE DILEMMA

Let's look first at the "R" and the "A." "R" is supposed to be, in the model, the person who does the work—a worker, a doer. Almost no one understands this correctly. The letter R is defined as standing for "Responsible," but the word responsible, to almost everyone, means the person who is in charge, who is supposed to lead the work, whose head will roll if things go wrong. Sorry, but in RACI, that is the definition of the "A" word—"Accountable."

Everyone we've ever worked with to try and use RACI, or who has already had RACI imposed on them, confuses the R and the A, to the point where deciding who is R and who is A becomes arbitrary, and therefore meaningless. Most importantly, things that are confusing, contradictory, or illogical become unmemorable, and that makes the whole RACI effort a costly waste.

The "C" and the "I" are also flawed. Can there be any less sincere roles for people than who is "Consulted" and who is "Informed"? The time spent delineating the C and the I in the standard RACI workshop is not only time wasted, it is the opportunity for more misleading behavior.

Too often, people labeled "C" are people who actually should be doing something, but don't want the responsibility. They are mollified with the C, as are those who don't want to do anything, but want

to be able to express an opinion about what others are doing. Should we be officially codifying such wasteful and passive-aggressive behavior?

Meanwhile, what about "Informed"? Unless you're working in the National Security Agency, is there anyone who shouldn't be informed, and is there anyone who needs to be officially informed they qualify for this obvious, passive position?

RACI's "C" and "I" are simply a fancy justification for the phenomenon I call "everybody into the loop!" (i.e., if you aren't actually responsible for anything, we don't want you to feel left out, so we will keep you "informed"; and if you're someone we're afraid of, we will make sure you are "consulted").

This is much like everyone on the kids' soccer team getting a trophy for "participation." Maybe we could give everyone on the project team a trophy at the first meeting, and then disinvite them for the rest of the project! I can see that my replacement for RACI should be "RDT"—Responsible, Doing something, gets a Trophy.

RAMIFICATIONS OF RACI

Because of these misunderstandings, the worst aspect of using RACI in real life is that no one is actually assigned to do any work. You can be the one who is blamed (RA), you can be the one who gets to kibbitz (CI), but no one is assigned to do anything specific, which was the original point.

There are only two roles worth delineating when designing clinical development processes: the person who governs the work, and the person who does the work.

If you are redefining or creating new processes in your research organization, there are many other techniques other than RACI that will clarify responsibilities. Stick to the two categories: Govern and Do. If someone or some function falls into neither bucket, they get the trophy and can go home. Finance? See you at budget time. Quality Assurance? You have your own chance to Govern and Do in QA processes. Information Technology? Make sure the Intranet is working.

It's very important to clarify roles in the multiplexed world of clinical development. The key is to clarify for the sake of simplicity, not for the sake of inclusion. Productivity over Ego; Govern and Do. Erase the RACI and get back to working smarter.

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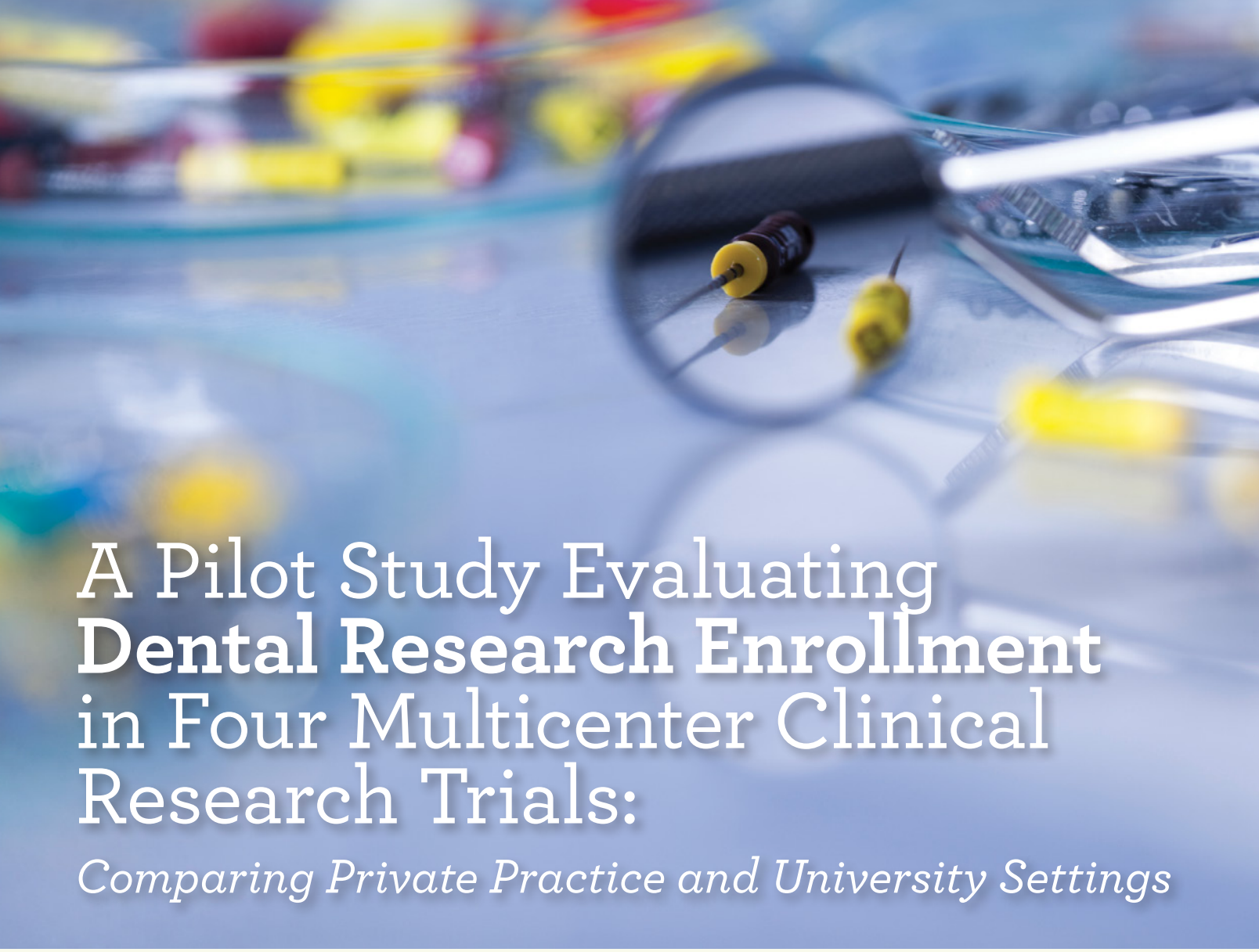

A Pilot Study Evaluating **Dental Research Enrollment** in Four Multicenter Clinical Research Trials:

Comparing Private Practice and University Settings

PEER REVIEWED | Rebecca Dean Showalter, RDH, BS, MS | Carol Nguyen, MS, RDH
William J. Curtis, DDS | JoAnn Diaz Jordan, MA, RDH | Melanie V. Taverna, MSDH, RDH

[DOI: 10.14524/CR-14-0057]

When the managers of a periodontal clinical trial experienced a large gap between the projected number and the actual number of enrolled subjects within a planned time period, successful completion of the research was threatened.[1] This gap occurred when inclusion and exclusion criteria were too restrictive. Although the goal seemed straightforward, the enrollment of subjects was still challenging.

Historical atrocities against human research subjects such as in Nazi war crimes and the syphilis study at Tuskegee brought about the Nuremberg Code and Belmont Report, respectively. These regulations developed ethical principles and guidelines for the protection of human subjects in research[2-4]; however, they have resulted in unintended consequences.[2-5]

One unintended consequence in current clinical research is often-unmet enrollment goals due to more stringent criteria for adequate representation of sex, age, race, and ethnicity.[5] In order to protect human subjects, entire demographics, such as women of childbearing potential, are often excluded from enrollment in trials. Such exclusions directly affect the ability of research teams to reach desired enrollment numbers.[5]

Background

Narrow study design and strict inclusion and exclusion criteria have affected the delicate balancing act between patient protection and the advancement of research in the United States.[3,4] For example, the aforementioned exclusion of women of childbearing potential creates demographic misrepresentation in gender, as well as age and race, which contributes to the lack of diversity in research findings.[5]

Overall, the Institute of Medicine's National Cancer Institute recently reported that 40% of its funded trials failed to complete enrollment.[3,4]

Enrollment into periodontal research trials has also been challenged by strict inclusion criteria. Examples include enrollment of patients for studies with a split mouth design, which requires defects to be located in a mirror image pattern, thus allowing for control and tests sites that are very similar within the same patient population. However, individual research sites were encumbered with screening numerous patients to identify relatively few qualified subjects.[6,7]

Such challenges to enrollment goals in clinical trials threaten the ability to produce timely data, cause delays in the transfer of knowledge, and limit the generalizability of research. There is also a significant financial expenditure when research fails due to low enrollment.[8]

Researchers typically do not report enrollment challenges and their solutions when publishing their data. Consequently, there is very little literature that discusses the effects of human protection regulation on enrollment success. Therefore, this study evaluated enrollment differences in multicenter academic and private practice periodontal dental clinical research trials; in particular, the influences of regulations on enrollment success.

Methods

A two-part quantitative survey was designed and reviewed by expert periodontal researchers and a statistician. The survey was sent via e-mail using Survey Monkey to a convenience sample of four sponsors of multicenter periodontal research trials in the United States and Canada, representing both private practice and academic sites. The four participants were study managers of the sponsoring companies, and were informed of the voluntary nature of the survey. The participation of the sponsor representatives implied consent.

The survey gathered data regarding the success of academic and private practice research sites in meeting enrollment goals. Part one (the sponsor portion) addressed study protocols governing all of a sponsor's sites and asked questions about the number of participating sites, initial enrollment goals, and time periods. Sponsors were also asked their opinion about current regulations' impact on their ability to meet their goals.

TABLE 1: Demographics and Enrollment Goals

	Sponsor 1		Sponsor 2		Sponsor 3		Sponsor 4	
Number of Sites per Sponsor	4		8		6		4	
Private Practice (p) versus Academic Sites (a)	1p	3a	8p	0a	3p	3a	2p	2a
Study Enrollment Goal	141		120		94		96	
Enrollment Goal per Site	~35		15		~16		24	
Enrollment Time Period Goal	12 months		12 months		12 months		12 months	
Private (p) versus Academic (a) Enrollment Goals Met	0p	0a	4p	0a	3p	2a	2p	2a
Worked with Site Previously	2		3		1		1	
CRC Continuity	4		8		4		3	
Enrollment Goals Met	0 (0%)		4 (50%)		5 (83%)		3 (75%)	
Were enrollment numbers met?	No		Yes		No		No	
If initial enrollment goals were not met, what were the reasons?	• Study design • Enrollment period too short • Enrollment numbers too high		• Did not report		• Inclusion criteria too limiting (no women of childbearing potential)		• Enrollment period too short	
If initial enrollment goals were not met, what changes were made?	Extended time period		Competitive enrollment		Competitive enrollment		Competitive enrollment	

Part two (the research site portion) gathered data that applied specifically to participating clinical research sites. Questions targeted the success of each site in meeting enrollment goals, what changes were made to meet the goals if initial enrollment failed, and the experiences and continuity of principal investigators (PIs) and clinical research coordinators (CRCs) at the sites.

Responses were de-identified; where applicable, data were aggregated to ensure anonymity. Items in the survey were summarized using descriptive statistics, and categorical items were summarized using counts and percentages; continuous and quasi-continuous items were summarized using measures of central tendency. Data were analyzed using descriptive statistics in Microsoft Excel 2007®. Narrative data were analyzed for recurrent concepts. This study was approved by the University of Texas Health Science Center San Antonio Institutional Review Board as an exempted study (IRB) HSC20140407E.

Results

A knowledgeable representative (study manager) from each of four sponsors responded to the survey, reporting on four recent periodontics studies involving a total of 22 sites with varying numbers of subjects per site. There was a consistent enrollment period of 12 months for all studies (see Table 1).

Three of the four studies did not meet initial enrollment goals (number of subjects enrolled within enrollment period). Of the 22 total sites, 14 were private practices (64%) and eight were academic institutions (36%). Twelve (55%) of the total sites met their enrollment goals, including nine of the 14 (65%) private practice sites and three of the eight (38%) academic sites (see Table 1).

Of those sites that did not meet initial enrollment goals, the primary change made was an extension of the enrollment period (56% of sites). The other change listed by sponsor managers was competitive enrollment (opening up other successful sites within the study for larger enrollment). The Fischer's exact test (two-tailed p=0.377) explored the potential relationship between private versus academic study sites and enrollment success.

A sponsor's previous experience with a site did not appear to provide an advantage or correlation with enrollment success. Seven of the sites had previous experience with the sponsors. However, of these sites only three met enrollment goals. Also the number of CRCs per site did not appear to relate to enrollment success. Two-thirds of the sites with multiple CRCs met initial enrollment goals.

Though one might have predicted that continuity of CRCs at any given study site would have influenced enrollment success, the three sites with coordinator changes during a study all had successful enrollments. Likewise, the enrollment success did not appear to be influenced by the number of investigators per study site; of the nine sites with multiple investigators, only five were successful.

TABLE 2: CRC Continuity and Previous Experience

	Sponsor 1	Sponsor 2	Sponsor 3	Sponsor 4	Total
Number of Sites	4	8	6	4	22
Worked with Site Previously	2	3	1	1	7
CRC Continuity	4	8	4	3	19
Enrollment Goals Met	0 (0%)	4 (50%)	5 (83%)	3 (75%)	12 (55%)

The primary reason sponsor managers gave for choosing a study site was "space to accommodate research and administration of project study" (17 of 22 sites). The other reason given (five of 22 sites) was marketing and/or PI preferences. However, three of these five sites did not meet initial enrollment goals. The sponsor with the most subjects per site (sponsor 1, with about 35 subjects/site) stated the number of subjects required and the enrollment period as the reasons the sponsor was unsuccessful with initial enrollment goals at *all* of its study sites.

Although this investigation attempted to explore the relationship between PI continuity and enrollment success, all sites maintained their original PIs throughout the duration of the studies. Therefore, investigation of this possible association could not be explored.

Discussion

Historically, there have been multiple changes to enrollment practices in periodontics research due to regulations intended to protect human subjects.[5] Since researchers typically do not report enrollment challenges or solutions when publishing their data, there is very little literature that discusses the effects of human protection regulation on enrollment success. Therefore, this study evaluated enrollment challenges found in multicenter private practice and academic periodontal clinical research trials, in an effort to stimulate future reporting.

This study supports literature suggesting that enrollment for periodontics research is challenging.[1] Findings demonstrate that only one of the four studies considered had success with enrollment.

None of the surveyed factors appear to influence enrollment success except, perhaps, private versus academic institutions and the subject

Narrow study design and strict inclusion and exclusion criteria have affected the delicate balancing act between patient protection and the advancement of research in the United States.

enrollment goals, yet the data failed to show an association ($p = 0.377$). However, the only study (sponsor 2) to meet enrollment goals at all of its study sites chose only private practice and no academic sites. Sponsor 2 also had the fewest subjects per site (15) and the greatest number of sites (eight).

Given this information, one might be tempted to speculate that a combination of the selection of private practice and lower subject enrollment goals per site would improve enrollment success. However, this investigation was not designed or powered to allow inferential statistics, only "descriptive" statistics, as provided herein. Inferential statistics would have required, for example, quantifying error and providing a predetermined and appropriate sample size rather than the "convenience" sample allowed by this investigation.

In this regard, statistical associations like the Fischer's exact test employed "after the fact," while interesting, are not entirely valid and present the possible danger of inferring causal relationships where they do not exist, or are actually caused by factors not considered or not available for consideration within the available convenience sample.

One weakness in this study is the survey design, which utilized a convenience sample and could not obtain predetermined sample sizes, preplanned comparisons, or pre-established and corresponding inferential statistics. Strengths of the study included the knowledgeable study sponsor managers, who responded about quite recent, large-scale studies. In this regard, this investigation presents valid trends on which future research may follow up.

Within the limits of the design of this investigation, the large disparity of enrollment success observed between the sponsors points to possible causal factors worthy of further exploration in a future, prospectively designed study. This future study could investigate the possible relationship of private versus academic study centers and lower versus higher enrollment goals per center for greater enrollment success.

Conclusion

It is important to continue to explore the enrollment challenges of clinical research trials in order to learn what is necessary to increase successful enrollment in future studies. If further studies support a supposition that enrollment is more reliably successful in private practice than in academic settings, it would shift the paradigm of future research.

There is a need to conduct larger studies comparing private practice and academic settings. In addition, based on the findings of this study, further investigation is needed to specifically evaluate the challenges of conducting research in academic settings. More importantly, there should be a requirement and a mechanism for reporting enrollment challenges and remedies for success.

Determining and reporting the factors that challenge enrollment will serve not only to increase the success of future research trials, but also to increase the efficiency of research processes.

References

1. Milgrom PM, Hujoel PP, Weinstein P, Holborow DW. Subject recruitment, retention, and compliance in clinical trials in periodontics. *Ann Periodontol* 1997;2(1), 64–74.
2. National Institute of Health, NIH training. 2008. Protecting Human Research Participants. https://phrp.nihtraining.com/introduction/01_intro.php
3. Centers for Disease Control and Prevention. U.S. Public Health Service Syphilis Study at Tuskegee. [Internet] 2014. www.cdc.gov/Tuskegee/after.htm
4. Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Protection of Human Subjects. Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. [Internet] 2014. http://search.usa.gov/search?query=Belmont+report&action=search&utf8=%E2%9C%93&affiliate=cdc-main&searchButton.x=58&searchButton.y=9
5. U.S. Department of Health and Human Resources, Food and Drug Administration, Center for Devices and Radiological Health, Center for Biologics Evaluation and Research (2014). Evaluation of Sex-Specific Data in Medical Device Clinical Studies Guidance for Industry and Food and Drug Administration Staff. Document issued August 22, 2014.
6. Imrey PB. Considerations in the statistical analysis of clinical trials in periodontitis. *J Clin Periodontal* 1986;13:517–32.
7. Jones CS, Billington RW, Pearson GJ. The advantages and disadvantages of running a clinical trial in general practices. *Br Dental J* 2004;197(6):311–3.
8. Kitterman DR, Cheng ST, Dilts DM, Orwoll ES. The prevalence and economic impact of low-enrolling clinical studies at an academic medical center. *Acad Med* 2011;1360–6. [doi: 10.1097/ACM.0b01333182306440]

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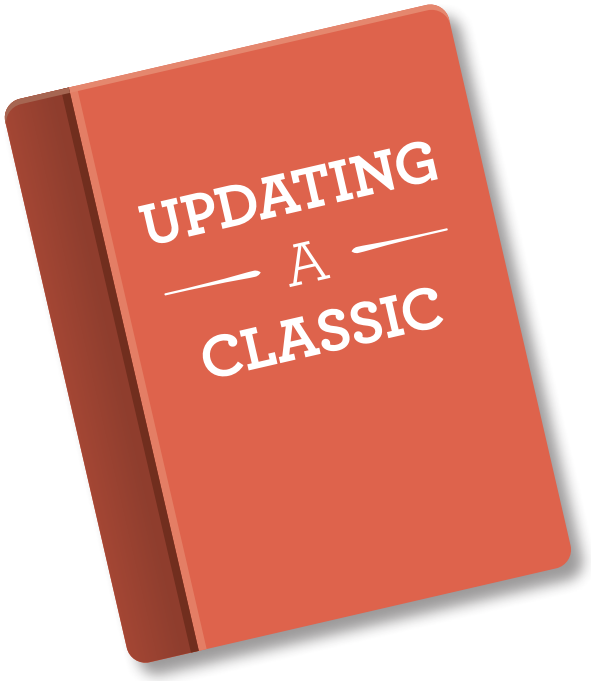

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Having temporarily run out of "Qs" to kick off a true "Q&A" lineup for this issue's column, I will instead describe the recently released draft of the Addendum update to the International Conference on Harmonization's (ICH's) Guideline for Good Clinical Practice (GCP) E6 document, which has many implications for quality assurance efforts in clinical research. *If you have a QA question, please email me at gcp@moriahconsultants.com.*

As with the recent change to the monitoring guidance describing the new risk-based approach to monitoring now endorsed by FDA, EMA, and other agencies, the ICH E6 guidance was in need of an update.

In June 2014, the ICH Steering Committee endorsed a concept paper for revising and updating the landmark GCP guidance, also referred to as the ICH Harmonized Tripartite Guideline. This guidance was first finalized in May 1996, so it is approaching 20 years old.

To complement the harmonized ICH GCP E6 Guideline, the Addendum is proposed to modernize the guideline and to enable implementation of innovative approaches to clinical trial design, management, oversight, conduct, documentation, and reporting that will better ensure human subject protection and data quality. In this "integrated" Addendum, changes were integrated directly into several sections of the parent E6 Guideline.

Why and How to Update

Since the adoption of the ICH GCP E6, clinical trials have evolved substantially, with increases in globalization, study complexity, and technological capabilities. To keep pace with the scale and complexity of clinical trials and to ensure appropriate use of technology, it is important to update our approach to GCP. This will enable implementation of innovative approaches to clinical trial design and oversight that will better ensure human subject protection and data quality.

An Expert Working Group was established by the ICH, consisting of members nominated by the European Medicines Agency (EMA), European Federation of Pharmaceutical Industries and Association, U.S. Food and Drug Administration (FDA), Pharmaceutical Research and Manufacturers of America, Japanese Ministry of Health, Labor, and Welfare, Japan Pharmaceutical Manufacturers Association, Health Canada, and Swissmedic. Members included experts in GCP who also had experience in clinical trial quality management.

The ICH has a multistep review and evaluation process leading to a final version of a guidance document. The new ICH E6 Addendum is at Step 2 of the ICH process. At Step 2, a consensus draft text, agreed upon by the Expert Working Group, is transmitted by the ICH Steering Committee to the regulatory authorities of the ICH regions (the European Union, Japan, the United States, Canada, and Switzerland) for internal and public consultation, according to national or regional procedures.

A Preview of What's Coming

As with the recent change to the monitoring guidance describing the new risk-based approach to monitoring now endorsed by FDA, EMA, and other agencies, the ICH E6 guidance was in need of an update. Back in 1996 when it was finalized, computer systems were available, but not as widely used as today. The Addendum recognizes the implementation and use of technology to facilitate high-quality and reliable data from clinical studies and taking a risk-based approach to quality.

Check out the ICH website **(www.ich.org)** for deadlines and further details on how to comment.

In fact, section 5.18.3 on "Extent and Nature of Monitoring" advocates a risk-based approach to monitoring:

> The sponsor should develop a systematic, prioritized, risk-based approach to monitoring clinical trials. The flexibility in the extent and nature of monitoring described in this section is intended to permit varied approaches that improve the effectiveness and efficiency of monitoring. A combination of onsite and centralized monitoring activities may be appropriate.

Some other examples of new language in the Addendum being proposed to be added to the guidance follow.

Under Section 4.2 on "Adequate Resources," the Addendum adds two new items:

> 4.2.5 The investigator is responsible for supervising any individual or party to whom the investigator delegates study tasks conducted at the trial site.

> 4.2.6 If the investigator/institution retains the services of any party to perform study tasks, they should ensure this party is qualified to perform those study tasks and should implement procedures to ensure the integrity of the study tasks performed and any data generated.

Under Section 4.9 on "Records and Reports," the Addendum adds language about the adequacy of source documents:

> 4.9.0 The investigator should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

The Addendum also adds language in Section 5 on "Sponsor" matters regarding quality management of the clinical trial, including a risk management approach to quality:

> 5.0 "Quality Management" The sponsor should implement a system to manage quality throughout the design, conduct, recording, evaluation, reporting, and archiving of clinical trials. Sponsors should focus on trial activities essential to ensuring human subject protection and the reliability of trial results. Quality management includes the efficient design of clinical trial protocols, data collection tools and procedures, and the collection of information that is essential to decision making.

> 5.0.2 "Risk Identification" Risks to critical study processes and data should be identified. Risks should be considered at both the system level (e.g., facilities, standard operating procedures, computerized systems, personnel, vendors) and clinical trial level (e.g., investigational product, trial design, data collection and recording).

Finally, a section on "Noncompliance" requires that the sponsor implement appropriate corrective and preventive actions (CAPAs). A robust CAPA process should now be an integral part of any company's quality systems.

> 5.20.1 When significant noncompliance is discovered, the sponsor should perform a root cause analysis and implement appropriate corrective and preventive actions. If required by applicable law or regulation, the sponsor should inform the regulatory authority(ies) when the noncompliance is a serious breach of the trial protocol or GCP.

A revised version of the Integrated Addendum to ICH E6(R1) document with the changes integrated directly into the document can be found at www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Addendum_Step2.pdf. The following are the sections of the parent guideline that have been revised: Introduction, 1.11.1, 1.38.1, 1.39, 1.60.1, 2.10, 4.2.5, 4.2.6, 4.9.0, 5.0, 5.0.1, 5.0.2, 5.0.3, 5.0.4, 5.0.5, 5.0.6, 5.0.7, 5.2.1, 5.2.2, 5.5.3 (b), 5.5.3 (h), 5.18.3, 5.18.6 (e), 5.18.7, 5.20.1, and 8.1.

Download a copy now and read the current thinking by the ICH Expert Working Group on the proposed changes to the guideline. It is also possible to submit your comments/suggestions to the ICH committee.

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Electronic Informed Consent (eConsent) in Clinical Investigations

Clinical research continues to evolve from pen and paper to stylus and computer. The U.S. Food and Drug Administration (FDA) recently released draft guidance on "Use of Electronic Informed Consent in Clinical Investigations." The guidance "provides recommendations for clinical investigators, sponsors, and institutional review boards (IRBs) on the use of electronic media and processes to obtain informed consent for FDA-regulated clinical investigations" and defines electronic informed consent (eConsent or eIC) as the use of electronic media and processes to obtain informed consent.[1]

eConsent can be used to complement the onsite consent process as well as to facilitate remote informed consent. However, it is critical to note that, for informed consent to be legally valid, it must satisfy all of the essential elements of informed consent and comply with local policies and state law for the state where consent is obtained (see Table 1).

TABLE 1: Regulations Relevant to eConsent

Regulation	Citation
Electronic Records and Electronic Signatures	21 CFR Part 11
Elements of Informed Consent	21 CFR 50.25
Documentation of Informed Consent	21 CFR 50.27
General Requirements of Informed Consent*	45 CFR 46.116
Documentation of Informed Consent*	45 CFR 46.117
Investigator Record Requirements	21 CFR §§ 312.62 and 812.140(a)
Sponsor Record Requirements	21 CFR §§ 312.57 and 812.140(b)

** U.S. Department of Health and Human Services regulated research*

How, When, and Where

The draft eConsent guidance notes that for electronic consent, the "interview process should allow subjects the opportunity to ask questions about the study," and describes that this may be accomplished through "in-person discussion with study personnel or by using a combination of electronic messaging, telephone calls, videoconferencing, or a live chat with a remotely located clinical investigator or appropriately delegated study personnel."[2]

The draft guidance also describes how, when, and where eConsent may be obtained:

> The consent process may take place at the study site where both the investigator and subject are at the same location, or it may take place remotely (e.g., at the subject's home or another convenient venue) where the subject reviews the consent document in absence of the investigator. The eIC materials may be provided for both onsite and remote access.

It is critical to note that, for informed consent to be legally valid, it must satisfy all of the essential elements of informed consent and comply with local policies and state law for the state where consent is obtained.

> If the entire process takes place at the study site, the study personnel can personally verify the subject's identification, review the eIC content, answer questions about the material, have follow-up discussions, and witness the signing of the eIC.
>
> If any or all of the process takes place at a remote location, all interactive responses by subjects, witnesses, or other involved parties should be documented electronically using software systems to ensure that responses cannot be altered. In addition, if the consent process is not personally witnessed by study personnel, the computerized system should include a method to ensure that the person signing the informed consent is the subject who will be participating in the research study (or the subject's [legally authorized representative]). Whether the eIC is obtained from the subject onsite or remotely, the subject should have the opportunity to ask questions and receive answers prior to signing the eIC to participate in the study.[1]

Regardless of how eConsent is obtained, federal regulations mandate that "[a]n investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence."[3]

Sign Here: _____

Informed consent is documented by the use of an IRB-approved consent form that is "signed and dated by the subject or the subject's legally authorized representative" with a copy of the consent form given to the person signing the form.[4] The draft guidance suggests several alternatives to a wet-ink signature for informed consent, including an encrypted digital signature, electronic signature pad, voice print, or digital fingerprint.[1]

In the *Code of Federal Regulations,* 21 CFR Part 11 describes the essential criteria for electronic signatures and electronic records to be considered trustworthy, reliable, and equivalent to paper records and handwritten signatures. A Part 11–compliant signature on an electronic record must contain: (1) the printed name of the signer; (2) the date and time when the signature was executed; and (3) the meaning (such as review, approval, responsibility, or authorship) associated with the signature.[5]

A Part 11–compliant signature must be unique to one individual, and may either utilize biometrics or combination of a unique identification code and password. Biometrics is defined as a "method of verifying an individual's identity based on measurement of the individual's physical feature(s) or repeatable action(s) where those features and/or actions are both unique to that individual and measurable."[6]

Authorizations for the use of protected health information under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) are frequently combined with research informed consent documents. The HIPAA authorization and research consent may be combined into one electronic document; however, a copy of the signed authorization must still be given to the subject.[1]

Investigational Device Exemption eConsent

While Investigational New Drug regulations do not require sponsors to submit informed consent documents to the FDA, Investigational Device Exemption regulations require the submission of "all forms and informational materials to be provided to subjects to obtain informed consent."[7] Therefore, the draft guidance suggests that:

> The sponsor should submit to FDA the same eIC materials that will be presented to subjects to obtain eIC for their participation in the clinical investigation. For example, as part of an electronic submission to FDA, copies of all forms and informational materials should include any videos and Web-based presentations provided on a compact disk (CD) or as a link to the eIC Web page that is accessible to FDA for viewing these eIC materials. In addition, the sponsor should also provide a copy of the informed consent document as a paper copy or an electronic PDF format document that can be emailed that includes a transcript of the eIC audiovisual presentation.[1]

Conclusion

Paper-written informed consent forms with wet-ink handwritten signatures may soon be a relic of the past like the carbonless triplicate case report forms. In its March 2015 draft guidance, the FDA is signaling its intent to allow electronic means to obtain and document informed consent for participation in clinical investigations. However, sponsors, sites, and IRBs need to ensure that the entire informed consent process results in legally effective consent for research if part, or all, of the process occurs electronically.

References

1. U.S. FDA. Use of Electronic Informed Consent in Clinical Investigations (March 2015). www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM436811.pdf
2. See also International Conference on Harmonization Guideline for Good Clinical Practice, ICH E6(R1) 4.8.7.
3. 21 CFR 50.20 and 45 CFR 46.116.
4. 21 CFR 50.27(a). See also 45 CFR 46.117(a).
5. 21 CFR 11.50.
6. 21 CFR 11.3(b)(3).
7. 21 CFR 812.20(b)(11).

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Pharmacovigilance: *Implementation and Beyond*

Pharmacovigilance is defined as the science of, and activities related to, the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems.[1] However, this system was long in a dormant stage, with infamous adverse drug incidents such as the sulfanilamide disaster (1937), thalidomide disaster (1962), and many more helping over time to make the case for more effective safety monitoring.

Regardless of the global development and technological growth of pharmacovigilance, the numbers of adverse drug reactions are considerably large and of major concern for public health systems. The present postmarketing reporting system finds difficulty in identifying risk associated with marketed drugs within the required time frames.

Furthermore, the monitoring of drug safety in vulnerable populations (i.e., pregnant women, the elderly, and children) is difficult. Similarly, determining safety of off-label or inappropriately packed medicines is challenging. For example, extensive use of generic drugs causes problems in determining product safety.[2]

Highly irregular and inconsistent processes and standards, complex and varied global regulations, regulatory warnings, limited integration of data and data quality, public scrutiny, and negative media coverage also significantly influence pharmacovigilance efforts.

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...there are countries where 90% of the medicines on sale are considered to be counterfeit.

Nevertheless, rising and unpredictable adverse event case volumes, coupled with increasing case complexity and costs, and a shortage of well-defined metrics, make pharmacovigilance more difficult in terms of proactively managing the fluctuations inherent in the process. For better development of pharmacovigilance, implementation of effective and modern policies is necessary.

The Effects of Globalization

Owing to globalization, many pharmaceutical organizations have started distributing their products in newer markets. One historic risk of this scenario was that existing drugs may not have been clinically evaluated in certain ethnic groups to which they were newly being offered; therefore, the risk of adverse events was substantially high. However, today, most firms take steps to alleviate this risk, and issues related to complex supply chains and management of product quality are more prominent.

Shortcomings in the timeliness or technical specifications of supply chain processes may lead to contamination of a product (e.g., vaccines), which can affect large numbers of people if undetected before administration. Often, shortages of drugs in particular regions are due to supply chain issues that may also cause difficulties in the management of adverse events and hinder the implementation of systemic pharmacovigilance.

Generally, the word globalization is viewed in the context of low-cost outsourcing models that are used to earn more profit. However, the spirit of globalization takes advantage of current developing and growing markets, and indicates the current issues, challenges, opportunities, and problems of newer markets.[3]

Globalization not only deals with rising competition from more, and more distant, regions of the world, but also helps to develop quality products for needy populations; drives global innovation by addressing the problems of talent acquisition in areas with limited breadth and depth in the available workforce; and ultimately makes firms' pharmacovigilance efforts faster and more compliant while keeping a watch on cost.[4]

On the Lookout for Counterfeit Products

Medicinal products must meet the highest of quality standards to assure patient safety, so the prevalence of counterfeit medicines has always been a matter of concern to authorities and healthcare professionals. The incidence of counterfeit drugs in the legal supply chain among industrialized countries is around 1% of market value,[5] and is likely to increase. Indeed, there are countries where 90% of the medicines on sale are considered to be counterfeit.[6]

> Regardless of the global development and technological growth of pharmacovigilance, the numbers of adverse drug reactions are considerably large and of major concern for public health systems.

To the casual eye, counterfeit medicines typically are similar to the original brands they seek to pass for, and may include lifestyle drugs and routine medications such as cough syrups, painkillers, and even vitamin supplements. However, they often have less or more than the required amount of active pharmaceutical ingredients (APIs), contain expired APIs that have been repacked to extend the expiry date, and have undergone limited or no quality control checks.

Sometimes, a counterfeit medicine's contents can be dangerous enough to pose a health risk.[7] For example, a counterfeit version of the drug Avastin for cancer treatment that lacked the proper API affected various medical practices in the United States in one case of detected fraud.[8] It should come as no surprise that high demand for such medicines and the low cost of manufacturing counterfeits can make the practice very profitable for the criminals involved.

Counterfeit drugs challenge the goals of pharmacovigilance, but various anti-counterfeiting measures offer hope for the future. For example, the World Health Organization launched the IMPACT (International Medical Products Anti-Counterfeiting Taskforce) in 2006 to combat the production and distribution of counterfeit medicinal products by building coordinated global networks between countries.[9] Similarly, the Bilcare packaging research organization, based in India, has created an anti-counterfeiting technology called nonClonableID™, which helps authenticate products within the context of supply chain processes.[10]

Data Quality and Its Management

The results of pharmacovigilance efforts include data collected on various drugs, therapeutic conditions, and numbers of adverse events within or beyond the environment of systematically managed clinical trials. Pharmacovigilance also extends to examination of over reporting of data for publicity purposes or to increase legal burden, under reporting to hide truths about a drug that may be seen as unfavorable to its marketers, and the reporting of insufficient and/or contradictory information.[11]

TABLE 1: Reasons for Medication Errors

Type of Error	Nature of Error
Storage	• Look-alike/sound-alike medicine • Improper storage • Inappropriate prescribing
Prescribing	• Poor handwriting • Use of abbreviations • Transcription error
Dispensing	• Computer entry error • Compounded incorrectly • Filed incorrectly
Administration	• Label incorrectly • Wrong drug • Drug omitted
Monitoring	• Wrong time • Inappropriate monitoring of patient vitals • Inappropriate monitoring of response

Source: Chris Olson, unpublished data

Generic drugs should have roughly the same bioavailability as that of the brand product; they are allowed a variance of 10% (more or less), which could affect the safety records. In addition, questions may be raised about the correctness and completeness of pharmacovigilance information pertaining to adverse events involving a generic drug, such as its dose, dosage form, start and end date of the event, duration of the event, any follow up to the event, and details on the background rates of any similar adverse events. Extraction, organization, management, analysis, and interpretation of such raw data have been challenging tasks.

Harmonization of healthcare standards and standards for minimum reporting requirements is necessary, and is possible to achieve through the collaboration of pharmacovigilance organizations, regulatory authorities, and the Clinical Data Interchange Standards Consortium (see www.cdisc.org/) at various levels. Information technology has opened new doors for national and international collaborations that may strengthen pharmacovigilance activities.

Drug Consumption, Marketing Trends, and Self Medication

Drug consumption patterns also affect issues of drug safety. For example, the parenteral route of drug administration can cause severe local or systemic adverse reactions if administered by untrained personnel using inadequately sterilized equipment and/or incorrect methods.

Meanwhile, illegal (and often irrational) use of drugs for anything other than their intended purposes has become a worldwide problem, with online marketing efforts encouraging use of over-the-counter sales of drugs without valid prescriptions and the sale of banned drugs under false health claims, among other serious concerns to authorities and healthcare professionals.

Each country has its own policies for the purchase, marketing, and sales of medicines. For example, in Germany the mail-order business related to medicinal products was legalized in 2004, which has led to increased levels of counterfeit medicinal products in the country.[12] Meanwhile, Internet pharmacies are often exploited by those seeking access to controlled substances such as anabolic steroids and narcotics. In such situations, users often won't report occurrences of adverse events, which makes signal detection and pursuit of appropriate actions (e.g., warnings to others) difficult to manage.

However, the Internet can be useful for experts in terms of them providing potentially important safety information to consumers, as well as for monitoring evidence of safety issues brought forth by consumers. Both activities can tie into today's social networking sites, blogs devoted to healthcare issues, and chatrooms of different medical awareness groups.

To be sure, sponsors, regulators, and other professionals should be cautious about sharing and accepting drug safety information through social media. Such activity must be supported with strong laws aimed at preventing the dissemination of possibly misleading information. On the other hand, one still expects that the official website of any pharmaceutical company would provide important and thoroughly detailed safety information about the firm's drugs.

Medication Error

A medication error is defined by one source as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer."[13] Due to medication errors, nearly 100,000 deaths occur per year and at least 1.5 million people are left injured.[14] Such incidences may be due to negligence of healthcare professionals, labeling issues, shipment problems, dispensing errors, or poorly trained staff members. Examples of important and common medication errors are highlighted in Table 1.

The joint efforts of patient safety organizations, vigilance centers, and related adverse event control groups aid in the detection of medication errors.

Medicinal products must meet the highest of quality standards to assure patient safety, so the prevalence of counterfeit medicines has always been a matter of concern to authorities and healthcare professionals.

The main goal of pharmacovigilance is to increase the overall safety of any marketed medicine. However, the process of carrying out vigilance activities, the legal and regulatory requirements, and the available methodologies and approaches keep evolving.

Also, healthcare providers who are aware of the problem and encourage reporting of medication errors help to improve patient care. At the same time, the development of an improved safety culture will certainly bolster patient safety.

Lack of Harmonized Regulations

The main goal of pharmacovigilance is to increase the overall safety of any marketed medicine. However, the process of carrying out vigilance activities, the legal and regulatory requirements, and the available methodologies and approaches keep evolving (see Table 2). Pharmaceutical companies must continually update their resources to keep pace with these other changes.

The U.S. Food and Drug Administration Amendments Act of 2007 highlighted new requirements for integrating risk evaluation and mitigation strategies into the review of new drugs and postmarketing activities.[15] Similarly, the European Union has implemented legislation for collecting and reporting adverse events.[16] Unfortunately, regulations for pharmacovigilance are not harmonized on a more global scale (see Table 3).

Effective pharmacovigilance practices must stay up to date with changes in the healthcare environment in general, and with changes from across varied regulatory agencies affecting all phases of the drug life cycle.

Adverse Drug Reaction Occurrence and Handling

All noxious and unintended responses to a medicinal products related to any dose are considered adverse drug reactions (ADRs).[17]

Polypharmacy is one of the causes of ADRs; it includes the redundant use of different dosage forms of the same medication by patients, use of unnecessary and/or unwanted prescriptions clinically not required for treatment of disease, and simultaneous administration of multiple drugs that are clinically indicated for treatment of a patient's various conditions, but which should be spaced out.

As suggested above, sometimes, the use of a chosen or assigned treatment is not even based on good medical evidence. Polypharmacy is common in aged patients, patients with manic conditions, patients receiving treatments from multiple physicians, patients suffering from multiple disorders, patients recently admitted to hospitals, and more.

TABLE 2: Updating Pharmacovigilance Regulations

EVOLVING REGULATIONS

Regulatory agency	Year of last updates
Vietnam	March 2009
Russia	November 2008
Brazil	February 2009
US	2001
Mexico	2007
EU	Vol 9A - September 2008
Ukraine	2007

Source: GVK Biosciences

TABLE 3: Variation in Global Pharmacovigilance Regulations

Activity	Variation	Country
Pharmacovigilance obligation start date	From date of authorization	U.S., Canada, European Union (EU)
	From date of product launch in market	India, Australia
Electronic (E2B) reporting requirement	Mandatory	EU, EMA
	Not mandatory	Rest of the world
Periodic Safety Update Report (PSUR) submission requirement	Mandatory requirement	U.S., EU, India
	On request by regulatory agencies	Canada, South Africa
	At license renewal only	United Arab Emirates
PSUR submission cycles	Quarterly, annually	U.S.
	Quarterly, semiannually, annually, re-registration	Mexico
	Three years	EU
	Annually	Australia
Timelines for PSUR submission from data lock point	30–60 days (quarterly/annual)	U.S.
	60 days	EU, Brazil
	30 days	India
Risk management plan submission mandatory	For all new registrations	EU
	Not mandatory for all registrations	Rest of the world

Source: GVK Biosciences

The reported reactions due to polypharmacy are usually incomplete. Reasons could include insufficient/unreliable available information, unpredictable methods for analyzing such information, and misstatements of the benefits of a treatment as compared to its associated risks by various sources during its evaluation and analysis in development.[18]

Another cause behind reported ADRs concerns negative effects caused by a drug in addition to its intended therapeutic effect. This phenomenon is called a "paradoxical reaction." For example, increased willingness to hurt themselves was observed in patients who used diazepam.[19]

Today, generic versions of many off-patent drugs easily gain approval without being critically evaluated for safety, and this may cause exposure of the general public to the possibility for more ADRs. There is a need for sufficient research on ADRs globally, with results gathered from all nations with modern drug controls, which will help to identify the exact reasons for occurrences of ADRs, wherever they are detected.

Lack of Education and Training

As pharmacovigilance is a complex system, many healthcare professionals are not well versed in, or even keen to learn, its workings. Furthermore, poor literacy and healthcare education levels among consumers can affect the implementation of pharmacovigilance efforts.

While current literacy rates are showing satisfactory results among educated populations around the world, more than half (51.8%) of the residents of South and West Asia are illiterate, and together they account for nearly half of the illiterate population globally. More than one-fifth of all illiterate adults (21.4%) live in Sub-saharan Africa.[20]

Meanwhile, medical practices are not standardized across the Asian nations, and their diverse cultural practices, patient population, lack of financial resources, and poor reporting standards may result in ineffective pharmacovigilance.[21]

Under-reporting of ADRs by patients who do not understand the importance of doing so also raises a concern about the quality of pharmacovigilance data produced, so educational outreach on this issue to illiterate populations is warranted. Indeed, the concepts tied to pharmacovigilance are relatively new in many countries, and few academic courses cover all of the topic's aspects. Therefore, it is essential to ensure proper training for all those who are associated with pharmacovigilance.

> The results of pharmacovigilance efforts include data collected on various drugs, therapeutic conditions, and numbers of adverse events within or beyond the environment of systematically managed clinical trials.

However, with lack of appropriate trainers, infrastructure, and funds, training becomes more difficult. Education and training outreach at all levels to illiterate—and even literate—people through developing pharmacovigilance training centers in key locations will be helpful.

Traditional Medicines

Also of concern in relation to pharmacovigilance and ADRs is the extensive worldwide use of traditional medicines such as herbal remedies.

There is a common belief that "herbal" means "safe," and that long-term use of traditional medicine assures its efficacy and safety.[22] However, several adverse reactions following administration of herbal medicines have been reported. For example, the use of Ginkgo biloba causes bleeding, while Ephedra has caused hypertension, insomnia, headache, and seizures, among other reactions.[23]

Even as many once-localized traditional and herbal medicines are now being manufactured for global use, there have been more and more cases of these medicines being adulterated or contaminated with other medicines and substances. When traditional and herbal medicines are used with other medicines, there is the potential of adverse drug interactions,[24] so just like other pharmaceutical products, herbal medicines should be incorporated into the regulatory framework and into a strong pharmacovigilance system.

Nevertheless, challenges related to the presence or absence of (or access to) commonly understood adverse reaction terminology, safety information, signal detection capabilities, concomitant medications, quality assurance/quality control efforts, counterfeit and spurious herbal drugs, information about the APIs and mechanisms of action of herbal medicines, and more will remain. Monitoring the safety of herbal medicine through well-developed channels will help to restore confidence in those products that may be truly considered safe for their marketed uses.

Cost Considerations

Costs associated with research and development, production, and preclinical and clinical trials are huge, and the cost of pharmacovigilance activities represents an additional burden.

Effective pharmacovigilance practices must stay up to date with changes in the healthcare environment in general, and with changes from across varied regulatory agencies affecting all phases of the drug life cycle.

A good pharmacovigilance system depends upon a teaming of high-quality software applications and human resources. The software systems are considerably expensive just when considered alone, whereas the personnel required for data entry, quality processes, therapeutic assessment, signal detection, and software maintenance contribute to making this an even more significantly laborious and costly affair.

At the same time, poor product quality and/or programmatic errors may increase the frequency of ADRs and their associated costs. Thus, companies try to do more with the help of limited resources. Moreover, many countries do not have a formal pharmacovigilance system because of lack of budget support. However, for better financial control of pharmacovigilance efforts, a real-time understanding of their total costs is necessary.

Conclusion

Pharmacovigilance is the backbone of product safety; however, its effective implementation poses many challenges. As a fundamental contributor to the quality of marketed medicines and safety of human beings, pharmacovigilance needs to have reliable and meaningful metrics around which related initiatives can be developed, governed, and executed.

To improve operational efficiency, quality, and compliance, pharmacovigilance organizations should proactively develop and implement a capacity management strategy and the tools to successfully execute that strategy. Furthermore, pharmacovigilance systems and their regulatory requirements must be synchronized and updated, so they can use the information generated from rapidly growing sources.

Meanwhile, uncontrolled use of drugs should be prevented by strict regulations. Intensive training that raises awareness of the issues addressed in this article before implementation of any pharmacovigilance program can be an effective tool.

To facilitate pharmacovigilance, all stakeholders must focus on new imperatives out of the box. This would ultimately improve collection of medical and scientific data, which will enhance overall safety mechanisms.

DISCLAIMER

All opinions expressed are those of the authors and do not reflect the views of their organization.

References

1. www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/. Accessed on March 28, 2015.
2. Campbell RR, Spehar AM, French DD. Proactive post marketing surveillance: overview and lessons learned from medication safety research in the veterans health administration. In: Henriksen K, Battles JB, Keyes MA, et al., editors. Advances in Patient Safety: New Directions and Alternative Approaches (Vol. 1: Assessment). Rockville, Md.: Agency for Healthcare Research and Quality; August 2008. Available from www.ncbi.nlm.nih.gov/books/NBK43650/
3. Mojmir Mrak. (2000). Chapter 2: The world as a global economy. Globalization: trends, challenges and opportunities for countries in transition.
4. George Botsakos. (2012). The future of pharmacovigilance: five imperatives that will drive improved business outcomes. Cognizant 20-20 insights. Available at www.cognizant.com. Accessed on March 27, 2015.
5. WHO Fact sheet No. 275, January 2010.
6. Schweim, Prof. Dr. rer. nat. habil. Harald G (2010). Arzneimittelkauf im Ausland – dasann gefährlich sein! *Deutsche Apotheker Zeitung,* 21: DAZ.online.
7. Javier Sanz (2013). Counterfeit medicines: a real danger to patients. *International Pharmaceutical Industry*; 5(1): 96–7.
8. U.S. Food and Drug Administration. 2012.
9. www.who.int/impact/about/en/. Accessed on June 15, 2013.
10. www.bilcare.com/businesses/bilcare_technologies.htm. Accessed on June 24, 2013
11. Nelson RC, Palsulich B, Gogolak V. (2002). Good pharmacovigilance practices: technology enabled. *Drug Safety*; 25: 407–14.
12. Schweim, Prof. Dr. rer. nat. habil. Harald G; Fuchs, Jörg (2011) Arzneimittelfälschungen und Scheinsicherheit – Wie effektiv ist das Sicherheitslogo für Versandapotheken? *Deutsche Apotheker Zeitung,* 10: DAZ.online.
13. National Coordinating Council for Medication Error Reporting and Prevention. www.nccmerp.org/about-medication-errors
14. www.alcooklaw.com/practice-areas/medication-error-injury/medication-error-stats-examples/. Accessed on November 2, 2013.
15. Food and Drug Administration Amendments Act of 2007.
16. European Medicines Agency; Good Pharmacovigilance Practices Guidelines.
17. International Conference on Harmonization E6-Good Clinical Practice Guidelines.
18. R. Chou, M. Helfand. (2005). Challenges in systematic reviews that assess treatment harms. *Ann Intern Med,* 142(12 Pt 2): 1090–2000.
19. M.E. Berman, G. D. Jones, M. S. McCloskey. (2005). The effects of diazepam on human self-aggressive behavior. *Psychopharmacology* (Berl.), 178 (1): 100–6.
20. UNESCO Institute of Statistics (UIS) Fact Sheets, September 2011; No.16.
21. Biswas, P. (2013). Pharmacovigilance in Asia. *Journal of Pharmacology & Pharmacotherapeutics,* 4(Suppl1), S7–S19. doi:10.4103/0976-500X.120941
22. Vijay Kumar (2013) Challenges and future consideration for pharmacovigilance. *J Pharmacovigilance* 1: 102. doi:10.4172/jp.1000102
23. Melanie Johns C. (1999). Herbal remedies: adverse effects and drug interactions. *Am Fam Physician.* 1; 59(5): 1239–44.
24. Zhang L, Yan J, Liu X, Ye Z, Yang X, et al. (2012) Pharmacovigilance practice and risk control of traditional Chinese medicine drugs in China: current status and future perspective. *J Ethnopharmacol* 140: 519–25.

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AMC ROUNDTABLE
Rhonda Jensen, RN

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Research Billing in an Academic Medical Center

Clinical research is one of the important missions of any academic medical center (AMC). There are many levels of experience and support that can contribute to this mission. It is exciting and gratifying to be able to offer new and cutting-edge therapies to our patients.

However, the reality is that, in a large organization, with many areas and departments involved, research billing can face any number of challenges. Developing relationships and effective lines of communication with and among all stakeholders is vital to an efficient research billing process.

Types of Trials

The many different types of clinical trials that can be conducted at AMCs add another layer to the challenge.

AMCs will typically offer more investigator-initiated trials than industry-sponsored ones. These trials usually take longer to develop and require more resources, so their funding needs to be carefully evaluated.

Federally funded trials and cooperative group trials will typically provide a set amount of funding, and may also need to be evaluated for funding support.

Phase I trials will bring the newest and developing therapies, but can be more complicated and require more resources and higher expenses in research-related services.

Pharmaceutical industry trials are typically funded, but may require additional time and resources for budget negotiations.

High-profile clinical trials will draw potential participants from throughout the country; insurance reimbursements and out-of-network issues may need to be evaluated and addressed. Those involved with research billing should be engaged from the beginning with the initial clinical trial evaluations, and ideally be able to follow through with the budgeting and finally the billing.

The Process

The research billing process should begin with the coverage analysis—a thorough evaluation of the clinical trial to determine the routine clinical care services that are billable to insurance and the research-related services that will need to be funded by the study. There are a number of resources that can be used to support the coverage analysis determinations, including National Comprehensive Cancer Network guidelines, Medicare national and local coverage determinations, Medicare billing guidelines, and more.

It is also important to reach out to and include a trial's principal investigator in any billing-related communication, as well as any ancillary departments that may be involved for research-related

There should be established lines of communication between the research billing staff conducting the coverage analysis and the budget and contracting staff.

When a trial is ready to open, education and support need to be provided to its assigned clinical research coordinators in relation to research billing and compliance.

services, such as radiology, pharmacy, and surgery, to ensure that the research-related services are being captured correctly. The coverage analysis will also evaluate and document that the trial is a "qualifying clinical trial," according to Medicare standards, and that routine costs are billable.

Once the coverage analysis is completed, the clinical research budget or "billing grid" is developed and incorporated into the overall study budget. There should be established lines of communication between the research billing staff conducting the coverage analysis and the budget and contracting staff.

Research-related procedures may need to be clarified and funding issues may need to be addressed. This all requires open and timely communication, in order to keep the most current information available.

There also needs to be open lines of communication with the regulatory staff. At my institution, the informed consents are reviewed by the staff conducting the coverage analysis, to ensure that information about costs presented in the consent accurately conveys to the patient what his or her financial responsibility will be while participating in the clinical trial. This is key communication to the patient, and clear understanding should help avoid research billing questions as the trial moves forward.

Getting the new clinical trials "up and running" can be a big challenge, and requires open communication with all involved in the process, including the research billing staff. As part of a larger process improvement project at my institution last year, several new processes were developed that have resulted in breaking down some of the barriers and providing more transparent and open communication.

For example, an internal "dashboard" is available for all involved to view and enter comments and/or issues of concern regarding the progress of the new clinical trial through the pipeline. A brief weekly conference call is also held; different groups of trials are reviewed and discussed each week, which also helps to communicate progress and/or any issues that need to be addressed.

Moving Forward and Closing the Loop

When a trial is ready to open, education and support need to be provided to its assigned clinical research coordinators in relation to research billing and compliance. They should have information specific to their trials available to them that outlines research-related procedures and routine clinical procedures, and should be encouraged to contact the research billing staff with any questions or concerns.

After the trial opens, the research billing staff should be involved in the ongoing review of protocol amendments, to evaluate the updates and any potential budget additions and/or changes for research-related services.

To close the loop, research billing staff are involved with clinical trial patient account reviews, ensuring that all research-related services are correctly moved from the patient accounts to the associated study research accounts, before any billing out to third-party payers.

And...Adding in the Information Technology Layer

Most, if not all, of these processes and activities will also involve the integration and use of the institution's clinical trial management system (CTMS) and electronic medical record (EMR) system.

The coverage analysis process can be integrated into the CTMS system, which can help streamline the clinical trial budgeting process. Research billing staff will utilize the EMR system to help verify documentation of research-related services, and to be able to review and reconcile research billing work queues and reports. This all involves resources for initial and continued training and support for the research billing staff.

Conclusion

The set-up and ongoing process for research billing will probably not look the same for every AMC. At my institution, these activities involve a centralized department within the Financial Services division of the hospital working closely with the Budget and Contracts area of the Clinical Trials Office. Other institutions may have a more decentralized approach to the research billing process.

Whether a centralized or more decentralized approach is used, open and effective lines of communication among all stakeholders across the process are vital to an efficient and effective research billing and compliance program.

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Voices from the Field

Risk-Based Monitoring: *Hope or Hype?*

James Michael Causey

[DOI: 10.14524/CR-15-4085]

Buzzwords are funny things. Like rumors, they seem to come out of nowhere; and, like rumors, they can either fizzle out or herald an important new truth.

Risk-based monitoring (RBM) is certainly a clinical trial buzzword these days. But is it something more?

Jill Petro

"I love RBM, but I have concerns, too," says Jill Petro, BS, CRCP, CCRA, CCRC. She comes at RBM from the perspective of an in-house monitor for a contract research organization (CRO) who used it from 2008 to 2013, while trying to work with sites by performing remote monitoring.

"It's definitely for real," adds Julie Qidwa, a research coordinator at the University of Iowa. Mostly relying on tight National Institutes of Health grants, her academic CRO is always under pressure to do more with less. "We're very attracted to it because we've never had a huge onsite budget for monitoring."

Will Competition Drive Adoption?

The gap between interest and adoption will continue to close this year, according to "Top 10 Clinical Development Trends for 2015," from Health Decisions. "Continued reliance on traditional monitoring will increasingly place sponsors at a competitive disadvantages as they spend more on SDV and monitor travel rather than sponsors that have embraced" RBM.

Julie Qidwa

Barely one-third of sites are currently conducting RBM, according to an ACRP-CenterWatch Survey. **Find out how your site compares at www.acrpnet.org/statements**


Ann Meeker-O'Connell

"It is as important as it sounds," explains Ann Meeker-O'Connell, head of risk management and external engagement with Johnson & Johnson's BioResearch Quality and Compliance group. She spoke to a packed house on RBM at DIA's 51st Annual Meeting event in Washington, D.C. in June. "It's the way we should be going."

What's Old is New?

Some, however, wonder what all the new fuss is about. "I think it's interesting that so many people seem to think that this is a new and radical idea that will transform the industry," says Laurin Mancour, CCRA, CCRP, formerly of Duke University and now with the Center for Information and Study on Clinical Research Participation as an account representative for the Communicating Trial Results program and project manager for AWARE for All educational events. Stressing that she's an RBM proponent from way back, she points out that some companies and sponsors have been leveraging it for late-phase, observational, and device trials for years now.

RBM "is something that companies have been doing for years, or should have been doing all along," suggests Nikki Christison, president of Clinical Resolutions, Inc.

Putting that valid point to one side, the U.S. Food and Drug Administration's (FDA's) August 2013 guidance on "Oversight of Clinical Investigations—A Risk-Based Approach to Monitoring" was an important, tangible factor propelling RBM forward, most agree. "It helps us clarify regulatory expectations; it fills in another piece of the puzzle," says Qidwa's University of Iowa colleague, Dixie Ecklund, associate director at the Clinical Trials and Statistical Data Management Center.


Nikki Christison


Dixie Ecklund

The FDA guidance "opened the door," Nicole Stansbury notes, but people are still "craving" details. Stansbury is executive director of adaptive and intelligence monitoring, PPD. She did emphasize that the FDA move represents a high-level suggestion to shift toward centralized RBM (see "Clinical Trials: The Future is Now" on page 62).

Romiya Barry, a clinical trial manager at CeQur Corp., thinks the FDA's guidance was clear, and that the agency "wants to help sponsors monitor and carry out research more efficiently." In other words, it's about clean data, not clean cash.

Still, Christison is skeptical of the RBM moniker. "Whether a company calls it RBM, Signal

ARE WE LOSING THE HUMAN TOUCH?

I am sure there are many opinions about RBM. Some call it "remote monitoring," but I think the terms are synonymous. I think it depends on whether you are a site or a sponsor/CRO as to one's opinion. From a sponsor view, the bottom line is about saving money. From a site's view, this is my opinion from coordinating research for 17 years.

I understand the need for RBM, but do not like remote monitoring where sites are literally monitoring themselves. I participated in one study that was entirely remote monitoring, and it took me hours to prepare the documents the sponsors expected to be faxed in prior to the calls. Temperature logs, delegation logs, source documents, investigational product dispensing logs, etc.; all had to be pulled and faxed which caused a huge amount of extra work on the site's end without reimbursement for the extra work because it was "the cost of doing business."

A simple study turned into extraneous work for our site. I am more comfortable having monitors come to the site to make sure an adverse event/serious adverse event/endpoint isn't missed. Coordinators are human, and do miss events and endpoints, and it's good to have an independent person physically look at the data.

From a site perspective, RBM significantly reduces the relationship with sponsors, which is important in the communication and understanding of the protocol and success of the trial. I have empathy for new coordinators and sites starting up without having the opportunity to develop a relationship with the sponsor, because many initiations are web-based and remote. Web-based presentations will never have the same effect for a site as an in-person site initiation or monitoring visit.

Terri Campbell, RN, CCRC, *Genesis Healthcare System, Pharmaceutical Research Specialist, Malta, Ohio*

WEATHER REPORT: CLOUDY TODAY, CLEARER SKIES AHEAD?

A project that I'm on is moving in this direction (not there yet), and I love the reduced source data verification. It lets me actually spend time looking at the forest instead of the trees. While I've always tried to do this, checking the minutiae always took a lot of time.

I am concerned that sponsors are going to look at RBM as a big money saver. I think it is just going to change where the money is spent, not reduce it. Instead of money spent for travel, more central monitors are going to need to be employed in a project to look for the major trends at specific sites and overall in the study.

I am concerned about who will be employed as central monitors. In my past experience, central monitors are frequently the new monitors, to give them in-house experience. However, it will require the experience to be able to find the trends and to get the sites to respond to offsite communications.

In the long run, I think it will improve clinical trials, but I see a lot of short-run challenges.

Lorene Ward, CCRA, *INC Research*

Detection, Adaptive Monitoring, Quality Risk Management, or Remote Monitoring, it all means the same thing; it is the analysis of potential risk factors in a study and identification of proactive measures to address that risk."

More, With Less?

Anina Klein, a clinical research associate at the Nathan Kline Institute, is a big RBM fan. "It's helped me even in the limited scope where I can apply it," she says. She usually has funds for two to three interim trial visits onsite, and using RBM, she can shift some of her resources with confidence and add one or two visits to a more high-risk site.

RBM certainly offers a lot of advantages—but only if it is executed properly, says Barry, joining a chorus of comments elsewhere. "What I'm hearing is that it is being looked at as just a money-saver first," and that means "we won't get the benefits we should be getting." Too many sites, she says, look at RBM as a way to save funds. "Sponsors aren't doing a good job of telling sites this isn't about saving money." Instead, she emphasizes, it should be leveraged with an eye toward emerging with cleaner data because inspection efforts are less scattershot and more focused.

Romiya Barry

WILL CROs LEAD THE WAY?

RBM is not permission from regulatory authorities to decrease monitoring. It is about doing certain aspects of it in a better, smarter way, based on aspects of the project and quality systems.

I hear some sponsor/CROs say "we will only do RBM for certain projects." Maybe they are referring to their specific data analytics, but using the term that way is very confusing, and makes it appear that RBM is centralized monitoring only. RBM, better stated as clinical quality risk management (QRM), should be within the quality system, and from that lends a decision on the monitoring approach.

QRM is a way of doing business to promote efficiencies not just at the beginning of a trial set-up, but as changes occur and challenges arise that were not anticipated. Monitoring is not just the monitor, it is all aspects that a sponsor organizes to monitor the trial (e.g., quality assurance, quality control, data management, etc.). The concepts of RBM are not rocket science; they are logical, and when trained can be applied at any level.

For many smaller sponsors, CROs will likely lead the way, and many of these companies are looking to them.

Commonly, monitors receive the blame for inadequate sponsor monitoring. The root cause is very unlikely the "monitor." So, monitors should like the RBM movement, because up to now, they've gotten a bad rap, often blamed for items cited in Warning Letters [from the FDA] when, in fact, it is more about whole quality system failure. A lot of the problem is poor monitoring plan development, poor training of monitors related to site monitoring, misunderstanding source document review, and failure of sites to follow protocol.

Sandra (SAM) A. Sather, RN, BSN, MS, CCRC, CCRA, *Treasurer, Academy of Clinical Research Professionals Board of Trustees*

DO WE NEED MORE TOOLS IN THE TOOLKIT?

The [FDA's] 2013 RBM guidance provided much needed monitoring cost and time relief for sponsors. We've seen a meaningful (~50%) percentage of the industry begin the process of implementing RBM in their trials within the past two years. About half of those (~25%) transitioned to RBM on the majority of their Phase II+ studies. Sponsors we've met with say the benefits in cost reduction and time to closeout are real.

With those benefits, why isn't more of the industry doing it? We think the answer comes down to remote data access. To date, many sponsors rely on only one data tool in support of RBM—the electronic data capture (EDC) database. The trouble is this only provides access to, and analysis of, data points entered by the sites. The EDC ignores the mountain of data that has been historically available via source data verification (SDV) from onsite visits.

As a consequence, there are many sponsors (about half the market, in fact) that still insist on 100% in-person SDV for their studies. Remote SDV can help here. Remote access to source is the way to help this side of the market realize the benefit of RBM. In fact, if you look at the FDA, European Medicine Agency, and TransCelerate guidance, they all recommend a hybrid of risk and remote activities. It's this blend that will make RBM real for the other 50% of the industry.

Mike Kassim CEO, *Florence Healthcare, Atlanta, GA*

Stansbury agrees that there's too much vagueness out there. "What are the right risk indicators?" she asks. "It's very trial and error right now. We have to learn from each other."

Klein is also nervous about what she hears at trade shows. "When I speak to my colleagues, it seems like they think this might be a way for sponsors to cut down on site monitoring." That's not what RBM should be about, she adds.

Angelo Sambunaris, medical director at the Atlanta Institute of Medicine and Research, takes a somewhat more cautious view of RBM. "I think that companies have a misconception that remote monitoring gives them the same level of insight." However, RBM users aren't able to interact with site staff as much, he says (see "Are We Losing the Human Touch?" on page 60).

On the other hand, Sambunaris acknowledges another pressure to adopt

Angelo Sambunaris

RBM: "Younger workers don't want to travel, they'd rather sit in an office and check data." He sees a generational gap, in that "younger people are into this, older ones say the risk-based approach is terrible."

Todd Davies, director at the Marshall Clinical Research Center, lauds RBM for giving professionals a way to identify the 20% of data carrying more risk and enabling them to focus the laser beam on those data, instead of diluting resources by trying to sift through the vast amounts of data that are already solid.

Todd Davies

No Silos Allowed

RBM shouldn't be attempted in a vacuum, warns Mike Caswell, vice president for clinical evaluation at the Consumer Product Testing Company. It's key to "obtain viewpoints from different stakeholders—not only the sponsor of the trial, but also [people at] the site," including the principal investigator, research staff, and financial officers.

"If you can't get buy-in from sites, RBM won't work," Barry says flatly.

Meeker-O'Connell cautions not to forget about other factors that could impede RBM expansion. Those include:

- Realizing that the industry may have underestimated how big the effects of RBM could be on sites.
- Addressing a real fear out there that this means cutting back on monitoring.
- Understanding that a successful RBM rollout is about people, processes, and technology—in that order.

Davies also worries that industry misunderstandings could undermine RBM. "The problem I'm seeing is that CROs and others think of RBM simply as remote monitoring, but they aren't the same thing. There's a lot of confusion out there."

The Road Ahead

What does the future hold for RBM? Most crystal ball readers see increased adoption, though there's some argument about whether that will look like a rocket's explosive trajectory or an airplane's gentler ascent. Stay tuned.

James Michael Causey, a former Editorial Director at *FDAnews*, is the Editor-in-Chief at *Clinical Researcher.*

CLINICAL TRIALS: THE FUTURE IS NOW?

RBM is a logical approach to clinical trial monitoring. RBM combines risk assessment with development of a custom monitoring plan. These plans are based on those identified risks using the likelihood they will happen, the detectability of them through various methods, and the impact they will have on the safety of subjects or integrity of the trial. The plans are fine-tuned with additional risk mitigations using data analysis and other more efficient mechanisms (centralized monitoring) and roles. The industry's recent activity in this area is a breath of fresh air.

The results are real. While it is still early in the implementation of these techniques and many risk indicators are still being tested and evaluated, the limited audit results to date are showing a trend in RBM studies with fewer critical and major findings than traditionally monitored studies. Is it because the sites are improving their processes through monitors focusing more on process improvement than on source data verification? Is it because we are identifying errors earlier through remote and centralized monitoring methods and preventing repeated mistakes? We cannot say for sure that these trends will sustain over a longer duration and greater volume of assessment, but we are not detecting "red flags" because of RBM.

RBM solutions will continue to be a vital part of clinical trials in the future. More efficient use of resources, coupled with an additional focus and attention to time and those sites that need remediation will allow for reduced costs—if not immediately, certainly as processes and tools mature. This is critical as we continue to improve healthcare, but it also makes matters more complex, with multiple providers, digital records, and devices. The future of clinical trials needs RBM.

Nicole Stansbury, *Executive Director of Adaptive and Intelligence Monitoring, PPD*

It's Not About the Money, But...

The future of clinical trial monitoring is at a crossroads, according to a 2015 white paper from Quintiles. Traditional methods continue to dominate, but RBM has "emerged as a new way forward." Touting its more than 100 studies across more than 20,000 sites and more than 250,000 patients, the company says RBM can bring as much as 25% cost reduction over traditional trial approaches.

ARTICLE SUBMISSION GUIDELINES

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

The Peer Review Process

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

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

Submission Requirements

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

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

Check out the Editorial Calendar for 2015, at acrpnet.org/Editorial-Calendar

TRAINING OPPORTUNITIES

eLEARNING COURSES

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

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

GCP for the Experienced CRA: Improving Monitoring Efficiency and Effectiveness

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

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

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

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

Risk-Based Monitoring: The Essentials for CRAs

Risk-Based Monitoring: The Essentials for CRCs

Risk-Based Monitoring: The Essentials for Investigators

Theory to Practice: Operationalize Your Clinical Study Protocol

NEW IN 2015

Inspection Readiness: Best Practices for Managing Clinical Trial Inspections

Site Quality Management Tools: SOPs, Metrics, and Training

ICH Gap Analysis Tool

GCP Test-Out Challenge

Form FDA 1572: Get it Right the First Time

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

LIVE WEBINARS

OCTOBER 7, 2015

Informed Consent Procedure: What Can We Learn from Inspection Findings?
Janet Holwell

OCTOBER 14, 2015

Investigator-Initiated Sponsored Research (IISR): Current Challenges and Evolving Solutions
Mary Voehl Hirsch and Ashley Willis

OCTOBER 21, 2015

FDA Inspects the Site: Are You Ready?
Deborah Copeland

WEBINAR REPLAYS

Investigator-Initiated Sponsored Research: Global Collaborations with Industry and Academia
Alex Kostek
ORIGINAL AIR DATE: JULY 22, 2015

Patient Navigators in Cancer Clinical Trials
Margo Michaels and Lucy Gansauer
ORIGINAL AIR DATE: JUNE 3, 2015

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

FDA Inspection of a New Drug Clinical Investigator: From A to Z
Robert Young and Leah Andrews
ORIGINAL AIR DATE: FEBRUARY 18, 2015

One Size Fits All? Not for Small Sponsors and CROs
Katie McCarthy and Laurie Halloran
ORIGINAL AIR DATE: FEBRUARY 4, 2015

Grant Management Web Based System for IISR Programs to Manage the IISR Lifecycle from Concept through Publication
Pat Westergren and Scott Cunningham
ORIGINAL AIR DATE: JANUARY 28, 2015

Communicating Trial Results: Data Sharing that Engages Patients as Partners
Laurin Mancour and Kenneth Getz
ORIGINAL AIR DATE: JANUARY 14, 2015

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

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

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

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

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

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

Standardizing Principal Investigator (PI) Delegation Records to Balance Site Operations and Regulatory Requirements
Nadine Nemunaitis and Staci Horvath
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FXM RESEARCH

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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.

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