Clinical Researcher™

The Authority in Ethical, Responsible Clinical Research

March 2019 (Volume 33, Issue 3)

Finding Your Financial Footing in the Clinical Research Enterprise

All contents © 2019 ACRP. All Rights Reserved (The Association of Clinical Research Professionals)
Clinical Researcher™

Association of Clinical Research Professionals

Editor-in-Chief
James Michael Causey
mcausey@acrpnet.org
(703) 253-6274

Managing Editor
Gary W. Cramer
gcramer@acrpnet.org
(703) 258-3504

Editorial Advisors

Suheila Abdul-Karrim, CCRA, CCRT, FACRP
Freelancer
Johannesburg, South Africa

Victor Chen, MSc
Principal
The CK Clinical Group
Director, Clinical Affairs
Align Technology, Inc
Mountain View, CA

Fraser Gibson, CCRC, CCRA, CCRP
President
Advantage Clinical
London, Ontario, Canada

Stefanie La Manna, PhD, MPH, ARNP, FNP-C
Assistant Professor and Advanced Registered Nurse Practitioner
Nova Southeastern University
Lake Worth, FL

Christina Nance, PhD, CPI
Assistant Professor
Baylor College of Medicine
Houston, TX

Paula Smailes, DNP, RN, MSN, CCRP, CCRC
Visiting Professor
Chamberlain College of Nursing
Senior Systems Consultant
The Ohio State University Wexner Medical Center
Columbus, OH

Jerry Stein, PhD, ACRP-CP
President/Owner
Summer Creek Consulting, LLC
Fort Worth, TX

Shirley Trainor-Thomas, MHSA
President and Principal Strategist
Phase Up Research
Mount Pleasant, SC

Heather Wright, CCRC
Research Coordinator
Tampa Bay Clinical Research Center
Brandon, FL

Advertising
Tammy B. Myers, CEM
Director, Advertising & Exhibition Sales
(703) 254-8112
tammy.myers@acrpnet.org

https://www.acrpnet.org/advertising/

For membership questions, contact ACRP at office@acrpnet.org or (703) 254-8100.
Table of Contents

4 Executive Director’s Message—Maintaining the Human Touch in Clinical Research
Jim Kremidas

PEER REVIEWED

6 The Training Challenges in Billing and Research Compliance
Kelly M. Willenberg, DBA, RN, CCRP, CHRC, CHC

11 Paying Subjects to Take Part in Research: A New Perspective on Coercion and Undue Influence
David Borasky, MPH, CIP; Jeffrey A. Cooper, MD, MMM; Kelly FitzGerald, PhD

SPECIAL FEATURE

21 Pitfalls and Solutions on the Way to Finding Your Financial Footing in Clinical Research
Esther Wei-Yun Landhuis, PhD

COLUMNS

25 Good Management Practice—Creating Accountability at Research Sites: Step by Step
David J. Morin, MD, FACP, CPI, FACRP

31 Research Compliance—Show Me the Documentation
Jan S. Peterson, MS, CCRA, RAC, ASQ CBA, ACRP-CP

37 Site Strategies—Protecting Cash Flow: How Site Investigators and Staff Can Keep Site Payments on Track
Shaun Williams, PMP

Clinical Researcher is your platform. Interested in writing a peer-reviewed article or guest column? You’ll find our submissions guidelines at https://www.acrpnnet.org/resources/clinical-researcher/.

Credit-granting Home Study tests based on Clinical Researcher articles are available for purchase at https://www.acrpnnet.org/home-study/, along with downloadable PDFs of the relevant articles and questions from each issue. The test based on this issue should be posted by the end of March.
New technologies are impacting the clinical trial landscape in ways almost unimaginable 20 years ago. Whether it’s widespread use of wearable devices, remote monitoring, artificial intelligence, or the promise of virtual trials, we’re clearly on the verge of revolutionary change where the very role of the clinical trial workforce is being called into question.

Some of the recent headlines I’ve seen seem to hint that technologies will gradually supplant most of the human beings actually conducting the trials. Frankly, I think that’s all wrong. Make no mistake, technology is going to change the way we conduct some aspects of trials. For example, it’s already making it easier to identify patients in smaller, disparate disease populations and enabling trials that might not have been feasible just a few years earlier.

However, technology won’t help us achieve lofty goals if we’re not all working in unison. Clinical trial practitioners have been somewhat technology averse in days past. There are some obvious reasons, including the fact that ours is a heavily regulated industry engaged in activities that can literally be matters of life and death.

**Bridging the Gap**

We all know that ignorance and misunderstanding can breed fear and confusion. At ACRP, we’re working to bridge the gap between tech innovators and clinical trial practitioners by bringing them together in settings where they can help each other overcome trial management barriers hindering better job performance.

Next month at [ACRP 2019 in Nashville](https://www.acrp.org), for example, among other tracks we’re offering a [Technology Track](https://www.acrp.org) of educational sessions, beyond which we’ll feature something new to our annual meeting, the [techXpo](https://www.techxpo.org). Through techXpo, leading industry suppliers will address many of
the technology challenges facing clinical research and spotlight innovative solutions from their firms. These suppliers will share customer case studies and product demos to help you and your team leverage technology to improve clinical trial operations. During these give-and-take sessions, we hope attendees will have the chance to learn about new tools, while providers will get a better understanding of what users most want and need.

Technology is here to serve the workforce and ultimately patients. Let’s work together to make it as valuable a tool as possible!

Jim Kremidas (jkremidas@acrpnet.org) is Executive Director of ACRP.
Clinical trial billing is the process of ensuring that, from the coverage analysis to a claim reimbursement, you have revenue integrity. From the negotiation of a budget and contract against the coverage analysis to the revenue charge review and adequately coding claims, a site must ensure teamwork and communication for all stakeholders.

However, billing compliance is sometimes an overlooked component at clinical operations sites. What are the challenges with the process of billing compliance, and how do you train team members adequately? This article focuses on how determining when training is necessary and when it is lacking is a successful component of a compliant research billing process.

Challenges Ahead

A research billing compliance professional faces challenges every day, and sometimes they are insurmountable. Understanding why a coverage analysis is necessary, and its importance to the development of the contract, budget, and informed consent is key. Although some sites have this process designated to someone on the research team, the necessity for having the proper training cannot be overstated.

Asking study coordinators to perform this task is truly difficult without the proper training and clinical expertise. Analyzing a protocol’s study procedures from the billing perspective is not an
easy task for anyone, least of all someone who has no idea what a coverage analysis is. However, their knowledge base from the clinical side in evaluating a study calendar and protocol for the clinical services can be extremely valuable to the process. Can they make an adequate evaluation and perform the necessary steps?

In some ways, having little or no training can be riskier, because once you start documenting using a bad process, you open the door for mistakes to be recorded and replicated. To be successful in research billing compliance, all staff need to accomplish many things, including an investment of time into professional development activities around the billing process.

**Validation and Evaluation**

How do you validate and evaluate your process of billing compliance? First, you must know all the types of clinical trials open at your site and whether they are considered “deemed and qualifying” under the National Coverage Decision of the Center for Medicare and Medicaid Services. Beyond the more familiar types of drug trials, understanding what types of device trials, if any, your site has open (including those carried out under Category A or B Investigational Device Exemptions [IDEs]) and if they have approval from Medicare is vital to your success in reimbursement.

Recognizing the types of studies and promoting awareness of them among all participants at every visit will set you up for success. Identifying each study with a coverage analysis is best practice, and should be implemented to procedurally process claims in a compliant manner. This does not occur without dedication and knowledge on many levels in the billing compliance spectrum.

While training is important, staff turnover for the billing compliance team can lead to big issues if there is not a hand off of information. The consequences can impact accrual and compliance with the protocol. There are many steps to ensure that ultimately, a claim is submitted correctly; the regulations are intense and cannot be learned overnight. Each state Medicaid plan varies, and all commercial payers have different medical management policies that can cover or not cover clinical trials. Accepting that Medicare is the payer that you should follow with intention from the beginning will make the process smoother.
Targeting Training Needs

What training is necessary for success? The first part of the billing compliance process is the coverage analysis. Training on a coverage analysis is absolutely necessary for best practice with a review of the protocol services against National Guidelines, National Coverage, and Local Coverage Decisions. This justification is documented and serves as justification when a claim is processed for a study participant with billable services.

The coverage analysis is the basis for a solid budget, contract, and informed consent. Knowing that the patient should be told what services their insurance or payer is going to be covering for a trial is part of the consent process, as they may end up with outstanding balances. This is why the person doing the consent should be trained on the coverage analysis so they can describe correctly to the participant what their expected cost will be in the consent form, and ensure that this description is understandable to a person with an 8th grade education.

Another area that is important to the billing compliance process is ensuring that all coordinators receive education on how the coverage analysis impacts the consent. Explaining that something is covered by a sponsor is easy, but when it is documented as a routine cost in the coverage analysis, the consent process is marred by disagreement with the financial documents. Participants will be confused when they receive an explanation of benefits that shows something itemized that they thought was provided by the study sponsor. By building appropriate infrastructure around this process, everyone is informed about what is expected to be paid by Medicare or insurance and what the sponsor is paying for or providing for free, and ultimately the transparency helps the participant to understand their financial responsibility.

Another problematic area for billing compliance is claims processing, when the research coordinator is contacted to help segregate charges on a participant claim. If the coordinator does not understand how the coverage analysis directly impacts submission of the claim, they can direct charges to the wrong payer. When they are not trained adequately, they may not order the services correctly. Asking one if something is “standard of care” might get an incorrect answer, thus a wrong claim is processed.
If the services are set as billable under the rules to a payer as a “routine” costs, the claim should be processed in that matter. Without the ability to track these visits, some sites find themselves overwhelmed and coordinators are relied on to make decisions on segregating charges with no knowledge or training of the billing compliance process. Making the wrong decision can separate hospital and physician billing into two different methods for one visit. Research staff must understand that how a service is ordered and documented can be the reason for a denial.

These types of services can be just as important in an inpatient device study and an outpatient drug trial. The government wants to know that you are billing both drug and IDE device studies correctly; both have unique challenges that must be understood. Anyone who deals with the claim at the patient care level needs information on the coverage analysis regardless the type of study you are dealing with when there is treatment. The communication flow is sometimes the biggest challenge for billing compliance teams, and often a lack of training can cause many discrepancies.

**Considering the Three C’s**

The “three C’s” of billing compliance can be described as meeting the Challenges, fostering Collaboration, and accepting a spirit of Compromise. Once you decide to meet the challenges of billing compliance, collaborating with colleagues will help in answering questions that arise. Keeping training on the agenda for all team members and encouraging them to attend conferences that have billing compliance, revenue cycle, and reimbursement on the agenda is key. There are many conferences that have sessions on these topics.

There also are many opportunities for training. Finding opportunities where all staff—including coders, study coordinators, billing compliance managers, regulatory compliance experts, and accounting team members—can learn together is recommended. Having everyone work together and collaborate on how to face the challenges in billing is gratifying for billing compliance personnel.

Compromise involves reaching an understanding of how each department’s procedures can impact others. Working together to face simple process issues with compromise for who is responsible can make the difference within a compliant billing process.
Conclusion

Put training on your team’s calendar and you will reap the benefits! Delving into networking opportunities, mentoring programs, and training will help staff to achieve career goals and make research billing compliance programs stellar. Attending clinical trial billing compliance conferences will strengthen your team members’ abilities to meet the challenges that come with this important aspect of clinical trial management.

Reference


Kelly M. Willenberg, DBA, RN, CCRP, CHRC, CHC, (kelly@kellywillenberg.com) is Manager of Kelly Willenberg, LLC in Greenville, S.C.
Paying Subjects to Take Part in Research: A New Perspective on Coercion and Undue Influence

David Borasky, MPH, CIP; Jeffrey A. Cooper, MD, MMM; Kelly FitzGerald, PhD

Under U.S. Department of Health and Human Services (HHS) and Food and Drug Administration (FDA) regulations and the International Council on Harmonization guidelines for Good Clinical Practice, for an institutional review board (IRB) to approve research with human subjects, it must determine that investigators will obtain informed consent from each prospective subject or the subject’s legally authorized representative, under circumstances that minimize the possibility of coercion or undue influence.\(^1\)–\(^4\) Payment for participation in research represents a mechanism to induce subjects to take part in research when they otherwise might not take part. Therefore, payment is part of the consent process and any payment provided to subjects must take place under circumstances that minimize the possibility of coercion or undue influence. However, how should IRB members determine that this is, in fact, the case in the studies they review?

Defining Undue Influence

To determine whether any payments to participants minimize the possibility of coercion or undue influence, IRBs should apply the definitions of “coercion” and “undue influence.” The
Belmont Report defines “coercion” as an overt threat of harm that is intentionally presented by one person to another to obtain compliance, where compliance in this case refers to agreeing to take part in research.\cite{5} The Belmont Report further defines “undue influence” as an offer of excessive, unwarranted, inappropriate, or improper reward or other overture to obtain compliance. In this context, “compliance” refers to agreeing to take part in research or to continue participation in research. “Influence” means to impact, determine, guide, shape, alter, change, or transform and “undue influence” is influence that is excessive, unwarranted, inappropriate, or improper.\cite{6–8} Under the regulations and guidance, undue influence is ethically unacceptable, whereas influence that is not undue is allowable.

As parts of the HHS, the Office for Human Research Protections (OHRP) and FDA have released guidances regarding subject incentives that state, “Paying research subjects in exchange for their participation in research is a common and, in general, acceptable practice.”\cite{9,10} The FDA guidance goes on to state that payments made to offset or reimburse out-of-pocket expenses do not raise issues of coercion or undue influence. This guidance also informs IRBs to look carefully at payments to ensure that they are neither coercive nor unduly influential.

**Proposing a Different Approach**

Most IRBs are cautious about payments and reject those that are out of the norm as coercive or unduly influential. However, two recent papers cast doubt on this approach, and suggest that IRBs need to take a different approach to evaluating whether the circumstances of payments to subjects minimize the possibility of coercion or undue influence.\cite{11,12}

The first issue noted by the authors of these papers is that studies of IRB members indicate that they commonly reject the use of monetary incentives because they categorize such incentives as coercive.\cite{7,8} However, these authors note that IRBs should abandon the idea that incentive payments can be coercive.\cite{11,12}

As noted in the Belmont Report, coercion involves the intentional threat of harm.\cite{5} Although a threat to withdraw a payment to which a subject is entitled can represent an intentional threat of harm, subjects taking part in research are not entitled to incentive payments. Therefore, the offer
of an incentive payment is a benefit and cannot represent a harm, no matter how large the payment.

Offering an incentive payment for participation cannot meet the definition of “coercion.” Therefore, IRBs should stop using coercion as a basis for requiring investigators to reduce the amount of payment to subjects. Instead, IRBs should focus on whether the influence presented by incentive payments represent influence that is acceptable or influence that is undue.

**Considering Payment Impact**

While coercion is relatively easy to recognize because subjects are threatened, distinguishing undue influence from mere influence is more difficult. Undue influence implies that individuals will agree to take part in research without a rational consideration of the information provided in the informed consent process, such as the risks and procedures involved in the research.

IRBs cannot consider an incentive payment to be unduly influential solely because an individual would not take part in the research but for the payment; this is precisely the reason investigators use recruitment incentives. Moreover, this logic would compel IRBs to determine that many acceptable incentives are unduly influential, such as advertising or a physician telling a patient that they might want to talk to the investigator to learn about taking part in a clinical trial.

If an IRB has approved a study, the IRB has determined that the risks are acceptable in the absence of payment. Adding payment to a research study cannot affect the acceptability of the research risks. In both cases, reasonable individuals can use good judgement and decide to take part in research with incentive payments, where in the absence of those payments, they would have declined.

Undue influence must lead to poor judgement. The question is: How does an IRB determine whether a payment causes prospective subjects to make a decision that is against their interests?

**Recognizing Context Plays a Part**

A problem with payments is that an offer of payments designed to incentivize participation in research will not affect all individuals the same way. Subjects will have different perceptions of
the financial reward based on the burden of the research in terms of costs of transportation, length of study visits, and degree of risks and discomforts. The offer may result in poor judgement by some individuals, but may not affect the judgement of others.

More specifically, what is unduly influential to one subject might be merely influential to another. As OHRP guidance states, “because influence is contextual, and undue influence is likely to depend on an individual situation, it is often difficult for IRBs to draw a bright line delimiting undue influence.”{9} Meanwhile, the IRB must approve the research for all individuals who meet the selection criteria, even if an incentive payment may cause poor judgement in a minority of subjects.

Since the theoretical likelihood of undue influence goes down with a decreasing incentive, many IRBs minimize the possibility of undue influence by mandating payments low enough to prevent any possibility of an incentive payment affecting someone’s judgement. This is problematic for two reasons. First, there is no threshold of payment below which no person would ever be unduly influenced. If the goal is to protect against such outliers, no payment can ever be free of undue influence. Second, there are other influences on a subject’s participation in research, and if the same paradigm is applied to these influences, one reaches an illogical conclusion.

Acknowledging Influence of Potential Benefits

Lee points out factors other than incentive payments that influence subjects, and notes that if payments can be unduly influential, so can these other factors.{11} For example, a common influence on subjects’ decisions to enroll in research would be potential benefit.

The potential benefit may be a therapeutic misconception or may be reasonably expected, based on reality. For example, early trials may have shown a high rate of complete remission in a lethal cancer that otherwise had no effective treatment, such as seen with early trials of imatinib and ipilimumab. This potential benefit, or the incorrectly perceived potential benefit, may be enough to cause an individual to make a decision contrary to his or her own best interest. Research staff who run active Phase I oncology units see this not infrequently.
Minimizing All Possible Sources of Influence

Lee observes that the standard IRB approach to reducing the likelihood that payments will unduly influence subjects is to reduce them. If IRBs were to apply their standard approach to payments to other research benefits, Lee notes that IRBs would have to reduce potential benefits to minimize undue influence. For example, the IRB would require protocols to randomize a greater percentage of subjects to placebo or require lower doses of drug in the treatment group to the point where individuals would be less motivated to take part.

Factors such as the possibility of closer follow-up, less expensive medical care, or access to medical care also influence subjects to join trials. IRBs could minimize the possibility of undue influence by reducing follow-up visits or requiring subjects to pay for the study drug; clearly, however, this is absurd. The IRB would be penalizing all subjects based on the behavior of a subset of individuals, and would be interfering with science that otherwise meets the criteria for approval.

Factoring in Fairness

There is an issue of fairness at stake when denying a subject reasonable compensation because of the behavior of a minority. If an insufficient number of subjects enroll in a research study, the likelihood of gaining important knowledge is reduced.

One can argue that reducing payments to subjects is different from reducing benefits in research. However, that does not solve the problem that potential benefits may present undue influence and that, to approve research, the IRB is obligated to ensure that such undue influence is minimized. Can IRBs use a single strategy to minimize undue influence related to incentive payments and potential benefits?

Obtaining Legally Effective Consent

One solution to this issue is to go back to the definition of undue influence. Undue influence implies that individuals will agree to take part in research against their own best interest. The
unduly influenced subject may have agreed to participate in the research without any consideration of the risks or the procedures that would take place.

The FDA and HHS regulations refer to “legally effective consent,” which generally means that an individual has been provided sufficient information about the research, understands that information, has considered that information, can understand the implications of a decision to take part, can make a decision, and can communicate that decision.\[1,2,5\] The unduly influenced subject fails these criteria, based on not considering the information and not understanding the implications of a decision to take part.

Essentially, unduly influenced subjects are in a state where they cannot provide legally effective consent. This applies not only to subjects who are unduly influenced by incentive payments, but also to subjects unduly influenced by actual or perceived potential benefits, advertisements, and recommendations of a treating physician that participation in a specific research trial would be in that patient’s best interests.

**Determining Capacity to Consent**

Another situation in which individuals are unable to provide legally effective informed consent arises when subjects are cognitively impaired and lack the capacity to provide informed consent. Typically, protocols require subjects to be able to personally provide informed consent, or in some cases, require a legally authorized representative to provide consent on behalf of such subjects.

Although some protocols involve the expectation that prospective subjects may or may not lack capacity to consent, almost all protocols involving adults are based on the idea that the research team knows whether a subject taking part has the capacity to provide legally effective informed consent. If they do, subjects must personally provide informed consent and permission by a legally authorized representative for the subject to take part in the research is insufficient. If they don’t, the investigator cannot enroll the subject or must obtain the permission of a legally authorized representative, depending on the specifics of the protocol.
Many IRBs have dealt with situations that require the research team to evaluate during the consent discussion whether the prospective subject has the capacity to consent. This involves the research team listening to the prospective subject’s statements and questions to assess whether he or she understands the information being provided, is considering that information, understands the implications of a decision to take part, can make a decision, and can communicate that decision.

IRBs can apply the same process to undue influence, which like capacity to consent, is another factor that interferes with the ability of an individual to provide legally effective informed consent.

**Recognizing Undue Influence**

Some IRBs may scoff at the idea that the research team can evaluate whether a subject is providing legally effective informed consent, but the fact is that IRBs often rely on research teams to make this decision. If the research team can determine whether a subject is providing legally effective informed consent based on capacity to consent, it can follow the same process to exclude subjects being unduly influenced by incentive payments or by perceived or actual prospect of benefit.

In our travels, we have met investigators from clinics that exclusively conduct Phase I oncology trials. They commonly run into patients who are looking for a cure and are not interested in learning about or considering the risks. These investigators recognize undue influence, and will not enroll subjects who ignore the information required to provide legally effective informed consent.

Researchers can follow the same process for incentive payments, and it is not hard to detect subjects whose judgement is impaired by the promise of dollar signs. There is no doubt that many researchers would benefit from training and mentoring in this regard. However, changing the behavior of research teams is the only way to address undue influence caused by perceived or potential benefit, and has the side effect of addressing undue influence caused by incentive payments.
Identifying the One Percent

This process directly addresses OHRP’s aforementioned observation that “because influence is contextual, and undue influence is likely to depend on an individual situation, it is often difficult for IRBs to draw a bright line delimiting undue influence.”\(^9\) Most IRBs understand that capacity to consent depends on both the protocol and the individual.

A subject may have the capacity to consent to a study involving a single blood draw, but may lack the capacity to agree to take part in a complicated clinical trial. Ninety-nine percent of individuals may have the capacity to take part in a trial, while one percent do not. The same is true for undue influence—a subject may be unduly influenced by a $2,000 incentive for one trial, but not another. Ninety-nine percent of individuals might not be unduly influenced by a $2,000 incentive for one trial while one percent are. The IRB can never draw a bright line, but the research team is in the ideal situation to detect and minimize undue influence.

Conclusion

In summary, IRBs should understand that incentive payments can never be coercive. The issue with incentive payments is that they can be unduly influential. Undue influence is not unique to payments, but also occurs because of perceived or actual potential benefit.

Because undue influence depends on the subject, IRBs cannot define when a payment, a perceived potential benefit, or actual potential benefit will be unduly influential to a specific subject. Nonetheless, IRBs are required to determine that the consent process is conducted in such a way that incentive payments minimize the possibility of undue influence.

For undue influence related to perceived or actual potential benefits, the current process is for researchers to not enroll potential subjects who are being unduly influenced. Rather than restricting incentive payments to low levels, IRBs can use the same process to address undue influence caused by incentive payments as a unified and reasonable approach to minimize all forms of undue influence.
References


**David Borasky, MPH, CIP, (dborasky@cgirb.com)** is Vice President for IRB Compliance at WIRB-Copernicus Group in Durham, N.C.

**Jeffrey A. Cooper, MD, MMM,** is Vice President for Process and Strategic Improvement at WIRB-Copernicus Group in Washington, D.C.

**Kelly FitzGerald, PhD,** is Vice President for IRB and IBC Affairs at WIRB-Copernicus Group in Puyallup, Wash.
Working out timely and appropriate revenue flows for clinical trials can often prove just as challenging as conducting the study itself. Here are examples of several pitfalls and potential solutions from the perspective of providers and study sites that are trying to keep their financial footing in today’s topsy-turvy clinical research enterprise.

In Search of Clarity

About five years ago, The Ohio State University received a stream of customer service complaints regarding a research study testing cardiovascular imaging. “Patients were calling in saying they got billed for something that was research,” says Jennifer Lanter, MSPH, BSN, RN, CCRC, the university’s director of revenue cycle clinical support and research billing.

The ambiguous language of the consent form likely contributed to the problem. Often these forms “will just say ‘you will not be billed for any research services,’” Lanter says. “Patients don’t know what that means.”
This particular scenario had an additional complication: The study’s principal investigator was also the treating physician. That made it hard for patients to distinguish between services that were part of their clinical care and those done for research purposes, Lanter says. “Patients would come in for an office visit...but they would end up getting billed for it,” she explains. “In the investigator’s mind, this was a standard of care thing. In the patient’s mind, it was research.”

As a result of the incident, the university amended the consent form to clarify which services were part of the research study and which were standard of care. They worked with the research staff to make sure they were explaining the distinction to patients. To rectify the billing situation, they administratively adjusted the charges so they were covered by the provider instead of by the research sponsor, even though the services were still considered standard of care. “So we were out money because the researchers didn’t communicate well,” Lanter says.

**Getting Paid**

Clinical research sites—especially smaller ones without a dedicated finance specialist—can also lose money if they don’t stay on top of their billing and invoicing. Kristi King Etchberger, a corporate executive with expertise in pharmaceutical law, discovered this in 2012 when she was hired to handle billing for several doctors who had gotten in over their heads with a study site they had set up.

The doctors were not using a clinical trials management system (CTMS), and the site had grown to a point where they didn’t have the administrative support to keep up with invoicing. They “were writing checks on Sunday afternoon from their kitchen table,” Etchberger says. “It was not a good use of their time, and they knew that.”

Once she helped the site get a CTMS up and running, staff sifted through volumes of historical and open studies and “found probably a million dollars for these three doctors that were un invoiced,” Etchberger says.

It’s not surprising; generally, study sites are run by medical professionals who focus on the medicine and the research. They’re busy dealing with study sponsors, the U.S. Food and Drug Administration, and contract research organizations over protocols, safety issues, patient
recruitment, data handling, and the like. “The research is very demanding—and that is, and should be, their focus,” Etchberger says. “But they also need to get paid for it.”

In 2015, Etchberger helped launch Clinical Research Billing, headquartered in South Florida, to help clinical research sites set up and manage CTMSs, negotiate budgets, and invoice for extras such as screen fails, unscheduled visits, and past-due visits that often don’t get paid if sites do not go after them. Her team works on a contract basis. “We’ve tried to leverage our experience and talents to smaller sites, to give them the advantage of large sites who can hire an expensive finance person,” she says.

**Billing Compliance**

Things get really complicated for large hospitals that in-house their research. For each service, staff need to decide if it’s a standard-of-care procedure or a research procedure. “And they have to decide who to bill—you can’t bill the pharmaceutical company for a procedure you’re billing the insurance party for,” says Nikki Couturier, BSRT (T) (CT), CCRC, ACRP-CP, contract and budget manager at IACT Health in Columbus, Ga., which manages a network of study sites.

Making these decisions can be tricky. “Standard of care itself can be subjective,” notes Couturier. “It’s not always laid out in black and white. It changes by region. It changes by physician, by practice, by hospital. So that makes it very confusing.”

The confusion can intensify even further for study sponsors. “You’re doing a study all over the country, and each region can differ based on the local coverage decision policy,” says Kelly Willenberg, DBA, RN, CCRP, CHRC, CHC, of Kelly Willenberg & Associates. Her firm trains people how to look up guidelines and understand what to do with them.

“We step through everything you need to know—how to look up coverage analysis, how to validate it, how to make sure you have documents to defend what you’re going to bill out on a claim,” Willenberg says. “You want the proper payer to pay what they pay on a claim, based on a coverage analysis at the beginning. It’s a huge process to get it right.”
Esther Wei-Yun Landhuis, PhD, is a freelance science writer based in the San Francisco Bay area.
GOOD MANAGEMENT PRACTICE

Creating Accountability at Research Sites: Step by Step

David J. Morin, MD, FACP, CPI, FACRP

Accountability is the process by which an individual or organization is held responsible for a set of accepted rules. Sites should develop thorough accountability processes for the protection of subject welfare and data as a good management practice internally, and because they are held accountable by external regulatory agencies. There is also a chain of accountability connecting site staff to their manager, the manager to the organization, and the organization to governing agencies.

For such an important process, however, there is very little information available on how to create it.

Take a minute and ask if your research site has methods in place which genuinely allow individuals to be held accountable for their actions. For example, when addressing an issue, have you ever heard, “That’s not how I was taught to do it” or “I didn’t know that was my responsibility”? However, what if their training failed to address a task or they were not assigned the authority to perform a particular function?
This brief article will detail the steps required to create accountability at the research site level. Such accountability allows sites to hold individuals responsible for their assigned roles, but also to bring managers to account for gaps in the process and for updating the system when required.

The Essential Steps

Accountability begins by assigning responsibility in your standard operating procedures (SOPs). Though SOPs are not regulatory requirements, they are essential to creating a uniform standard of behavior across the spectrum of research site actions. They follow the regulations and allow the site manager to assign tasks to individuals based on their study roles as a result of their level of education, training, and experience. They define expectations and delegate authority inherent in the company role. SOPs can be acquired commercially and then modified to your site requirements or thoroughly developed internally. However, if you have SOPs, you are required to follow them.

Once each role is appropriately assigned, this information is listed directly from the SOP to create a job description. The job description is separately added to the SOP and sent to prospective employees before a first interview. By sending this information at the pre-employment phase, you are setting expectations very early. I added this process where I work.
years ago, after hiring a promising new clinical research coordinator who was shocked to learn on her first day that she was expected to have contact with people! We never said the position was purely lab based, but hadn’t provided a list of job expectations. Because this wasn’t clearly written down, wrong assumptions were made on both sides. Providing the list of job duties very early in the process fixed that issue. However, it also had the possibility of discouraging novice applicants, so we reassure a promising candidate that we will train them to perform all assigned tasks.

As soon as a prospective candidate is hired, begin the training process to include all tasks assigned in their job expectations. Also, include ancillary items required of all employees. At our institution, we use a training program developed internally and appoint an experienced mentor. To preclude boredom and keep the training relevant to the roles, it is a mix of didactic and clinical education. Also, training programs may be obtained commercially.

Mentoring allows supervision and oversight to help verify competency, which is the ability to perform one’s job effectively. We utilize a training checklist and regularly meet with the new employee to assess progress and skill. Each training section is divided into separate areas which are initialed and dated by the mentor and manager once completed. Finally, we keep this training record on permanent file should we need to verify training at some future date.

Verifying job performance is an ongoing process which is used to assure regulatory compliance and employee competency. Examples of a “proactive” quality assurance (QA) process are the secondary review of all source documents before screening subjects, and of subjects before
randomization. This process is used to help prevent protocol deviations. Reactive or “retroactive” QA processes review completed work; they may respond to an internal concern or an issue discovered by the study monitor, and may be done in preparation for an external audit or on a routine basis. Competency is confirmed when the quality of the work is acceptable.

Finding an activity which falls outside the scope of acceptable practice, or outside the boundaries as defined by the protocol, requires immediate attention. There are many good articles on “Corrective Action and Preventive Action” (CAPA) for readers to review. Whether the improper action requires a CAPA or process involving the Human Resources (HR) department is determined by the manager, based on the severity and intent of the action.

CAPAs are used to address a process that is inconsistent with the expected performance tasks. They are part of an administrative process used to show “due diligence.” It’s possible that the action occurred as a result of inadequate training. In this case, the new process is added to the SOP along with documented training for all affected employees.

While CAPAs are educational, a “Warning” or “Write Up” is more disciplinary in nature. We strictly follow the recommendations of our HR department when disciplinary actions occur.
Figure 1 depicts how I see this process as continual. New regulations are entered into the SOP and assigned to those responsible. The defined expectations for a given job position are used as the basis for training. The next section along the “wheel” is to assess job performance and verify competency through QA programs. The final part is to address and correct any deficiencies by site actions, which include CAPA for processes requiring additional training and due diligence to actions which are more punitive. Any methods which are new or updated add to the SOP (at the top), and the process begins again.

**Figure 1: Closing the Circle of Accountability**

A recent example of changes to our SOP occurred when we received a study which randomized the subject the same day of screening. We allowed some flexibility to review the first two subjects within 24 hours after randomization if it could not be done earlier. By following these general processes, all levels of the organization are held accountable to their roles and expectations, including management.
Conclusion

Developing a thorough accountability process may take time, but it is not complicated. It permits modification at any time based on the site needs. Moreover, the time invested will reap big rewards by creating an environment of stability.

David J. Morin, MD, FACP, CPI, FACRP, is Director of Research with The Holston Medical Group in Kingsport, Tenn., and a member of the Association Board of Trustees for ACRP.
Q: My institution is currently in the process of amending its standard operating procedure (SOP) for CITI Program training. We have been having trouble keeping key personnel compliant, and are wondering what the federal requirement is for training in research. I was under the impression that training in Good Clinical Practice (GCP) and human subjects protection (HSP) was required, but another member on my team thinks only GCP is required. I am not able to find any guidelines/regulations that specify exactly which training is needed.

A: Even a diligent search for specific U.S. Food and Drug Administration (FDA) “requirements” for GCP and HSP training will not provide a clear answer, as there are none. Don’t be shocked! Even the broader Common Rule (45 CFR 46 in the Code of Federal Regulations), in effect at all federally funded institutions like universities and most hospitals, says nothing about specific investigator training requirements for clinical research activities. If you are conducting clinical studies funded by any institute in the National Institutes of Health (NIH), there is a Human Subjects Education Policy that requires individuals involved in the design or conduct of the studies (i.e., “key personnel”) to receive education on the protection of human subjects. But the institution that receives the grant or contract must determine what is adequate to meet the education requirement, and NIH does not specify or endorse any particular program. The U.S. Department of Health and Human Services, under which both NIH and FDA are organized, has a directive that calls for “appropriate research bioethics training and human subjects research training” for investigators, but again, no specifics about what is appropriate are provided.
However, there is a recognized cascade of responsibilities for documented training that do stem from specific FDA regulations and guidance documents, including the International Council for Harmonization (ICH) E6(R2) Guideline for GCP, which is endorsed by the FDA. In addition, there are what some would call accepted “industry practices” not published by FDA or ICH. For example, you may find the TransCelerate Biopharma “Minimum Criteria for ICH E6(R2) GCP Investigator Site Personnel Training” document as a useful resource, but I reiterate that those criteria do not constitute a regulatory requirement.

Comprehensive GCP training often covers most, if not all, of the topics many also consider as HSP (or what CITI refers to as Human Subjects Research, or HSR) training. So, you have to see the various course curricula to assure you are getting what you want/need without unneeded overlap. Separation of GCP and HSP/HSR courses can be useful to isolate topics more useful for different personnel, and also to break up the learning modules into more digestible portions.

Many institutions have their own requirements, of course, independent of commercial clinical study sponsors. This is most common at institutions like universities and hospitals receiving federal funding, and the relevant institutional review board (IRB) for the institution may provide (or at least review) the specific minimum education requirements.

If you start with regulatory obligations, all sponsors of FDA-regulated clinical studies are responsible for “selecting qualified investigators” (see regulations at 21 CFR 312.50 as a base starting point for drug studies; medical device studies have parallel regulations to quote, like 812.43(a)). At 312.53(a) a bit more detail is given, as drug study sponsors “shall select only investigators qualified by training and experience as appropriate experts to investigate the drug.” Not so helpful yet, right? What training? What experience? What is an “expert”? What about everyone else on the research team?

Note: If you prefer the ICH E6(R2) GCP citations (I often do), please look at Sections 2.8, 3.2.1 (for IRB members), 4.1.1, 5.0.4 (this section is new in the E6(R2) update and here the “risk control” concept is noted as a sponsor decision process), 5.5.3(b) Addendum (for computerized systems), 5.6.1, 5.7, 5.18.7 (also an R2 update section), and 5.19.2(b) (which relates to auditors). If you/your sponsor claim to be following GCP (it probably says this in most protocols or the
sponsor’s SOPs), then you have to consider what it says in these GCP sections about training and experience for study personnel.

Back to the FDA obligations: What is meant by “qualified,” being an “expert,” or “training and experience” is not detailed in the regulations, GCP, or in FDA guidance. Nor is what might be considered specifically as adequate documentation for these (other than in an investigator’s CV “or other statement of qualifications” as quoted in 312.53(c)(2)).

So, we (i.e., everyone in the clinical research enterprise) all are faced with both determining what is appropriate training for study personnel (like, just the basic concepts or more of the details of GCP, HSP/HSR, and research ethics) and how to document that training so someone else can evaluate it upon review—and hopefully they will then consider it adequate. (The contemporary approach is to use “risk-based” methodologies to assess and plan for your training/documentation requirements. That’s a longer and separate discussion, though in reality, everyone has always been using risk-based methods to some extent, whether they called them that or not.)

Further on in the FDA drug regulations at 312.53(c)(1)(vi)(g), an investigator's responsibility is extended to the study team, as the investigator will “ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations...”. This “ensuring” part, as well as the need for them to be “informed,” is what most recognize as creating a generalized training requirement for study personnel at the site level.

Now, exactly what constitutes adequate training to “ensure” things will be done right (you know, things like the sponsor’s and investigator’s obligations to conduct the study according to the investigations plan and protect the rights, safety, and welfare of study participants, etc.) and what constitutes adequate documentation for this, is in general left to the sponsor and investigator, respectively, or according to the institution’s policies. Some would say ultimately this always rests with the study sponsor. Fine—and many commercial sponsors (and institutions) will tell you explicitly what they consider “their” requirements for training and the requisite documentation.
Sponsors and contract research organizations (CROs) should not be claiming their specific training requirements are “FDA requirements” *per se* (as I mentioned, these are nonexistent), but they certainly can be the institution’s, sponsor’s, or CRO’s own requirements. Each party must consider how others (in particular, FDA or other regulatory body inspectors, monitors, and auditors) will look at this training issue through some future review of documentation as they seek evidence that the involved study personnel were indeed trained and qualified to perform their study-related activities. It’s always a “show me the documentation” situation.

Depending on the role of the study personnel (investigator, receptionist/scheduler, nurse, physician, scribe, coordinator, data clerk, technician examiner, clinical lab chemist, research lab chemist, pharmacist, IRB member…the list is quite long) someone needs to evaluate what aspects of GCP and HSP/HSR, in addition to protocol-specific instructions, are needed to meet the “ensuring” target for those various personnel. Some sponsors take a broad approach (perhaps unnecessarily so) and say “everyone at the site involved in our study needs comprehensive GCP and HSP/HSR training” and it must meet minimum criteria for the training time commitment and obtaining a passing score on some evaluation. Other sponsors are willing to scale the requirements according to levels of responsibility, roles, or involvement.

Perhaps the training needs to meet some “industry standard,” like a curriculum outlined by TransCelerate or another body, or be sourced through specific vendors, like CITI, or through the institution. Even if you use CITI, many participating institutions can and do tailor the basic CITI GCP course modules collection (by addition or subtraction of specific modules) making their GCP course institution-specific.

Some sponsors give no useful instructions for training at all. Other sponsors may direct investigators to be more selective (as some FDA guidance documents suggest) and focus more comprehensive training on “key personnel” (as NIH policy implies) who really need a stronger, more comprehensive GCP and HSP/HSR training experience. This routinely applies to the lead investigator and their coordinators, most subinvestigators, and the research pharmacist. Policies may allow those in other, less research-responsible roles at the site to receive less comprehensive GCP training but keep at least the HSP/HSR privacy modules if they handle the research data or subject medical charts, for example.
How sponsors/investigators/institutions choose the type and extent of the training they require for site study staff is also an enforcement issue, to be sure. Does training ever expire? Is re-training needed at some interval? For which staff members? Why? (I had someone ask me once if re-training was needed to update training documentation that had just expired after all the last study visits were completed and close-out was occurring. I said no; be sensible.)

Not all sponsors are very good about explaining their desires and requirements clearly (through SOPs or the investigator contracts, for example). So, when monitors report that staff training and the related documentation are inadequate, what is to be done? What standards are being applied to judge noncompliance? Whether training is completely lacking or perhaps out-of-date, we know sponsors are still stuck with their obligations to bring sites back into “compliance.”

Compliance, it should be noted, has two primary masters: regulatory compliance for FDA and compliance with the sponsor’s own SOPs (and often the site’s SOPs, as well) and protocol. Few sponsors are very good at the compliance side of this issue, despite their monitors’ reports describing lack of adequate and documented training or re-training for study staff, assuming the requirements were clear to begin with.

When sites are noncompliant with the stated training requirements, the hammer never seems to fall often enough on the investigator/site in a way to risk investigator payments from the sponsor, or stopping shipments of study drug and termination of study participation at the site. (This is about the only leverage the sponsor really has, according to the regulations at 312.56(b). Institutions may have other enforcement options, as does NIH.) I’m complaining here, but in my opinion, this section of the regulation is exercised too rarely by sponsors. Perhaps because their investment has already been high, clearly many noncompliant sites are allowed to continue on in a state of noncompliance for a variety of reasons (not just lack of appropriate training, to be sure).

I’ll stop here. As you can see, the sponsor and/or the institution should be driving this training/training documentation issue using clear, written requirements. I hope sponsors in particular (perhaps through their CRO and monitors) provide reasonable instructions about their “requirements” for investigator and relevant staff training, in advance, and are willing to enforce
what they consider really necessary for study quality, safety, and overall ethical human research. I also hope sponsor requirements are thoughtfully considered (in conjunction with any institutional policies), and not so onerous for everyone at a site that they inhibit qualified investigator participation in clinical research.

I have observed (as perhaps you feel) that many investigators and research staff are not provide adequate time for GCP and HSP/HSR training, or are somehow resistant to re-training, as our question writer noted. But if research staff, including the investigator, are not given (or refuse to accept) adequate time to be trained properly, I feel the site in general should not become a research site. You can base this decision on the need for sites to have adequate resources (see ICH E6(R2) GCP Section 4.2), which includes not only the necessary facilities but also having properly trained personnel. This commitment to adequate training is a part of the high (but necessary) costs of time and expenses associated with clinical research, and something that must not be ignored by sponsors or investigators.

**In Conclusion…**

As I have mentioned in other writings, being a good study site with qualified investigators and staff requires a significant expansion of understanding, skills, and procedures beyond the “good clinical practice” associated with routine clinical care. Good Clinical Research Practice (GCRP) is the way we should think of the clinical research endeavor, and as the complexity and regulatory controls for GCRP continue to increase, what we now call GCP and HSP/HSR training becomes even more important each year.

**Acknowledgement**

Some of the above details on training requirements and the role of IRBs were adapted from information posted to the ACRP Online Community by Erica Heath, MBA, CIP, in response to the author’s feedback on an Open Forum thread which serves as the basis for this column.

**Jan S. Peterson, MS, CCRA, RAC, ASQ CBA, ACRP-CP,** (jan@tpsrv.com) is a consultant and Vice President of Regulatory Affairs and Quality for Global Regulatory Partners, Inc., and a former Chair of the ACRP Regulatory Affairs Committee.
SITE STRATEGIES

Protecting Cash Flow: How Site Investigators and Staff Can Keep Site Payments on Track

Shaun Williams, PMP

Clinical site payment technology is moving steadily toward automated systems and processes to help sites and sponsors/contract research organizations (CROs) track expenses, resolve invoices, and reconcile payments. Until such technology is perfected, standardized, and widely deployed, however, sites especially must contend with a number of payment-related issues.

Considering the “Payn” Points

Chief among the payment pain points for sites can be cash flow volatility. In its 2018 Site Landscape Survey, the Society for Clinical Research Sites (SCRS) found that 64% of responding sites had less than three months of operating cash on hand.{1} Similarly, the survey reported that more than 20% of sites made less than 5% net profit in 2017.

Payment delays cause financial hardships for research sites—so much so that the Clinical Trials Transformation Initiative (CTTI) found that as many as 40% of sites drop out of studies due to lengthy payment delays.{2} Taking a closer look, Forte surveyed 119 sites, and 21% of respondents cited “the invoicing process” as the driving reason for delayed payments.{3}

Many factors make sites’ invoicing difficult; for example, most small sites do not have dedicated financial staff, leaving invoice preparation and payment tracking to administrative or clinical personnel who are juggling many other duties. Trial logistics can pose billing challenges, as can
the fact that investigators may operate out of multiple office locations. Further, sites frequently run multiple studies, each with its own unique invoicing demands; keeping up requires significant administrative organization and monitoring.

**Streamlining the Invoicing Process**

With approximately 50% of study budgets attributed to site payments, sponsors and CROs are working toward standardization and automated solutions. In the meantime, sites can take the lead in making sure they are paid all that they are owed on time. More specifically, sites should:

- **Negotiate an appropriate start-up payment.** It is important to get off to a strong start on every study. By requesting funds up front and tied to a milestone achievement, such as a successful study initiation visit, you will best position your site to do just that. Be ready to justify your true costs as part of your negotiations.

- **Ask for monthly payments as part of the contract negotiations.** Although 77% of the respondents in the SCRS Site Landscape Survey preferred monthly payments, only 39% were contracted to that frequency. The sponsor may insist on quarterly payments, but you will not know until you ask. In addition, by asking you will help raise sponsors’ appreciation of this issue.

- **Study the payment section of the clinical trial agreement (CTA) closely.** At the start of the trial, ask questions to be certain you understand the terms and effort required to manage the payment process start-to-finish. All sites, especially those outside the U.S., should also be clear on what costs are issued via a pro forma invoice.

- **Be prepared to handle amendments.** Amendments to the CTA, which are very common, should be negotiated as swiftly as possible, and all parties need to be clear on how the amendments will affect payments. Create and implement standard operating procedures specific to amendments and track amendment activities.

- **Recognize that patient visits drive the majority of invoicing, but not all.** On average, 30% of billable items include fees associated with non-study visit tasks, such as institutional review board (IRB) submissions and advertising. Patient-related costs can often be triggered automatically from electronic data capture (EDC) systems, and sites should create a
mechanism for flagging invoices for other events. Such triggers will help you secure faster payments for all billable study activities.

- **Keep trial participants’ records up to date in the EDC system.** EDC and remote monitoring enable sponsors/CROs to track individual clinical activities in real time. Depending on the study’s payment management system, that information may also trigger an automated payment once the predetermined, contract-specific milestone has been met.

- **Collect billable activities data from the clinical team in the clinical trial management system (CTMS) and invoice only what has been approved within it.** Your site’s or institution’s clinical and finance teams should meet regularly to review what is billable.

- **Invoice often and on time.** Build a simple tracker in Excel that lists all of the categories of billable work/items and the datapoints that will demonstrate that the activity has been completed. Such a tracker should be populated with data from the CTMS and with information from the detailed remittance notification that accompanies payments. Ask the sponsor/CRO if they can provide such a tracker for your use.

- **Include all necessary details in your invoices.** To ensure prompt processing, include all required details in every invoice. Included should be activity references, which will enable accurate and timely reconciliation of money received. Always list the account e-mail and contact telephone on the invoice, which will allow remittances to be set up automatically.

- **Create an invoice template.** Ask your sponsor/CRO for a template or create your own to streamline your ongoing payments management tasks.

- **Establish a strong communication channel with the trial sponsor/CRO.** At study start, identify the appropriate contact for all payment-related issues. Make sure you have a central contact for payment escalation.

- **Use every tool you are given.** If the sponsor/CRO has an established payments portal, register and use it. Being able to check payment status in real time—and on your schedule—will save you time and frustration while ensuring better cash flow.

- **Follow up on delayed payments.** Timely attention—and persistence—are keys to successful collection of late payments. Post reminders in your calendar and follow up every week until you see payment.

- **Praise effective payments providers to your sponsor/CRO.** Should you work with a payments provider that meets or exceeds your highest expectations, be sure to thank the sponsor/CRO
managing the study. You might also recommend the vendor to other sponsors whose payments processes are not as well orchestrated.

Conclusion

The clinical development industry is well aware of the importance of developing payment solutions that work for investigators and their staff. Specialty payments firms and select CROs are developing technology and processes that will lessen site burden. Adopting the suggestions above, in parallel with the ongoing technology changes, will increase the benefits and satisfaction your site gains from conducting clinical trials—now and in the future.

References


**Shaun Williams, PMP**, is Executive Director of Investigator Management Solutions for Syneos Health.