ACRP

FOR LEARNING FOR LISTENING FOR LIFE

Clinical Researcher™

The Authority in Ethical, Responsible Clinical Research

January 2020 (Volume 34, Issue 1)

Rising Expectations in Research: Are You Sinking or Swimming?

Clinical Researcher™

Association of Clinical Research Professionals

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Clinical Researcher—January 2020 (Volume 34, Issue 1)

EXECUTIVE DIRECTOR'S MESSAGE

You Are the Association's Vital Signs

Jim Kremidas

One of the best parts of my job here at ACRP is the opportunity to meet so many of our interesting members and "take the pulse" of what belonging to the Association means to you. I've been inspired countless times since I became Executive Director by your dedication and commitment to helping deliver the most innovative therapies to patients.

I've always welcomed the opportunity to get your input on ACRP as an organization. Whether it's a request for additional educational offerings or new certification opportunities, or something more basic like more coffee breaks at the annual conference, I always take your ideas and concerns back to our team in the Alexandria, Va. home office.

In 2019, we conducted a massive member survey. I'd like to thank you if you found the time to participate. The data it yielded represent the vital signs of this organization, and serve as a diagnostic tool for us to know where we are helping you to do your job better and thrive in your career, and to learn where we can improve.

I'm happy to report the member survey told us there are a lot of things you are happy about with your organization. Perhaps more importantly, however, it alerted us to a few areas where we need to get better.

I'd like to use my first column of 2020 to address a few of those core areas:

- **Customer service.** You told us you sometimes had difficulty navigating our website, especially when it came to finding our services online. We heard you loud and clear, and I'm excited to report we're making important strides toward vastly improving your user experience in 2020. It's a big project and we ask for your patience as we hone it and build out a better website to help make it easier to access all the benefits of being an ACRP member.
- **A revitalized eLearning program.** You asked for upgrades and improvements, and we're just about to deliver them. You'll soon have access to more interactive, simulated training modules, culled from the best practices and most innovative adult learning techniques. Watch this space for a big announcement in February.
- **Member communications.** We're working toward better targeting our communications with you. Translation: fewer, but more on-point e-mails from us to you in 2020.
- **Exciting news on the Chapters front.** We're launching innovative pilot programs in the Research Triangle Park region of North Carolina, in Las Vegas, and in New Orleans designed to remove much of the business and administration burden from chapter leadership, freeing them up for more networking and educational events. The early returns are good, but I'll report back on these pilots in the months ahead.

Finally, allow me to take this opportunity to once again thank you both for your valuable work, and for giving back to the clinical trial enterprise by being a member of ACRP. As always, I welcome hearing from you directly at jkremidas@acrpnet.org.

Jim Kremidas is Executive Director of ACRP.

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CHAIR'S MESSAGE

With Your Involvement, It's a Wonderful Association

Paul Evans, PhD

In the holiday classic *It's a Wonderful Life,* hero George Bailey learns what the world would have been like had he never been born. For the few of you who haven't seen it, I won't ruin the film. Suffice to say, the world is better for George Bailey being part of it.

Watching the film recently got me to thinking about ACRP. What if it didn't exist?

As the incoming chair of the Association Board of Trustees for ACRP, our organization has been on my mind a lot recently. I'm so impressed with the caliber of people working in this industry and the passion I so often find for the important work you do, but what if we weren't here? What would change?

I think ACRP's purpose is clear and two-fold: providing development opportunities for individual members, whether that is certification, training, or networking, and helping to raise the professional bar for the entire clinical trial workforce. These aren't mutually exclusive goals by any means, and we need to make sure we don't lose sight of our dual purpose.

Over the past few years, ACRP has become established as a leader in workforce development in the pharmaceutical industry. We will continue to extend initiatives such as our Workforce Innovation Steering Committee (WISC), which saw us provide input to lawmakers on Capitol Hill developing the Cures 2.0. Act.

At an individual member level, I'm excited about our plan for working more closely with our vital ACRP Chapters in 2020. As Jim Kremidas mentions in his first Executive Director's Message of the new year elsewhere in this issue, we're launching three pilot programs this year that we hope will reinvigorate our Chapters and reduce some of the administrative burden on their leadership. The idea is to free them of the administrative burden of running a Chapter to do the more important work of raising awareness of ACRP and clinical research as a vital profession.

We're also in the midst of a massive website upgrade. I know some of you have been frustrated at times when interacting with ACRP online. We heard you. We've made major strides toward improving your user experience and the investment we will be making in our back end systems this year will go further in providing the service you deserve. I welcome your feedback on past or current experiences. We're always looking for ways to further enhance the value you get from membership in ACRP.

Ultimately, we're all part of the same important mission: Speeding the safe delivery of lifesaving and life enhancing drugs and devices to patients. I look forward to working with old friends and colleagues and meeting new ones throughout 2020. A great place to meet is of course at ACRP 2020 in Seattle from May 1–4, and if you haven't already made plans to join us there for what I'm sure will be a great event and a great party, then add it to your New Year's resolution list.

If you have any thoughts about how you can contribute to ACRP, or how we can help the clinical trial industry, please don't hesitate to reach out to me at pevans@velocityclinical.com.

Paul Evans, PhD, is President and CEO of Velocity Clinical Research, and Chair of the Association Board of Trustees for ACRP in 2020.

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PEER REVIEWED

Optimizing Medical Records Collection in Clinical Research: Lessons Learned from Two Pediatric Cohort Studies

Marina Albuquerque de Souza Dantas, MD; Lacey B. Robinson, MD; Elie Mitri; Catalina Gallegos; Ashley F. Sullivan, MS, MPH; Carlos A. Camargo Jr, MD, DrPH

Medical records are a valuable source of data for clinical research, and the ongoing shift to electronic medical records (EMRs) allows for increased access to important data sources.{1} In 1996, privacy rules were established through the Health Insurance Portability and Accountability Act (HIPAA) to safeguard medical information and protect patients' privacy.{2} The HIPAA Privacy Rule is frequently misinterpreted by healthcare providers, contributing to difficulties in medical records collection and complicating research execution.{3} A national survey of clinical scientists in the U.S. showed that the HIPAA Privacy Rule was perceived to add uncertainty, cost, and delay to the conduct of health-related research.{4}

To date, little has been published on strategies for medical records collection in clinical research, which may discourage investigators from conducting robust studies relying on medical records, such as large multicenter studies. Therefore, a better understanding of the applicability of the HIPAA Privacy Rule, along with possible solutions to commonly encountered problems in records collection, would be of substantial benefit to clinical researchers.

To address this scientific gap, we describe our experience of collecting medical records in two multicenter pediatric cohorts, known as the 35th Multicenter Airway Research Collaboration (MARC-35), a prospective cohort study of severe bronchiolitis and risk of recurrent wheezing and asthma, and the 43rd Multicenter Airway Research Collaboration (MARC-43), a study of the airway microbiome asthma phenotypes in healthy infants. We have faced several challenges in medical records collection, but with experience, we have overcome many problems and improved our processes to obtain a high level of completeness of medical records. These experiences encouraged us to share the lessons we have learned for the benefit of future studies.

The MARC-35 and MARC-43 Cohorts

MARC-35 and MARC-43 are multicenter cohort studies following children from early infancy to approximately age 6 years for multiple outcomes, including clinician-diagnosed asthma. From 2011 to 2014, 1,016 infants (age < 1 year) were enrolled in MARC-35 in 17 U.S. hospitals (enrollment sites) during an inpatient hospitalization for bronchiolitis. In 2013 and 2017, a total of 720 healthy infants were enrolled in MARC-43 in five U.S. hospitals.{5,6}

Study procedures in these two parallel cohorts include serial telephone interviews with the legal guardians every six months, in-person physical exams every few years, and complete medical records review from birth to study completion at age 6 years or older. Complete medical records review includes physician review of records from all primary care providers (e.g., pediatrician) and specialists (e.g., pulmonologist, allergist), along with all urgent care visits, emergency department visits, and hospitalizations. All study activities are coordinated by the Emergency Medicine Network (EMNet) at Massachusetts General Hospital.

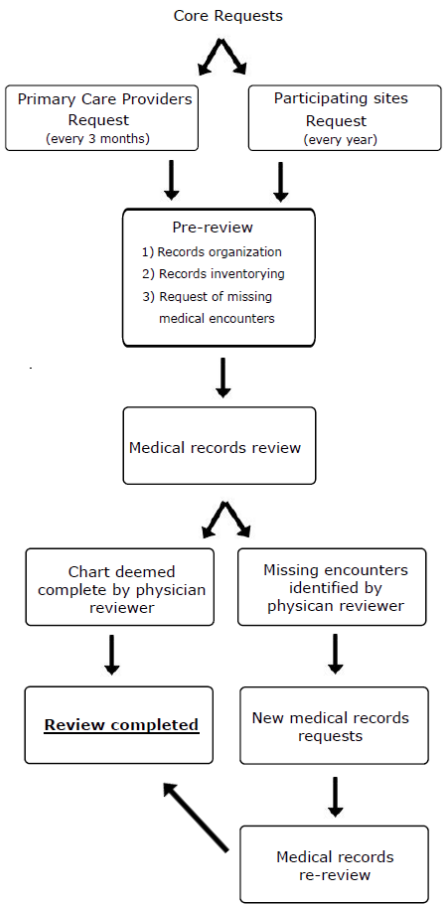
Informed consent and HIPAA-compliant authorization forms for records release were obtained at enrollment, authorizing the EMNet Coordinating Center to obtain all records for participants

from birth until study completion. Per the HIPAA Privacy Rule, authorization forms may be valid until an established date (e.g., until the end of the research study) or never expire. We decided to use a form that was valid until one year after completion of participant follow-up.

Medical Records Collection

We used a systematic approach for medical records requests and inventory (see Figure 1). Core medical records include records from the participating enrollment sites and the children's primary care providers (PCPs). Requests for these core records are made regularly on a predefined schedule. In November of each year, due to the existence of a Data Use Agreement, the EMNet Coordinating Center requests all medical records on file for the previous year from each participating enrollment site, including all visits to site-affiliated facilities within a shared EMR system.

Figure 1: A Systematic Approach to Medical Records Requests and Inventory



PCP information is confirmed and updated every six months by serial telephone interviews with legal guardians and stored in REDCap,{7} a HIPAA-compliant, web-based data capture tool. Time points for PCP requests were predefined at ages 1, 3, 5, and 6 years. Every three months, we query which participants meet these specified age timepoints and send medical records requests to the PCPs they saw in the interval of interest. The requests are submitted twice by mail to PCPs, and any non-responders are then contacted by telephone.

After the core medical records are received, EMNet coordinators conduct a pre-review of the records by age section (e.g., 0–0.9 years, 1–2.9 years, and so forth). Pre-review includes checking medical records for consistency (e.g., ensuring available records match healthcare encounters reported by legal guardians) and identifying missing or incomplete records. Information regarding completeness of each age range, dates of submission, and details about problems with collection are recorded in Microsoft Access, a database management system.

During pre-review, medical records not obtained from PCPs through the initial core request (approximately 15–20%) are re-requested and followed up until the missing medical records are obtained. Urgent care visits, emergency department visits, specialist visits, and hospitalizations not obtained through participating enrollment sites are also requested at this time. The medical record is deemed complete when we have no chronological gaps and all well-child checks and sick visits are present for a given age section.

When complete, the medical records are assigned for review by trained physicians who extract relevant data portions and enter them in REDCap. If the physician reviewer identifies any remaining missing medical records, medical records requests are sent to the identified facilities.

Challenges

We encountered multiple challenges during the process of medical records collection (see Table 1). We will discuss our most common and difficult challenges and share our solutions.

Table 1: Medical Records Collection: Challenges and Solutions

CHALLENGES	SUGGESTED SOLUTIONS
DELIVERY OF MEDICAL RECORDS REQUEST TO THE CORRECT PROVIDER	Maintain periodic contact with participants after enrollment to update information about past and current healthcare providers. Maintain a database with contact information for all participants' PCPs, including preferred method of contact.* Ensure knowledge of records allocation rules in the case of facility closure.
LACK OF RESPONSE TO MEDICAL RECORDS REQUESTS	Perform systematic follow-up after submission with telephone calls. Track submission of requests and all subsequent contacts in an EMR tracking system.** Use Data Use Agreements to make large bulk requests when possible.
DECLINED AUTHORIZATION FORMS FOR RECORDS RELEASE	Use multiple checkpoints to ensure accuracy of authorization forms at time of completion. Adapt authorization forms to follow state-specific requirements. Avoid making authorization forms provider-specific and instead use broad authorization from many care providers. Set authorization form date of expiration after outcome of interest to allow additional time for medical records collection. Contact participants periodically to obtain a new authorization form if needed. Use an electronic system for authorization form signature.

*We use REDCap for this purpose. **We use Microsoft Access for this purpose.

Delivery of Medical Records Requests to the Correct Provider

During the many years of follow-up, children's PCPs frequently change, and facilities relocate or undergo closure, complicating delivery of medical records requests to the correct provider. Often, updated PCP information is provided by legal guardians, but at other times we only suspect PCP changes have happened due to gaps in the received medical records.

The HIPAA Privacy Rule forbids providers to release any protected health information by phone, including the name of other providers, and prevents facilities from sending records of others, thus hindering medical records collection in cohort studies that do not have longitudinal contact with participants. The serial telephone interviews with legal guardians included in both cohorts enable us to obtain updated contact information for PCPs in a timely and efficient manner. This process is aided by recording of alternate contacts for all legal guardians, increasing our ability to complete the serial telephone interviews.

However, in some cases, we are unable to obtain updated PCP contact information from the legal guardian (e.g., participant lost to follow-up) and then rely on information in the available

medical records. For example, PCP names may be recorded on hospital discharge summaries or immunization records.

After the PCPs and other healthcare providers are identified, the submission of medical records requests is complicated by other factors, including inaccuracies in the contact information for PCPs or other healthcare providers received from legal guardians. To decrease errors, when the correct contact number and address of any healthcare provider are identified, we update REDCap and Microsoft Access with this verified information. Additional notes are entered, including best mode of communication (e.g., telephone vs. fax).

Although uncommon, some healthcare facilities undergo closure. Many factors influence the transfer of medical records upon closure, such as state and/or federal laws, Medicare and/or Medicaid requirements, recommendations from state licensing boards and professional societies, and the general circumstances of closure.{8} Therefore, medical records may end up with another healthcare provider, the state Department of Health, in commercial storage, or even destroyed if no transfer is possible.

When a closed facility hasn't released a public note listing the new custodian of its medical records, we contact the Department of Health for the state for further information. A summarized list of each state's requirements for medical records disposition after facility closure can be found via the American Health Information Management Association website.{9}

Lack of Response to Medical Records Requests

Even upon identification of the correct healthcare providers and their contact information, medical records request submissions frequently do not result in transfer of requested records to the research facility. In many cases, there is no direct communication on the status of requested records. The initial request to PCPs, submitted by mail, usually obtains a response rate of approximately 50%, with rates for a second mailing of requests typically increasing to 70%, and with the final requests by telephone, the response rate rises to at least 80%.

During the medical records pre-review, additional medical records requests to newly identified PCPs or other healthcare facilities are submitted first by fax, and then by telephone call if no response is received. After two attempts, the overall response rates for these groups is > 95%.

To increase the response rate for initial medical records requests to PCPs, we have established a systematic telephone follow-up system, in which EMNet coordinators call facilities that did not respond to the initial requests once per week to identify potential issues. All activities are registered in Microsoft Access, giving an overview of what has already been performed and what is due, and enabling monitoring of the status of submitted and pending requests in an organized system that can be accessed by all key personnel.

Through the use of Data Use Agreements with enrollment sites, yearly bulk medical records requests can be completed for all study participants at each enrollment site. Records from sites and all affiliated healthcare facilities are then sent directly to the EMNet Coordinating Center for review, with a uniform response rate of 100%. This process increases efficiency, as there is a decrease in the overall number of individual requests.

Declined Authorization Forms for Medical Records Release

Even when medical records requests are received by healthcare providers, many authorization forms are declined, often due to different interpretations of the adequacy of the form. We use strictly HIPAA-compliant forms, but to decrease rates of declined forms we suggest attention to state-specific requirements, allowance of multiple providers to release records, and an expiration date after study completion.

Despite emphasis on the importance of accurate completion of the authorization form, we found that many returned forms have blank fields or incorrect dates which invalidate them. To decrease these errors, we performed additional training and established multiple checkpoints during the completion of the form, improving their completeness and validity.

Several facilities require use of a specific authorization form or report more strict state laws than the HIPAA Privacy Rule. Examples of these stricter rules include protections for specific conditions such as sexually transmitted disease, substance abuse and psychiatric

conditions.{10,11} In these cases, we create new forms that account for these specific rules; these must be approved by the respective enrollment sites' institutional review boards and then signed by legal guardians. This process significantly delays collection of medical records.

In our experience, many legal guardians only include the participant's current PCP on the authorization form, and thus a new form has to be obtained to request information for any other providers. This is problematic because participants frequently switch PCPs or obtain care from multiple healthcare providers (e.g., from specialists, in urgent care settings, or various hospitals). One strategy we employed to minimize the need for separate forms for each medical provider is to authorize "all providers" at "all healthcare facilities" to release records. Stating a class of providers (e.g., all primary care providers or all providers) in the authorization form is allowed by the HIPAA Privacy Rule.{2}

Another common source of rejection of authorization forms is tied to the form's expiration date. In our experience, many facilities are unfamiliar with the fact that the HIPAA Privacy Rule allows the form to expire at the end of the research study or to never expire, thus facilities often refuse to provide medical records for service after the date of the signature on the form. This obstacle is problematic for prospective cohort studies, in which the form is usually signed at enrollment and meant to be valid for many years (e.g., until the end of the planned study period).

When facilities decline authorization forms because of signature dates, we discuss the applicability of HIPAA Privacy Rules directly with the facilities' medical records department staff by telephone. When necessary, we fax the federal HIPAA Privacy Rule to the facility, highlighting the specific paragraphs related to the flexible expiration date of the authorization form for research use. If the form was still declined, we would then contact the legal guardian and ask him/her to complete a new form.

Due to these reasons for rejecting an authorization form, it is not rare to need to obtain a new form outside a prespecified study visit. Initially, when a new form was required, we contacted the legal guardian and requested completion of a new form to be returned by mail. However, using this system we had very low rates of returned forms. We thus implemented a HIPAA-compliant electronic system (Ingram Micro Adobe Sign) to obtain a signature on the form, which

has proven to be extremely helpful, as the rates of completed forms have increased. Our ability to contact subjects periodically during the study period is instrumental in our success in receiving updated forms when needed.

Conclusion

Medical records collection is a time-consuming activity that may become the rate-limiting point of any study without careful logistical planning. In the MARC-35 and MARC-43 multicenter studies, we faced many problems with records collection—from successful delivery of medical records requests to providers to declined authorization forms—but were able to develop and implement many successful solutions.

Some studies are solely based on medical record review, but in our experience the ability to periodically contact legal guardians has been vital to our success. This longitudinal follow-up allows us to update providers' information and obtain new authorization forms when required. Through use of electronic databases (REDCap and Microsoft Access), the information given by legal guardians is complemented by our experience contacting each provider, increasing the chances of successfully reaching these providers in the future. In the unlikely event that a healthcare facility closes, we recommend contacting the state's Department of Health to locate the medical records.

Before requests are submitted, it is crucial to have a medical record tracking system such as Microsoft Access in place, as it will provide an up-to-date view of which records are ready for review and which need to be requested. This tracking system provides the basis for systematic follow-up of already submitted medical records requests—an important strategy to achieve a satisfactory response rate. Similar systems for medical record completeness documentation have been previously applied with success.{12} For multicenter studies, having a Data Use Agreement with participating enrollment sites decreased the number of individual requests and increased the rate of medical record collection.

Finally, much focus has to be devoted to the components of the authorization form, since they are the main source of medical records requests rejection. From the beginning of a multicenter study design, investigators should make sure the authorization forms contain state-specific

elements, are not provider-specific, and expire after the outcome of interest, allowing time for medical record collection. Despite these precautions, authorization forms may still be declined, and thus we recommend having the ability to contact legal guardians to obtain a new form.

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PEER REVIEWED

The Data of Subject-Reported Adverse Events

Robert Jeanfreau, MD, CPI; Nathan Best

Attributes of the thorough documentation of research data, endorsed worldwide by the U.S. Food and Drug Administration (FDA), the International Council for Harmonization (ICH), and the World Health Organization (WHO), are embodied in the ALCOA acronym, first used by an FDA Bioresearch Monitoring staff member.{1} "A" stands for accurate; "L" for legible; "C" for contemporaneous; "O" for original; and "A" for attributable. In 2010, the European Medicines Agency (EMA) added four additional attributes: **C**omplete, **C**onsistent, **E**nduring, and **A**vailable, thereby creating the more cumbersome acronym, ALCOACCEA.

The importance of thorough documentation is perhaps best appreciated by a closer inspection of the underlying rationale. As described in the following sections, there are three major, albeit related, reasons why adverse events (AEs), like all research data, should be thoroughly and consistently documented.

The Evaluation of Severity and Causality

First, a complete description of an AE is critical for the principal investigator's (PI's) evaluation of an AE's relatedness, or causality, and severity to the investigational product (IP). A one-word description is useless in this regard.

Even in those situations in which a very brief description might appear to be adequate to determine causality, a careful description is still necessary. Let's take as an example a study involving an IP to control atrial fibrillation. During the study, a subject is involved in a motor vehicle crash and reports that event to the coordinator. The subject denies any injury and provides no further description.

If no additional information is solicited, the PI may conclude that there was no AE and that the crash could not have been related to the IP. However, upon careful questioning, the subject thinks that he may have fallen asleep at the wheel. The subject is instructed to come to the site for an evaluation that reveals that the subject is having episodes of intermittent, complete heart block, which likely caused the subject to briefly lose consciousness.

Similarly, the PI cannot determine severity without an adequate description of the AE and its effect on the subject. Furthermore, based upon a good description of the AE, coupled with a thorough knowledge of the IP (including the mechanism of action, the half-life, and other information from the Investigator's Brochure), along with background information on the subject's medical history and any available laboratory studies, the PI may be able to formulate a differential diagnosis which then serves as a defensible basis for determining causality.

The Statistics of AEs

Secondly, this information serves as the starting point for the future statistical evaluation of a drug's safety profile.

The pursuit of medication safety is a complicated and a never-ending process that encompasses the entire lifespan of a drug. Understandably, the younger the drug, the more intensive the

scrutiny. The greatest number of safeguards are in place for experimental drugs in their infancy, since safety information on risks and benefits is at its nadir.

Although the specific process will vary depending upon the stage of the drug's lifecycle, statistics plays an indispensable role at every step. Statistics require solid data, and critical to every phase is the reliable garnering of data which first begins with the collection of AEs at the research site level. The entire subsequent process of safety evaluation could be flawed if the initial data are inconsistent or incomplete.

One cannot help but wonder if various problems encountered in pharmacovigilance, at least in part, could be traced back to the inadequate description of AEs obtained during clinical studies. According to one source, "In an attempt to solve this problem, many systems have been developed for a structured and harmonized assessment of causality. None of these systems, however, have been shown to produce a precise and reliable quantitative estimation of relationship likelihood. Nevertheless, causality assessment has become a common routine procedure in pharmacovigilance."{2}

Although the description of AEs is an essential component of source documentation, the far-reaching importance of completeness in the description of AEs and the subsequent causality assessment are not only underappreciated, but also being questioned outright. An article from 2017 suggests that the PI process of determining causality is so subjective that the practice should be abandoned. According to the authors, their analyses demonstrate that assigning causality to AEs "is a complex and difficult process that produces unreliable and subjective data. In randomized double-blind placebo-controlled trials where data are available to objectively assess relatedness of AE to treatment, attribution assignment should be eliminated."{3}

The determination of causality would then become purely a statistical exercise utilizing double-blind placebo-controlled studies. This view is supported in the FDA's Clinical Investigator Course of 2018. One slide states: "Individual assessment (is) unlikely to help determine attribution for common AEs, i.e. headache, nausea, MI in elderly. Such AEs require aggregate analyses using a population approach (risk or rate with study drug vs. control)."{4}

Subject Safety

Even if causality assessment of AEs by PIs is abandoned in the future, there remains a third, compelling reason for the thorough description of AEs. A complete description is necessary for the PI to ensure the totality of a subject's safety.

The PI's responsibility extends beyond ensuring that the potential risks attributable to the IP are minimized. In the ICH's Good Clinical Practice (GCP) guideline, ICH-GCP 4.3.2 states: "During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values**,** related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware."

To determine if a patient-reported AE is indicative of a significant health threat, the PI must have an adequate description of the AE. Let's take, as an example, a subject having a headache. Causes of headaches are legion, and range from the relatively innocuous tension headache to the potentially life-threatening headache of a sentinel bleed.

Although the PI may feel that the IP is not causing the subject's symptom, the PI's involvement does not end there. If the subject's description is suggestive of a sentinel bleed, the PI must act. As one source observes, "Patients with subarachnoid hemorrhage (SAH) frequently describe the occurrence of an underestimated or even ignored severe headache in the days or weeks preceding the bleeding. If recognized early, this warning headache might lead to specific investigations and, if indicated, a surgical approach might avoid a dramatic hemorrhagic event."{5}

The Current Practice

Despite the clear importance of the proper collection of AEs, there are a number of challenges to its implementation, including the skill and time required.

Coordinators at research sites collect the vast majority of the data on subject-reported AEs and then present the information to the PI for evaluation of severity and causality. Interviewing

subjects to obtain a complete description of an AE requires a complex skill set. Not only must the coordinator know which questions to ask for any given symptom, but also how to ask them and in what order. The result is lack of uniformity in how AEs are documented.

Bias, which can be nearly impossible to detect during an interview, can be bi-directional and requires considerable skill to avoid.

Admittedly, there has been an increasing emphasis on education and certification for coordinators. Moreover, many coordinators are nurses with the requisite skills. Nonetheless, the need for reproducible uniformity remains a concern. The amount and quality of information regarding AEs can vary widely within an organization's sites and may even vary within a single site.

Another roadblock is the amount of time required for this process. The duties of coordinators are broad and increasing. The thorough collection of information for an AE can be a time-consuming process for a coordinator who is already overburdened with other duties. The frequent result is that the coordinator attempts to collect the information as quickly as possible. This pressured approach sometimes results in incomplete data. The frequency with which the PI, when presented with inadequate data, requests additional necessary information underscores the inefficiency of the current method.

A Different Approach

A potential solution is the use of well-crafted, electronic, self-administered questionnaires for the most common AEs. The questionnaires are loaded onto tablets available to subjects in the waiting room before a scheduled visit. These same questionnaires could also be accessed as an app on the subject's phone for home use. The information is then presented as a summary for the PI's review.

Importantly, in collecting subject data, the questionnaire presents qualifier questions with appropriate descriptions that a subject can easily process. Questions are layered into symptom tiers which are further layered into specific inquiries. The system is interactive in that answers to a question can alter which questions are subsequently presented.

The information within the questions is parceled to avoid overwhelming the subjects. The questions are also sequenced in such a way to make the flow of information intuitive. The questions and the sequence of questions are also fashioned to minimize the introduction of bias.

These goals, in part, are accomplished through logic trees and by presenting subjects with rational follow-up questions. The information is then processed in the background and sent to the PI in a narrative format, as can be seen in a sample questionnaire available online for a subject's reported symptom of fever.

Advantages

This system offers a number of other advantages over the current approach.

First, because the template could be utilized across a wide spectrum of clinical trials, this type of approach presents a much-needed standard for the uniform collection of data for AEs. There is a long-standing, recognized need for the standardized characterization of AEs. In 2001, in an article addressing variability in the assessment of AEs, the authors conclude: "There was considerable variability in categorization of AEs in an exercise following training for AE data collection. Type of report, relatedness, and severity were found to have more variability in reporting than did action taken or outcome."{6}

The past nearly two decades since that article have brought little progress in resolving this issue. In a recent review article of the analysis and reporting of AEs in randomized controlled trials (RCTs), the authors present similar conclusions: "This review highlighted that the collection, reporting, and analysis of AE data in clinical trials is inconsistent and RCTs as a source of safety data are underused. Areas to improve include reducing information loss when analyzing at patient level and inappropriate practice of underpowered multiple hypothesis testing. Implementation of standard reporting practices could enable a more accurate synthesis of safety data and development of guidance for statistical methodology to assess causality of AEs could facilitate better statistical practice."{7}

A second advantage is that the system will save time for research staff, resulting in decreased sponsor costs. The technology, as used in electronic diaries for patient-reported outcomes, is

readily available. Data security is ensured by not entering any identifiable subject information and by using vendors with a secure data exchange.

Lastly, such a platform offers a key component for the evolution of virtual clinical trials, which hold the promise of decreased trial costs, greater access to volunteers, and improved data quality.

For use on a wider scale, the questions could be approved by a panel of experts in the respective fields, with input from those in pharmacovigilance as well.

Conclusion

Laboring in an environment where there is no standard for approaching causality, the PI has no option but to rely on his or her own subjective approach. The first step in formalizing the approach to determining relatedness is to systematize the description of AEs.

Presently, the responsibility for the safety of current subjects and future patients rests squarely on the shoulders of the PI. A uniform system for collecting data will hopefully advance the industry's search for safety.

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SITE STRATEGIES

Leave No Site Behind: How Sites, Sponsors, and CROs Can Speed Clinical Research Together

Bree Burks

As the age of blockbuster drugs has given way to precise, impactful treatments that are customized for rare diseases and individual patients, the volume of clinical trials has compounded. In 2007, there were 48,290 clinical trials recorded worldwide while more than 322,100 trials are expected to be tallied for 2019.{1}

With clinical studies flourishing, sponsors have shifted to an outsourcing model to drive greater efficiency. More than 70% of all clinical trials are expected to involve a contract research organization (CRO) in 2020,{2} and analysts predict the CRO market will reach nearly $55 billion by 2025.{3}

Clinical research sites are also becoming increasingly vital in helping sponsors and CROs keep pace with bringing new treatments to market. Sites, however, face significant hurdles in meeting the demands of this new era of drug innovation—hurdles that may discourage the all-important participation of principal investigators in studies. In fact, more than half of first-time investigators do not conduct a subsequent trial.{4}

Going forward, there is a significant opportunity for the industry to improve collaboration and execution of clinical trials. Sites have the most to gain, especially with improving productivity and reducing delays that impact trial execution. Recently, leading investigators from a range of

different sites identified three key opportunities for improvement: communication and collaboration, information sharing, and streamlining common trial processes.

Improve Communication and Collaboration to Drive Productivity

Good communication often starts with mutual understanding. By getting to know one another and establishing common ground, clinical trial partners can be more productive and develop stronger working relationships. While the ability of sponsors and CROs to meet the needs of sites has progressed in recent years, most sites say there is room to improve communication,{5} especially around the day-to-day responsibilities and workloads that impact timelines at sites.

"Sponsors don't have visibility into the many things on my plate to understand that their timelines are sometimes not achievable," said Katie Seehusen, a regulatory specialist with the Iowa Diabetes & Endocrinology Research Center. "I am the only regulatory specialist at my site, and we currently have 30 ongoing drug and device studies with seven new studies coming soon. So, it's important that I structure my time to get everything done."

Seehusen frequently balances the critical deadlines of various sponsors and CROs, and ultimately has to make difficult judgement calls about which jobs get done first based on priorities and available resources. "I am pretty good at multitasking," she said, "but sometimes there just isn't enough time in the day. Just because we work at high volume, doesn't mean we have a high volume of staff."

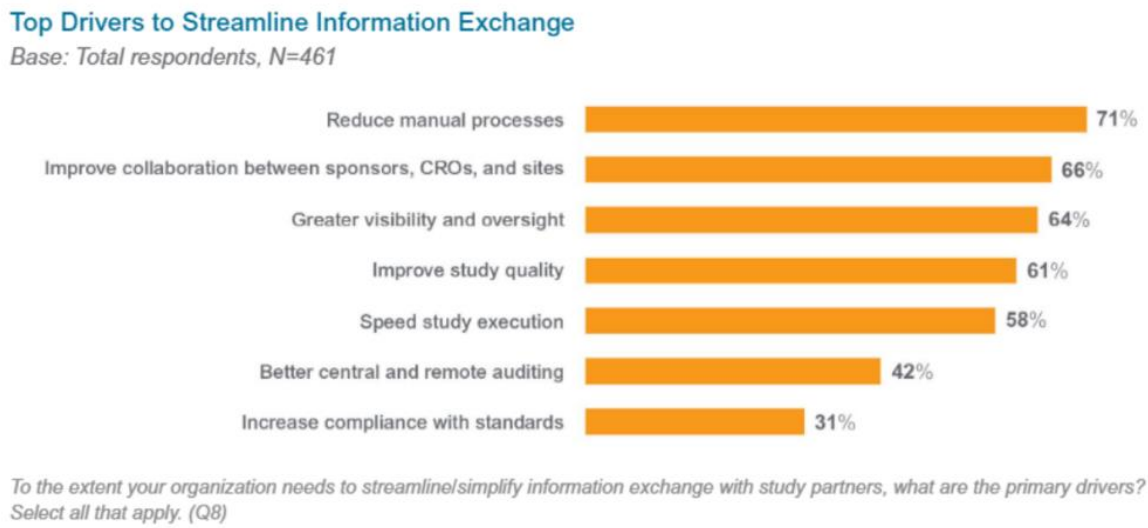
The demand on sites to get more done, faster can be overwhelming. Sites acknowledge that better communication on timelines and even collaborating with sponsors and CROs on how to work more efficiently can alleviate some of the pressure they're feeling.

Jeff Kingsley, CEO of IACT Health, a clinical research network based in Columbus, Ga., said part of the communication and collaboration breakdown often stems from the outsourcing model itself. "There's sometimes a big gap between the sponsor and clinical trial sites with separate companies handling labs, oversight, and so forth," he said. "If sites and sponsors become more strongly connected, we could better support the tremendous growth happening throughout the industry. Bridging the communication gap is critical to this."

Streamline Information Exchange for Faster Trials

One of the most common needs among researchers is improving information exchange with sponsors and CROs.{6} Key drivers included reducing manual processes, improving collaboration among study partners, and better visibility and oversight (see Figure 1).

Figure 1: Top Drivers to Streamline Information Exchange



Sites often depend on sponsors and CROs to provide technology for managing trial activities and collaborating during a study. Sponsors and CROs on average use three different systems—including e-mail, portals, file sharing, and eTMF applications—to exchange trial data and documents with study partners.

Meanwhile, sites support multiple studies at one time. With each sponsor providing a unique system to sites running dozens or even hundreds of trials, the use of technology can become overwhelming. In fact, the average site uses a minimum of 12 different electronic systems to collect and capture clinical study data.{7}

“One of the biggest challenges we have as a site is that most technology comes from sponsors, and the sponsors select the technology that serves their needs,” said Rachel Sheppard, clinical research director for the Clinical Trials Units at the University of Louisville. “We’re running

trials for hundreds of sponsors, so we have to learn all those various systems and be agile in them. So, it's been difficult for us to transition to electronic regulatory systems because of that."

Several sites noted that better information sharing could be addressed by newer cloud-based tools that are capable of streamlining trial activities and accelerating research.{8} Sheppard said that administrative minutiae are holding sites back and preventing trials from getting started quickly. "These setbacks could be resolved with better technology," she added.

Nelson Rutrick, CEO of Adams Clinical, a site outside Boston specializing in psychiatric research, said sponsors collect large amounts of information on site data quality during patient enrollment. Making these data available helps sites understand where they're doing well and where they need to improve.

"Sites know how well they are doing relative to other sites on recruitment metrics, but they often lack visibility into their performance on quality metrics," Rutrick said. "Most electronic data capture and eSource products have reporting features that display some statistics to sites, but these features are usually turned off. Sponsors and CROs should turn these features on so sites can see where improvement is needed."

Some sites also said making information sharing more efficient would enable them to focus more time and energy on other important matters—most notably training.

"I never want to be so busy that I stop learning," said Seehusen. "Research is always changing. There are always new things to learn. We have a job where we constantly need to learn about what's changing. I would love to have more time to train and be better at my job."

Better training is an opportunity to improve clinical trials. Researchers want a roadmap for the right qualifications to do their job—the skills they should have and the related competencies. There's a big movement among sites around competency-based roles. With so many specialized roles, the industry could benefit from sites having more ways to get credentialed for their unique roles.

Katrina Quidley, a regulatory manager with IACT, said she would like more sponsors and CROs to consider waiving redundant requirements for good clinical practice (GCP) training for staff with Certified Clinical Research Coordinator (CCRC) or Certified Principal Investigator (CPI) credentials through the Association of Clinical Research Professionals (ACRP). In 2014, the TransCelerate BioPharma Inc. initiative began acknowledging these ACRP certifications as an equivalent to any GCP course. Accepting ACRP certifications for GCP fulfillment streamlines the training process and allows sites to move forward with completing all personnel requirements and meeting expected timelines.

Simplify Operational Processes to Reduce Delays

With more study partners in the mix, trials have become increasingly complex. More people are involved in trial processes, each wanting to review and approve a site's work. This often leads to trials being underbudgeted or delayed.

"There are many parties involved these days," said Kingsley. "Innovation can stagnate because of so many in-betweens. CROs typically prefer that all communication be filtered through them, so we often lose the emotional connection with sponsors. Sponsors and sites don't have much contact anymore."

Seehusen said she often finds herself dealing with more people than she can count—all needing the same information. "Sponsors and CROs have a lot of people working on the trial, so there can often be a lot of redundant steps that cause delays," she noted. "Centralizing coordination and improving organization could save me hours; and if you multiply that across all the studies happening at any given time, it could add up to days of improved productivity."

Working Better Together to Improve Patients' Lives

The pressure to innovate specialized products and get them to market quickly will only become harder as the ecosystem of clinical trial stakeholders continues to expand. Improving efficiency among study partners will enable the entire industry to better support the growing number of trials and, ultimately, bring innovative new therapies and drugs to market much faster for the patients who need them.

In our conversations with expert sources at sites, they underscored their desire to work with sponsors and CROs to improve trial processes. In the end, they said everyone just wants to achieve more positive results.

“Our biggest focus is on improving the lives of patients,” Seehusen said. “So, if we’re working at a capacity of maybe 15 studies a year and we can get to 20 studies a year because we’re working more efficiently and effectively, then we can see more patients and help more people. That’s really our end goal—just being able to help more people.”

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RECRUITMENT & RETENTION

Delving into eConsent: Industry Survey Reinforces Patient Centricity

Neetu Pundir; Mika Lindroos; Jenna McDonnell; Bill Byrom; Spencer Egan

With the objective of learning more about the industry's global experiences and perspectives with electronic informed consent (eConsent), Signant Health conducted a survey in 2019 that sought to obtain insights from more than 130 respondents working in sponsor settings and with contract research organizations (CROs). This column presents findings from this key piece of industry research.

Background

For several years now, eConsent has been making a name for itself as a technological gamechanger in clinical trials. With industry groups, academic research centers, and, crucially, regulators advocating its innovative advantages, it is no surprise that many of the major pharmaceutical companies are keen to explore eConsent initiatives.

In 2017, CRF Health (now Signant Health) conducted its first survey to dig a little deeper into the industry's attitudes toward eConsent. This enabled industry experts to understand and to benchmark its current use, better understand adoption hurdles and challenges, and anticipate future use and adoption. Two years on, it is interesting to take a fresh look at how those in the industry view eConsent, and to learn from the experiences of companies employing the technology—from extensive use to pilot testing.

The 2019 Industry eConsent Survey received responses from personnel at sponsors and CROs who have had hands-on experience with implementing eConsent or were working with teams

directly involved in its planning and implementation. The survey was not specific to any eConsent solution or provider.

The profiles of respondents covered a wide range of therapeutic area responsibilities as well as functional groups, including executives, clinical operations, regulatory, data management, innovation, information technology, clinical sciences, and procurement. Some of the key areas from the survey presented and discussed in this article include uptake rates by study phase, experiences, and feedback on operational services provided by eConsent solution providers, and which aspects of eConsent solutions were considered to have a high impact on patients' comprehension and engagement.

The results also demonstrate increasing demand to integrate consent data with other eClinical systems (e.g., electronic data capture [EDC] systems) and key market trends and perspectives on eConsent deployment in clinical trials by early adopters. Other highlights include areas of improvement, level of satisfaction, and remaining challenges for eConsent solutions and implementation. Finally, the report provides some clarity on the business drivers behind decisions about whether to implement eConsent.

The Respondents

The survey captured the opinions of 134 respondents from predominantly biotech and pharmaceutical companies (60%) and CROs (34%). Thirty-nine percent of respondents worked in clinical operations functions, with a further 13%, 8%, 7%, and 7% in health outcomes, procurement, data management, and regulatory functions, respectively. Therapeutic area responsibilities covered a broad range including oncology, central nervous system, immunology, gastrointestinal, pediatrics, hematology, endocrinology, respiratory, and dermatology, amongst the most common.

eConsent Experience and Adoption

Respondents varied in their levels of experience with implementing eConsent solutions (see Figure 1). Thirty-one percent had implemented an eConsent solution in anywhere from one to five studies, 18% in six to 15 studies, and a further 18% had implemented more than 15 studies

(remainder not answered or unsure). Fifty-five respondents (41%) indicated usage in Phase III trials, with 19%, 32%, and 22% in Phases I, II, and IV, respectively (see Figure 2).

From those asked, North America was the most popular region where eConsent has successfully been implemented (72%), followed by Europe (37%).

Figure 1: Profile of Respondents—How Much Experience Does Your Business Unit Have with eConsent?

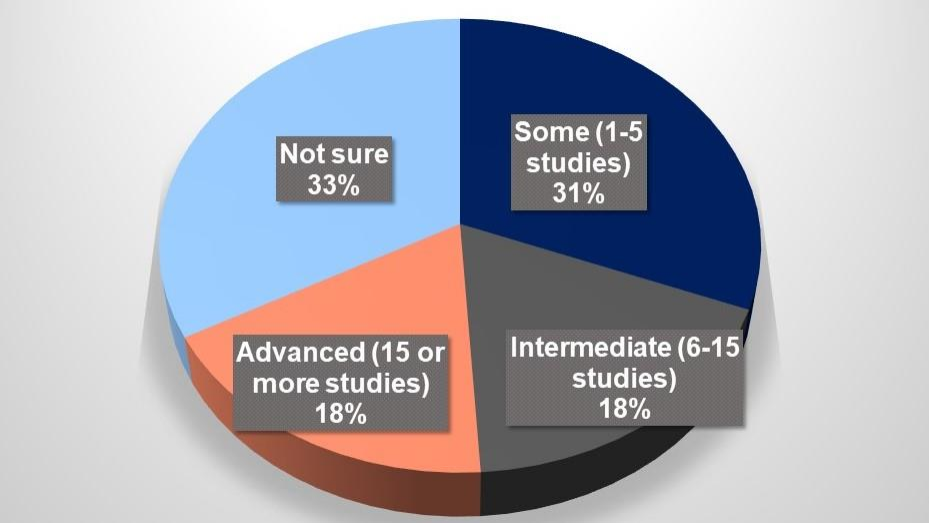
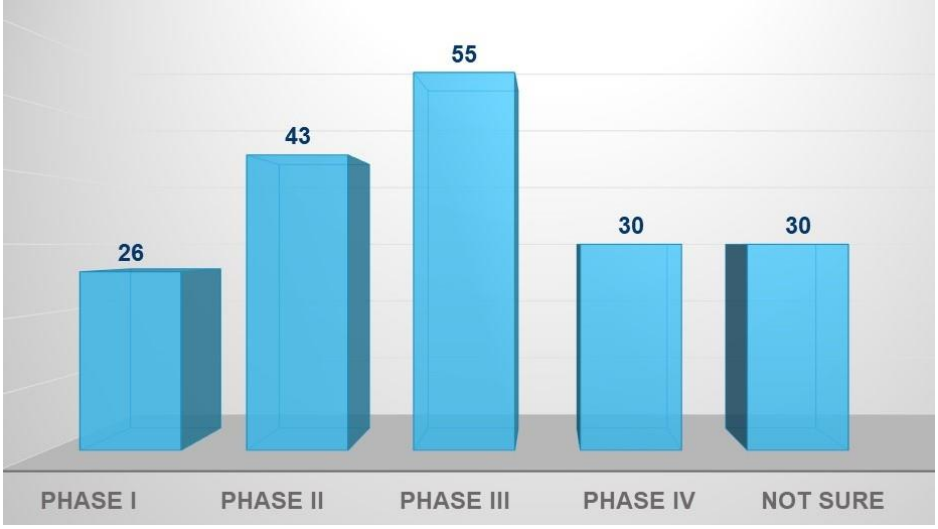
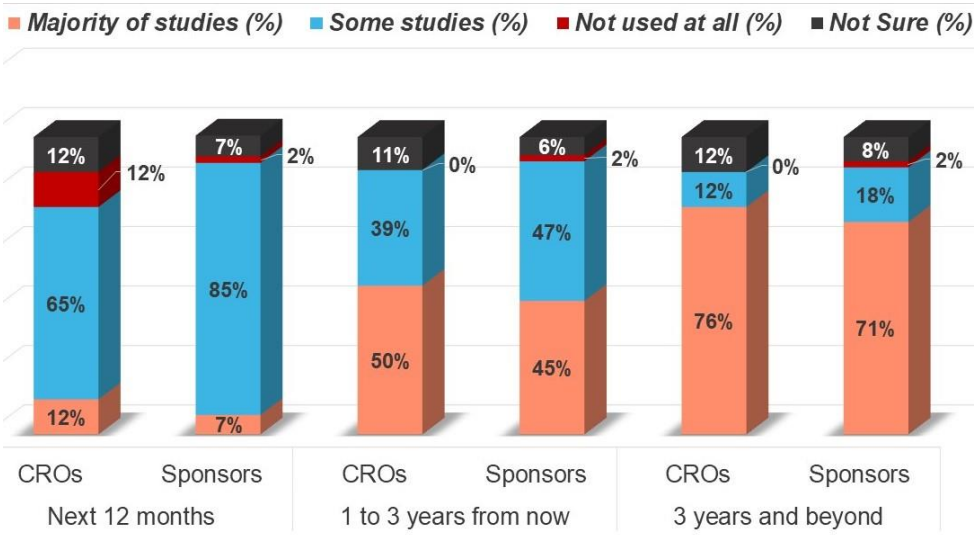


Figure 2: For Which Phase is eConsent Typically Used at Your Organization?



Indeed, the momentum of adoption looks set to continue with 65% of CRO respondents and 85% of sponsor respondents saying that their organizations will adopt eConsent for some studies over the next 12 months. While in the long term, 76% of CRO respondents and 71% of sponsor respondents state that their organizations will adopt eConsent for the majority of studies in the next three years and beyond (see Figure 3).

Figure 3: The Future of eConsent—How Do You Predict eConsent Use at Your Organization?



Business Drivers and Impact of eConsent

Respondents were asked to rank the importance of a number of potential business drivers for implementing eConsent in their organizations. Most commonly identified in the top three business drivers were improved patient comprehension, efficiencies through digitization, improved patient retention, and reduced regulatory risk and audit findings. The top drivers identified were similar between biopharmaceutical company respondents and CROs.

Related to these top business drivers, further exploration of aspects of eConsent that may impact patient comprehension and engagement found 91% of CRO respondents and 73% of sponsor respondents reported a user-friendly and interactive interface (e.g., glossary of complex terms) was a highly impactful feature. Other features of eConsent thought to highly impact patient comprehension and engagement were the ability for patients to flag questions to

discuss with site staff (73% and 69%), multimedia tools (91% and 50%), and the ability to read consent documents at home (64% and 56%) (figures are CRO and sponsor respondents, respectively).

This is in line with what the U.S. Office for Human Research Protections (OHRP) and the U.S. Food and Drug Administration (FDA) stated in a December 2016 guidance document on the use of eConsent in clinical trials. It was noted that "electronic processes to obtain informed consent may use an interactive interface, which may facilitate the subject's ability to retain and comprehend the information."

Satisfaction and Challenges

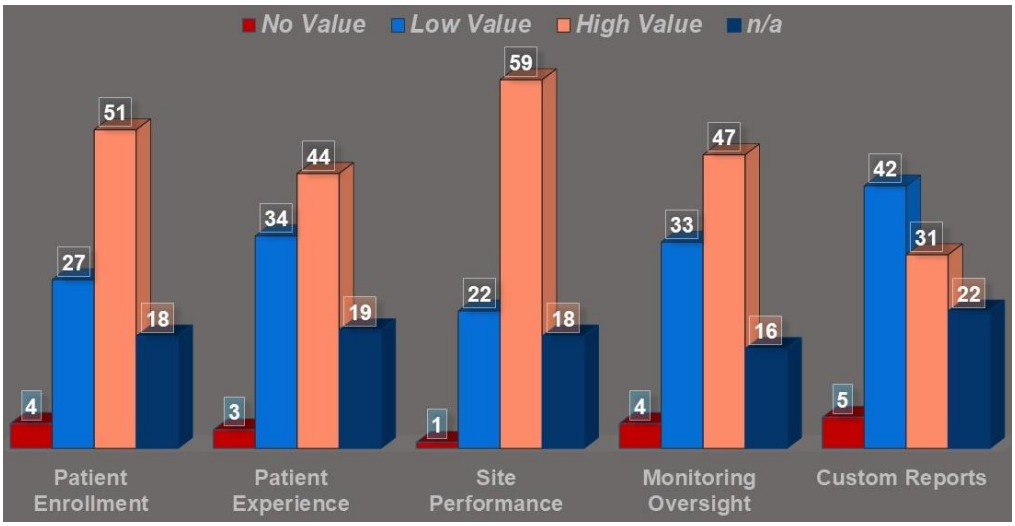
From an eConsent design and development perspective, 63% of respondents reported that they were satisfied with the setup processes such as procuring digital tablets for site use, training sites, and creating site users. However, 16% were not satisfied with the ability for study teams to easily configure and self-author eConsent without vendor involvement (see Figure 4).

The reliance on outside vendors to design and program eConsent can slow down implementation and create longer timelines in making the eConsent "live." Consequently, sponsors and CROs are looking for adaptable solutions and support models that enable them to control and manage the design, development, and deployment of eConsent without the need for continuous vendor support. While the majority of respondents were largely satisfied, there is room for improvement to get to "very satisfied."

Figure 4: eConsent Experience—Rate Your Organization's Level of Satisfaction on Items Related to Design and Development of eConsent Forms

From a data reporting perspective, 59% of respondents placed high value on site performance reporting, such as enrollment rate, pending re-consent. This was closely followed by patient enrollment data (51%), monitoring oversight (47%), and patient experience (44%). Most data are considered highly valuable, while custom reports were identified as relatively low in value (see Figure 5).

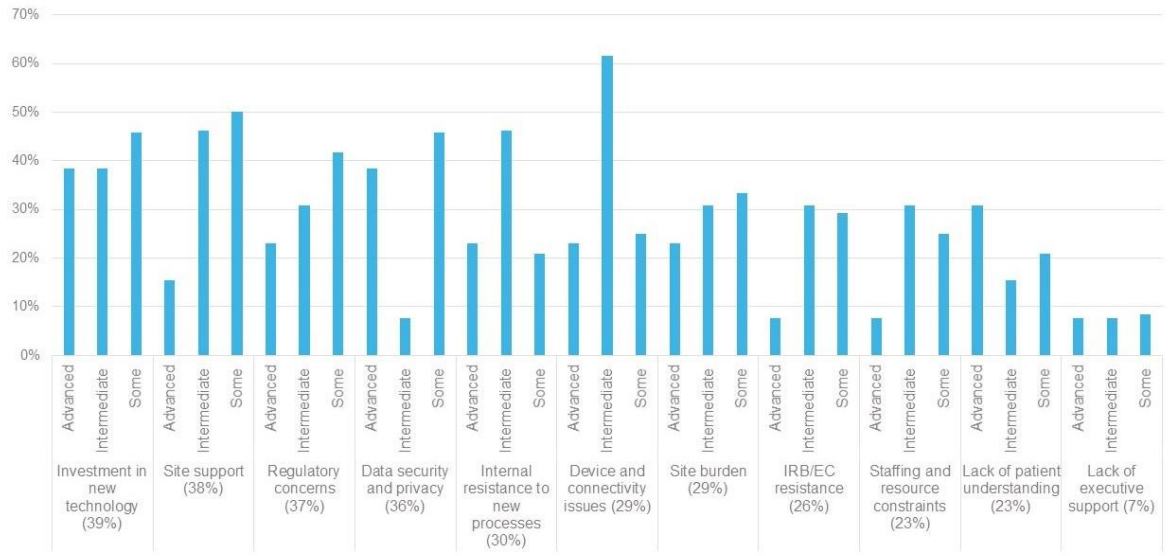
Figure 5: What Reporting Data from eConsent Systems Have Been Most Valuable to You?



One of the biggest challenges reported with using eConsent in clinical trials was investment in new technology. As with all new technology, perceived high costs and uncertain return on investment can prove to be a barrier and prevent some organizations from adopting eConsent, with 38% of respondents reporting that investment in new technology can be challenging.

Often, the costs of existing processes associated with consent form development, implementation, and monitoring are not measured, nor the costs of loss of data due to ambiguous or incomplete informed consent documentation or resulting regulatory findings. While site support was identified as a potential challenge by 37% of respondents, those with more experience (>15 studies using eConsent) reported this less often—with only 15% of these advanced users citing this as a challenge (see Figure 6). This demonstrates the learning curve during the adoption phase, common to the implementation of all new processes or technologies.

Figure 6: What Have Been the Biggest Challenges with Using eConsent for Your Studies?



The Importance of Data Integration

Perhaps giving a more revealing glimpse into the industry's current mindset were the responses around eClinical systems integration. Twenty-eight percent of respondents had integrated an eConsent solution with an EDC product, with the same number (28%) reporting integration with a clinical trial management system. A further 26%, 19%, and 17% had integrated eConsent with electronic clinical outcome assessment, electronic trial master file, and randomization and trial supply management solutions. Integration experience was largely positive.

Surprisingly, 36% of respondents had not integrated eConsent with other eClinical systems, and this may be a feature of the early adoption phase for this technology as the importance and drive to simplify processes and limit reconciliation through eClinical integration continues to be a focus within our industry.

Conclusion

Reflecting on the findings of the survey, eConsent is a valuable technology for many organizations in the drive to improve clinical trial processes, efficiency, and quality, and to generate a better patient experience impacting patients' comprehension and ongoing

engagement. This is further underlined by the intent of many companies to significantly ramp up their use of eConsent solutions in the next three years, as illustrated by our survey findings.

Understanding the features of solutions that most impact the improvement of patient comprehension and patient and site experience helps to focus ongoing development of these solutions. It is encouraging to see the continued and increased interest in eConsent now being realized with increased utilization within biopharmaceutical companies and CROs—a trend that is growing rapidly.

With increased adoption, companies can expect to benefit from internal efficiencies in addition to the secure knowledge of well-informed and engaged patients; transparency, clarity, and regulatory adherence around the consenting event; and simplified monitoring oversight in terms of consent tracking, document version control, and revision implementation remotely.

The benefits reflected clearly by responses to this survey act as a pulse check on attitudes and intent around eConsent. As a result, as an industry we will soon transition from the early adopter stage to mainstream use of this technology.

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GOOD MANAGEMENT PRACTICE

You've Earned It! 10 Tips to Help Clinical Research Sites Recognize Earned Revenue in 2020

Beth Scharmer

As a manager for a clinical research site, you dedicate a lot of time to negotiating budgets and performing your other duties. Now it's time to follow through, stop leaving money on the table, and recognize all the revenue you have earned.

Here are 10 steps you can take to help collect all your research program revenue:

1. Budget Review: Prior to a fully executed contract, thoroughly read through the budget and payment terms. Identify any areas that are vague or not clear. For example, your site may have "combination" visits (e.g., Visit 1 and Visit 2 could occur on the same day). How will the sponsor pay for multiple visits on the same day? Will the sponsor pay the full amount for both visits, or will it pay less because of the timing? Other budget areas that can be vague are payments for screen failures and unscheduled visits. How will they be paid (flat amount/per procedure) and when? Some sponsors will delay payment until trial end for screen failures; not only will this reduce the revenue you have available now, but you could have less leverage at trial end to dispute how the sponsor paid for those screen failures and what procedures should be covered.
2. Track and Reconcile Payments: It's a common misconception that sponsors and contract research organizations (CROs) do not pay on time. However, you will probably find that

roughly 72% of payments are paid in accordance with the terms in the contract.{1} Setting up a process to track activity and payments before work begins is critical. Frequently, patient visit payments are made upon monitored data (no invoice required). This leads many sites to put off tracking and reconciling these payments. Do not fall into this trap—you will be scrambling at the end to reconcile a mountain of data. It also may be too late to receive sponsor payments on any discrepancies found at that point. The process should include tracking every item on the budget, along with its cost, patient activity, any non-patient activity you should be compensated for (audit fees, dry ice, etc.), invoices, and payments. Additionally, be sure to include periodic audits of your site's receivables management performance.

3. Stay Organized: Keep all finance-related matters in one place. Establish a "research only" lock box or another way of isolating study payments so that co-mingling of funds between business operations and/or departments is minimized. Create a reconciliation report for every study for tracking purposes. Scan copies of invoices, checks, etc., and store them on a computer in dedicated folders. Use a consistent naming convention for those files so that everything can be found quickly and easily. For example, keep all scanned checks along with payment details for those checks in one folder with the file name containing the check date, amount, payor, etc., so your team can quickly find a copy of any prior check. It is important to have check details stored and easily accessible along with the checks; a copy of the check is of little use if you do not know what it covers.
4. Assign Resources: Entrust the receivables management process to a study coordinator who is responsible for entering/managing/reporting activity to your finance team. Identify someone on your team who likes working with data and numbers. Assign collections to someone on your team dedicated to following through until payments come in. Have a collections schedule in place for that resource, and establish an escalation process for use when payments are delayed and/or there are disagreements regarding amounts paid.
5. Be Aware of Billable Items: Patient visit payments often are automatically paid (no invoice required); however, this is not always the case. Frequently, there are items that require invoices to be submitted, and those can vary greatly from study to study. Carefully review the budget and identify items that require invoices; ensure that a

dedicated resource on your team is notifying your financial person that these items occurred so they can promptly submit an invoice for them. Once you receive payment for billable items, ensure it is accurate.

6. Review Invoice Requirements: Be aware of each CRO's/sponsor's invoicing requirements; some of them are very specific. If your invoices do not match their requirements exactly, some sponsors/CROs will simply reject your invoice without even notifying you. Don't be surprised if approximately 33% of invoices need to be resubmitted.{1} Even if you re-submit the invoice (which will cost your staff additional time and effort), you may have to wait until the next payment cycle for the sponsor to review it again. Set up an invoicing template right away that includes all necessary formatting/information in your accounting software or alternatively in Excel/Word if you do not have specific software.
7. Communication: Good communication is critical between finance staff and coordinators who enter the data. The finance staff will not know to invoice for serious adverse events, unscheduled visits, etc., if they are not informed when those events occur. This goes back to having a system in place for communicating all events that are reimbursable.
8. Push Back: You can generally expect that only about 70% of all payments will be paid correctly.{1} Even with well-negotiated budget and payment terms, there can still be items for which payment is unclear. If a sponsor declines to pay for something that you should be compensated for, or you feel it is under-compensating your site in some way, push back. It does not hurt to ask, and many times you will find that the sponsor is willing to be flexible for high-performing sites that make reasonable requests.
9. Escalate: If you push back and the request is still denied, bring in a senior-level manager; sometimes an extra push from management can help sponsors re-consider.
10. Final Audit: At the end of a study, have specific staff members assigned to perform a final audit in order to ensure that all costs have been captured. Often, studies come to an end and sites simply forget to invoice for close-out/archiving or don't follow up on withheld payments. This seemingly small oversight can result in thousands of dollars not being collected.

While many of these steps may not be considered high priority, missing even small items can result in significant lost revenue over time. Ensure that your site recognizes all revenue available in 2020—you've earned it!

Reference

1. WCG PharmaSeek 2019 aggregated client audit results.

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PI CORNER

What Doesn't Kill You Makes You Do More Paperwork

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Explorations into another person's job are always eye-opening experiences. I have fostered my self-perception of being a generalist in clinical research by spending a year or more embedded in most departments found in clinical research sites—particularly regulatory, human resources, business development, marketing, pharmacy, and quality assurance departments at independent clinics and academic medical centers. Yet somehow, over those 15 years, I never pursued the same deep dive into accounting.

Wow. What a trip.

I knew that sites are treated like commodities, where most investigators (novices and experienced alike) are offered the same budget, despite the quality of work or timeliness of enrollment they had proven. What I didn't know was that research sites have to fight tooth and nail to get paid for some items that are *in* the fully executed budgets. Do you find it shocking that a contract can be fully executed by both parties and yet be disregarded?

Who Thought These Were Good Ideas?

Let's go through some of my discoveries:

- Investigational New Drug safety reports are generally negotiated such that we are to be paid a flat fee, incrementally—for example, $25 per 10 safety reports issued to the investigator. For some reason, in my site network we are fought continuously on these, and often don't get paid at all for them. Despite the fact that our client (the sponsor or clinical research organization [CRO]) submits these reports to us, they require that *we* provide their accounting people with proof of the reports. Unless the sponsor/CRO has a portal that contains the reports, this has proven to cost more in time spent creating lists than it is worth for the money we might receive.
- The same is true of protocol amendments, where we can only receive payment if we list the date and version of the amendment…which was sent to us by the institutional review board and is thus part of the sponsor's/CRO's records already.
- Dry ice for shipping lab specimens is likewise a negotiated line item in a budget, and the likelihood of being refunded for this is even worse. Oddly, although our client has record of the frozen shipments they have received from us, requests for payment are routinely denied. We are very frequently asked for detailed dry ice purchases, which is excessively burdensome.
- A little better are procedures. Sites are asked for proof of the procedures (such as endoscopies), despite the data about the procedures having already been entered into the sponsor's/CRO's electronic data capture (EDC) system. Again, this is added work on the site for information the sponsor/CRO already has.
- Most ridiculous of all is the invoicing system itself (see below).

Real-World Frustrations in Invoicing

If we frame our minds around client/vendor relations, then a clinical research site is a vendor of the sponsor or CRO. With that in mind, I accept that it is reasonable that a site would have to invoice for certain work performed. That said, nearly every client we have rejects invoices if there is any sort of error (such as using the investigator's first name of Alex instead of

Alexander), or even if we invoice for too many budget items at a time. There is also the curious case that some of our clients require us to use a purchase order number that they have to provide us, and we cannot submit an invoice until we ask them for the number we should use.

If you work for a sponsor or CRO, please take your mind away from work and into your home life for a moment. Now ask yourself: Do you get to disregard a bill from your utilities company because they spelled your name wrong? My water bill comes to Kristine Senn; I still pay it. Could you tell the phone company you won't pay them unless they send you separate invoices for each instance? That would be like me arguing to Verizon that I won't pay them unless they send me separate bills for each of the phones I have on the account. Would any of these companies wait for you to give them an invoice number, and accept that they wouldn't get paid until you took the time to respond to them? That's frankly ludicrous.

Spinning Wheels Go Round and Round

I'm sad to say these are not all of the examples I discovered, but these are the ones evident in 87% of the trials we conducted in 2018–19. (The rate would be worse/higher if we tracked the issues involving invoices rejected for trivial reasons, but we did not track those.)

In general, it takes approximately three months of us re-invoicing, obtaining proof, following up, obtaining additional proof, and re-invoicing in order to get approval for payment—and that's *if* we don't decide to just write off the cost due to the extent of the proof required. (Don't get me started on payment timelines. Small sites don't have the cash flow, credit, or vendor relationships to support the lengthy delays between invoicing and payment.)

It's curious that sites, which typically have the fewest resources of all of the companies in the human trials pipeline, should have to do the extra work of proving so much of the work performed. On top of that are the delays in paying. For every sponsor or CRO director who thinks their payment timelines meet their company's policies, I want to break it to you that your definitions of the timelines are flawed.

My guess is that your company's measurable is "time from approved invoice" to "date check sent." I would argue that you would see that site payments are delayed by an *additional* 90 to

180 days if the timeline started ticking at “invoice received from site” because of the silliness described in the scenario above that results in lengthy invoice approval times.

No Wonder “One and Done” is a Problem

These issues dovetail precisely into the reasons investigators leave research; they lose money doing it and/or the burden is too high.

In my experience, investigators are willing to do what is necessary to ensure patient safety and document data, but the regulatory and financial expectations are definitively onerous. When many providers need to see four non-research patients each hour just to stay profitable, what is the message from the industry when they are expected to spend multiple hours proving that they should be paid?

On the positive side, I learned during my foray into our accounting department that startup and closeout fees are always paid without difficulty. Patient data that end up in EDC systems are likewise usually paid without difficulty. This implies that good systems are in place for those portions of the accounting processes, and it would not be difficult for sponsors and CROs to add processes for the remaining budget items as a means of improving customer service.

Sites might be “vendors” to sponsors, but they are important and necessary vendors, and keeping more sites in business is key to the entire clinical research process.

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