

# Clinical Researcher

**The Authority in Ethical, Responsible Clinical Research**

**April 2024 (Volume 38, Issue 2)**



## **The Benefits of Breaking Out of Comfort Zones**

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## Clinical Researcher

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## Clinical Researcher—April 2024 (Volume 38, Issue 2)

Contributors to this issue invite you to consider “The Benefits of Breaking Out of Comfort Zones,” whether by making new friends and colleagues at ACRP 2024, tackling diversity challenges in your trials through new recruitment tactics and site locations, exploring new or underappreciated approaches to research training and benefit-risk calculation, leaning into better relationships and technology practices across the site-sponsor/CRO divide, absorbing lessons from real-world research ethics cases, and more.

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Curated by Gary W. Cramer, Managing Editor for ACRP

## **Making Your Profession One of Your Happy Places**

Susan P. Landis, Executive Director of ACRP



Where is your happy place?

Many members and stakeholders in ACRP and its mission will soon [GO to ACRP 2024 for inspiration, education, and connection](#) in Anaheim, Calif., near what some say is “The Happiest Place on Earth.” ACRP has held independent conferences all over the U.S., and sometimes in Canada, since 1984, but the happy (sometimes approaching magical) moments of attending an ACRP conference come from making or rekindling professional friendships, learning about the latest resources that are key to excellence in your clinical research career, and sharing valuable lessons for your success in the workplace.

Wherever your happy place(s) may be, in terms of both your professional and private sides of life, your ongoing membership in and [commitment to volunteer engagements with ACRP](#) are a big part of what keeps the Association’s lifeblood happily flowing all year long. We thank you for making life better for your organizations, participants, and community at large through your dedication to upholding the highest standards of quality and safety in our profession. To keep the momentum going, whether or not you can join in on the fun and learning in Anaheim, we invite you to consider how you can be an agent of happiness in your clinical research setting the rest of the year. Let me offer one timely suggestion...

[Clinical Trials Day 2024](#) is coming up fast on the heels of the conference on May 20. This year, we are celebrating the “Trailblazers Among Us” through our observance of Clinical Trials Day—those who are forging a path forward in the profession through the relentless pursuit of knowledge, an exacting application of best practices, and an unwavering commitment to championing patient well-being. Please visit the event website for a bevy of downloadable resources and ideas for drawing attention onsite and through social media to the importance of clinical researchers in your workplaces and communities—and you need not wait until May to

start “flying the flag,” as we have begun promoting the big day already and it will have a major presence in our activities at ACRP 2024.

Meanwhile, no conference on the scale of ours comes together without the generous donation of time and talent from volunteers helping ACRP staff spread the news about the upcoming event, select content from proposals for workshops and sessions, lay the groundwork for activities onsite, greet and assist incoming attendees, and meet behind the scenes for such purposes as tending to item writing for certification exams, Chapter management updates, workforce development initiatives, and much more. In that vein, we are also already in preparation for ACRP 2025 in New Orleans, La., and if you are interested in helping out in any way, [please let us know](#)—and keep an eye out for the [Call for Proposals for 2025](#), which will open May 3.



PEER REVIEWED

## Barriers to Clinical Trial Enrollment: Focus on Underrepresented Populations

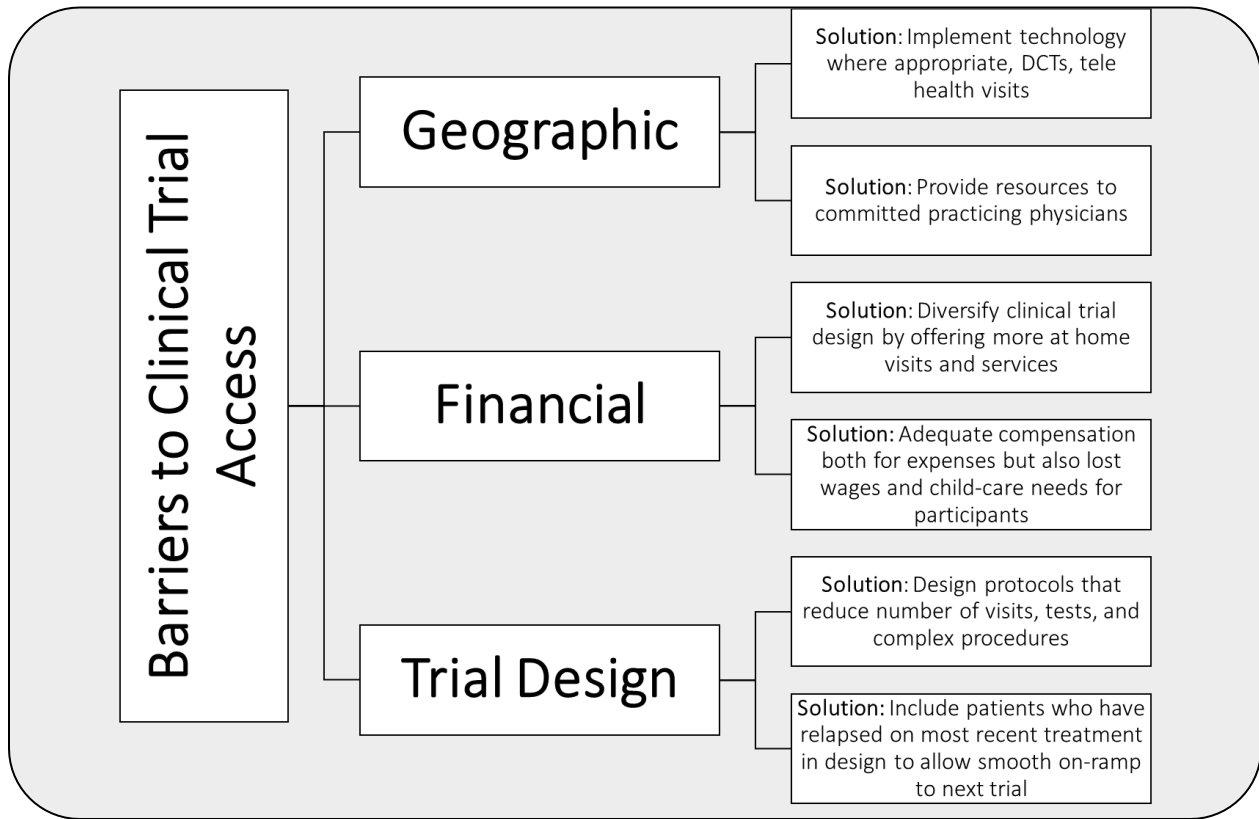
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Clinical trial enrollment of representative populations is critical to the successful completion of a trial. Key to this is ensuring that traditionally underrepresented populations are included. According to Cornell Law School, “[t]he term ‘underrepresented population’ means a population that is typically underrepresented in service provision, and includes populations such as persons who have low-incidence disabilities, persons who are minorities, poor persons, persons with limited English proficiency, older individuals, or persons from rural areas.”<sup>{ 1 }</sup> Throughout this examination, we identify common barriers that prevent underrepresented patients from enrolling in clinical trials and offer practical solutions, focusing on both future suggestions and evidence-based success stories.

Barriers such as the sparsity of clinical trial sites in rural and underserved communities, inadequate patient reimbursement, and stringent inclusion/exclusion criteria hinder the enrollment of patients from diverse and underrepresented populations (see Figure 1). The strategies we outline are not a comprehensive solution to all issues facing diversity enrollment, but we intend to stimulate conversation within our industry to ensure these barriers are addressed during the design and implementation of clinical trials. Lastly, we will also draw upon our collective firsthand experiences managing a variety of trials of distinct phases and complexities, where relevant, to support our claims.

**Figure 1: Common Barriers to Equitable Clinical Trial Access and Potential Solutions**



DCTs = decentralized clinical trials

**Geographic Limitations**

Seidler et al. found geographic proximity is a barrier preventing equitable access to clinical trials. They analyzed ZIP Codes of 174,503 research sites from 2002 to 2007 and discovered most sites are concentrated in urban areas with academic research institutions, large hospital networks, and other established social services; conversely, rural areas had few, if any research sites. {2}

From our experience, even sites in urban areas face recruitment challenges. In general, patients, especially those in underrepresented backgrounds, refrain from traveling long distances to sites. For example, sites in Cincinnati informed us that recruitment was challenging because few patients wanted to travel to the site from the suburbs.

In response, decentralized clinical trials (DCTs) have helped address geographical barriers by extending the reach of novel therapies to rural and underrepresented populations and increasing trial patient diversity. For instance, Sedhai et al. conducted a large, decentralized, randomized controlled COVID-19 trial at a rural satellite hospital in which patient visits were conducted by telehealth and videoconferencing.<sup>{3}</sup> The trial was successful and enrolled many diverse participants, of which 62.5% were Black and 37.5% female.

In our trials, we noticed underrepresented patients do not always benefit from DCTs because they lack internet connection, and found that providing these patients with Wi-Fi hotspots, ports, and/or computers was a viable solution. Further, implementing technology into clinical trial design has allowed existing rural hospitals to expand their patient reach, but rural areas lack adequate research infrastructure and committed practicing physicians. Addressing this barrier requires cooperation from numerous stakeholders, including government officials, the medical establishment, and the clinical research industry.

Scholars contend that the industry must incentivize physicians to conduct clinical research in rural areas. Woodcock et al. assert that both industry and the medical establishment must provide community-based clinicians in rural areas with the resources, mentorship, and training necessary to run successful clinical trials. These physicians serve local populations and maintain strong rapport with their patients, which are factors critical for enrollment and retention.<sup>{4}</sup> Moreover, an Elsevier survey revealed that 72% of patients are more likely to participate in a trial that their physician recommends.<sup>{5}</sup>

Legislators in certain states have recently passed bills increasing the number of physicians in rural areas. A 2023 Texas law allocated resources to rural hospitals incentivizing them to train physicians committed to practicing medicine in rural and underserved areas, but results have yet to be seen.<sup>{6}</sup> Regardless, more rural physicians present opportunities for the clinical research industry to establish partnerships with these medical providers, introduce them to clinical research, and extend needed clinical care to vulnerable populations.



## Financial Issues

Patients find clinical trials appealing because they may receive compensation for their participation, but compensation alone does not imply equitable remuneration. For instance, trial compensation may be insufficient to justify the obligations and burdens patients accrue while enrolled in a study.

Patient liabilities may include time spent away from income-generating activities, along with travel costs to and from the research site. Patients informed us of their inability to attend study visits that conflicted with their work schedules, and that, over time, study participation became more difficult. They also indicated an absence of childcare services was another factor that either prevented them from enrolling in the study or led to them dropping out of it.

Most importantly, Bierer et al. showed that patients from lower socioeconomic backgrounds incur significant wage losses when participating in a trial.<sup>{7}</sup> Therefore, underprivileged and/or underrepresented patients often cannot afford trial participation costs, which may compel them to either prematurely leave the study or not participate. Moreover, drug sponsors underpay participants or simply provide no compensation at all, which limits the inclusion of diverse and underrepresented populations. Hence, these groups are understudied and less likely to receive the benefits of novel therapies.<sup>{8}</sup>

To address this, we believe patients should be offered at-home services as an option, not a requirement, and this is because while many patients preferred in-home services, many of our trial patients openly declined them. The evidence justifies the inclusion of at-home services in a trial's design where appropriate, but also aligns with our conservative view. For example, a CenterWatch survey found half (51%) of 1,129 respondents preferred home services.<sup>{9}</sup> Such visits are beneficial since a nurse can draw blood samples, take vitals, and perform other assessments. We realize the impracticality of having every assessment done at home, but patients can nevertheless benefit from shorter wait times and fewer clinic visits, which could help underrepresented patients increase their income-generating activities.

Nipp, Hong, and Paskett outline how patients participating in U.S.-based trials experience financial difficulty stemming from fees not covered by insurance or study reimbursement.<sup>{10}</sup>

Trials often reimburse patients for travel expenses and pay for any necessary procedures outside the standard of care criteria. However, this does not consider that many procedures considered standard of care may not be fully reimbursed by a patient's insurance or Medicare coverage. As a result, a patient who would have normally needed a single blood draw each month at an out-of-pocket cost of \$10 for a standard treatment regimen may now have to pay for multiple \$10 draws per month.

These out-of-pocket costs can financially devastate underrepresented patients, especially if they lack insurance. To address this barrier, we recommend that the industry works with legislators to establish a clinical trial insurance program aimed at low-income patients, to minimize unexpected costs and expand access.

### **Clinical Trial Design and Awareness**

Another barrier we witnessed is an overly complex and burdensome schedule of assessments requiring multiple visits outside treatment days. For example, we managed a kidney trial with a pharmacokinetic sub-study mandating urine draws every 12 hours. Although nurses and study coordinators informed us that many protocols were impractical, their feedback was never considered. This is a mistake because these health professionals can provide valuable insight into designing less burdensome and more feasible protocols. We contend that protocols should be patient-centric and include insight from numerous stakeholders, not just scientists and board members. Thus, protocols should enable sponsors to obtain the minimum scientific data necessary to establish an accurate safety profile and efficacy.

Our industry must address how clinical trial protocols are designed, which can exclude patients from specific populations. All clinical trials contain baseline criteria that patients must satisfy, commonly referred to as eligibility criteria. These criteria can help the sponsor ensure that patients with the appropriate diagnosis are enrolled, but a criterion too stringent can restrict trial enrollment for underrepresented patient populations. According to Sae-Hau et al., one barrier is patients being more likely to enroll if they had relapsed on their most recent treatment, as opposed to those patients who were undergoing current therapy, or in a maintenance period.<sup>{ 11 }</sup> This is an opportunity for our industry to engage sites early in the process by reviewing the

protocol prior to patient enrollment. Physicians and site staff can present their opinions if the criterion is too stringent and consider patients who meet most of the inclusion and exclusion criteria, which will also present a streamlined enrollment approach to expedite initiation into the trial.

Desai et al. showed that clinical trial patient recruitment is undoubtedly a major challenge for the industry, as 80% of clinical trials fail to meet initial enrollment timelines. {12} Likewise, clinical trials are in dire need of effective marketing and advertising strategies to bolster awareness among various patient populations. {13} Some traditional recruitment methods include media campaigns, advertisements, and physician referrals; online recruitment methods may include social media ads and search engine advertisements, which can allow research teams to target more specific and nuanced patient populations.

Brøgger-Mikkelsen et al. conducted a meta-analysis which found that studies utilizing online recruitment methods recruited patients much more quickly than traditional methods and were more cost effective. {14} Conversely, traditional methods fared much better when it came to enrolling screened participants into the trial. Taken together, the findings suggest that study teams should consider using online recruitment methods to target patients, and then scheduling in person visits to assess those patients.

However, recruitment challenges also stem from the community's lack of awareness of clinical trials. One study found that, among a representative sample of 3,772 U.S. adults, 41.3% had no knowledge of clinical trials. {15} Addressing the public's lack of awareness in clinical trials poses challenges, but it is a necessity that the government, industry, and academia should collaborate to address. A starting point would be greater promotion and awareness of ClinicalTrials.gov as a free online resource, as the site contains information on clinical trials across the globe, including their requirements and locations.

A final key consideration is that, if we recognize the difficulties above, including low potential for enrollment at rural clinics, financial circumstances, and unnecessarily limiting trial design, there is still potential for improved awareness of existing clinical trials to which rural clinic providers may refer their patients. There remain massive hurdles for many patients to travel to

large urban centers that carry most clinical trials, but this is still an option. To accomplish this, we need to improve outreach to rural clinics to ensure that patients are at least being made aware of potential options. This, coupled with travel reimbursement plans where the guidance is laid out explicitly for patient referrals, would help to alleviate some of the burden to help patients reach critical and potentially life-saving trials.

## **Conclusion**

If the clinical research industry is to ensure that lifesaving therapies have greater efficacy and safety, industry leaders must address the barriers preventing individuals from diverse, socioeconomically disadvantaged, and/or rural backgrounds from participating in trials. We have discussed three barriers to accessing clinical trials for underrepresented patient populations—sparsity of clinical trial sites in rural and underserved communities, inadequate patient reimbursement, and stringent inclusion/exclusion criteria—which all hinder the enrollment of patients from diverse and underrepresented populations (Figure 1). We outlined the necessary initiatives to combat these barriers, starting with industry leaders engaging with rural physicians and providing them the resources and support to conduct trials in under deserved areas.

Additionally, the clinical trial protocol design itself could be diversified to include telehealth visits and traditional onsite visits, where appropriate, to capture the widest range of patients. Moreover, the industry must design protocols with fewer restrictive inclusion/exclusion criteria and minimize the number of tests and/or patient visits. Lastly, we considered reducing the travel- and economic-related burdens on patients by offering more home visits and services. This is a necessity given that patients from low-income backgrounds cannot afford to cease working for extended periods.

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PEER REVIEWED

## **Using Simulation to Teach Research**

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Using simulation to demonstrate the theoretical and practical aspects of research design has yet to be explored. Identifying what simulation can achieve for educational and research objectives that other modalities cannot achieve is essential. This review discusses whether simulation can be used to teach the research process. The value of simulation can't be determined by randomized trials alone. A qualitative approach to assessing the value of teaching research via simulation adds a well-rounded perspective.

Simulation has tremendous potential and can be used as a research tool. This review aims to develop the fundamental research question, namely, can we use simulation to educate about the research process?

### **What is Simulation?**

“Simulation is a methodology by which we recreate a portion of the healthcare delivery experience to educate and assess people, groups of people, teams, and environments of care.”<sup>{1}</sup> Simulation creates a practical context in which skills can be learned, applied, and mastered. It has emerged as an effective teaching methodology.<sup>{2}</sup> It is increasingly employed to improve knowledge and skills.<sup>{3}</sup> It has spread to almost every discipline and domain.<sup>{4}</sup> It represents an actual event for practicing, learning, evaluating, testing, or understanding systems or human actions.

In other words, simulation either mimics or amplifies real experiences with guided experiences that evoke or replicate real-world circumstances. <sup>{5,6}</sup> It is an ideal modality to practice and learn management of critical events.<sup>{7}</sup>

Several simulation applications have been in clinical practice (see Table 1). The Simulation Research Summit organized by the Society of Simulation in Healthcare guided the research-based use of simulation.<sup>{8,9}</sup>



## **Table 1: Application of Simulation**

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Clinical performance

Decision making

Clinical processes

Human factors

Training

Research

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### **Practice in Simulation First**

Simulation creates a safe learning environment that allows testing new clinical processes and enhancing individual and team skills before encountering actual patients. Since patient safety has become an essential agenda item, the clinical setting is no longer the only place to learn and practice skills. Human subjects should be protected whenever possible and not perceived as commodities for training conveniences. Simulation provides a structured training opportunity with defined learning objectives.

Simulation could support the investigation of phenomena that are difficult to study by more conventional methods. It is based more strictly on theories or conceptual frameworks. Several variables can be controlled in a simulated environment compared to actual situations where every component aspect varies.

Standardization of the environment allows the researcher to control many potential threats to internal validity.<sup>{10}</sup> In other words, the participants' performances comprise the only difference between actual and simulated situations. Indeed, the differences in performance are illustrative of an intrinsic human factor.

## **What Can be Simulated?**

It is not incorrect to say that almost anything and possibly everything can be simulated. In recent years, the research agenda has shifted from “if” simulation works to examining the “who, what, when, where, why, and how” of the simulation process. {11} Hence, the critical question is when should we use simulation? And how do we effectively use simulation?

Although a situation is simulated, this approach may produce emotional realism, allowing the participants to learn “as if it were a real situation.” This requires establishing a “fiction contract: acting as if things are real.” In other words, a voluntary commitment from the learner to do what they would do to act as if the experience is real.

## **Research Using Simulation**

The simulation research process is similar to the conventional research process. It has become commonplace in clinical education. The focus of simulation research is education, as well as an assessment of processes and performance. Identifying what simulation can achieve as educational and research objectives that other modalities cannot achieve is essential. We believe simulation is an effective instructional method for teaching the research process. Simulation-based research can be classified into two categories {12} (see Table 2):

- Research about simulation allows for testing or improving simulation techniques. Here, simulation is the focus or objective of the research and serves as a dependent variable. This approach also involves the clinical impact of simulation as an educational tool.
- Research uses simulation to study other issues, such as human performance, clinical cognition, or clinical care processes. This means that simulation is used to investigate other research questions. Simulation is used as a research tool and serves as an independent variable. It offers unique features and can be considered a complementary window into the clinical world relative to other modalities. It can be applied, for example, when complex phenomena such as medical team processes are studied. For instance, how teams adapt from routine to non-routine situations and how such adaptations are related to performance, communication

processes such as information processing, problem-solving and decision-making, and coordination requirements during resuscitation. Using simulation as a research method and choosing a simulator or tool depends on the research question or objective.

**Table 2: Types of Simulation Research**

	<b>Research About Simulation</b>	<b>Research Using Simulation</b>
<b>Focus</b>	Investigates simulation	Investigates other research questions
<b>Purpose</b>	Simulation is the objective	Simulation serves as a research method
<b>Variable</b>	Dependent	Independent
<b>Outcome</b>	Improves simulation	Depends on the study question/objective

### **Creating a Simulated Environment**

Simulation recreates the actual situation and provides an experience that closely mimics the conditions encountered in the real environment. The most important step is carefully designing scenarios that align with the objective. Researchers should ensure the scenarios are realistic and relevant to the skill taught. This helps the participants to immerse themselves in the simulation.

Scenario-based simulation is a structured activity with a timeline of events and clear learning goals that aim to replicate a clinical situation. Since the simulated environment can be standardized, simulation is a robust research methodology for studying clinically relevant issues in a controlled manner. Unlike in the actual clinical setting where all these elements would be variables, they are precisely controlled in the simulated environment.

The difference between the simulated and real environments is the absence of real human subjects. However, “standardized subjects” are recruited to perform role play using simulation.

These individuals are carefully coached to present their illnesses in a standardized way. Standardized patient rooms can be incorporated into simulation centers to improve fidelity.

Virtual models created by software can be used for teaching research. These can be customized to meet the needs and experiences of learners. Also, these can be adapted, allowing them to interact with the simulation. This is especially well-suited to conduct research that is difficult to accomplish in a real clinical environment.{ 13 }

Simulation research can help determine what works best for training purposes. Additional benefits include research regarding patient outcomes, improving safe health delivery practices, and error reduction.{ 14,15 } This can further the analysis of system issues that yield successful outcomes or result in failure.

### **Teaching the Research Process**

Simulation is used to study clinical settings. It helps to facilitate controlled studies, which expose one group but not the other(s) to intervention. Simulation can be used to learn about implementing new processes or protocols. In that sense, it can be applied to teach the research process. It can study human factors and improve knowledge of human error and system performance. We believe it can enhance work systems in an organized manner by helping to identify and remove systemic sources of error.

Simulation in the research context provides clarity and improves participation in the research process. Research process integrity depends on the planning and organization of the process. The institutional review board (IRB) for a study site oversees all research activities involving human subjects and monitors regulatory compliance. The board's primary responsibility is to protect the rights and welfare of human subjects. Studies have shown that IRBs operate at different levels of efficiency, and decisions made by IRBs and their members may not always be in accord with regulatory guidance.{ 16 } Simulation can also assess the consistency of IRB decisions and help to identify latent issues.

A simulation environment allows for uncovering latent errors, especially under extreme circumstances and unexpected outcomes. Early research efforts justify simulation as a modality for teaching multiple aspects of research{17} (see Table 3).

**Table 3: Required Elements of the Research Enrollment Process**

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Objective and Purpose of the Research

Research Design and Methods

Study Procedures

Recruitment of Subjects

Informed Consent Process

Adequate Protection of Human Subjects

Risks/Benefits Assessment

Privacy and Data Confidentiality (Health Insurance Portability and Accountability Act's Privacy Rule outlines individuals' rights regarding their protected health information)

Regulatory Compliance and Record-Keeping

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In recent years, simulation has been used to retest clinical randomized trial hypotheses. This repeated the clinical trial in a simulated environment. The purpose is to determine whether the conclusion will remain the same as that of the clinical trial.{18} Computer simulation of clinical trials has been used to improve the drug development process.{19}

## Teaching the Consent Process

Simulation can be used to teach about the informed consent process. An informed consent is necessary for the successful conduct of a research project. It takes some time before one becomes competent and comfortable with this process, and this is a risk-free way to iron out the kinks before approaching real human subjects.

Human subjects must enter the study voluntarily, with sufficient information and adequate understanding (see Table 4). The consent process and associated concepts can be taught and practiced using simulation. Informed consent is an essential ethical safeguard, ensuring prospective subjects fully understand any research protocol's study procedures, risks, and benefits. It is not merely a form that is signed and documented. It is a process in which the subject understands the research and its risks. The voluntary expression of consent and adequate information disclosure about the research procedure are essential to the informed consent process.

### Table 4: Core Elements of Consent Process

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Adequate disclosure of information

Comprehension and understanding

Voluntary participation

Informed decision-making without undue influence

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The consent process uses simulation with volunteers (simulated research participants) by role-playing. A checklist can be used to identify the essential elements of informed consent (see Table 5).

## Table 5: Informed Consent Checklist

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Research and experimental status

Purpose of the research

Expected duration of the subject's participation

Procedures to be followed and identify any experimental procedures

Foreseeable risks or discomforts to the subject

Benefits to the subject or others that may be expected from the research

Disclosure of appropriate alternative procedures and treatment

Extent of confidentiality maintenance

Identification of contact person

A statement that their participation is voluntary, refusal to participate will involve no penalty, and they can withdraw at any time

Additional costs to subjects or compensation paid (if any)

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Electronic informed consent (eIC) creates opportunities to improve the consenting process. {20}

This format improves participants' engagement and enhances their understanding. {21}

Computer-based platforms with audio-visual and interactive features are available. It is much more than obtaining a subject's signature; it's a process by which participants understand the study and its risks. The research team must assess the subject's understanding of the information presented during the eIC process. This should allow adequate opportunity to ask questions and consider whether to participate.

The aforementioned Health Insurance Portability and Accountability Act of 1996 ([HIPAA](#)) is a required component that operates in tandem with the consent process. It is a federal law that

requires the development of national standards to keep sensitive, protected health information (PHI) from being disclosed without a patient's consent or knowledge. The HIPAA Privacy Rule was issued by the U.S. Department of Health and Human Services to implement the requirements of HIPAA. It establishes the conditions under which covered entities may use or disclose PHI for research purposes. It also defines how individuals will be informed of the uses and disclosures of their medical information for research purposes. Its implementation is imperative as we engage in more complex research, particularly genetic testing. Periodic monitoring to assess safeguards protecting PHI is essential. Simulation exercises can be used to achieve this goal.

Some limitations must be recognized. Although it may be helpful in research, this analogy may not work for everyone as a person's way of learning may vary. One potential disadvantage of using simulation as a research method is becoming overwhelmed by technology, assuming that simulation almost always involves technology. Also, simulation research assesses outcomes in simulated environments. It remains to be seen how findings in simulated environments will translate into the real-world environment.

## **Conclusions**

Simulation is a beneficial but rarely employed research strategy. The current use of simulation in healthcare hasn't reached its full potential. We need to explore its potential applicability further to make it more effective.

Moving simulation research forward requires thoughtful planning and organization. This modality is well-suited for conducting research that is difficult to achieve in a real-world environment. It can contribute to a better understanding of how simulation can provide education regarding research principles in a clinical work environment. Given the multiple and diverse uses for simulation, it is essential to expand its implementation. Furthermore, research can be advanced by embracing simulation-based training.



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PEER REVIEWED

## An Approach to a Benefit-Risk Framework

Robert Jeanfreau, MD, CPI; Robyn Harrell, MS; Paul Pati, MSN, FNP-C



All rational behavior, driven by an incentive to obtain a desired goal, is tempered by an evaluation of the attendant risk of harm. In common parlance, safety is sometimes misunderstood to be the condition of being free from the risk of any harm; however, even a superficial examination of this definition reveals its inadequacy. Every human activity, including medical therapeutics, involves the possibility of harm. Safety, in an absolute sense, simply does not exist. Every evaluation of safety must involve an estimation of the potential for benefit as well as for harm.

The weighing of benefit and risk is how stakeholders—the pharmaceutical industry, regulatory agencies (including the U.S. Food and Drug Administration [FDA]), institutional review boards (IRBs), study participants, practitioners, and patients—evaluate, in one way or another, safety.

In the past, evaluations have involved, to a greater or lesser extent, a qualitative, intuitive component performed by a stakeholder. For example, in clinical research prior to a protocol being initiated, it must be approved by an IRB. A scientific reviewer, one of the panel members, has the primary responsibility of determining if the benefits justify the risks. Each IRB must perform its own, individual benefit-risk assessment *de novo*. Although the reviewer carefully evaluates the scientific data, there is no standardized framework available for deliberations.

More recently, there has been a shift from qualitative assessments toward a more quantitative approach. A quantitative framework is a method for arranging numerical data in a standardized format to assist in the decision-making process.

Formalized evaluation of benefit and risk of harm is referred to as the benefit-risk framework (BRF) (the term we will use hereafter), or the benefit-risk assessment, and has been structured in a variety of different ways. The lack of wide acceptance of a particular BRF underscores the significant challenges.

There is, however, a general opinion regarding the desired features of a BRF{1–5}. It should:

- be as quantitative as possible;
- incorporate the patient’s perspective;
- be transparent; and
- be applicable throughout the lifecycle of the drug.

### **Quantitative**

The shift from qualitative assessments is based upon certain deficiencies inherent in that approach, making the last three features of a desirable BRF difficult to achieve. For example, one of the encumbrances for some formal, qualitative assessments is the requirement for convening an expert panel. If a BRF is to be utilized throughout the lifecycle of a drug, it will be necessary to perform serial assessments as new risks and benefits become apparent. Routinely utilizing expert panels is excessively onerous and time-consuming. A structured, quantitative approach, however, allows for repetitive and timely determinations.

Another major advantage of a fully quantitative BRF is the opportunity for mathematical analysis, enabling its consistent application. This advantage is, of course, based on the premise that the components of the framework, specifically benefits and risks, are, in fact, measurable and, therefore, quantifiable.

### **The Patient’s Perspective**

If benefits must outweigh risks throughout the lifecycle of a drug, inclusion of a participant’s perspective is not just desirable but imperative. In some early-phase studies, there are no recognized benefits from the study drug to the enrolled participants. Since there are no objective benefits, any question about the benefits justifying the risks is meaningless.

In these situations, the widely promulgated concept that the benefits must outweigh the risks is abandoned in favor of the assertion that the risks must be minimal. What is being overlooked is the fact that, although there may not be recognized benefits to receiving an investigational product (IP), there are study benefits to the participant, albeit entirely subjective. For example, the desire to help find a cure for a disease affecting a participant's loved one would be a powerful motivator.

### **Transparency**

Transparency implies that the “inner workings” of a BRF are readily apparent and understandable. In the case of a qualitative assessment, transparency dictates that the intuitive reasoning of an expert panel is available and clearly described.

Transparency of quantitative assessments requires that the framework is also understandable to the stakeholders. A quantitative framework cannot be deemed to be truly transparent if its computations are so complex as to defy the understanding of the most important stakeholder—the patient. An approach based upon basic algebra satisfies this requirement.

### **The Drug's Lifecycle**

If a BRF is to be utilized throughout the entire lifecycle of a drug, it is reasonable to examine how these concepts are addressed near the very beginning of drug development (i.e., in clinical research).

Ensuring the effectiveness of investigational drugs and devices and the safety of human participants are two primary pillars of the FDA. Effectiveness is the likelihood that, under specified conditions, an IP will result in a desired therapeutic *benefit*. Therefore, the benefits of drugs are initially verified in clinical trials. Harms are determined by the evaluation of adverse events collected during clinical studies. The evaluation of benefits and the risk of harm is at the very core of clinical trials. The BRF would also need to address any additional, longitudinal risks and benefits recognized after drug approval.

## A Possible Approach to a Benefit-Risk Framework

Every BRF seeks to compare benefits and risks. Do the potential benefits outweigh the potential risks? A common opinion, as discussed in the quotation below, is that these two factors cannot be directly compared, although that is precisely what a quantitative BRF strives to do.

Consider this perspective: “Risk–benefit ratio: The most common expression for the comparison of harms and benefits. It is a technical term that assumes that a ratio can indeed be calculated. Because the benefits and harms of an intervention are often so different in character or are measured on different scales, the term ‘risk–benefit ratio’ has no literal meaning. In addition, there may be several distinct benefits and harms. We advocate using ‘balance of benefits and harms’ rather than ‘risk–benefit ratio.’”{6}

If the above statement is, however, true (i.e., if there is no common ground for comparing risk of harms and benefits), then there can be no basis for quantification, rendering a quantitative BRF completely untenable.

Benefits and risks *can* be expressed as probabilities of comparable scales. The common ground is, of course, health. Harms diminish whereas benefits promote health. Clinical research provides guideposts as to how these two entities might be compared as a ratio.

Benefit

Risk

An example follows. A hypothetical, investigational arthritis drug relieves joint pain in 99 of 100 patients with only one reported adverse reaction (AR).

The equation can then be written as:

Frequency of Benefit

Frequency of AR

Initially, the benefit-risk ratio looks acceptable—until it is disclosed that the AR was a death. Clearly, more than just the frequency of the AR must be considered.

Severity of the AR is a critical factor. The equation is modified as noted below.

Frequency of Benefit

Frequency of AR x Severity of AR

Another example follows with a different drug in a terminal setting. With this drug, there is again a single AR out of 100 patients and again that AR is a death. However, the drug was completely effective in the other 99 patients. Consider that all 99 patients had a diagnosis of terminal lung cancer and were, therefore, subsequently cured. So now the benefit- risk ratio is remarkably positive. Clearly, not only the frequency of the benefit and the severity of the AR, but also the severity of the underlying disease are necessary factors to consider. The equation is modified to include four specific factors.

Frequency of Benefit x Severity of Disease

Frequency of AR x Severity of the AR

At first glance, this appears to be a simple, usable equation. When the numerator is larger than the denominator, the benefits “outweigh” the risks.

Important questions remain. How is “benefit” determined? How is the severity of an AR determined? How is the severity of a disease determined? Clinical research may provide answers to these questions.

The FDA defines disease as:

“...damage to an organ, part, structure, or system of the body such that it does not function properly (e.g., cardiovascular disease), or a state of health leading to such dysfunctioning (e.g., hypertension); except that diseases resulting from essential nutrient deficiencies (e.g., scurvy, pellagra) are not included in this definition.”{7} In this definition, the emphasis is on normal functioning.

The FDA defines an adverse event as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an adverse event could be a symptom, an abnormal lab finding, a physical finding, or a clearly defined disorder or

disease. If it should be determined that the adverse event is, in fact, caused by the drug, then the adverse event is termed an AR.

Clinical research provides grading scales for the evaluation of ARs. A grading scale is a type of rank order and is the first step toward assigning weights.

A common grading scale for symptoms, physical findings, and diseases is based upon the effect that the AR has on activities of daily living (ADLs). Grading scales for the evaluation of abnormal lab results are also found in clinical research.

### **Frequency of Adverse Reactions**

The collection and characterization of ARs, an integral part of clinical research, continues even after drug approval. Therefore, the frequency of ARs, often contained within the package insert or in systematic reviews, is subject to change as additional, longitudinal data become available. As more long-term evidence accrues, a dynamic framework would make updating benefit-risk assessments throughout the drug's lifecycle a much less daunting task.

### **Severity of Diseases and Adverse Reactions**

One of the biggest challenges in formulating a workable equation is in defining severity of ARs and severity of diseases. For ease of interpretation, these terms will be defined such that they are "like-terms." The commonality of diseases and ARs is that they both affect health. Therefore, the challenge becomes to define both in terms of health. Health can be defined as the "ability to function normally."

The severity of diseases and ARs can thus be operationally described in terms of the impact on a person's ability to function normally, taken here to mean the ability to carry out ADLs.

An excellent example of how these concepts are utilized in clinical research is the Common Terminology Criteria for Adverse Events v5.0 (CTCAE). The CTCAE, originally formulated for oncology trials, provides a grading system for all categories of ARs, including symptoms, lab abnormalities, physical findings, and disease states. The grading system is described in the introduction of the document:



“Grades: Grade refers to the severity of the [adverse event]. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each [adverse event] based on this general guideline:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.\*

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.\*\*

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to [adverse event].

Activities of Daily Living (ADL)

\*Instrumental ADL [refers] to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

\*\*Self-care ADL [refers] to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.”{8}

This approach has become standard practice in oncology trials which routinely rank subjects according to The Eastern Cooperative Oncology Group (ECOG) Performance Status Scale.

The CTCAE grading system can be implemented in this approach to grade the severity of disease states and ARs. Since there can be little argument (i.e., the effect of subjectivity is minimal) that the worst possible harm is death, death will be assigned the highest weight for ARs. The numeral, 1, will be arbitrarily chosen as the highest weight. The other categories of ARs, therefore, will be assigned values less than 1. In this way, the weights for ARs are defined as “constants” as opposed to variables.

Although severity of disease can also be expressed by its impact on health, it cannot be assigned as a constant in clinical practice. The reason is that the severity of a particular disease can vary widely from patient to patient (e.g., the manifestations of multiple sclerosis can range from minimal to life-threatening). Another example is COVID-19, which has gradually mutated into a less virulent disease. For a specific patient, the particular weight for the severity of disease would be assigned by the treating clinician. In the clinical trial setting, however, the weight for the severity of disease could be assigned by the sponsor in concert with the FDA.

### **Frequency of Benefit**

For the purpose of defining this variable, benefit will be understood to mean how well the drug does what it is purported to do. It is obvious that some types of benefits have a more profound effect on health than others. What drugs do can be broadly categorized in rank order of increasing importance as follows: 1) alleviates symptoms, 2) ameliorates (or slows down) disease, 3) halts disease progression, 4) cures disease, and 5) prevents disease. Therefore, the frequency of benefit is the frequency with which the drug achieves its primary goal. Ranking of these five categories will later serve as the basis for assigning weights to benefits.

The benefit variable can now be further defined as the frequency of the benefit x the weight of the benefit.

$$\frac{(\text{Frequency of Benefit} \times \text{Weight of Benefit}) \times \text{Disease}}$$

$$\text{Frequency of AR} \times \text{Severity of the AR}$$

Because the weight of the benefit is defined as a constant, specific weights have to be assigned. Since there can be little argument (i.e., the effect of subjectivity is minimal) that the best possible category of benefits is prevention, it will be assigned the highest weight for benefits. Again, the numeral, 1, will be chosen as the highest weight. The weights for the other categories of benefits will be assigned values less than 1.

Similarly, because the weight of ARs is defined as a constant, specific weights have to be assigned. Since there can be little argument (i.e., the effect of subjectivity is minimal) that the

worst possible AR is death, death will be assigned the highest weight for ARs. The weights for the other categories of ARs will be assigned values less than 1.

The remaining weights for the other benefits and ARs would be assigned by a panel of experts. However, for demonstration purposes only, the following weights will be assigned for benefits and ARs:

<b>Benefits</b>	<b>ARs</b>
0.0032 Alleviates symptoms	0.0032 Mild
0.252 Ameliorates disease	0.252 Moderate
0.501 Halts disease progression	0.501 Severe
0.75 Cures disease	0.75 Life threatening
1.0 Prevents disease	1.0 Death

Examples follow. Any value > 1.0 will be seen as a positive benefit-risk ratio for the drug. An antibiotic which has, as its most common AR, diarrhea, is being used to treat pneumonia. This AR occurs in 10% of patients, and its severity is considered moderate (i.e., a weight of 0.252). We will further postulate that the antibiotic cures pneumonia in about 90%. The pneumonia is graded as severe.

$$\frac{(\text{Frequency of Benefit} \times \text{Weight of Benefit}) \times \text{Severity of Disease}}{\text{Frequency of AR} \times \text{Severity of AR}}$$

Substitute the numerical values for the variables:

$$\frac{(0.9 \times 0.75) \times 0.501}{0.1 \times 0.252} = 13.5$$

As another example, alter the above equation as follows. The AR is colitis due to *clostridium difficile* with an occurrence rate of 30% with a severity of severe. The numerator will be the same.

$$\frac{(0.9 \times 0.75) \times 0.501}{0.3 \times 0.501} = 2.25$$

The result is a positive risk-benefit profile, although not as pronounced as the preceding example.

Alter the variables once more. Instead of pneumonia, the disease will be pharyngitis with a designated severity of mild with the other variables remaining the same.

$$\frac{(0.9 \times 0.75) \times 0.0032}{0.3 \times 0.501} = 0.0144$$

Now the benefit-risk ratio becomes 0.0144, clearly an unacceptable treatment option. Clearly, any framework is dependent upon reliable data drawn from well-conducted clinical trials with sound statistical analysis (e.g., appropriate sample size, etc.). If a study is subsequently found to be flawed, the data would simply be expunged from the calculations.

## **Discussion**

In addition to the previously mentioned advantages (i.e., quantitative, incorporates patient's perspective, is transparent, and applicable throughout the lifecycle of the drug), this approach is also versatile.

For example, for drugs having multiple ARs and/or multiple benefits, the computations can be carried out in a single equation, yielding a composite ratio.

$$\frac{(\text{Frequency of Benefit} \times \text{Weight of Benefit}) \times \text{Severity of Disease}}{(\text{Frequency of AR}_1 \times \text{Severity of AR}_1) + (\text{Frequency of AR}_2 \times \text{Severity of AR}_2)}$$

Additionally, there are some situations in which the drug has an AR that some participants may actually view as a benefit. For example, a drug for migraines may be found to have mild weight loss as an AR. However, some participants might consider mild weight loss to be a benefit rather than an AR. This approach is versatile enough to account for this type of participant subjectivity.

To be sure, there are certain limitations to this approach; among them, in its current format, it does not address the issue of uncertainty. For example, a Phase I study with a sample size of 30 subjects yields data on risks and benefits of an IP for migraine. Three of these subjects (10%) developed nausea felt to be secondary to the IP. A larger Phase III study with 500 subjects also yielded a 10% rate for nausea along with the same benefit profile. Although the results of the benefit-risk ratio will be exactly the same, the certainty associated with each study is markedly different. Uncertainty is inversely proportional to the amount of reliable data.

Additionally, this approach assumes that drugs are only used for disease states. There are, however, drugs (primarily those used for cosmetic purposes) that are not used to treat a disease but to improve the quality of life. The approach would have to be modified to evaluate these medications.

This approach utilizing well-established concepts in clinical research is not a definitive solution, but is intended to stimulate discussion regarding a viewpoint that has been prematurely dismissed.

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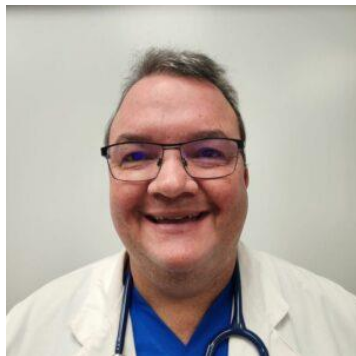
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## Clinical Trial Technology: A CRO's Perspective

Malia Lewin, JD



When I was working in the technology space, it was understood that if a sponsor's contract research organization (CRO) had a role in supporting the implementation of our product at sites, it meant the end of its usage and adoption in those settings. Why would that be? Well, CROs are responsible for protecting study timelines, budgets, and quality. This means that isolating and eliminating variables that could distract sites with perceived time-drainers such as technology training, requirements for additional passwords, risks to data quality, or other contributions to site burden is part of the job.

My tech friends often ask me how to effectively partner with CROs and my answer is “give me something to improve clinical trial outcomes while driving faster timelines with reduced costs.” CROs don't hate all technology, just point solutions that contribute to user burden without significant benefit or integration into already complex workflows and data management challenges.

Legacy technologies are no longer fit-for-purpose, and we must follow the lead of other sectors like manufacturing and consumer packaged goods in adopting generative artificial intelligence (AI) and other technology and data advancements to support pain points around patient experience, data integrity, quality, and the supply chain. A recent MIT report of senior executives in the healthcare and life sciences sector showed that 38% of us consider our use of generative AI and other advancements to be very slow to moderate.<sup>{1}</sup> This is simply not good enough.

## Things to Pack for the Journey

In the journey from drug discovery to approval, a significant amount of information is collected. The persistent problem is generating and actioning insights from these data in a manner that allows us to take quick, decisive action. About 61% of those surveyed by MIT are increasing investment in data and AI analytics up to 25% over the next year and 38% expect an even larger increase.<sup>{1}</sup> The large majority (about 72%) will leverage these investments to support streamlining workloads and accessing real-time information. Others see greater potential to push substantive scientific breakthroughs and data mining in areas of high growth, such as biomarker identification, genetic variant targeting, and personalized medicine applications.<sup>{1}</sup>

Another timeless challenge up for a good technology solution is the persistent issue of data integration across the diverse network of sites and systems on a given clinical trial. More than half (52%) of the industry's respondents in the MIT survey said having a single system for structured and unstructured data used for AI is "very important" to achieving their organization's technology goals, and yet one third of the MIT respondents say their organizations support 10 or more data and AI systems.<sup>{1}</sup>

AI and natural language processing will help bridge multiple datasets and allow for the democratization of insights across stakeholders. Clarity around the location of real-time information with a user interface allows all study stakeholders to query the data with minimal training and hassle. This can have a positive impact on patient outcomes and the time, quality, and cost of running clinical research.

Leveraging AI methods like machine learning and natural language processing can also help meet the complex challenge of reducing bias in clinical research and ensuring equitable accessibility for all communities of stakeholders across therapeutic indications.

Hispanic/Latinx patients make up 18.5% of the population but only 1% of typical trial participants<sup>{2}</sup>; African American/Black patients make up 13.4% of the population but only 5% of typical trial participants.



Further, between 2011 and 2020, 60% of vaccine trials{3} did not include any patients over 65, even though 16% of the U.S. population is over 65.{4} To fill diversity gaps like these, companies like Johnson & Johnson are leveraging AI to identify new sites for accessing underserved populations{5} and others are using AI to build screening, enrollment, and retention models to close diversity, equity, and inclusion (DEI) gaps and meet data traceability and transparency goals aligned with U.S. Food and Drug Administration guidance and regulations.{4}

## Conclusion

Leveraging technology in clinical research to drive advanced analytics, integrate and query data across multiple data sources, and improve DEI in clinical research are unifying causes for CROs and the technology sector. If we put our heads together on effective and efficient solutions that leverage AI, as other sectors outside of healthcare and life sciences have done, we will drive a faster, cheaper, safer path from discovery to clinic and benefit millions of patients globally.

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**ON THE JOB**

**The Art of Investigational Site Relationships with Sponsors/CROs**

Elizabeth Weeks-Rowe, LVN, CCRA



Investigational sites are the crux of a clinical trial: the origin of study data, patient recruitment, and procedure execution. The principal investigator (PI) leads the investigational site study team as its members facilitate study activities and patient care/education. The investigational site facilities store the investigational treatments under study, hold essential documents that support the ethical chronology of trial activities, and house the diagnostic and trial management equipment necessary to achieve the study endpoint(s) and maintain timelines. The clinical trials lifecycle, as part of the overall drug development process, would not progress without investigational sites.

Study sponsors or contract research organizations (CROs) working on their behalf follow a methodical process to select appropriate investigational sites for study participation (study start-up), and effective relationship development is key to transforming a preliminary meeting into a flourishing partnership between these stakeholders.

The first impression created during site selection will impact the course of the ensuing relationship between the sponsor/CRO and investigational site, and this selection process must be conducted professionally at all costs. This effort does not subside once the proverbial dust of study start-up has settled. The following periods of study enrollment, maintenance, and close-out

require equal finesse to continue an efficient collaboration between the parties that promotes patient safety and credible data collection throughout the study lifecycle.

### **CRA and CRCs at the Epicenter**

There is no predictive algorithm to ensure optimal relationship creation, development, and sustainability between the sponsor/CRO and the investigational site. It is influenced by such intangibles as perception, impression, and circumstance. It is impacted by such diverse variables as study budget, protocol feasibility, patient enrollment, data collection, reporting, and overall study conduct. The players involved can only control their efforts toward study success in an otherwise unpredictable environment, and a key component of the partnership's success or failure is the clinical research associate (CRA)/site dynamic.

More specifically, the CRA/clinical research coordinator (CRC) dynamic is the epicenter of the overall relationship between sites and sponsors/CROs. The success of this relationship hinges on the willingness of the CRA and CRC to collaborate for the common goal of trial success. There are core absolutes to this relationship—one cannot fulfill his/her study responsibilities without the other, as the relationship is interdependent. One is not subordinate to the other; the relationship must be equitable—a dynamic commitment to an equal partnership, rooted in respect for collective experience over individual ego.

While there is no secret formula to guarantee success, there are intentional steps/behaviors that will help transform a fledgling introduction into a strong relationship between the CRA and CRC, which may lead to a lasting partnership between the sponsor/CRO and investigational site.

### **Respect, Professionalism, Transparency, Positivity, and Follow-Through**

*Respect* and *professionalism* must be displayed in both directions from the inception of the relationship. The CRA must open the initial dialogue with the site cordially and continue that way. E-mails/instant message/telephone or video platform communications must display professional salutations, preliminary/constant courtesies, and clear content until conclusion. When this frames site communications, almost any challenge can be overcome as the relationship developed from a place of mutual respect.

For example, if a CRA is assuming site management from another CRA, the most professional move would be for the CRA to call the investigational site to make the initial introduction. This may seem old fashioned when e-mail is more efficient; however, electronic communications are impersonal. Think about this—the investigational site personnel could be feeling out of the study loop as they had not had sponsor contact for a while, and an introductory call from their new CRA shows effort and helps build preliminary trust that may have been lacking from an absence of communication. Subsequent communication can be completed via electronic mediums, but the initial reach out should be personalized.

In terms of *transparency*, when it comes to following the protocol, investigational sites are only as good as the information they are provided. CRAs are duty-bound to provide sites with clear sponsor instructions, accurate protocol directions, and transparent study updates. This is accomplished when the CRA keeps abreast of important study information and provides their investigational site partners with timely and factual updates. This will prepare sites during data deadlines and when implementing corrective action, and will promote efficiency during future monitoring visits. The sites rely on CRAs to provide the answers they seek, and transparency in information will perpetuate this reliance.

Meanwhile, an attitude of *positivity* is a true morale booster in the most challenging of situations. This does not mean artifice, or adopting a manner that seems disingenuous; this means providing encouragement to site personnel who may seem to be overwhelmed.

Overcomplimenting and false flattery diminishes genuine praise for a job well done, and makes it more difficult to discriminate between the two. However, a sincere compliment inspires effort and the desire to go the extra mile for our colleagues. CRAs should try complimenting CRCs in front of their PIs or site directors. A CRA should ask the CRC his/her opinion on how to resolve an issue. A CRA should remain open minded and encourage creative problem solving with their sites by maintaining an environment where all voices are encouraged to “bring forth” and contribute. This will transform a checklist/directive mentality sometimes assumed when disseminating information into a spirit of collaboration with their sites.

When thinking about how to be effective with *follow-through*, remember that, first, we are our words, then we are our actions. The phrase, “we are only as good as our word,” was never so apropos as it is for sponsors/CROs managing/maintaining successful relationships with their investigational site partners. There is no question that CRA responsiveness promotes site action by providing critical support for a site’s ability to proceed in the face of multiple challenges and accomplish the tasks set before it. A lack of responsiveness shows a lack of care; it inhibits site progress, which may impact patient safety and data quality.

Whether providing an answer to a critical protocol eligibility question or providing a range of dates for an impending site visit, CRA follow-through delivers clarity and control for site partners, which are critical tools for building trust. Even if the CRA does not yet have the answer for the site, a status update can alleviate worry that comes with the unknown. Further, when sites sometimes rely on this information for their livelihood, it is the least they deserve.

### **When Personalities Collide**

Challenges are inevitable with interpersonal relationships. Individuals may be personally vested in an outcome which may elicit a stronger, more sensitive reaction. One individual may have caused or contributed to the underlying problem, while another may be experiencing illness or external stressors unrelated to work but affecting behavior on the job. No matter the situation, we must remain professional, even if everyone around us is not. That is the impression most remembered and is a strong negotiating tactic for resolving issues.

For example, I had a colleague who was assigned as a CRA at a large academic site, and the research manager was notoriously difficult. She would raise her voice to monitors and disagree with every directive. At first, my friend took everything personally, and alternated between frustration and anxiety after each monitoring visit. After a particularly challenging day, my friend was in the monitoring area stewing over recent events, when a contract CRA who had worked at the site for years gave her some sage advice.

“Stop taking the situation personally, for you will never get anywhere that way,” the contract CRA said. “You must be the bigger person, take your ego out of the equation, and stop trying to win every argument. Instead, be kind and compromise as much as you can. Uphold the protocol

and patient safety, and report your observations factually. Offer solutions and always listen, even when you don't agree with the opinion. That is all you can do.”

These simple measures enabled my colleague to deal more effectively with the research manager. She was able to control emotional reactions by a subtle shift in perception. This was not about being right or winning, but about ensuring study success for the site. She was able to better manage her expectations with the research manager by demonstrating extra patience, kindness, and compromise as previously recommended. This eliminated the “emotional” element and preserved the professional aspect of the salvaged relationship.

## Conclusion

Trust is built with intention, focus, and consistent action. Trust is the cornerstone of a successful sponsor-site partnership—one that flourishes when the traits discussed earlier are demonstrated.



**Elizabeth Weeks-Rowe, LVN, CCRA**, has broad experience as a clinical research consultant, trainer, site evaluation and selection expert, content creator, and conference presenter. She is the author of *The CRA's Guide to Monitoring Research*. Based in California, she last wrote for *Clinical Researcher* in June 2023 about “[CRA Soft Skills for Pre-Study Evaluation Visits](#).”

RESOURCES & REVIEWS

**Lessons Learned from Challenging Cases in Clinical Research Ethics**

Lindsay McNair, MD, MPH, MSB



[A review of [\*Challenging Cases in Clinical Research Ethics\*](#). 2024. Wilfond BS, Johnson L-M, Duenas DM, Taylor HA (editors). CRC Press (Boca Raton, Fla.)]

*Challenging Cases in Clinical Research Ethics* may not be a book you take to the beach for a light read, but if you have a role, or an interest, in how we analyze the complex ethical challenges that are an integral part of conducting clinical research, it may be a good book for you. This is a reference book, a teaching tool, and, in some ways, a historical record.

While healthcare institutions have long had ethics committees or even trained clinical ethicists to provide consultation to staff and families during difficult situations in clinical care settings, the specialized practice of clinical research ethics consultation is much more recent. As described in the foreword of the book, the development of this kind of resource was spurred by the National Institutes of Health’s (NIH’s) Clinical and Translational Science Awards (CTSA) program, a funding mechanism which supports a network of almost 60 medical institutions across the United States to facilitate collaboration that expedites the design and dissemination of new medical advances. Since a requirement of the funding program is that the institutions must have ethical support services, the CTSA-funded institutions created ethics consultation services that focused on the research ethics issues likely to arise from the CTSA-funded work.

In 2014, the leaders of the clinical research consultation services across the organizations formed a group to share information and best practices, called the Clinical Research Ethics Consultation Collaborative (CRECC). The CRECC continues to be an active group, and membership is open to anyone who is in a role related to clinical research ethics practice, including representatives not just from the CTSA-funded institutions, but also from biopharmaceutical companies and independent contributors.

This book arose from the work of the CRECC. The cases discussed in the book are real situations at research institutions across the U.S. for which the persons involved sought advice from their local consultation services, and the consultants brought the case to CRECC for discussion. The editors make a point of saying that by the time of the finished case discussion, each case involved 30 to 50 consultants, and they recognize almost 170 contributors to the book, including most of the best-known and most well-respected research bioethicists.

Each year, the *American Journal of Bioethics* has published up to four of these case presentations, along with two to four commentaries on the case from different ethicists to provide a variety of approaches, perspectives, and opinions. These cases and the accompanying commentaries comprise this book.

The editors have organized the book around the ethical principles for research ethics that were described in a seminar paper by Emanuel, Wendler, and Grady in 2000, resulting in five main sections focused on collaborative partnerships, respect for participants, fair participant selection, favorable risk-benefit ratio, and informed consent. Because they also recognize that there were many possible ways to organize the material and that someone looking for discussion of a specific topic may want to be able to search in more detail, the book includes three separate appendices; one that lists cases by primary and secondary ethical principles involved, one that lists cases by topic keywords (e.g., pediatrics, Phase I trials, social media), and one that lists cases by values relevant to the discussion (social value, equity, and trustworthiness), as well as a standard index which lists topics, people, policies, and keywords and the pages on which the terms appear or are discussed.



In each section, an editor presents a brief description of the unifying theme of that section, and then short summaries of each of the five to eight cases under that theme. The section then delves into each case in more detail with an introduction that includes any necessary background context (disease details, standard of care framing, existing policy), a case description (often just a page or two), references, and then one to four commentaries.

The commentaries, each by different authors, approach different considerations or aspects of the case, together providing a variety of opinions and a well-rounded discussion. For example, there is a case focused on a request from a study team to unblind a participant's treatment assignment after an adverse event (to help determine relationship to study drug and whether other participants were also at risk, or whether the event was a symptom of the underlying condition). The commentaries are presented by two ethicists from a sponsor company discussing the ethical issues of unblinding and the impact on study data; an ethicist from the NIH discussing considerations of a data monitoring committee in making decisions that will impact studies; and an ethicist involved in health monitoring programs for chronic illness who discusses issues of community trust and communication. The editors and commentators are careful to focus on the relevant ethical issues and conflicts, and not on operational or regulatory requirements, although they do address those considerations.

Although the cases all stem from situations that developed at research institutions, almost all of the content is relevant to other audiences in the clinical research ecosystem, including situations encountered in biopharmaceutical-sponsored studies that industry leaders have to think about. For example, there are cases that discuss ethical implications of advertising for research participants on social media, whether compensation for participation can (or should) be withheld from a participant who was intentionally deceptive to get enrolled in the study, how extensive the "alternative options" presented in a consent form should be, and whether a patient with advanced cancer must exhaust all possible treatment options before being allowed to enroll in a Phase I study of a new immunotherapy.

There are a number of ways that teachers, trainers, and leaders could use the content of this book both for education, and as the basis for case-based discussions. Overall, I would recommend this book as a resource for anyone in a training or leadership role, both for personal education and as a useful tool for developing training content that will likely prompt thoughtful discussion.

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**Lindsay McNair, MD, MPH, MSB**, is a physician, research ethicist, and Founder and Principal Consultant of Equipoise Consulting LLC, which provides consulting for projects related to the scientific and ethical conduct of research studies and drug development programs. She joined the Clinical Research Ethics Collaboration Collective, from which the authors of the reviewed book drew their case discussions, in 2023, when the book was already in the process of publication.

RECRUITMENT & RETENTION

**Enhancing Participation in Digital Therapeutics Clinical Trials with a Decentralized Model**

Anthony Brogno



Since 2021, there has been an increase among the general public in willingness to participate in clinical research studies. However, participants want the trials to be more convenient, closer to home, and more accommodating of their schedules.

Those are among the findings of the [2023 Perceptions & Insights Study](#) from the [Center for Information and Study on Clinical Research Participation \(CISCRP\)](#), which surveys clinical trial participants every two years to collect information on individual experiences during participation.

These findings are instructive for digital health companies and contract research organizations (CROs) which, by and large, are still modelling clinical trials for digital therapeutics (DTx) on those used for pharmaceutical and biotech studies. Switching to a decentralized clinical trial (DCT) model will encourage greater participation and result in more participants completing the trial. While DCTs can be used for many studies, they are particularly suited for DTx products since they are widely regarded as presenting low risk to participants, and such trials can operate under a less strict regulatory framework and be designed with a more patient-centric approach.

## **Background**

The pandemic proved that many more work- and health-related activities can be accomplished remotely more conveniently than we once thought possible, including accessing healthcare. People now guard their time more carefully, with staying at home often the preferred option for work, doctor appointments, shopping, entertainment, and more.

Bearing this out, the 2023 CISCRP survey of more than 4,500 individuals globally who have participated in a clinical study found that traveling to the clinic for procedures was the greatest burden for participation. Among those who quit trials before they were completed, the location of the study site was the second-most cited reason. Asked what would have encouraged them to complete their trials, 32% of respondents replied, “more virtual visits.”

## **Healthcare as a Commodity**

None of this should come as a surprise to those who have noticed the growing trend toward the consumerization of healthcare. After decades of working around providers’ policies and schedules, patients are asserting themselves as consumers, treating healthcare like a commodity and prioritizing convenience above all. While trial participants are perhaps more magnanimous than the average patient, they, too, value their time and convenience.

Modern CROs have taken note of this and now offer hybrid or [fully remote \(decentralized\)](#) site capabilities for DTx sponsors to create real-world settings in which patients can carry out study activities. Much of the data collected from DTx technologies involve satisfaction measures such as emotional affect, user experience, and quality of life variables that can easily be captured without traveling to a brick-and-mortar facility. CROs are also using networks of travel nurses and study staff to perform physical assessments and collect bodily samples from participants’ homes to mitigate the need for in-clinic study visits.

Most clinical research participants today are also discovering opportunities to be in clinical trials online. CISCRP’s study reports that, of the individuals who learned about their studies online, 46% were made aware through social media channels and 26% through web advertising. DTx

sponsors can ensure they are implementing a well-rounded digital marketing strategy by using a CRO that is experienced in acting as a DCT site to accelerate recruitment.

This model enables DTx sponsors to screen potential participants and allow them to participate in their trial regardless of geographic location, ultimately producing a more diverse patient population. These CROs are set up to attract the right participants through in-house clinical operations and marketing teams that screen for DTx patients who meet study inclusion/exclusion criteria and that run multi-channel recruitment campaigns.

Lastly, 86% of participants in the CISCRP survey reported they felt appreciated for their involvement in clinical studies. Even in virtual DTx trials, CROs in this space maintain excellent rapport with trial participants. Decentralized sites, although fully remote, are staffed with knowledgeable clinical research coordinators who act as the first point of contact for anything trial-related, from technical questions about the DTx technology being used to more pressing health concerns. At the end of the day, a trial is nothing without patients who are willing to participate and contribute.

## **Conclusion**

Decentralized trials create an overall better experience for both sponsors and patients. Due to the nature of digital therapeutics technologies and their journey to market, there's no reason most DTx sponsors can't execute fully decentralized trials. When people have the autonomy to complete study activities and manage their healthcare in a real-world setting, they are happier and less likely to drop out before completion.

It's time for DTx trial sponsors and CROs to modernize their operations and design trials to be as convenient as possible for participants.



**Anthony Brogno** is Director of Clinical Operations at [Lindus Health](#).

## **Discovering Diversity: Why Puerto Rico Stands Out for Clinical Trials**

Amarilys Silva-Boschetti, PharmD



Clinical research is the cornerstone of medical progress, propelling innovations that transform healthcare landscapes. However, the imperative for inclusivity and diversity in clinical trials has only gained prominence in recent years. In this context, the Puerto Rico Consortium for Clinical Investigation (PRCCI) emerges as a beacon of progress, providing a unique and advantageous platform for researchers and sponsors seeking to enhance diversity in their studies.

Nestled in the heart of Puerto Rico, a vibrant U.S. territory with a cultural tapestry reflecting Hispanic, African, and Indigenous influences, PRCCI stands at the intersection of rich diversity and cutting-edge biomedical research. The organization has evolved over time, having transitioned from its roots as a consortium to establishing its own Clinical Research Center. This strategic expansion equips PRCCI with the capability to conduct independent trials, a particularly pertinent development given the U.S. Food and Drug Administration’s (FDA’s) endorsement and encouragement for organizations to initiate and conduct diverse clinical trials.

In April 2022, the regulatory agency released preliminary guidance titled “Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials,” referred to as the Diversity Plan. The recommendation calls for sponsors to include a “Race and Ethnicity Diversity Plan” when submitting applications for investigational new drugs, biologics licenses, or investigational device exemptions.

Puerto Rico’s unique blend of cultures provides fertile ground for understanding how different populations respond to medical interventions. By conducting clinical trials in this environment, researchers gain access to a more nuanced understanding of how cultural factors may impact

treatment outcomes. This cultural diversity extends beyond ethnicity, encompassing language, traditions, and healthcare beliefs, enriching the data and insights generated from clinical studies.

Additionally, thanks to its rich bioscience legacy of more than 65 years, the island stands out as an optimal partner for pharmaceutical and medical device companies seeking to conduct clinical trials. Renowned as the “Medicine Cabinet of the USA,” the island has played a pivotal role in the pharmaceutical industry, contributing more than \$60 billion in manufacturing, creating more than 18,000 jobs, and accounting for approximately half of the country’s total exports.

Furthermore, the island boasts a highly skilled labor force, with a strong emphasis on STEM education in both public and private academic institutions, producing more than 25,000 STEM graduates annually. Notably, the University of Puerto Rico Mayagüez campus serves as a top talent pool, with NASA consistently selecting more engineers from this campus than any other college in the United States.

PRCCI boasts a team of seasoned and skilled staff members and operates within the regulatory framework established by the FDA. As a U.S. territory, Puerto Rico adheres to the same rigorous regulatory standards, ensuring that clinical trials conducted at PRCCI meet the highest levels of quality and ethical practices. This regulatory alignment provides sponsors and researchers with confidence that their studies are conducted in a compliant and reputable environment.

In essence, Puerto Rico invites you to see beyond its tourist allure—it’s not merely a destination but a dynamic workplace, especially poised to revolutionize the landscape of inclusive clinical trials. With its customs-free operations, bilingual population, and scientific know-how, it stands as a paradise for researchers and sponsors seeking diversity in their trials.



**Amarilys Silva-Boschetti, PharmD**, is Executive Director of the Puerto Rico Consortium for Clinical Investigation, a subsidiary of the Puerto Rico Science, Technology & Research Trust, and has held diverse roles in research, medical affairs, global product safety/pharmacovigilance, and regulatory affairs.



## **In Case You Missed it, You Haven't Missed (Most of) it Yet...**

Curated by Gary W. Cramer, Managing Editor for ACRP



What you probably *haven't* missed, if you've been paying any attention at all to the ACRP website, publications, e-mails, and social feeds lately, is the fact that the [ACRP 2024 gathering in Anaheim, Calif.](#), is racing your way with all the speed of a learning, networking, and resource-gathering juggernaut. There's a multitude of upcoming sessions, Signature Series discussions, workshops, exhibitors, sponsors, and ceremonies to brag about, and we're trying to spotlight them all in one way or another

before the event itself arrives, but there just aren't enough days left on the calendar between now and then. So here are a few sessions you may not have heard about yet that will be happening at the conference, plus some recent announcements you might have missed in all the excitement.

### **Let's GO! (to ACRP 2024)**

Are you hoping to make the most out of attending your first ACRP conference but feeling a little anxious about the “sit down next to someone you don't know and introduce yourself” ritual of such big gatherings? Take heart—if you drum up some courage and [listen to the wisdom of those who have gone before you](#), you will find yourself looking back on your time at ACRP 2024 with the pride of accomplishment that comes from putting your best foot forward, getting in the game, and making great professional strides in your clinical research career. A key opportunity for networking will come on Friday afternoon at the conference, when the [First Time Attendee Get-Together](#) is held. Anyone interested in attending this informal session is requested to RSVP by April 25.





When Monday rolls around on the conference calendar, look on the schedule for the one hour when a collection of five-minute [Rapid-Fire and Poster Sessions](#) will offer a change of pace from the many longer educational presentations on tap. Among the posters to be presented is one from Paula Smailes, DNP, RN, CCRP, on “Evolving Training for and Satisfaction with Electronic Medical Record [EMR]

Systems,” showcasing how one academic medical center made the switch from instructor-led training to eLearning for training approximately 300 clinical researchers per year on the functionality of the institution’s EMR system for clinical research fundamentals, documentation, billing, and scheduling.

Smailes will also present a poster on “Interpreting and Capitalizing on Research Participant Satisfaction Surveys” with Lisa Hafer, Deanna Golden-Kreutz, PhD, Holly Bookless, BSN, RN, NE-BC, and Emily Brown. The team members will discuss a clinical research center’s use of surveys housed within REDCap to solicit feedback from participants as a quality improvement initiative to better the research services offered by the center, as well as to collect their motivating factors to participate in clinical research, demographics, perceptions on the informed consent process, and feedback on questions pertaining to the research experience.

Rapid-fire topics scheduled for Monday at the conference include “Mind the Gap: Achieving and Maintaining Effective Communication Between Sites and Sponsors” by Morgan Heck; “Tools and Measurements for Driving Diversity in Clinical Trials” by Cameron Davis; and “What We Can Learn from Minority Experiences in Clinical Trials” by Heidi Green, PhD.



A regular-length session that you may not have heard about for Monday focuses on “[Are Hybrid Trials the Answer to Aligning Decentralized Methods with Diversity Goals?](#)” Nadina Jose, MD, will examine how the message that seems to surface from recent U.S. Food and Drug Administration draft guidances is that the agency wants the biopharmaceutical industry and its stakeholders to be more focused and

targeted with their approach of lessening the gaps in the overall composition of patients invited to participate in clinical trials and with their conduct of trials through the adoption of improved methodologies. The best obvious place to start would be to get these parties to design protocols that not only reflect diversity but also include the appropriate use of decentralized clinical trial methods, which can affect data collection and quality, trial speed and efficiency, and site costs, Jose notes.

Another full-length session to be aware of on Monday is “[Integrating Clinical Research into a Community-Based Practice](#),” which comes from Ashley Moultrie, CCRP, and Charlotte Grayson-Mathis, MD, who ask, “What if we could bring clinical trial opportunities right to where potential participants get their annual physical, their flu vaccine, and the majority of their care?” They will discuss the challenges and how they overcame them to build a successful research partnership in a community-based primary care practice.

Already have an idea for a presentation you’d like to give at ACRP 2025 in New Orleans? We [start accepting proposals on May 3](#) of this year! You should submit your proposal(s) by June 17. You don’t have to be an ACRP member to participate, but you must create a free user account with us to use the proposal system if you don’t already have one.

### **Celebrating Clinical Trials Day 2024**

You know what also comes our way in May? Why, Clinical Trials Day on May 20, of course. The message we’re sharing through Clinical Trials Day 2024 is that, as clinical researchers, we celebrate YOU! YOU are the ones who interpret and apply the guidelines that keep studies viable and on track. YOU play a vital role in protecting patients. YOU see challenges as new opportunities for discovery. YOU bring unique perspectives and expertise to blaze new trails that lead to new possibilities—and new reasons for hope. YOU Are the Trailblazers Among Us!

[Learn More About CTD2024 >](#)

### **Seeking Volunteers for Educational Programs**

ACRP is looking for professionals to serve in the new Educational Programs Ambassador initiative. Among other contributions, Ambassadors will serve in working groups to contribute to

new ACRP educational programs, provide comments on regulatory guidance, and review existing resources for needed updates. ACRP members and non-members are welcome to apply.

[Learn More >](#)

### **In Memoriam**

[Laurie Halloran, BSN, MS, passed away](#) on February 29. She was a former member of ACRP, a frequent attendee and speaker at our conferences, and holder of a Certified Clinical Research Associate (CCRA®) designation through ACRP from 1995 to 2015. She founded Halloran Consulting Group in 1998 and led it for 25 years before stepping down.

### **Got Fraud?**

In connection with [a recent ACRP blog](#) on how to spot and deal with applicants and new hires who turn out not to have the clinical research expertise they claim, we conducted a simple poll on LinkedIn asking, “Have fraudulent claims in resumes and applications found after hiring resulted in serious consequences in your clinical research organization?” Out of the 87 respondents, 48% said YES, this has happened; 44% said NO, luckily not; and 8% said OTHER, though they did not provide details. Something to think about, anyway!





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