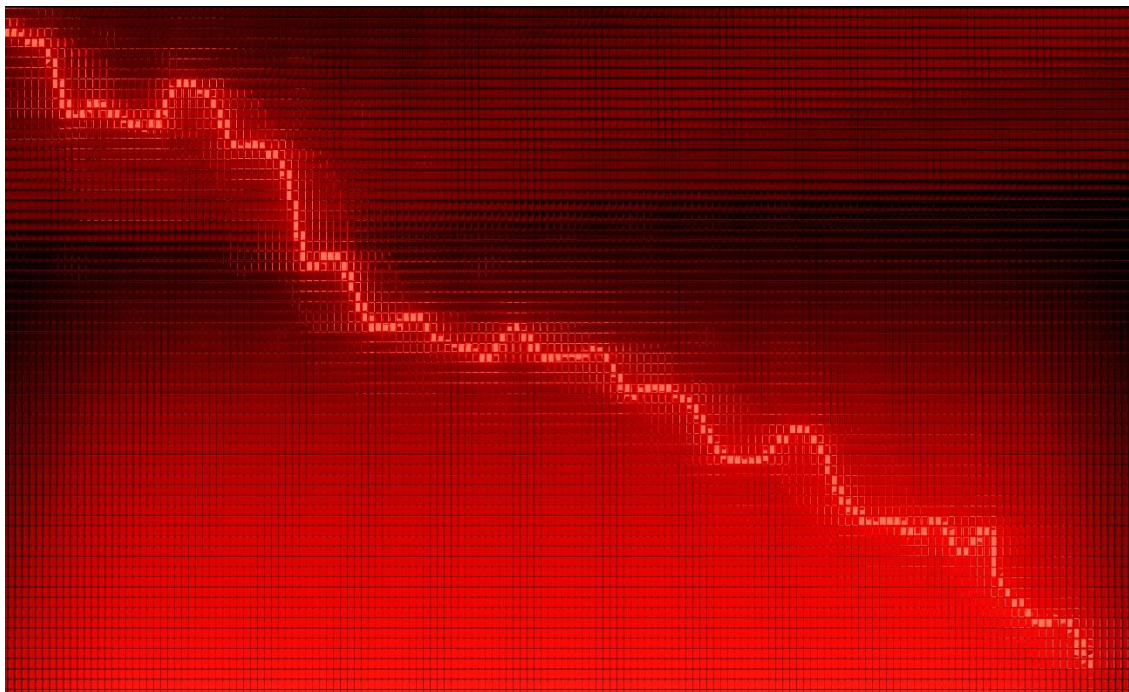




Clinical Researcher™

The Authority in Ethical, Responsible Clinical Research

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Taking Aim at Adverse Events

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Clinical Researcher™

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EXECUTIVE DIRECTOR'S MESSAGE

Applauding the Clinical Research Workforce

Jim Kremidas



Clinical research is a valuable profession, and it deserves to be treated as such. Whether the members of its workforce are saving lives, alleviating suffering, or helping people live healthier, more active lives, it is difficult to think of a more important calling.

Your Association is committed to advancing standards, certifications, and best practices to further professionalize the clinical research workforce. We announced several progressive initiatives last year, and we've got many more on tap in 2019. Watch this space for regular updates.

I'd like to take this opportunity to focus on one initiative that I'm particularly excited about.

Earlier this year, [we announced the finalists](#) for the second annual ACRP Innovation in Workforce Development Award. In April, we'll recognize industry-leading organizational commitments to innovation in clinical research workforce development during the [ACRP 2019](#) annual conference in Nashville, Tenn.

Representatives from each organization will present their workforce development initiatives during the conference to a panel of expert judges, who will determine the award recipient. Finalists will also [present their innovative workforce development ideas in a special session](#) Monday, April 15, during ACRP 2019.

ACRP's Workforce Innovation Award is the only such program in clinical research to recognize an organization exemplifying the spirit of creativity and innovation through adaptation,

improvement, or development of new processes or tools that result in improvement in workforce development quality.

Throughout the conference and during the [ACRP Awards & Recognition Ceremony](#), we will also recognize recipients of the following awards:

- Outstanding Leadership by a Clinical Research Coordinator
- Outstanding Leadership by a Project Manager
- Outstanding Leadership by a Principal Investigator
- Advancing Public Awareness
- ACRP-Avoca CRO Quality Award (as selected by research sites)
- ACRP-Avoca Sponsor Quality Award (as selected by research sites)

Clinical research professionals are driven more by a desire to give back than they are for glory or hearing applause. Still, at ACRP we believe it is important to recognize those professionals and their organizations who are leading the way. Not only are they to be encouraged, but it's our fervent hope they will serve to inspire others as we work together to deliver the best possible trials to patients.

I hope to see you in Nashville in April.

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

CHAIR'S MESSAGE

Off to the Races

John P. Neal, CRCP



We've had a strong start out of the gate for 2019, and the year ahead looks good for ACRP. In January, we held the year's first ACRP Association Board of Trustees (ABoT) meeting at ACRP headquarters in Alexandria, Va. After recapping some of the accomplishments of 2018 ([see my message](#) in the January issue of *Clinical Researcher*), we spent time examining how to make the most of them in 2019 and beyond.

For example, it was exciting to see energy, enthusiasm, and consensus continuing to coalesce around our plans for building on our newest, highly successful certification (the [ACRP Certified Professional](#) [ACRP-CP] program introduced in 2017) and our new subspecialty designation (the [ACRP-PM](#) introduced in 2018 for project managers). We are also developing a variety of innovative professional development programs and training opportunities to help our members remain up to date with the changes we are experiencing as an industry.

The ABoT is [a strong group of gifted professionals](#), and I'd like to thank each of them for sharing their time and expertise as ACRP works to raise the bar for conducting ethical, responsible clinical research around the world.

Just as the highlight of this year will be the [ACRP 2019 annual meeting](#) in Nashville, Tenn., we are already preparing for ACRP 2020 in Seattle, Wash. The conference expands each year, with new tracks and new voices. It will continue to provide you, our valuable members, with unparalleled opportunities to hone your knowledge, network with your peers, and make new friends.

I hope to see you in Nashville!

John P. Neal, CRCP, is Founder and Chairman of PCRS Network, LLC, and the 2019 Chair of the Association Board of Trustees for ACRP.

PEER REVIEWED

Assessing the Impact of Online GCP Training on CRC Perceptions of Adverse Events

Linda S. Behar-Horenstein, PhD; Lissette Tolentino; Huan Kuang; Wajeeh Bajwa, PhD; H. Robert Kolb, RN, MS, CCRC



In response to the growing complexities of clinical research as it converges with new technologies and regulatory intricacies, the International Council for Harmonization (ICH) published the Integrated Addendum to its Guidelines for Good Clinical Practice (GCP) in 2016.^{1} This amended guideline was intended to address the impacts of the online era on study conduct, while preserving the elements of human subject protection and data integrity.

The ICH GCP E6(R2) addendum offers a unified international standard providing reassurance that “the rights, safety, and well-being of trial subjects are protected.”^{1} Key components of these GCP guidelines and protections emphasize the investigator’s trial-related responsibilities and, within this context, includes the reporting of adverse events (AEs).

Many institutions, such as those with study sites participating in the U.S. National Institutes of Health (NIH) Clinical and Translational Science Awards (CTSA) program, rely on standardized online GCP training systems that are provided by the Collaborative Institutional Training Initiative program (CITI) and the Association of Clinical Research Professionals (ACRP). The CITI and ACRP platforms are two of the dominant online platforms designed to equip learners with GCP core concepts.

GCP training is also part of a growing movement toward establishing a set of core competencies from which to build standardized didactic curriculum.^{2} These core competencies have been vetted by investigators with the CTSA hubs in the Enhancing Clinical Research Professionals' Training and Qualification (ECRPTQ) project, and subsequently have been accepted by the NIH's National Center for Advancing Translational Science (NCATS).^{3}

ECRPTQ has two central goals; one has been to implement a standardized training process for professionals involved in CTSA clinical research. The second goal has been to advocate for a collaborative approach leading to the development of consistent training and qualification strategies to generate additional best GCP practices across academic institutions.^{3} As a result of this work, the NIH mandated that all of its funded investigators and clinical trials research staff be trained in GCP.

Learning About Learning

Little is known about the effectiveness of the dominant CITI and ACRP GCP online learning platforms, or how they impact core GCP competency. Whether clinical research coordinator (CRC) interactions with their principal investigators (PIs) on reporting AEs is better facilitated through online teaching or structured work experience and mentoring has not been shown. For this study, "online learning" refers to module-driven training sessions absent real-time interaction.

Eight research questions were analyzed in this study to determine the efficacy of online training in influencing CRC perceptions of, and their actions toward, handling AEs. The research questions are as follows:

1. What is the relationship between the frequency of CRC reporting AEs to PIs when compared by (a) coordinator primary responsibility, (b) training background, and (c) length of time involved in clinical research? Hereafter referred to as: **Observing AE to PI by Demographics.**
2. What is the relationship between bringing AEs to the PI's attention (Yes/No) when compared by (a) coordinator primary responsibility, (b) training background, and (c)

- length of time involved in clinical research? Hereafter referred to as: **Bringing AE to PI Attention by Demographics.**
3. What is the relationship between discussing the AE with the PI (1) verbally, (2) via e-mail, or (3) through both methods when compared by (a) coordinator primary responsibility, (b) training background, and (c) length of time involved in clinical research? Hereafter referred to as: **Format of Discussing AE with PI by Demographics.**
 4. What is the relationship between PI's response/action to the CRC reports of AEs when compared by (a) coordinator primary responsibility, (b) training background, and (c) length of time involved in clinical research? Hereafter referred to as: **PI Response to AE by Demographics.**
 5. What is the relationship between whether the PI took CRC's observation seriously and made the appropriate changes when compared by (a) coordinator primary responsibility, (b) training background, and (c) length of time involved in clinical research? Hereafter referred to as: **PI Actionable Response to AE by Demographics.**
 6. What is the relationship between whether the PI simply acknowledged the CRC's concern, but did not act on it when compared by (a) coordinator primary responsibility, (b) training background, and (c) length of time involved in clinical research? Hereafter referred to as: **PI Non-Actionable Response to AE by Demographics.**
 7. What is the relationship between the PI rejecting CRC observation of the AE when compared by (a) coordinator primary responsibility, (b) training background, and (c) length of time involved in clinical research? Hereafter referred to as: **PI Rejection to AE by Demographics.**
 8. What is the relationship between how CRCs would handle a situation where an AE was observed, but the PI did not take any action when compared by (a) coordinator primary responsibility, (b) training background, and (c) length of time involved in clinical research? Hereafter referred to as: **CRC Future Response to PI's Rejection to AE by Demographics.**

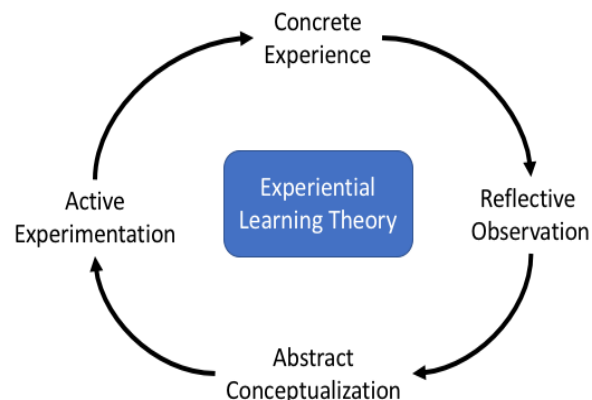
Experiential Learning Theory

This study is grounded in the Experiential Learning Theory, {4} which posits that knowledge and skill acquisition depends on a cycle of experiential learning (see Figure 1). Its underlying premise is that learning evolves via four types of engagement:

- 1) **Experiential** (i.e., concrete experience), whereby CRCs gather information from the world (e.g., observations of inappropriate methods of informed consent);
- 2) **Reflective** (i.e., reflective observation), whereby CRCs take time to think, process, organize, and relate inputs to other known factors that surround that experience (e.g., determining whether risk to the participant was great or immediate);
- 3) **Abstract** (i.e., abstract conceptualization), whereby CRCs create new meanings from developing unique ways of looking at existing information (e.g., how recording data incorrectly can jeopardize study integrity); and
- 4) **Action** (i.e., active experimentation), whereby CRCs actively test a hypothesis (e.g., responding to ethical misconduct, “I can test my emergent hypothesis that reporting it to an anonymous source leads to appropriate resolution”).

The ELT promotes reflective conversation (or executive consciousness) that helps to enable learners to shape responses to the goals of the project (e.g., creating a conversational space for members to reflect on their experiences). {5,6} ELT stimulates sharing functional leadership, {7} whereby personal needs are replaced by shared roles necessary for meeting project goals. Kolb showed that training groups or teams are cultivated by sharing experiences and reflecting on the meaning of those experiences together. {8}

Figure 1: Experiential Learning Theory (ELT) Cycle{8}



Methods

Participants completed one GCP online training program developed by CITI and another one developed by ACRP.

The CITI GCP training includes basic courses tailored to the different types of clinical research. {9} Refresher courses are also offered for retraining and advanced learning. The CITI program offers several GCP courses that satisfy the 2016 NIH policy. {10}

ICH GCP E6 Investigator Site Training courses from CITI also meet the minimum criteria for ICH GCP Investigator Site Personnel Training identified by TransCelerate BioPharma, Inc to enable mutual recognition of GCP training among trial sponsors. These courses, written and peer-reviewed by experts, have been updated to include ICH E6(R2) standards. {1,11}

Suggested audiences for the CITI GCP courses include IRB members, PIs, CRCs, research nurses, clinical research organization (CRO) staff, and other key study personnel based at study sites and sponsors. {9}

The ACRP GCP course is for all clinical research professionals. {12} This course is preparatory for those engaging in clinical research and a good review for seasoned professionals. It addresses

the globally accepted standard for conducting ethical and scientifically sound research, and for ensuring the use of universal language related to the conduct of clinical research.

The interactive ACRP online course incorporates real-world scenarios that the learner is likely to encounter during a clinical trial. This training also meets the minimum criteria for ICH GCP Investigator Site Personnel Training as identified by TransCelerate BioPharma, Inc. {11}

Learning objectives of the ACRP course are {12}:

1. List the key drivers that led to the formation of the ICH and its focus on GCP.
2. Explain the key considerations to be made with regard to GCP during a clinical trial.
3. Describe the roles and responsibilities of a sponsor, an investigator, and the IRB or institutional ethics committee.
4. Explain the AE reporting requirements for both the sponsor and the investigator.
5. List the core requirements for securing informed consent from study participants.
6. Describe the importance of protocol compliance and clear documentation in the clinical trial process.
7. Define the purpose of various documents and templates that members use in clinical trials.

Each of these training modules are based on the ICH Harmonized Tripartite Guideline – Clinical Safety Data Management: Definitions and Standards for Expedited Reporting and International Council for Harmonization (ICH) Harmonized Guideline: Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2), and they address E8, which includes safety reporting. More specifically, the training modules address Classifying Adverse Events, Investigator Reporting Requirements, Monitoring/Reporting Requirements for Sponsors, and Differences in Reporting AEs to Sponsors/IRBs.

“The objectives of reporting AEs are to identify new risk information as early as possible and to develop a profile of the drug. Investigators must immediately report [serious AEs], and sponsors must have processes in place to evaluate the events. Once new risk information is identified,

sponsors are required to report the information to regulators and stakeholders, and changes to the trial should be implemented, when appropriate, to reduce the risks associated with the trial.”{9}

Following the receipt of IRB approval, study participants were recruited by sending e-mails to the research community’s listservs and by placing posters on campus. The participant selection criteria were designated as people involved in human subject research at a large, CTSA-designated public university in the Southeastern United States, without differentiation for gender and race.

Volunteers (n=132) at any level indicated a willingness to take part in the training programs. Of those, 95 participated (72%) by completing the training program online as well as the pre- and post-survey in Research Electronic Data Capture (REDCap), a secure, web-based application designed to support the traditional case report form data capture. After finishing the training program and the pre- and post-surveys, the participants were contacted via e-mail six months later for a follow-up. Forty participants who finished the six-month follow-up survey constitute the dataset; the response rate was 42.1%.

The data did not meet the assumption of normality for parametric testing. Thus, the Wilcoxon Signed Rank and McNemar tests were conducted to determine if there were pre- and six-month follow-up test differences in the frequency of CRC reporting AEs, the actions taken by the PIs, and how CRCs would handle reporting AEs differently in the future. The Wilcoxon Signed Rank test was used to determine if there were any significant rank differences among pre- and six-month follow-up test for questions, “Reporting AE to PI by Demographics,” “Format of Discussing AE with PI by Demographics,” “PI Non-Actionable Response to AE by Demographics,” and “PI Rejection to AE by Demographics.”

Given their dichotomous response pattern, McNemar tests were used for questions “Reporting AE to PI by Demographics” and “PI Actionable Response to AE by Demographics.” A nonparametric bivariate Spearman correlation was used to analyze change scores from the pre- and the six-month follow-up by demographic variables. Mann-Whitney tests were conducted to compare any differences among the six-month follow-up scores when compared by the CRC’s primary responsibility, training background, and length of time involved in clinical research.

Effect sizes were also calculated for the Mann-Whitney tests using the formula from Figure 2, as cited from Fritz, Morris, and Richler. {13}

Figure 2: Effect Size Formula

$$r = \frac{z}{\sqrt{N}}$$

For purposes of data analyses, the “Coordinator Responsibility” variable was collapsed into two groups, where Group 1 consisted of those who self-identified as “Coordinator/Investigator/Other.” Group 2 consisted of those who self-identified as “Regulatory Coordinator/Research Compliance.” The “Other” label refers to those who did not fall into any of the other coordinator responsibility options.

Sample questions that participants were asked included “How would you handle a situation where you observe a serious deviation, but the PI does not take any action?” Text responses were analyzed and categorized by two groups: Non-PI Supervisor (including personnel in nursing or clinical team leader) and Institutional (including the IRB and the university’s Clinical Translational Science Institute (CTSI)). Content analysis and frequency counts were reported for each category.

Results

Of the participants in this study, 72.5% were self-identified as “Investigator/Research Coordinator/Other” group, whereas the “Regulatory Coordinator/Research Compliance” group consisted of 25%. The remaining non-respondent (2.5%) was denoted as missing. Most respondents (72.5%) had 0–9 years of research experience, while 27.5% of respondents reported having 10 or more years of research experience. Of the respondents, 40% hold a bachelor’s degree or below, 45% had a master’s degree or above, while 15% did not respond to this question.

Before and After Training Changes

There were no statistically significant differences seen in CRC reporting AEs, actions taken by the PIs, and how CRCs would handle reporting of AEs differently in the future from the pre-test versus six months after the training. Additionally, there were no statistically significant relationships between the demographic variables and how the deviations were discussed.

Training Performance by Demographics

There was a statistically significant difference ($U=90.00$, $Z=-2.25$, $p=.024$) on the six-month follow-up test scores related to “Bringing AE to PI Attention by Demographics.” The “Investigator/Research Coordinator/Other” group had a higher mean rank (21.29) than the “Regulatory Coordinator/Research Compliance” group (14.50). According to Cohen’s guidelines, the difference indicates a medium effect size ($r=-.36$).^{ 13 } The results indicate that the “Investigator/Research Coordinator/Other” group reported AEs to the PI’s attention more frequently than the “Regulatory Coordinator/Research Compliance” groups.

Second, there was a statistically significant difference ($U=71.00$, $Z=-2.51$, $p=.012$) on the six-month follow-up test scores for “Format of Discussing AE with PI by Demographics.” The “Regulatory Coordinator/Research Compliance” group had a higher mean rank (27.40) than the “Investigator/Research Coordinator/Other” group (17.45). A medium effect size difference between these groups was also observed ($r=-.40$). The “Regulatory Coordinator/Research Compliance” group reported discussing AEs with the PI verbally, by e-mail, or both more frequently than the “Coordinator/Investigator/Other” groups.

There were no significant differences in the six-month follow-up test scores related to the remaining research questions “Observing AE to PI by Demographics,” “PI Response to AE by Demographics,” “PI Actionable Response to AE by Demographics,” “PI Non-Actionable Response to AE by Demographics,” “PI Rejection to AE by Demographics,” or “CRC future response to PI’s rejection to AEs by Demographics.” Moreover, no significant difference was found in the six-month follow-up test when compared by training background and length of time involved in clinical research.

Regarding the open-ended questions, 40% to 52.5% of the sample responded. In the pre-test, 17 participants indicated that they would report to the PI and 21 mentioned that they would report to others. Representative pre-test comments among those who would report to their PI were:

- “I would try to approach the conversation from another angle to encourage the PI to understand the severity and how it could impact them and their studies.”
- “I would meet face to face with PI to make sure I understand their reasoning.”

Representative pre-test comments among those who would report to others were:

- “I would reach out to the compliance office at the [university].”
- “I would ... assess the risk to the participant. If I determined that the risk to the participant was great and/or immediate I would contact the IRB even through it would probably cost me my job.”

In the six-month follow-up test, the number of participants who indicated that they would report to the PI or to others was 16 and 21, respectively. Representative comments among those who would report to their PI were:

- “I would repeatedly bring it to his/her attention.”
- “I would personally explain to him/her again the seriousness and would also document in e-mail asking him/her for a response.”

Representative comments among those who would report to others were:

- “If action was not taken, I would report to the division Chief.”
- “I would let him/her know that I will be documenting and filing the response in regulatory binder so that sponsor can assess and discuss the situation with him/her if necessary. If still no action is taken, then I would notify the IRB.”

Discussion

Overall the findings showed that there were no significant differences in frequency of CRC reporting AEs, the actions taken by the PIs, and how CRCs would handle the reporting of the

AEs differently in the future. However, statistically significant differences on the six-month follow-up test scores by coordinator primary responsibility were observed:

1. The “Investigator/Research Coordinator/Other” group reported AEs to the PI’s attention more frequently than the “Regulatory Coordinator/Research Compliance” group.
2. The “Regulatory Coordinator/Research Compliance” group reported an increase in discussing AEs with the PI more often than the “Investigator/Research Coordinator/Other” group.

The differences in reporting by coordinator primary responsibility may represent the distinct roles that each CRC category plays in the process of clinical research. Members of the group bringing AEs to the PI’s attention more frequently have more direct participant contact, and are typically active in a clinic setting where events can take on the immediacy of need. Meanwhile, those involved in the administrative processes of regulatory and compliance activity are more likely removed from the direct experience of participant management. Given their regulatory role and that they likely do not work for the PI, they stand at a distance, and this might have resulted in their feeling *freer* to discuss AEs with the PI.

The results also show that the online training did not affect participants’ attitudes toward approaching PIs when faced with an AE. That is, the number of those who do not communicate with the PI is relatively the same for both pre-test and the six-month follow-up. Also, among those who do not report to the PI, the number of coordinators is greater than those who do speak with the PI about reporting an AE.

These findings suggest that training did not improve high-level, crucial communication. After observing an AE whereby the PI does not take any action, the number of participants who do not report to the PI remained fairly unchanged. Also, the number of coordinators who discuss reporting AEs with others, such as a non-PI supervisor or institutional personnel, was greater than those who report to the PI. However, overall the number of participants who indicated that they would discuss it with the PI versus others in the pre-test and the six-month follow-up remained relatively unchanged.

As defined by the ECRPTQ Communication Working Group, high-level communication skills entail being capable of crafting clear and effective communications through a variety of mechanisms (e.g., face-to-face, e-mail). This skill includes the ability to define constructive criticism and differentiate between positive or negative feedback, as well as criticism. {14} Communicating at this level requires the capacity to assess conflict in situations and the ability to implement constructive methods of resolution. All study-related correspondence to team members, regulatory officials, and sponsors must be clear, concise, and effective.

Repercussions

The lack of high-level communications skills and inadequate training can lead to poor data integrity and compromise research participant safety (e.g., AE reporting). As CTSA consortia move to implement unique versions of online environments to support standardized task-based training curriculums, there is a risk that online training platforms will miss the essential task of improving CRCs' vital responsibility in crucial communications and defeat the primary intentions.

The challenge of accurately assessing and evaluating online training and its capacity to promote competency remains. True competency is the ability to translate knowledge into effective action (i.e., report AEs) which is not easily measured by traditional multiple-choice questions proffered in online courses. Given the centrality of assessment in certifying instructional effectiveness, it is important that the evaluation of real-time, task-based learning includes metrics on both individual level learning and systems improvement, as well as a prospective assessment of its impact on the research enterprise at large.

Despite the emergence of a vetted core competency framework for the conduct of clinical research, the move to build online training platforms and populate them with competency content may miss the mark as long as we do not have a common rubric to evaluate all platforms and content. {2} As shown in this study, there remains a clear, unmet need for developing meaningful, standardized metrics and evaluations in the form of rubrics to assess individual training effectiveness and the utility of the various training platforms.

Online platforms can provide a substantial introduction to the clinical research environment and regulations. However, in and of themselves, these platforms are likely insufficient in inducing the crucial communications vital to safe study conduct. The study findings highlight the gap between knowing GCP and the natural, interpersonal interchange of experience—above and beyond the mere collection of cognitive competencies—which actualizes GCP.

Given the prevalence of online GCP training options and the NIH mandate, it is important to understand how CRCs learn and manifest GCP behavior. Previous findings highlight the fact that obtaining competencies cannot be solely achieved through online training, and that current training does not address the psychosocial and communication factors transcending regulatory understandings and conduct of GCP.{15}

A previous study showed participant preference for hybrid learning, which utilized classroom teaching in conjunction with online environments.{16} The interpersonal communication processes that a classroom learning environment fosters are simply not available in an asynchronous scenario. When it comes to promoting crucial communications with PIs on the imperative issue of AE reporting, online teaching simply appears insufficient.

High-level communication skills are essential for CRCs to efficiently report, and discuss AEs up the power gradient, to a PI; however, our findings suggest that online GCP training did not improve high-level awareness in this arena. These skills require a certain competence that comes from an integration of professional confidence with interpersonal values. These values are transmitted via forces of social presence and its impact on self-concept.{16} Social reinforcement plays a crucial role in conveying the values essential to responsible AE reporting.

In contrast to classroom settings, a lack of social presence and real-time interaction in online courses often leads to feelings of isolation and disconnectedness, thus diminishing opportunities for social reinforcement.{17} Sung and Mayer define online social presence as an experience of an individual's connectedness in a course.{18} Online social presence is the sense of others being present in the same experience that typically occurs via interpersonal interaction.{19} The integration of interpersonal values, which are essential to the role of a CRC, is transmitted via forces of social presence and its impact on self-concept.{20,21}

A sense of presence was largely absent in the online GCP training that we studied. These findings are consistent with a previous study in which CRCs articulated feelings of vulnerability to the PIs and expressed concerns around reporting AEs.{16} Addressing this vulnerability requires competency development that is defined by a professional attitude, knowledge, and skills necessary for a full realization of GCP advocacy of high-level communication skills. This level of skill attainment recognizes, respects, and solidifies the use of constructive methods of resolution.

Perhaps it is these values that elevate GCP competence—they are best represented by self-directed, autonomous individuals who are confident and capable of speaking up to authority (PIs) during crucial communications. Thus, the default GCP online approach is faced with a challenge in terms of how to ensure that working CRCs experience an active social presence, so that training produces self-directed and competent professionals.

Limitations

One limitation of this study is the relatively small sample size, which may decrease the representativeness of the entire population and lead to less accurate results. Non-parametric methods cannot support a strong statistical conclusion with few data. A lack of statistical power, owing to the sample size, might also increase the chance of a type II error. Although there were no statistically significant results related to the demographic variables, they may exist in the population.{22} Use of a larger sample size that would have sufficient power to draw statistical conclusions is recommended in future studies. While this study sought to assess the frequency of CRC reporting of AEs, actions taken by PIs, and how CRCs would handle reporting of AEs, it was not designed to promote the soft-skills essential to high-level communication.

Implications of the Findings

Limitations of course learning activities in conjunction with Experiential Learning Theory are apparent, in that the online modules place knowledge and skill acquisition outside a cycle of experiential learning. Online content, as evident in this study, tends to inculcate a learning stance of rote memorization in which mandatory training becomes an exercise in completing multiple-choice test questions. In its current form, the GCP online content does not promote reflective

conversation or the sharing of experiences. There was no accommodation in learning activities that fostered abstraction, hypothesis testing, or active experimentation.

Online content should be revised to promote CRC capacity through the use of reflective observation and abstract conceptualization. Use of staggered reflective writings to describe participants' perceptions over time is also recommended. The findings raise the question whether there is some kind of "cultural censor" that the online format cannot breach. To better understand the potential of this phenomenon, surveying and interviewing PIs is recommended.

Future studies should use bigger sample sizes across the nation's CTSA's to amass a large database of CRC outcomes and insight about GCP course content and learning activities. By implementing a standardized approach to evaluation, comparative findings from such studies can be used to advance the common metrics movement and to develop a body of institutional and intra-institutional perspectives that showcase GCP coursework outcomes. {23}

Conclusions

This study explored whether online GCP training influenced changes in the frequency of CRC reporting AEs, actions taken by the PIs, and how CRCs would handle the reporting of AEs differently in the future. The findings suggest that the online training platforms examined did not improve crucial communication.

This finding in and of itself is remarkable, and suggests two possibilities. First, it points out that alterations in these behaviors may be resistant to change. Second, it shows that a lack of experiential learning was tied to the absence of essential participant change. Increasing the level of experiential learning in online GCP courses coupled with robust evaluation is recommended.

Disclaimer

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References

1. The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). 2016. ICH Harmonized Guideline: Integrated Addendum To ICH E6(R1): Guideline For Good Clinical Practice E6(R2).
www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2_Step_4_2016_1109.pdf
2. Sonstein SA, Seltzer J, Li R, Jones CT, Silva H, Daemen E. 2014. Moving from compliance to competency: a harmonized core competency framework for the clinical research professional. *Clin Res* 28(3):17–23.
3. Shanely TP, Calvin-Naylor NA, Divecha R, Wartak MM, Blackwell K, Davis JM, et al. 2017. Enhancing clinical research professionals' training and qualifications (ECRPTQ): recommendations for good clinical practice (GCP) training for investigators and study coordinators. *JCTS* 1(1):8–15.
4. Kolb AY, Kolb DA. 2005. Learning styles and learning spaces: enhancing experiential learning in higher education. *Acad Manag Learn Edu* 4(2):193–212.
5. Dewey J. 2013. My pedagogic creed. In *Curriculum Studies Reader E2*. Routledge; 29–35.
6. Baker AC, Jensen PJ, Kolb DA. 2002. *Conversational learning: an experiential approach to knowledge creation*. Greenwood Publishing Group.
7. Mills TM. 1967. *The sociology of small groups*. Englewood Cliffs: Prentice Hall.
8. Kolb DA. 1984. *Experiential learning: experience as the source of learning and development*. Englewood Cliffs: Prentice Hall.
9. Good Clinical Practice (GCP) Course. 2018. CITI Program.
<https://about.citiprogram.org/en/series/good-clinical-practice-gcp/>

10. National Institutes of Health (NIH). 2016. Policy on Good Clinical Practice Training for NIH Awardees Involved in NIH-funded Clinical Trials (Notice Number: NOT-OD-16-148). <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-148.html>
11. Site Qualification and Training. 2018. TransCelerate BioPharma, Inc. www.transceleratebiopharmainc.com/assets/site-qualification-and-training/
12. Association of Clinical Research Professionals. 2018. Introduction to Good Clinical Practice. <https://www.acrpnet.org/courses/introduction-to-good-clinical-practice/>
13. Fritz CO, Morris PE, Richler JJ. 2012. Effect size estimates: current use, calculations, and interpretation. *J Exp Psych: General* 141(1):2–18. doi:10.1037/a0024338
14. Michigan Institute for Clinical and Health Research. 2015. ECRPTQ Meeting III - Competency Domain Working Group 8: Communication. Ann Arbor, Mich.
15. Behar-Horenstein LS, Bajwa W, Kolb HR, Prikhidko A. 2017. A mixed method approach to assessing online dominate GCP training platforms. *Clin Res* 31(5):38–42. doi:10.14524/CR-17-0013
16. Behar-Horenstein, LS, Potter JE, Prikhidko A, Swords S, Sonstein S, Kolb HR. 2017. Training impact on novice and experienced research coordinators. *Qualitative Report* 22(12):3118.
17. Rovai AP, Wighting MJ. 2005. Feelings of alienation and community among higher education students in a virtual classroom. *Internet Higher Ed* 8(2):97–110.
18. Sung E, Mayer RE. 2012. Five facets of social presence in online distance education. *Comps Human Beh* 28(5):1738–47.
19. Biocca F, Harms C, Burgoon JK. 2003. Toward a more robust theory and measure of social presence: review and suggested criteria. *Presence: Teleops Virt Envs* 12(5):456–80.

20. Zhan Z, Mei H. 2013. Academic self-concept and social presence in face-to-face and online learning: perceptions and effects on students' learning achievement and satisfaction across environments. *Comps Ed* 69:131–8.
21. Bowers J, Kumar P. 2015. Students' perceptions of teaching and social presence: a comparative analysis of face-to-face and online learning environments. *Int J Web-Based Learn Teach Techs* 10(1):27–44.
22. Lomax RG, Hahs-Vaughn DL. 2012. *An introduction to statistical concepts*. New York, N.Y.: Routledge Academic.
23. Rubio DM. 2013. Common metrics to assess the efficiency of clinical research. *Eval Health Profs* 36(4):432–46. doi.org/10.1177/0163278713499586

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Table 1: Bringing AEs to PI Attention and Format of Discussing AE with PI by Group Affiliation

Questions	Regulatory Coordinator /Research Compliance		Coordinator/ Investigator/ Other		Mann-Whitney U	Z	Effect Size r	p-Value
	N	Mean Rank	N	Mean Rank				
Bringing AE to PI Attention	10	14.50	28	21.29	90.00	-2.25	-0.36	.024*
Format of Discussing AE with PI	10	27.40	29	17.45	71.00	-2.51	-0.40	.012*

Notes: * Denotes $p \leq .05$

Table 2: Descriptive Statistics for the Sample (n=40)

Demographic Information	Category	n(%)	
Coordinator Responsibility	Investigator/Research Coordinator/Other	29(72.5%)	
	Regulatory Coordinator/Research Compliance	10(25%)	
	Missing	1(2.5%)	
	Years of Research	0-9	29(72.5%)
		10+	11(27.5)
Missing		0(0%)	
Training Background	Bachelor's or Below	16(40%)	
	Master's and Above	18(45%)	
	Missing	6(15%)	

Table 3: Pretest and Six-Month Follow-Up Comparisons by Research Questions

Statistical Test	Research Questions	Pre		Six-Month Follow-Up		Z	p-Value
		N	Mean Rank	N	Mean Rank		
Wilcoxon	Observing AE to PI	39	14.88	40	12.12	.458	.647
	Format of Discussing AE with PI*	40	12.06	40	11.97	1.32	.188
	PI Non-Actionable Response to AE	38	6.55	40	12.00	.702	.483
	PI Rejection to AE	38	4.50	40	6.50	.525	.599
McNemar	Bringing AE to PI Attention	38	---	39	---	---	1.00
	PI Actionable Response to AE	38	---	40	---	---	1.00

PEER REVIEWED

Opinion: Appreciating a Clinical Approach to the Evaluation of Nonserious, Laboratory Adverse Events

Robert Jeanfreau, MD, CPI



Recognizing the ongoing necessity for mitigating bias and improving the quality of reporting randomized controlled trials (RCTs), the SORT Group, comprised of medical journal editors, researchers, and epidemiologists, in 1994 published *A proposal for structured reporting of randomized controlled trials. The Standards of Reporting Trials Group*. This proposal, known as the SORT statement, consisted of a 32-item checklist and flow diagram to standardize the reporting of RCTs.

Three years later, the SORT Group, in collaboration with the Asilomar Working Group on Recommendations for Reporting of Clinical Trials in the Biomedical Literature, published the *Consolidated Standards of Reporting Trials (CONSORT) Statement*.^{1} The reporting of adverse events (AEs) had also come under closer scrutiny; a revised CONSORT Statement was published in 2001 with the addition of an item about reporting AEs.

When it became apparent that this single addition did not adequately address the importance of AE reporting, the CONSORT Group met again to remedy this shortcoming. The resulting second document on *Better Reporting of Harms in Randomized Trials: An Extension of the CONSORT Statement* was published in 2004.^{2} The most recent revision of the CONSORT Statement was published in 2010. The widely respected CONSORT Statement is currently endorsed by 585 journals, including more than 50% of the core medical journals listed in the Abridged Index Medicus on PubMed.^{3}

A like-minded organization, known as Medical Publishing Insights & Practices, is comprised of pharmaceutical companies and the International Society for Medical Publication Professionals (MPIP). It has recommended highlighting AEs of most relevance to practitioners and their patients. To this end, MPIP proposes that “authors develop a ‘clinical relevance’ filter.” The authors further state, “The intent of the ‘clinical relevance’ recommendation is to broaden [AE] reporting beyond what is mandated by regulators and to leverage the clinical experience and expertise of physician investigators to judge which [AEs] should be highlighted.”{4}

Applying Clinical Expertise to AE Evaluation

The clinical expertise of physician investigators has been grossly underutilized in the evaluation of AEs in RCTs. This is, perhaps, most clearly demonstrated in the evaluation of the clinical significance of laboratory data and is, in part, due to a poor understanding of the evaluative process.

The generally accepted view of clinical significance is described as follows:

“An abnormal lab value should be deemed clinically significant if either of the following conditions are met:

- The abnormality suggests a disease and/or organ toxicity that is new or has worsened from baseline.
- The abnormality is of a degree that requires additional active management, e.g., change of dose, discontinuation of the drug, close observation, more frequent follow-up assessments, or further diagnostic investigation....

Therefore, a clinically significant lab value is one that indicates a new disease process, an exacerbation or worsening of an existing condition, or requires further action(s) to be taken.”{5}

This viewpoint arises from an interpretation of the U.S. Food and Drug Administration’s (FDA) definition of AE:

“[AE] means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.”{6}

The term “untoward” is generally taken in this context to mean abnormal or outside the defined normal range. In fact, some protocols formally define clinically significant lab abnormalities based upon the amount of deviation from the normal range.

In clinical practice, however, any finding (laboratory result or physical finding) that differs from the “expected” is considered clinically significant. Unexpected findings are important because they suggest the existence of an underlying disorder. It is reasonable then to consider “unexpected” as being under the umbrella of “untoward.”

Clinically significant lab results may or may not be abnormal. Furthermore, even grossly abnormal results may not be clinically significant. The evaluation of laboratory data involves much more than deciding if an abnormal lab is far enough out of range to be of concern. A lab result is never considered in isolation, but in the context of the patient’s physical examination and available history (ideally including past and present medical problems, social history, family history, medications, and previous laboratory studies).

Putting Theory into Practice: Three Scenarios

Let’s take as an example a two-year study looking at a new diabetic medication for adults. Safety labs, consisting of CBCs, are obtained every four months. The reference lab gives the normal range of the hematocrit as 38.5% to 50%. The MCV normal range is set from 80 to 100. The first lab work shows a hematocrit of 50% with an MCV of 98. Since neither is outside the normal range, neither is reported as abnormal. At four months, the hematocrit is 48% and the MCV 95. These are again normal values. At eight months, the hematocrit is 45% and the MCV is 90. At one year, the hematocrit has fallen to 40% and the MCV is 85.

None of these labs would have been flagged as abnormal; therefore, they would not have been identified as AEs and may not have been evaluated for clinical significance. From a clinical standpoint, however, the lab values show a clear trend of deviating from the “expected” previous levels.

The study’s principal investigator (PI) is not considering one isolated set of lab values, but the trend of the results which clearly indicates a falling hematocrit and MCV. Beyond this, the PI

would have been reflecting on the subject's history—how the patient is 65 with no family history of colon cancer, and how his latest colonoscopy was normal.

The subject was taking no known ulcerogenic medications. The subject was experiencing mild episodes of intermittent nausea, and a review of the investigator's brochure for the drug under study shows that its most commonly related AE is nausea, occurring in 15% of subjects. A simple differential diagnosis is shown below:

- Lab error
- Gastrointestinal (GI) blood loss
- Anemia of chronic disease
- Investigational product (IP) (this is always listed in the initial differential diagnosis in a clinical trial)

When initially constructed, the differential diagnoses are not ranked. The second step in the evaluative process, which also follows as an important component of determining causality, is ranking the differential diagnoses by likelihood. Based upon clinical expertise and a review of the available information, the clinician would rank the above diagnoses as follows:

- 1) GI blood loss, possibly due to the IP causing gastric ulceration, suggested by nausea in the investigator's brochure.
- 2) Anemia of chronic disease, possibly due to worsening renal disease from diabetes.
- 3) Lab error, which seems unlikely considering that a trend was seen.
- 4) GI blood loss from other etiologies.

At this point, the PI stops the IP for three days and the nausea resolves. The subject is instructed to discontinue the IP until he can be evaluated by a gastroenterologist who, in fact, notes gastric ulcerations at endoscopy. By considering an "unexpected" lab finding as an AE, the PI has identified a potential adverse reaction of the IP.

Let's consider another example. Another subject in the same study has the very same sets of lab values. This subject is 42 and female. The PI requests that the subject return to the research site

after he reviews the third set of labs. The subject informs the PI that she has recently been to the gynecologist for a routine visit. At that visit, the gynecologist expressed concern regarding the hematocrit that the PI had faxed to him. She had explained to the gynecologist that her menses had always been heavy, but that she had stopped the iron supplement due to nausea.

A simple, initial differential diagnosis would have been:

- Lab error
- IP
- Menometrorrhagia
- GI blood loss
- Anemia of chronic disease

The differential diagnoses are quickly ranked as follows:

- 1) Menometrorrhagia
- 2) GI blood loss
- 3) Anemia of chronic disease
- 4) IP
- 5) Lab error

In this situation, it is possible that the PI may have felt that the diagnosis was quite obvious, and may not have even felt compelled to report the lab as a clinically significant AE.

Even lab results that show a trend toward “improvement” may be considered clinically significant. Let’s take an example of a middle-aged male in the same study. The subject’s initial hematocrit is 39%. The second set of labs again shows a hematocrit of 39%, which is within the normal range. The third set of labs shows a hematocrit of 43%, a deviation from the expected hematocrit of 39%. The PI considers this an unexplained increase in hematocrit that had been previously borderline low but stable.

In trying to develop a differential diagnosis, the PI concludes that he needs more information. The search for additional data is an important, but frequently overlooked aspect of the clinical evaluative process. The coordinator contacts the subject who explains that, during the week before the lab was drawn, he had a GI “bug” with nausea and diarrhea that was “going around his household.”

A simple, initial differential diagnosis would have been:

- Lab error
- IP
- Dehydration and subsequent hemoconcentration

The differential diagnoses are quickly ranked as follows:

- 1) Dehydration and subsequent hemoconcentration
- 2) Lab error
- 3) IP

In this context, the PI decides that the hematocrit of 43% is clinically significant since it was probably indicative of hemoconcentration due to dehydration. He reports the GI symptoms and the hematocrit as AEs and orders a repeat CBC along with a BUN and creatinine.

Considering the Options

As previously stated, grossly abnormal lab values may not be clinically significant. Let’s take a look at two examples.

Although the ALT has a lower limit of normal at 9 U/L, values beneath this level have no clinical significance because “abnormally” low values are not associated with a disease state. For a second example, suppose there is a study being conducted in subjects with pruritus and end-stage renal disease. Screening labs disclose a creatinine of 4. The PI does not consider this to be clinically significant since the subject has known end-stage renal disease and the lab result does not deviate from the expected.

The foregoing examples are not unlikely or contrived, but are very plausible scenarios that illustrate how complicated the process of determining clinical significance can be and how important it is for ensuring subject safety. These examples also underscore how critical it is for the PI to be able to evaluate serial laboratory data for trends.

Because of the way that labs are usually presented in research studies, the PI must locate previous labs and flip back and forth to establish trends in the data. A much more efficient way to accomplish this would be for the central lab to report serial lab data in charts, which would allow the PI to review all the data at a single glance.

It is unlikely that this change in reporting would incur any significant financial expenditures, since most large central labs already possess this ability. Integrating this change into clinical research would be a significant and practical advancement in leveraging the clinical expertise of PIs, thereby improving AE reporting and subject safety.

References

1. History: How CONSORT Began. www.consort-statement.org/about-consort/history
2. Ioannidis J, Evans S, Gotzsche P, O'Neill R, Altman D, Schulz K, Moher D. 2004. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 141:781–8. www.consort-statement.org/Media/Default/Downloads/Extensions/CONSORT%20Extension%20for%20Harms.pdf
3. Endorsers: Journals and Organizations. www.consort-statement.org/about-consort/endorsers
4. Lineberry N, Berlin J, Mansi B, Glasser S, Berkwits M, Klem C, Bhattacharya A, Citrome L, Enck R, Fletcher J, Haller D, Chen T, Laine C. 2016. Recommendations to improve adverse event reporting in clinical trial publications: a joint pharmaceutical industry/journal editor perspective. *BMJ* 355:i5078. <https://www.bmj.com/content/355/bmj.i5078>
5. Ceh SE. 2009. Documenting clinically significant lab values. *J Clin Res Best Pract* 5(1):1–4. https://firstclinical.com/journal/2009/0901_CS_Documentation.pdf

6. Statement of FDA Safety Reporting.

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32>

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SPECIAL FEATURE

A Fresh Take on the Adverse Event Landscape

Ann Neuer, MBA



The subject of adverse events (AEs) is often summed up as a series of definitions and reporting requirements, but more recently, there has been an effort to breathe life into this unwieldy topic, bringing greater understanding to the role of AEs in the clinical trial process. The U.S. Food and Drug Administration (FDA) provides guidance on the complex subject of AE reporting,^{ 1 } but at the same time, a growing body of literature details an inadequate level of reporting by stakeholders, especially of the more serious AE variety.

Perhaps this dilemma reflects the broad scope of this subject, as there are AEs, serious adverse events (SAEs), suspected adverse reactions, and unexpected AEs, and their proper reporting forms the basis of the critical risk/benefits analysis of investigational therapies. Even the simplest online search of AEs reveals the vastness of this topic, but most publications seem to focus on one aspect only—the industry-wide challenge of collecting complete AE information for already marketed products, known as postmarketing surveillance.

By comparison, the literature on the quality of AE and SAE reporting during ongoing clinical trials is scant, at best, and merits further exploration. In particular, do most investigators

understand their reporting responsibilities for various types of AEs? This is a fair question, considering that multi-year data from the Bioresearch Monitoring Program (BIMO), the FDA inspection plan, indicate that “failure to report AEs” is a continual clinical investigator deficiency, and falls under the category of “inadequate subject protection.”{2}

This article takes a look at the changing AE landscape from the clinical trial perspective. Stakeholders share their perceptions as to how clinicians interpret information that may or may not be a type of AE, and why there are reporting challenges. There is discussion on the underreporting of SAEs and AEs by investigators and sponsors, which leads to biased evidence and possibly serious consequences for patients.{3,4} Also presented are recent FDA rules and guidance on new standards for low-risk studies, which do not seem to be making changes to AE reporting. Finally, this article describes the importance of asking the right questions to study subjects in order to determine if an AE has actually occurred.

Figure 1: Definitions of Various Types of Adverse Events

Adverse event (AE): *Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.*

Serious adverse event (SAE): *In the view of either the investigator or sponsor, an event that results in any of these outcomes: death, a life-threatening AE, inpatient hospitalization, or prolongation of existing hospitalization.... (partial definition)*

Suspected adverse reaction: *Any AE for which there is a reasonable possibility that the drug caused the AE.*

Unexpected adverse event: *An event not listed in the investigator brochure or not listed at the specificity or severity that has been observed.... (partial definition)*

Source: 21 Code of Federal Regulations 312.32(a)

A Complex Picture

An AE is defined as *any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related*{5} (see Figure 1), and there are a whole host of reasons as to why the reporting of “untoward medical occurrences” during clinical trials can be less than optimal. These range from needing a better understanding of the various types of AEs, to how investigative sites should delineate between AE reporting requirements for the protocol and for their institutional review board (IRB), to differing reporting requirements for pharmaceutical and device trials.

To complicate matters further, it is possible that how AEs are observed is largely subjective. A thoughtful opinion piece was recently published in *Clinical Researcher* by Robert Jeanfreau, MD, medical director with MedPharma,{3} in which he explores how subjectivity, rather than objectivity, is commonplace among stakeholders and could be a root cause of problematic AE reporting practices.

Specifically, Jeanfreau writes about how the role of bias has been studied extensively in clinical trials, but when it comes to AEs, he claims there has been surprisingly little attention paid to how they are collected and how bias may determine whether AEs are viewed as such and whether they are reported at all. For example, he points out that an investigator may interpret a slight decrease in the hematocrit as an AE, and report it as such, but an increase in the hematocrit of similar magnitude may not be viewed as an AE, and therefore, not reported.

As a clinician with more than a decade of experience in conducting clinical trials, Jeanfreau notes that most scientific endeavors are based on objective techniques of the scientific method, whereas the collecting of AEs is not, and therefore allows for the introduction of bias. “In clinical trials, we don’t take a scientific, objective view of AEs because we are starting from the perspective that if something happens, it is an *adverse* event, suggesting something negative. That is already a biased view. It would be more objective to observe the event as a ‘change in health,’” Jeanfreau explains. (A new peer-reviewed article related to AEs by Jeanfreau can be found elsewhere in this issue of *Clinical Researcher*.)

Jeanfreau comments further that subjective perceptions of AEs are sometimes the result of overly simplistic thinking, especially when it comes to evaluating laboratory data for the possibility of an AE. “There is confusion as to how some clinicians and non-clinicians view blood work results. If a lab test is significantly out of range, it may be considered an AE. But oftentimes, the evaluation of lab data is much more complicated than that. For example, even a normal lab result can be an important finding. Over time, if there are four hematocrit readings, but each is lower than the previous one, yet still in the normal range, this is clearly a downward trend, and could be significant. This is different than simply assuming that *only* abnormal values can qualify as AEs,” Jeanfreau says.

Inadequate Reporting of SAEs and AEs

Making subjective judgments or failing to recognize AEs is only part of the story. There also is the reporting of SAEs, which seems to be a particular challenge.

According to clinical trial regulations for drug trials, investigators are to report SAEs immediately to the sponsor{6}, and in turn, sponsors are to notify FDA and investigators within 15 days of determining that a potential serious risk qualifies for reporting.{7} However, a number of published articles describe continual problems with the reporting of these events.

In particular, SAEs are to be reported to ClinicalTrials.gov by responsible parties—in accordance with the Final Rule of the Food and Drug Administration Amendments Act{8,9}—at various times, both during the trial and after its primary completion date. Too often, however, these results are not published in the medical literature.

Tang, et al. drew this conclusion after conducting a study that evaluated a random convenience sample of 300 trials from ClinicalTrials.gov.{4} All studies were either Phase III or Phase IV trials, and included at least one SAE. Of this sample, 78 (26%) lacked a corresponding publication, and 20 (7%) produced an article that did not match the ClinicalTrials.gov record. Of the 202 remaining studies, 26 (13%) published articles did not mention SAEs, four (2%) reported no SAEs, and 33 (16%) failed to report the total number of SAEs per treatment group.

Similarly, Hughes, et al. found substantial discrepancies between SAEs in Phase II, III, and IV psychiatric trials reported to the former ClinicalStudyResults.org trial registry and the number of corresponding journal articles about those same studies. { 10 } In retrieving 244 trial summaries for six antidepressant and antipsychotic drugs, researchers found 142 (58.2%) listed an associated article in the summary bibliography, and 72 (29.5%) listed no publication of any kind. Of 1,608 SAEs in drug-treated participants, 694 (43.2%) did not appear in associated articles, and almost 60% of SAEs counted in articles and 41% in trial summaries had no description. Also, most cases of death (62.3%) and suicide (53.3%) were not reported in articles. The authors concluded that SAE reporting is “incomplete, ambiguous, and inconsistent,” meaning that clinical decisions regarding drug use may be based on heavily truncated evidence.

This is but a small sample of the numerous studies documenting the pattern of ongoing problems with sponsors reporting study results to clinical trial registries { 11 } and to the literature. { 12–15 } Additional research is needed to explore why there is a major gap between the detection of SAEs and AEs, and how to include them in publications with adequate detail.

Regulatory Review

The current regulatory landscape for AE and SAE reporting is a mix of existing and newly minted FDA rules and guidances. For ongoing clinical trials, there have long been clear guidelines for stakeholders to report events, as spelled out in several Good Clinical Practice regulations and FDA guidances. The basic requirements for Investigational New Drug (IND) safety reporting appear in 21 *Code of Federal Regulations* (CFR) 312.32(c)(1){ 7 } and 312.64(b), { 6 } and describe sponsor and investigator reporting responsibilities. Guidelines for safety reporting in Investigational Device Exemption studies are found in 21 CFR Subpart G 812.150. { 16 }

Figure 2: Serious Events Unlikely to be Caused by Study Drug/No Safety Report Required

- SAEs (i.e., mortality or major morbidity) that were likely to have been manifestations of the underlying disease.
- SAEs that commonly occurred in the study population independent of drug exposure (i.e., strokes or acute myocardial infarctions in an elderly population).
- SAEs that were study endpoints.

Source: Safety Reporting Requirements for INDs and BA/BE Studies, 2012

For studies conducted under IND applications, in particular, the FDA guidance on “Safety Reporting Requirements for INDs and [Bioavailability/Bioequivalence] Studies”^{1} helps sponsors and investigators comply with requirements. The guidance also points out that sponsors often submit unnecessary reports to FDA, which drains agency resources and does little to aid a better understanding of the safety profile of an investigational therapy.

To address this issue, the guidance details how sponsors can determine if there is a reasonable possibility of linking a serious and unexpected event to the study drug, and if not, there is no need to submit an IND safety report. For example, sponsors have frequently reported SAEs that were likely to have been manifestations of the underlying disease, rather than the study drug (Figure 2 lists additional examples).

Recently, the FDA has been releasing additional rules and guidance designed to maintain safeguards that protect the rights, safety, and welfare of subjects. As for whether these new rules impact required AE and SAE reporting, they appear to be unchanged from current requirements. One proposed rule, released in November 2018,^{17} is a provision of the 21st Century Cures Act, and if finalized, would permit an IRB to waive or alter certain informed consent elements when clinical research poses no more than minimal risk to subjects.

At the same time, revisions to the Common Rule (“Federal Policy for the Protection of Human Subjects” from the U.S. Department of Health and Human Services) that went into effect in January 2019 intend to promote uniformity and compliance with human subject protections and

create a uniform body of regulations across federal departments.{18} Any confusion between the revised Common Rule and the aforementioned proposed rule that would allow for minimal risk clinical research without informed consent will hopefully be addressed during an ongoing harmonization process. As part of this initiative, the FDA released new guidance in October 2018 on how stakeholders can comply with both.{18}

Ask the Right Questions

Of everyone working in the heavily regulated world of clinical trials, those working at the investigative site have a front row seat to the reporting of AEs, SAEs, suspected adverse reactions, and unexpected AEs. It is the study coordinator and the investigator who hear, first hand, from study subjects about potential events that may or may not need to be reported. However, making this determination is often the result of asking the right questions.

Kaitlyn Roberson, clinical research site supervisor at IACT Health, a clinical research firm, explains, “It’s not enough to ask ‘How are you feeling?’ or ‘What’s going on?’ We have to be trained to ask the right questions, like ‘Have you had any new symptoms since your last visit?’ Using this approach, the patient may volunteer that he or she had a cold two weeks ago or maybe started taking a drug to treat it that could interfere with the study medication. At this point, it’s important to ask the right follow-up questions, such as, ‘Did you stop the study drug when you had your cold, and did you re-start it?’ Without the right questions, patients may forget to tell you these details.”

Similarly, Michael Marotta, manager of clinical monitoring services at IMARC Research, a medical device contract research organization, notes, “How a question is asked goes a long way toward capturing what could be an AE. With device trials, we would want to know if the patient had any unscheduled visits, say to a cardiologist, outside the realm of the study. This can be an important point because follow-up for device trials can occur over a number of years, and the further you get from the date of surgery, the greater time there usually is between follow-up visits.”

Marotta also provides insight into why study sites might miss AEs or draft incomplete AE safety reports. He points to the jam-packed schedules that typify many sites where multiple protocols

are being undertaken simultaneously for multiple sponsors, with each having different requirements and timelines.

“You can’t think of a trial as occurring in a bubble, which means that sites can have [conflicting] schedules [and] resourcing constraints, and even how the information is being collected can be confusing. And at a granular level, somebody at the site may not be acutely aware of all the requirements for a study. For example, a coordinator could be conducting five different trials, each with a different reporting requirement, so what is appropriate and accurate in one trial may not be appropriate and accurate for another,” Marotta says.

A Better AE Landscape

As the clinical trials industry works diligently to improve process flow and study conduct, there are signs that these efforts are spilling over into establishing more specific protocol-driven requirements for AE collection and reporting. According to Stephani Hulec, associate director of clinical monitoring services at IMARC Research, changes are happening.

“I’ve seen a definite shift in the industry in the last few years in terms of AE reporting. It’s shifting in a way that some sponsors are writing protocols more focused on the outcomes and what AE information is relevant to those outcomes. The protocols are more specific as to what AEs they require to be reported. This approach more clearly supports the objectives of the study,” Hulec comments.

Taken together, this change, new and existing regulatory guidelines on event reporting, and better training of site personnel represent critical steps in the industry’s attempt to create a more coherent framework for capturing AE-related information. What should follow are more informed evaluations of the risks and benefits of much-needed therapies and devices.

References

1. Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies. 2012. U.S. Food and Drug Administration. Center for Drug Evaluation and Research. <https://www.fda.gov/downloads/Drugs/Guidances/UCM227351.pdf>

2. Bioresearch Monitoring (BIMO) Fiscal Year 2017 Metrics. U.S. Food and Drug Administration.
<https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RunningClinicalTrials/UCM604510.pdf>
3. Jeanfreau R. 2017. Opinion: is bias inherent in the current reporting practices for adverse events? *Clin Res* 31(1):16–9. <https://www.acrpnet.org/2017/02/01/opinion-is-bias-inherent-in-the-current-reporting-practices-for-adverse-events/>
4. Tang E, Ravaud P, Riveros C, et al. 2015. Comparison of serious adverse events posted at ClinicalTrials.gov and published in corresponding journal articles. *BMC Medicine* 13:189. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4535304/>
5. 21 *Code of Federal Regulations* 312.32(a). U.S. Food and Drug Administration.
<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.32>
6. 21 *Code of Federal Regulations* 312.64(b). U.S. Food and Drug Administration.
<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.64>
7. 21 *Code of Federal Regulations* 312.32(c)(1). U.S. Food and Drug Administration.
<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.32>
8. Changes from Current Practice Described in Final Rule. 2016. Final Rule for Clinical Trials Registration and Results Information Submission (42 CFR Part 11). U.S. Food and Drug Administration. <https://prsinfo.clinicaltrials.gov/FinalRuleChanges-12Dec2016.pdf>
9. Frequently Asked Questions. 2018. ClinicalTrials.gov.
https://clinicaltrials.gov/ct2/manage-recs/faq#fr_7
10. Hughes S, Cohen D, Jaggi R. 2014. Differences in reporting serious adverse events in industry sponsored clinical trial registries and journal articles on antidepressant and antipsychotic drugs: a cross-sectional study. *BMJ Open*.
<https://bmjopen.bmj.com/content/bmjopen/4/7/e005535.full.pdf>
11. Enforcing reporting to ClinicalTrials.gov: what’s at stake for research transparency. 2017. *Ampersand* (The PRIM&R Blog). <https://blog.primr.org/enforcing-reporting-to-clinicaltrials-gov/>
12. Golder S, Loke YK, Wright K, et al. 2016. Reporting of adverse events in published and unpublished studies of health care interventions: a systematic review. *PLoS Med* 13(9).
<https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002127>

13. Pitrou I, Boutron I, Ahmad N, et al. 2009. Reporting of safety results in published reports of randomized controlled trials. *Arch Intern Med* 169(19):1756–61.
<https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/724471>
14. Prayle AP, Hurley MN, Smyth AR. 2012. Compliance with mandatory reporting of clinical trial results on ClinicalTrials.gov: cross sectional study. *BMJ* 344.
<https://www.bmj.com/content/bmj/344/bmj.d7373.full.pdf>
15. Anderson ML, Chiswell K, Peterson ED, et al. 2012. Compliance with results reporting at ClinicalTrials.gov. *NEJM* 372(11):1031–9.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4508873/pdf/nihms677071.pdf>
16. 21 *Code of Federal Regulations* 812.150. U.S. Food and Drug Administration.
<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.150>
17. Institutional Review Board Waiver or Alteration of Informed Consent for Minimal Risk Clinical Investigations. 2018. Proposed Rule. U.S. Food and Drug Administration.
<https://www.federalregister.gov/documents/2018/11/15/2018-24822/institutional-review-board-waiver-or-alteration-of-informed-consent-for-minimal-risk-clinical>
18. Impact of Certain Provisions of the Revised Common Rule on FDA-Regulated Clinical Investigation. 2018. Guidance for Sponsors, Investigators, and Institutional Review Boards. U.S. Food and Drug Administration.
<https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM623211.pdf>

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SPECIAL FEATURE

A Closer Look at FDA’s Proposed Rule on Informed Consent Waivers

Robert Barton



The U.S. Food and Drug Administration’s (FDA’s) [proposed rule](#) to allow an institutional review board (IRB) to waive or alter informed consent requirements in low-risk clinical trials is a good step toward streamlining the approvals process for drugs and medical devices, but the strategy is not without some potential pitfalls, according to several industry experts.

The proposed rule is controversial, according to Dr. Beverley Lorell, senior medical and policy advisor for the Washington, D.C.-based law firm King and Spaulding. The reason for that controversy has to do with the nature of FDA-regulated efforts on drugs and medical devices versus the broader spectrum of human investigations covered by the “Federal Policy for the Protection of Human Subjects”—more commonly referred to as the Common Rule—which was published in 1991 and codified in separate regulations by 15 federal departments and agencies.

“FDA regulations are much narrower [than the Common Rule],” Lorell said. “Those who are concerned about [the proposed regulation] are concerned that...since FDA regulations are solely focused on a human subject receiving an investigational drug or medical device, almost by definition that investigation does not meet the criteria of ‘no more than minimal risk.’ That is the

concern that some people have about applying the waiver of consent to [FDA-regulated] clinical research.”

Who Can Do What to Whom Now

Currently, according to an [article](#) in the *National Law Review*, the FDA allows IRBs to waive or alter informed consent requirements in only a few circumstances, including:

- Emergency use, which applies when human subjects:
 - Have a life-threatening condition
 - Suffer from a severely debilitating condition
 - Have a condition for which there is no standard acceptable treatment available
 - Are in a situation in which there is insufficient time to obtain IRB approval
- Planned emergency research, which applies when human subjects have a life-threatening medical condition that requires urgent intervention and cannot provide informed consent because of their condition. In addition, the research must involve an investigational product that has the prospect of direct benefit to the patient and must be administered before informed consent can be obtained. The research must also show that there is no reasonable way to identify eligible participants.
- *In vitro* diagnostic device studies using leftover human specimens that are not individually identifiable. The process for waiving informed consent is subject to a number of requirements aimed at the preserving the anonymity of the person from whom the specimen was obtained.
- When the subjects are U.S. Armed Forces personnel, which would apply only if the U.S. president waives informed consent for military personnel for the administration of an investigational product to members of the Armed Forces.

Who Might be Able to Do What to Whom Soon

Under the proposed rule, the FDA could permit IRBs to waive or alter clinical trial informed consent requirements for drug and device studies, if the IRB find and documents four key criteria:

- The clinical trial must involve no more than minimal risk to subjects.
- The waiver or alteration of informed consent will not adversely affect the rights and welfare of the subjects.
- The clinical trial could not practically be conducted without the waiver or alteration of consent.
- When appropriate, the IRB will provide the subjects with additional pertinent information after participation in the clinical trial.

“I think it’s a great idea,” said David A. Borasky, vice president of IRB compliance for the WIRB-Copernicus Group. “Human subjects research has been out of step with the Common Rule from the beginning.”

The FDA proposal is just part of an overarching effort—spurred in large part by the signing into law in 2016 of the 21st Century Cures Act, which was designed to help accelerate medical product development and bring innovations and advances to patients who need them faster and more efficiently—to streamline and speed up the approval process for the development of drugs, biologics, and medical devices.

Advantages to Taking a New Approach

“Typically, you wouldn’t want to waive the requirements for informed consent,” Borasky said. “However, the research landscape is changing. The FDA has expressed interest in seeing studies that involved the collection of real-world data to contribute to real-world evidence.”

For example, Borasky said, there is an increasing amount of data available from drugs and medical devices that have already been approved and are on the market. “Under current FDA regulations, you have to go through some funny contortions to be able to waive consent,” he said. “It’s about time FDA gets on board with this. It opens up the possibility to doing a lot of research on things like existing information in medical records that could potentially impact the labeling of currently approved drugs and devices.”

The FDA has been consistently saying for some time now that having access and seeing research with that sort of data being used is important to them, Borasky added. “It’s sort of a treasure

trove of information about what happens once these devices and drugs are approved and out on the market, and actually being used outside the narrow confines of a clinical investigation or clinical trial,” he said. “It allows this important research to go forward without adding unnecessary regulatory burden and without putting [anyone] at risk of harm by allowing access to this information.”

This type of activity is fairly common outside FDA-regulated research, Borasky pointed out. “Outside the scope of the FDA, there are all kinds of research projects that are done under the Common Rule regulation with full waivers of informed consent all of the time, because they don’t involve actually interacting or intervening with anybody. It’s looking at old medical records and abstracting data out of them. And that’s the most typical scenario I think that we’re talking about here. So, I don’t know that there are any actual disadvantages.”

In addition, Borasky stressed that the IRBs, not researchers, are the ones who get to make the call on waiving informed consent. “IRBs still have to approve these waivers and document that they have granted that waiver of informed consent, and those four criteria, I think, in practice have proved sufficient. It starts with the idea, first of all, that it has to be minimum-risk research, so, again, you’re not going to be initiating a clinical trial giving people an investigational drug and doing it with a waiver of informed consent and not telling them.”

Modernization and Harmonization

Lorell agrees that there is a school of thought in the industry that there are certain instances in which easing the informed consent rules could be helpful. “Proponents [of easing informed consent] believe there are, on occasion, certain types of FDA research where clinical studies are subject to regulation where the application of the ‘no more than minimal risk’ criterion could be beneficial,” she said. “An example of that might be FDA research that uses biological specimens from human beings.”

Another example might be certain kinds of cluster studies where researchers would be looking at already approved products and assessing outcomes. “In a nutshell,” Lorell said, “it’s the argument that not all FDA-regulated research involves the application of a high-risk, new medical device or high-risk, new drug or biological product to a patient or controlled subject.”

Other arguments center around ongoing efforts to harmonize FDA regulations and the Common Rule, as well as the intent of Congress when it passed the 21st Century Cures Act, Lorell said. “The third major argument is that, basically, the 21st Century Cures Act in 2016 not only gave very explicit permission to the FDA to modify its regulations, but was probably a mandate to do so,” she noted.

Further, Lorell believes the criteria listed by the FDA in its proposed rule to allow the waiver or alteration of informed consent are adequate to protect the rights and health of clinical trial subjects. She pointed out that both the FDA and its parent U.S. Department Health and Human Services define the “no more than minimal risk” standard identically in their respective regulations as constituting “harm or discomfort that are not greater than ordinarily encountered in life.” That’s the approved criterion, and that’s probably the most important one,” she said.

However, Lorell pointed out that IRBs are also going to have to consider the other criteria listed in the proposed rule, including that the waiver or alteration won’t adversely affect the rights and welfare of the subjects and that the research could not practicably be carried out without the waiver or alteration. Adding that the latter is especially open to interpretation, Lorell said “That’s been the subject of a lot of controversy over the years. What does that actually mean? It’s not [coming from] from an administrative point of view [that gaining consent is a hassle], but [from the viewpoint] that if you didn’t have the waiver, the effort to get consent would actually bias the outcome and the conduct of the study.”

Part of a Greater Whole

Indeed, the proposed rule is another example of a trend in which the FDA has been moving more toward a risk-based system, said Darshan Kulkarni, vice president of regulatory strategy and policy at Synchrogenix. “There are multiple instances where the FDA has actually done work [concerning] waivers for informed consent,” he said. “This is just another step in that direction, so I don’t see it as a departure from what the FDA has been doing,” but more of a continuation.

Meanwhile, the FDA’s proposed rule has some clear advantages, Kulkarni said: “The obvious advantage to waiving informed consent is that it speeds up the process a little bit, and the informed consent waivers are really being used in minimal-risk types of products.”

However, Kulkarni cautioned, IRBs should keep in mind that there are other requirements and regulations on not just a local, but a global, scale—such as the General Data Protection Regulation (GDPR) in Europe—which could apply despite the receipt of an FDA waiver or alteration.

“I think that the piece that people might forget is that just because you don’t need informed consent doesn’t mean that you aren’t [affecting] people’s privacy,” he said. “So, you may still want to get privacy waivers when you’re doing that. Usually, you’d incorporate that in an informed consent in many cases, but you may still be collecting retrospective data or certain types of prospective data, and that might require that people be informed that you’re going to be using their data.”

Even within the United States, IRBs will need to be cognizant of state and federal laws related to data privacy. “That is one of the things that I think is going to be important as you continue,” Kulkarni said. “I mean, California is doing its own version of GDPR, and there are various both federal- and state-level privacy laws that are implicated. So, in the bigger scheme of things, what have we really achieved? We’ve just gone from reviewing one document to reviewing another document.”

Subject to Change

The proposed rule is “a good start,” Kulkarni said. “I think the FDA is still evaluating what would really happen. This is just in proposed format, anyway. Chances are that people will comment, and there might be additional pieces [to come]. It might just be a change in wording, but it might become more inclusive as we continue [toward this risk-based system]. I think it’s just important to recognize the larger areas at play.”

Kulkarni also pointed out that FDA Commissioner Scott Gottlieb can be expected to address such issues within the framework of the Trump administration’s overall regulatory and policy goals. “The Trump administration came in and said, ‘We want to reduce the cost of drugs, we want to minimize the regulations that get applied,’” Kulkarni said. “[Gottlieb] came in, and he’s trying to match those thoughts and he’s trying to, again, match what the administration wants to achieve. This is very much in line with the administration’s thoughts in that they are reducing the

number of implicated regulations and reducing the amount of red tape that you have to go through, and still balancing the needs of people who may very well need consent.”

One area that does raise some level of concern is that of medical devices, Kulkarni said. He pointed out that, in the area of health information technology, the FDA has chosen not to review software, and now the proposed rule to ease informed consent raises some questions about the implications for the approved product. “That’s a worry for me, as we continue,” he said. “Not drugs, because I think that the drug world, for the most part, is conservative around these regulations. There are a lot more Wild West–type plays in the medical device world.”

In general, the process that will play out under the rulemaking procedures will require IRBs to determine just how to apply the FDA rule in practice, as opposed to theory, according to Lorell. “I think the IRBs are going to have a learning curve,” she said. “At one end of the spectrum will be research, such as federally regulated research on leftover biological specimens. At the other end of the spectrum will be something like a permanently implanted medical device or a drug with known life-threatening side effects. There’s going to be a whole lot in the middle between those goal posts.”

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DATA-TECH CONNECT

GDPR and U.S. Clinical Trials: What is the Impact?

Esther Daemen, MBA; Tine Wouters, MSc



The General Data Protection Regulation (GDPR) (2016/679) brought about the greatest change to European data security in 20 years. Applicable since May 2018 and repealing the Directive 95/46/EC, GDPR intends to strengthen and unify data protection for individuals within the European Union (EU).

All industries and sectors are bound by GDPR to re-think their privacy policies and data protection measures.

Businesses that conduct clinical research—and as such handle “personal data” and even more important “sensitive personal data”—are expected to meet standards of heightened vigilance for compliance with the data protection legislation, as the collection of the latter is forbidden under GDPR unless a valid legal basis for its collection and explicit consent from the pertinent subjects can be provided. Scientific research is fortunately one of the exceptions that allows for the collection of such data under these strict conditions.

Background

Key changes in GDPR from the previous Directive and related local legislations have to do with language touching on “increased subject rights” (right to access, correct, restrict or object data, right to be forgotten, explicit prior consent, data portability, breach notification, transparent plain language), “high fines,” “data minimization,” “privacy by design,” “Data Protections Impact Assessments,” and “Data Protection Officers.” However, which actions need to be taken for a clinical research project to be GDPR compliant? Is this covered by merely updating the informed

consent form (ICF) and being done with it? Not so. Protocols and Clinical Trial Agreements (for sites and vendors) also need adjustment, and the assignment of an aforementioned Data Protection Officer should be considered, as applicable.

Protocols should refer to the new legislation and to the trial's specific ICF. Protocol designs should avoid the collection of data not linked to the trial's endpoints and data breaches. Further, Clinical Trial Agreements should clearly describe "Data Processor" and "Data Controller" responsibilities, considering to what extent a joint controllership exists between the sponsor and the site regarding a subject's right to request access to data collected on them in a trial.

Data Protection Officers should be assigned within an overall company as well as at research sites, as applicable, to ensure the organization applies the laws protecting individuals' personal data independent from management. Detailed information must be kept on the categories of subjects involved in a trial, their individual trial-related data, and the purpose and duration of the data processing required to complete the trial.

Both site and sponsor sub-contractors must comply with GDPR. The current data protection clause of any contracts with vendors should therefore be revised by the organizations' legal departments.

This is only a rough outline of the impact of GDPR on clinical research. Each affected clinical research company is required to do a thorough Data Protection Impact Assessment before any trial commences to ensure full compliance.

As examined in the following section, when in the U.S., GDPR can also apply to trial conduct.

Impact for U.S. Companies Conducting Clinical Research

1. When the trial subjects are in the EU, GDPR applies.

This means that when a U.S. sponsor is processing data from subjects within the EU, GDPR mandates are to be followed. Sponsors should nominate in writing a representative within the EU who fulfills their responsibilities with regard to GDPR. (Even if subjects within the EU are not EU citizens, if data were collected on them while they were within the EU, this rule applies.)

2. When the sponsor is in the EU, GDPR applies.

When data on EU citizens is processed by a U.S. vendor, GDPR applies. Further, an EU sponsor might collect and process data from U.S. subjects; in this case, GDPR also applies, even when there are no subjects within the EU.

3. When the sponsor is in the U.S., it should carefully assess GDPR compliance.

If the U.S. sponsor has offices in the EU involved in some aspects of the trial, then they may be considered as established in the EU, and GDPR would apply.

Overall, if the clinical trial is intended to support a market authorization filing in the EU, this implies data-processing activity taking place in the EU for the purpose of data submission, and therefore GDPR applies.

Lastly, if a contract research organization established in the EU is part of defining the purpose of a clinical trial, it is considered a joint-controller, and thus GDPR applies.

What about transferring data between EU and U.S.?

Once an organization has established that GDPR applies to its clinical trial, it needs to ensure it has permission to transfer personal data to and from the U.S. Under GDPR, the U.S. is considered a “third country,” meaning a country outside the European Economic Area. As such, the U.S. is not considered a country for which EU-related transfer of data is allowed without further due diligence, possibly including registration by a U.S. company with the so-called Privacy Shield framework between the EU and the U.S. and/or demonstration of appropriate safeguards being in place through binding corporate rules.

GDPR and HIPAA: What is the Difference?

Compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) does not automatically mean compliance with GDPR. In a nutshell, GDPR has a broader scope than

HIPAA, and does not deal exclusively with health information. The two schemas also have different metrics for determining Protected Health Information. In HIPAA, this is any demographic information that can be used to identify a patient. In GDPR, this also includes racial or ethnic origin, religious beliefs, biometric or genetic data, and any data concerning health. Only for the latter is there some overlap between HIPAA and GDPR.

Furthermore, GDPR potentially applies to all international organizations that handle personal data of residents within the EU by setting standards for entire industries that deal with personal data, whereas HIPAA only applies to the relationship between covered entities and business associates.

Conclusion

A sponsor (controller) and vendor (processor) cannot avoid GDPR simply by being based in the U.S. They must perform a legal assessment based on the specific context of their activities and territorial business and organization, to determine whether GDPR applies before the start of a clinical trial. HIPAA and GDPR have some overlap, but are not the same, hence additional or other safeguards are needed to ensure compliance with both.



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Resources

Compliancy Group. 2017. GDPR compliance and HIPAA: how to address both.

<https://compliancy-group.com/gdpr-compliance-hipaa-software/>

TRIUM and DLA Piper. 2018. GDPR and clinical trials: how to ensure compliance before 25 May 2018 in a cost-effective way.

SCIENCE & SOCIETY

Engineering Heritable Changes in the Human Genome: Implications for Clinical Research

Daniel Kavanagh, PhD



This article will provide a brief overview of the state of genome-editing technologies as they relate to human genetic modifications that can be passed from parent to offspring (called “germline” genetic modifications). We will first look at what we *can* do with gene editing technology, and then look at approaches to the question of what we *should* do with such technology.

The answer to the former question can be reliably provided by molecular biologists and genetic engineers. The answer to the latter question must come from broad engagement of the scientific community, persons affected by heritable diseases, and the public at large. We will also consider recent reports from China regarding the alleged birth of human babies subjected to unethical gene-editing procedures by a rogue scientist.

Gene Editing Technology and Potential Applications

Genetic engineering—the deliberate modification of DNA to produce changes in an organism—has been around for decades, with early applications in the biology of microbes or isolated cells in culture, and later applications in animals and plants for research and agriculture. Some applications of genetic engineering are being used to modify cells in the human body for the treatment of disease.

As of this writing, the U.S. Food and Drug Administration (FDA) has already given marketing approval to several medical products whose mechanism of action involves genetic modification

of patients' cells. These include two Chimeric Antigen Receptor T cell (CAR-T) products for the treatment of B cell malignancies, and a gene replacement therapy to treat certain forms of inherited retinal disease.

A recent study suggests that there will be more than 40 such approvals by the year 2022.^{ 1 } Importantly, all of these therapies are intended to treat disease in individual patients; none are intended to induce genetic changes that will be passed on to future generations.

There are many techniques available to deliberately modify DNA; some of the most exciting recent developments in genetic engineering have been enabled by a set of technologies known as “gene editing” or “genome editing.” Genome editing technologies allow the genetic engineer to arbitrarily rewrite the sequence of chromosomal DNA with a degree of precision potentially comparable to a text editor or word processor. (Keeping in mind: texts produced with word processors frequently still contain errors.)

Of the various genome editing technologies, the ones receiving the most attention are those that involve CRISPR-based approaches. CRISPRs (clustered regularly interspaced short palindromic repeats) are a type of genetic sequence naturally found in bacteria. Bacteria use CRISPRs to naturally edit their own DNA to protect themselves from viruses.

Around 10 years ago, scientists first began to demonstrate that artificial CRISPR systems could be used to alter and edit the DNA of animal cells. Because functional CRISPR systems are relatively easy to design, it became apparent that various CRISPR-based systems could potentially be used to treat a wide variety of inherited diseases, and perhaps be brought to clinic much more quickly than preceding technologies. It is expected that some of the gene transfer medicines that will achieve FDA approval in the next few years will make use of CRISPR technology. It also became apparent that CRISPR techniques might be used not only to treat disease by targeting specific tissue such as lung, liver, or bone marrow, but also to induce genetic changes in cells that produce sperm or ova, or in living embryos. Such germline alterations in the human chromosome would potentially be passed on to children, grandchildren, and future generations.

In 2015, global experts met for the First International Summit on Human Gene Editing. As the conclusion to several extensive reports, the summit released a consensus statement on human germline gene editing.^{2} Six areas of special concern were identified:

- the risks of inaccurate editing;
- the difficulty of predicting harmful effects;
- implications for the individual and for future generations;
- the fact that over multiple generations, genetic alterations might cross national and cultural borders;
- broad social justice implications; and
- moral and ethical considerations for purposefully altering human evolution.

The report concluded that it would be irresponsible to proceed with intentional germline human genome editing until safety and efficacy issues have been addressed, until there is broad social consensus on appropriate applications, and until appropriate regulatory oversight is in place.

“CRISPR Babies” in China

In late 2018, a Chinese biophysics researcher named He Jiankui announced to the world that he had intentionally altered the genome of viable human embryos, at least two of which had been carried to term, resulting in a live twin birth. As of this writing, the scientific community has not seen definitive proof that such live births actually occurred. Recent statements from the Chinese government seem to indicate that the live births are real, and that the researcher is facing potential criminal charges in China as a result of his actions in this matter.

Almost all of what we know about this activity comes from the researcher’s own statements, as well as a few leaked documents from the hospital where the work was done. Based on this information, his actions are irredeemably flawed and inexcusable from the standpoints of science, medicine, and ethics. The defects in his approach are so comprehensive that there is no space to list them here. (For a list of important concerns, see Ed Yong’s article in *The Atlantic*.)^{3}

The molecular results presented by the researcher are technically deficient; the available version of the informed consent is deceptive; the scientific rationale is misinformed; and the medical justification is specious. Every aspect of this case is so tragically compromised that there is little we can draw from as part of an informed discussion of potential future legitimate germline gene editing projects.

This incident has raised strong feelings within both the bioethics community and the genetic research scientific community. Nevertheless, we can take comfort from the fact that, based on available information, there is a reasonable chance that the children produced from this rogue activity may live normal lives without significant ill effects.

Potential Legitimate Future Applications of Germline Editing

Millions of people around the globe are affected by inherited genetic diseases, and medical databases list thousands of genetic mutations that are associated with these diseases. Many of these inherited diseases result in death in early childhood, or in lifelong disability for surviving individuals.

As whole genome sequencing becomes more routine, increasing numbers of prospective parents are faced with the knowledge that any children they conceive as a couple will face the risk, and sometimes the certainty, of a devastating congenital condition. Current existing avenues available to such couples include options such as adoption, sperm or ova donation, or *in vitro* fertilization (IVF) with pre-implantation selection of disease-free embryos.

Understandably, many couples wish for the option to conceive and bring to term children who are free from the risk of inherited disease; some couples may not wish to utilize these options, and some options may be impractical for medical or social reasons. Genome editing offers a plausible alternative approach; nevertheless, the three criteria mentioned above (safety and efficacy, societal consensus, and regulatory frameworks) remain to be fulfilled.

As one example, a couple may discover that both prospective parents carry one copy of a disease-associated recessive allele for cystic fibrosis (i.e., both parents are asymptomatic *carriers*). This means that, on average, one-fourth of the embryos conceived by this couple will

be free of disease alleles, one-half of such embryos will be carriers like the parents, and one-fourth will be homozygous (receiving both copies) for the disease allele, and thus afflicted with cystic fibrosis, a devastating disease. The parents may plan to generate zygotes by IVF, test them for a disease allele, and then implant only disease-free embryos. Sometimes, however, too few viable zygotes are produced, and no disease-free option is available. As an alternative, parents might propose to use gene editing to attempt to alter the affected chromosomes and produce a disease-free child.

A Challenge for Scientists, Regulators, and the Public

At this point, the medical research community should be prepared to address crucial questions. Does the evidence indicate that this procedure is safe enough and effective enough to proceed? Is there a sufficient consensus in the community to allow such a procedure to go forward? Is there a regulatory framework in place to provide adequate oversight?

Further questions would include: How will researchers secure meaningful informed consent? Who would be liable for any social, psychological, or medical harm experienced by the child, or children in subsequent generations, that is possibly related to the gene editing procedure?

According to many authorities, the barriers posed by these concerns are essentially insurmountable. In other words, there are no foreseeable cases in which human germline gene editing would be justifiable. Other researchers are more sanguine, and feel that, as with IVF, initial public objections will fade away as new technology becomes more familiar, and that society has the tools to cope with risks associated with this and other emerging technologies.

Given the relative accessibility of the basic technology, and aside from the issue of legitimate research, society should prepare for the likelihood that increasing numbers of genetically altered children will be born in the coming decades, irrespective of popular opinion and regulatory oversight. The potential effects on the future of human society are profound. All participants in this discussion must do their best to maintain transparency regarding their own interests and biases, and research in this area must be guided by the basic principles of Respect for Persons, Beneficence, and Justice{4} at each step of the process.

References

1. Existing Gene Therapy Pipeline Likely to Yield Dozens of Approved Products Within Five Years. <https://newdigs-dev.mit.edu/2017/11/13/existing-gene-therapy-pipeline-likely-to-yield-dozens-of-approved-products-within-five-years/>
2. <https://www.nap.edu/catalog/21913/international-summit-on-human-gene-editing-a-global-discussion>
3. <https://www.theatlantic.com/science/archive/2018/12/15-worrying-things-about-crispr-babies-scandal/577234/>
4. <https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html>

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