ACRP

FOR LEARNING FOR LISTENING FOR LIFE

Clinical Researcher

The Authority in Ethical, Responsible Clinical Research

November 2021 (Volume 35, Issue 8)

Fine-Tuning Your Organization's Research Dynamics

Clinical Researcher

Association of Clinical Research Professionals

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

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

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

Media Kit
https://acrpnet.org/advertising/

For membership questions, contact ACRP at support@acrpnet.org or (703) 254-8100.

For information on writing for *Clinical Researcher*, visit https://www.acrpnet.org/resources/clinical-researcher/ or e-mail gcramer@acrpnet.org.

Credit-granting Home Study tests are available at https://www.acrpnet.org/home-study/, along with downloadable PDFs of the relevant articles and questions. The test from this issue should be online in December 2021.

Editorial Advisors for This Issue
Suheila Abdul-Karrim, CCRT, CCRA, ACRP-MDP, FACRP
(Freelancer)

Stefanie La Manna, PhD, MPH, ARNP, FNP-C
(Nova Southeastern University)

Paula Smailes, DNP, RN, MSN, CCRP, CCRC
(The Ohio State University Wexner Medical Center)

Clinical Researcher—November 2021 (Volume 35, Issue 8)

Table of Contents

Clinical Researcher—November 2021 (Volume 35, Issue 8)

EXECUTIVE DIRECTOR'S MESSAGE

Disruption, Disruption, What's Your Function?

Susan P. Landis, Executive Director of ACRP

The topic of disruption is everywhere these days. I don't know about you, but I'm feeling the pressure. There's a disruption in the supply chain—get those presents ordered now! There's disruption in the way clinical trials are being conducted—are you confused about decentralized clinical trials (DCTs)? And, like most of you I suspect, my planned routine is disrupted daily, be it by an unexpected meeting or a child calling from college worried about an economics exam.

Whether a mere distraction, a true disruption, or a delightful surprise, the purpose of an interruption is to, I believe, make us take notice. And that's not a bad thing. Here's how I have been handling the deluge of change that's been occurring recently for me on a day-to-day basis.

Listen and learn. ACRP members are on the front line of making clinical research concepts a reality. I'm excited about the perspectives being shared on many issues. Check out what some of our experts are saying on DCTs here and here. There's also a new study from the Tufts Center for the Study of Drug Development on how site personnel race and ethnicity correlate with the diversity of patients enrolled that will be showcased in an ACRP webinar on December 8.

Share. Recently, ACRP Fellows held an informative late afternoon session on DCTs. The presentation from a U.S. Food and Drug Administration expert was rich with detail. What made the event rewarding was the conversation among those who attended—who says virtual meetings can't be engaging! Whether you're speaking with colleagues about the challenges of a protocol or your strategy for ensuring holiday presents are ordered, the camaraderie that is built through sharing experiences is, well, priceless. An easy place to connect is through the ACRP Community, where there are daily discussions about hot topics in clinical research.

Take time and take care. A friend and colleague shared with me the other day that during an especially busy time, a study principal investigator called her to check in and to ask if she was doing well. This interruption in her day was an unexpected surprise, and it made a big difference in how she felt about putting in extra hours to deliver on tight deadlines. The next several weeks are only going to get busier, so take time to check in with those you care about—and especially with yourself. For me, that means prioritizing those unexpected personal calls in the middle of the day to calm nerves about college curriculums.

A big thanks to all our ACRP members—the disruptors and those making the disruption functional on the front line. We appreciate you and all that you do!

Clinical Researcher—November 2021 (Volume 35, Issue 8)

CHAIR'S MESSAGE

Making and Maintaining an Impact on Research Integrity

Erika Stevens, MA, 2021 Chair of the Association Board of Trustees for ACRP

How can ACRP impact research integrity?

Maintaining research integrity is a complicated process in clinical research. While regulations require protection of human subjects{1} and demand good clinical practice (GCP) in clinical research,{2} oversight of these activities in the United States sits with the U.S. Food and Drug Administration (FDA).{3}

The National Institutes of Health defines research integrity as performing research with verifiable methods and result reporting with adherence to regulations.{4} The Office of Research Integrity provides further clarification on shared scientific principles in the conduct of research to include honesty, objectivity, accuracy, and efficiency.{5} Noncompliance with federal regulations found through FDA inspections are classified as "No Action Indicated," "Voluntary Action Indicated," or "Official Action Indicated."{6}

Despite the regulations, potential inspections, and penalties, research misconduct exists in the clinical research industry. Research misconduct includes "fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results."{7} The *Code of Federal Regulations* established a final rule on research misconduct in 2005{8}; the possible administrative sanctions include debarment from federal funding and required corrective actions, inclusive of certification of research.{9}

While the FDA has oversight of inspections through the Department of Health and Human Services, the Office of Inspector General identified issues with FDA's ability to adequately oversee safety inclusive of biologics: "Ensuring that participants in clinical trials are protected from significant risk presents an additional challenge to the Department both during the initial approval process and after drugs, devices, and biologics are approved by FDA when post-marketing trials are conducted."{10} Unfortunately, even when reporting of misconduct to FDA occurs, the agency may not have the required resources to respond. For example, in September 2020, a report filed

with the agency indicated several concerns from a research organization participating in COVID-19 trials.{11}

ACRP provides simulated GCP training to support researchers' adherence to the regulations.{12} Further, ACRP offers pathways to certification for clinical research coordinators (CCRC), clinical research associates (CCRA), principal investigators (CPI), and ACRP certified professionals (ACRP-CP), and provides subspeciality designations for those working in the medical device (ACRP-MDP) and project management (ACRP-PM) arenas.{13} ACRP continues to be at the forefront in clinical research training and certification, and strives toward meeting its mission of "promoting excellence in clinical research" and its vision for clinical research to be "performed responsibly, ethically, and professionally everywhere in the world."{14}

I wish you all the best jusqu'a la prochaine fois (until the next time),

References

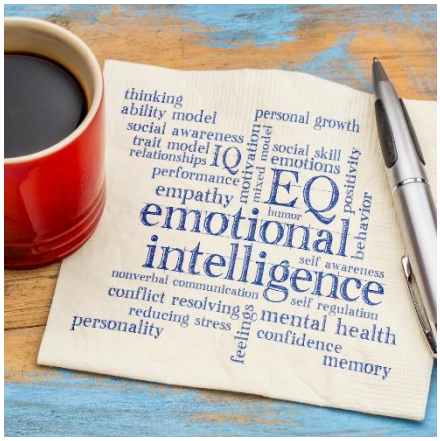
1. https://www.ecfr.gov/on/2018-07-19/title-45/subtitle-A/subchapter-A/part-46
2. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e6r2-good-clinical-practice-integrated-addendum-ich-e6r1
3. https://www.fda.gov/science-research/science-and-research-special-topics/clinical-trials-and-human-subject-protection
4. https://grants.nih.gov/policy/research_integrity/what-is.htm
5. https://ori.hhs.gov/education/products/RCRintro/index.html
6. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspections-database-frequently-asked-questions#classification
7. https://ori.hhs.gov/content/chapter-2-research-misconduct-federal-policies
8. https://ori.hhs.gov/public-health-service-phs-policies-research-misconduct-%E2%80%93-42-cfr-part-93-%E2%80%93-june-2005
9. https://ori.hhs.gov/federal-research-misconduct-policy
10. https://oig.hhs.gov/reports-and-publications/top-challenges/2011/issue12.asp
11. https://www.bmj.com/content/375/bmj.n2635
12. https://acrpnet.org/courses/good-clinical-practice-gcp-simulation/
13. https://acrpnet.org/certifications/
14. https://acrpnet.org/wp-content/uploads/dlm_uploads/2020/01/Mission-Vision-Goals.pdf

Clinical Researcher—November 2021 (Volume 35, Issue 8)

PEER REVIEWED

How the Pandemic Has Magnified the Importance of Soft Skills for Clinical Research Associates

Agnieszka Finlayson, MSc, MA



Before the COVID-19 pandemic, soft skills for use in clinical trial environments were already challenged,{1} with each clinical research associate (CRA) left to his or her own devices in forming and improving upon these skills. CRAs hardly, if ever, received formal training on what soft skills are needed to thrive in this demanding role; only with time and experience could they, like anyone else, strengthen their communication practices.

Without formal training, the most natural way for humans to communicate effectively is in person, which is what traveling CRAs relied upon. However, during lockdown, any sort of face-to-face communication was restricted. CRAs could communicate with busy sites only through digital means. Site staff still needed support and training, but CRAs no longer had the luxury of doing this while being present physically for utilizing both verbal and non-verbal cues to build rapport with site staff.

As with other industries, the clinical research enterprise turned to online tools to get important work done in pandemic conditions. Teleconferences became video calls, onsite visits became remote visits, and face-to-face conversation became e-mails. As these were not proper substitutes for the lack of physical interaction, the difficulty that CRAs already faced with training and motivating site staff was intensified.

While CRAs are intensively trained in hard skills such as source data verification or investigational medicinal product accountability, as well as the systems required to support their work on the study, soft skills are usually ignored. It was as if forgotten that a CRA's role is effectively dealing

with people—be they site staff, fellow CRAs, or vendors. The time for CRAs to start focusing on their soft skills has already passed us; however, the importance of not doing it has never been laid as bare as it is now.

The author of this article believes that post-pandemic online courses are a perfect medium to teach any required soft skills, as has been written about by others in *Clinical Researcher*.{2} By being better at communicating and dealing with people, CRAs (as with everyone involved in clinical trials) can not only improve the quality and efficiency of their studies, but they can improve the quality and efficiency of their lives.

What are Soft Skills?

Soft skills are human skills,{3} as Simon Sinek puts it. They are a combination of various capabilities and ways in which we interact with others. Empathy, communication, listening, and general "people skills" are all examples of soft skills. They are the qualities which distinguish us from each other and from any machine or a robot.

Through an optimal use of these skills, we can connect with other people. We can understand what is important to others and, through this, we can communicate in a way that motivates and inspires them. Soft skills can be improved with training, practice, and time.

The opposite of soft skills are hard skills—the things you need to know in order to do your job. These are normally industry- and job-specific skills and, as is the case with CRAs, are also attained through training, practice, and time.

How Do Soft Skills Apply to the CRA Role?

Empathy

CRAs work in a highly regulated yet dynamic environment. Functions around CRAs may be under various pressures while trying to meet conflicting deadlines. CRAs have to be empathetic to the people they work with to keep doing their work without being demotivated or taking things personally. If site staff are stressed and struggling and CRAs cannot empathize with them, it will be almost impossible for CRAs to build great collaborative relationships{4} with sites.

Communication

CRAs are a liaison between the sponsor and the site staff. Study management may sometimes need to achieve aggressive deadlines and inadvertently may put pressure on CRAs. However, site staff need to stay focused and motivated. It is therefore necessary for CRAs to communicate urgency to, and help set priorities for, site staff, but at the same time not induce panic or stress because that would be counterproductive.

Each site is different in what support it needs from CRAs to do the best work. For instance, some site staff like phone call reminders to do something, others prefer e-mail reminders, while others get offended by either. Some people require e-mails that are quick to read and a list of tasks that are arranged by priority, while others require explicit and detailed instructions.

CRAs must tailor their approach to each individual. Consequently, CRAs have to be able to listen carefully to all the messages that site staff convey, both verbally and non-verbally. CRAs have to look for cues about their site's level of workload in order to have the site prepared for a deadline and be confident it can meet that target.

Motivation

CRAs are in a unique position of having to motivate their site staff and create effective collaboration without having any mandate over them. Without soft skills, this will simply not be possible. Site staff are usually allocated to multiple studies and CRAs need to stay on top of them—no matter how many other pots they are stirring—for the good of their particular sponsor's study. CRAs can help site staff be effective, efficient, and motivated to do a high-quality job. This is a key area where CRAs with strong soft skills will prevail over those with weaker soft skills.

Before the Pandemic

Normally, people exercise their soft skills face-to-face. When next to another human being, we use our social skills and emotional intelligence to "read" people and respond appropriately in order to build rapport and communicate effectively. Once a relationship with a study team or site staff is established in person, that usually increases collaboration.

When CRAs or site staff find themselves inevitably under pressure, they will be more forgiving due to the rapport that has already been established. Because site staff have met their CRA in person, they will trust them in the future and vice versa.

When CRAs join a new company, such as a contract research organization (CRO), they get a lot of training. However, a vast majority of this training is about hard skills and technical aspects of the job: the tenets of Good Clinical Practice, creating and following standard operating procedures and study-specific procedures, etc. As CRAs develop and gain more experience, they are assigned to more complex studies and receive more study-specific training. CRAs become well-trained and well-prepared for the complexity posed by the indications and protocols they are working on, but only on a technical level.

Unfortunately, at no time are CRAs provided with extensive soft skills training, if they are provided with any at all. Often, CRAs need to rely on their own wits and support and advice from other CRAs through informal networks in order to get their tasks completed. This state of affairs is tolerated because at the end of the day, CRAs meet their goals and it is physical interactions that help get them over the line.

During the Pandemic

The COVID-19 pandemic brings challenges at every level for everyone. Lockdowns, travel bans, and social distancing each bring their own set of difficulties that CRAs, like anyone else, must overcome. In-person interaction, with all its fragile elements that were previously done subconsciously and taken for granted, is severely restricted.

CRAs can no longer attend site visits. Everything moves online and is done remotely. In addition, CRAs have to train site staff in this new way of doing things. Soft skills that were already lagging behind hard skills become even more essential. Across the industry, new tools and new processes are quickly adopted, causing friction and hassle in what was already a fragile network of relationships. These new tools bring with them new challenges.

Zoom Etiquette

Video conferencing comes to the fore to replace face-to-face meetings. Even though this mode of communication is not exactly new, the extent to which we are currently using it is unprecedented. Tools like Zoom, Teams, and Skype, all video-conferencing interfaces, become part of our human interaction with anyone who does not live in our household. Out of all the available video conferencing tools, Zoom is probably the most famous for both the right and wrong reasons. Therefore, this article will focus on Zoom as an example of all similar tools.

Because communicating face to face is nothing like communicating on Zoom, we needed some guidelines to convey our message via this medium as accurately as possible. Collectively and informally, participants in Zoom calls created a set of rules to communicate online effectively called Zoom etiquette. While Zoom etiquette is difficult to define and out of scope of this article, one key example is through eye contact.

When participating in a video call, each participant has to make a choice between looking directly into the camera (to give the other participants the illusion of having a real physical conversation) or looking at the monitor (to get non-verbal cues via their video streams). This means that it is now impossible to have a conversation and hold eye contact at the same time.

Any video conversation will always lack the synchrony of a conversation as you may miss facial expressions when looking at the camera, or other participants may miss your gestures as they are looking at their camera while mimicking physical eye contact (instead of looking at their monitor).

Zoom etiquette rules come about to lower expectations and tell participants that even if others are not “looking” at us through their cameras, it is because they are paying attention to what we say, hence looking at their monitor. This is particularly true if people’s setups mean their cameras are out of position relative to their monitors.

Through these video calls, soft skills are “working overtime.” The disconnect between video and face to face communication needs to be compensated with soft skills in order to foster a positive human-to-human interaction. To top it all off, the psychological reward that we would normally receive from physical communication which would make us alert is not really there.{5} This leads to Zoom fatigue.

Zoom Fatigue

Zoom fatigue is a term used to describe the tiredness, anxiety, or worry resulting from overusing virtual platforms. Video conferences are mentally exhausting.{6} Sensory overload may also be playing a part. We are now using our eyes, ears, and facial expressions in disjointed ways which we are not used to.

Staring at a monitor all day is tiring. The lack of movement and the required high level of focus all come together to exhaust us. On the top of it, we are forced to "overuse" our soft skills, foster attentiveness while on camera, and we have to do all this without the natural energy boost from a physical conversation.

Zoom fatigue can be contagious. When you are speaking to somebody who appears tired, that tiredness can transfer to you. If it is your first call for the day and their sixth, you will know it and start feeling their fatigue, too. This, unfortunately, is the flip side of being an empathetic CRA.

Languishing

There is also an emotional, long-term effect of the pandemic. A feeling of stagnation and emptiness that a lot of us are feeling is known as languishing. It is claimed to be the most dominant emotion of 2021.{7} Adam Grant explains languishing as an emotion that lies between depression and flourishing. Critically, we need soft skills to combat it—we need to feel connected to others, to be a part of a community.

CRAs are in a great position here because of the meaningful nature of the work they do. As an industry, we need to keep reminding ourselves of the good we are collectively doing and stay focused on achieving our goals. We need to make sure that we remember the bigger picture of getting the medicine to market and the patients who will benefit.

After the Pandemic

What will become of the skills and solutions that we used during the pandemic when the dust settles and we reach a "new normal"? It is hard to think that everything we learned during the

pandemic (e.g., communicating through video conferencing, remote working, and online training) will fade away as our state of practice reverts to how it was before.

A balance of the "old" and "new" must be the way forward. In this, the "old" will include tasks such as making traditional physical site visits when required or attending investigator meetings and seeing everyone involved in a study face to face. Meanwhile, the "new" may include further remote or flexible working, more remote monitoring visits than prior to the pandemic, and an appreciation of when to use video conferencing.

Ultimately, we will all organize our time differently and start prioritizing human connections above all. In-person interaction and time spent with family and friends will prevail over superficial interactions.

If these auxiliary interactions can be permanently shifted online, much like during lockdown, we can gain more valuable time for ourselves. Furthermore, if more "static" content can be consumed via online pre-recorded media, then we can further gain time and flexibility by eliminating commutes and pausing or playing back content as needed.

Time to Appreciate Soft Skills

No matter what the outcome is after the pandemic has subsided, what has been made clear is that our current lack of focus on soft skills in general, let alone their training and development, is not a sustainable position. We managed to stumble our way through awkward Zoom calls and e-mails without context or tone of voice. These lessons will not go away quickly, nor will the repercussions of not being prepared.

Soft skills training and development must go hand-in-hand with hard skills training and development. By ignoring effectively half of a CRA's role, pharmaceutical companies and CROs are only harming themselves, their studies, and ultimately the investigational medicinal product.

The Right Tool for the Job

One of the instrumental methods that CRAs, and indeed anyone else in clinical research, should be utilizing going forward is the medium of online courses. We have collectively enjoyed not losing

time on commutes or long travel to training sessions at the office where in-person training can have negligible results.

Instead, taking our lessons learned from the pandemic, we can shift all of this online. Online courses allow CRAs to complete them at their leisure, working in-between their personal and professional needs. As new training is made available, it is simply posted online for CRAs to complete. Much like hard skills training, more advanced soft skills courses can be made available to CRAs as they progress in their careers.

While it took a global pandemic to shake the status quo, ultimately this disruption will be of benefit to the industry as a whole. CROs and pharmaceutical companies massively benefit by having CRAs trained in both hard and soft skills, as this will lead to having more efficient sites, reduced study costs (compared to before the pandemic), and higher quality studies with the potential of going to market sooner. Meanwhile, CRAs are more likely to be happier with their roles leading to lower churn and creating an upwards spiral of skill and experience. Ultimately, a healthy work-life balance for CRAs (and indeed all clinical research professionals) means better studies and better results.

References

1. https://acrpnet.org/2017/06/20/soft-skills-hard-part/

2. https://acrpnet.org/2018/01/16/training-crcs-cctrn-using-online-learning-platform/

3. https://www.youtube.com/watch?v=o9uzJ0LgvT0&t=201s

4. https://www.forbes.com/sites/amyblaschka/2019/02/19/the-soft-skill-gary-vaynerchuk-simon-sinek-and-oprah-winfrey-say-is-crucial-for-leaders/?sh=28ca76d84e9b

5. https://www.psychiatrictimes.com/view/psychological-exploration-zoom-fatigue

6. https://www.psychologytoday.com/us/blog/the-desk-the-mental-health-lawyer/202005/virtual-platforms-are-helpful-tools-can-add-our-stress

7. https://www.nytimes.com/2021/04/19/well/mind/covid-mental-health-languishing.html

Agnieszka Finlayson, MSc, MA, (aga@whitewisteriaacademy.com) is Founder and Director of the White Wisteria Academy, which focuses on training for clinical research associates and is based in the United Kingdom.

Clinical Researcher—November 2021 (Volume 35, Issue 8)

PEER REVIEWED

Documenting Training Using REDCap

Carol Brooks, BHS, ACRP-CP; Robin Ryan, MPH, CCRP

The International Council for Harmonization (ICH) Guideline for Good Clinical Practice (GCP) states, "Each individual involved in conducting a [clinical] trial should be qualified by education, training, and experience to perform his or her respective task(s)."{1} It is of great importance that the trial can be reconstructed as it happened. An external observer should be able to confirm that the current protocol was followed, the data and information collected were accurate, and the staff conducting the trial were properly qualified and trained to do so. Proper documentation will provide an audit trail that will validate the trial if, and when, required.

Protocol-specific training can delay the activation of a study as well as a potential subject's enrollment. Systemizing and documenting staff training for multidisciplinary trials is challenging. For those cooperative group studies with multiple investigators and other study staff, it can especially be quite challenging. Schedules are full and often are geographically scattered. Accommodating time to schedule an in-person group training or finding time for individuals to complete self-training is difficult. For some individuals, completion of training can be overlooked since it is not necessarily a top priority for busy clinicians.

Children's Mercy Hospital is a pediatric medical center located in Kansas City, Mo. that integrates holistic care, translational research, breakthrough innovation, and medical education to provide care for those 21 years old and below. The not-for-profit hospital has received national recognition from *U.S. News & World Report* in 10 pediatric specialties.{2} Its mission is to "transform the health, well-being, and potential of children, with unwavering compassion for those most vulnerable." The research program at the hospital includes nearly 100 physicians and scientists actively participating in research studies. Research is especially important in the oncology section, as most of the active trials are treatment options for patients to whom they could be beneficial.

Past Training Methods at Children's Mercy

Prior to 2018, the Oncology Section at Children's Mercy did not have a systematic method of training and documenting protocol-specific training compliance. Pediatric oncology research includes numerous treatment and non-treatment protocols for the various types of cancer. Children's Oncology Group (COG) is the main consortium that sponsors research in the Oncology Section. Efforts to maintain current training and documentation among our COG team were difficult, as we have more than 30 active COG protocols and more than 60 COG site personnel to train. While in-person trainings and e-mail documentation were utilized, these were not consistent or easily validated. Additionally, e-mail created extra work for the coordinator—to keep track of the progress of each team member and forwarding reminders for those pending completion.

In 2017, the research team within the Division of Hematology/Oncology/BMT was restructured to create a separate regulatory coordinator role. Part of the rationale for this separation of regulatory work from patient-facing study coordination was to be more rigorous with training and documentation thereof. The oncology research team wanted to identify an efficient way to distribute and track completion of protocol-specific training for study team members.

An informal review of training options was undertaken by the institution's research leadership. This involved looking at available technology for possibly accommodating the needs. In 2018, it was decided to determine if REDCap could effectively document training.

Elements of REDCap

REDCap (Research Electronic Data Capture) is a secure web application from Vanderbilt University that can be used to build and manage online surveys. There is no special software installation needed for utilization. If institutions have this application available, there are no fees charged to use it. This web application is versatile and is used widely among different fields. At Children's Mercy, REDCap was already being used for databases, survey tools, research data collection, and e-consenting. If the team could utilize REDCap for training, it would provide an easily available option.

Rationales for choosing REDCap as a training platform included the fact that the survey tool is able to track the progress of completion. Using the survey feature, the regulatory coordinator can send protocol training to the identified study team. Survey recipients do not need special access to REDCap to get a link to review the training and attest to completion. For each personnel added to the participant list, REDCap will show if they have responded to the survey. REDCap will also show if there will be an upcoming invitation that is scheduled to be sent.

Further, REDCap can be set up to send automatic e-mail reminders. Keeping up with manually reminding delinquent personnel to complete training is time consuming. With REDCap, the frequency of the reminders, date, and time are all customizable.

REDCap also features an application that can generate a report of those who have submitted the surveys which can then be used as a training log. The reports are customizable, but can contain the date training was complete, timestamp, names, e-mail, and/or signatures (see Figure 1).

Figure 1: Example of a REDCap-Generated Training Log

Record ID record_id	**Survey Identifier** redcap_survey_identifier	**Survey Timestamp** redcap_training_template_timestamp	**I have reviewed the [PROTOCOL #] training [MATERIALS].** reviewed	**After reviewing the [MATERIALS]** questions	**Questions or comments** comments	**Name** name	**Please add your email address to attest to your completion. You wil ... s form without this completed.** email	**Date** date	**Provide Signature:** signature	**Complete?** redcap_training_template_complete
1		06-22-2020 12:10	Yes (1)	I have no questions or comments (1)		Test 1	test1@gmail.com	06-22-2020	Download	Complete (2)
2		06-22-2020 12:11	Yes (1)	I have questions or comments (2)	Insert questions here.	Test2	test2@gmail.com	06-22-2020	Download	Complete (2)

Development of a Training Template

There are a few important items that should be included in the survey for training. At our site, initial training includes a PowerPoint module reviewing the important aspects of the protocol. This PowerPoint is usually provided by the sponsor, but, if one is not available, it can be created by the site's principal investigator (PI). Attaching the written protocol and/or manuals for reference and as supplemental material is always a good idea.

For amendment training, the survey includes a summary of changes, an updated PowerPoint module, and the newly amended protocol. Within the survey, a section is included to attest that review of training materials has been completed, a block to include questions and/or concerns, a name stamp, an e-mail address stamp, and a date stamp (see Figure 2 for the training template).

Implementation of REDCap for the Oncology Team

Implementing this new format for the COG team was challenging due to the large number of team members. A simple workflow, however, was established and made to fit to accommodate the various COG protocols.

As new protocols are activated, the regulatory coordinator pushes out initial protocol training surveys to appropriate team members. The team member roster is determined at the time of protocol start-up. Required amendment training is determined based on content of the amendment.

Any amendment changing therapy, eligibility, or other major changes to the protocol will be forwarded as a REDCap survey training by the regulatory coordinator. All training surveys include a deadline date for completion.

As the training deadlines pass, the regulatory coordinator will communicate to the PI the list of delinquent team members. The PI alerts these individuals, and if failure to comply continues, repercussions will include the removal of the team member(s) from the study. Figure 3 is a representation of the workflow explained above.

Figure 2: REDCap Training Template

As a person involved in [DEPARTMENT] research, you are asked to review the training for [STUDY TITLE]

Thank you!

Because you participate or may participate in the conduct of [DEPARTMENT] trials at Children's Mercy, you are required to complete this training. Please review the [LIST MATERIALS SUCH AS PROTOCOL OR SLIDES] attached. At the end of this survey, you will be required to attest to having completed the review.

If you have any questions or comments, there is also a place to note that.

[PROTOCOL Number/Title] Required Training

Attach training slides

Attach protocol here

ATTESTATION

I have reviewed the [PROTOCOL #] training [MATERIALS]. Yes

No

* must provide value

Reset

After reviewing the [MATERIALS] I have no questions or comments

* must provide value

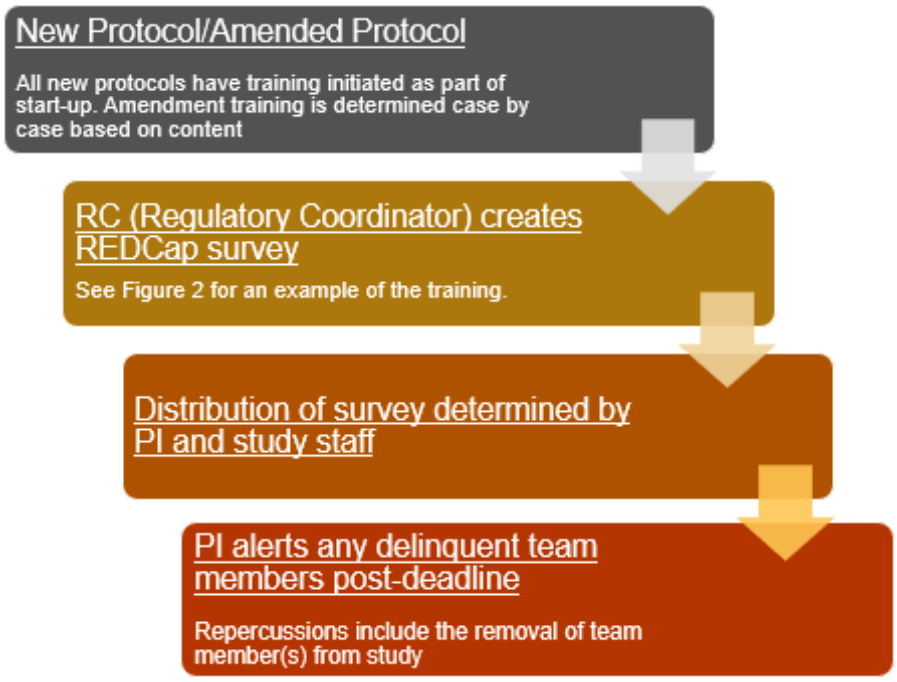
I have questions or comments

Reset

SIGN AND SUBMIT

Please add your e-mail address to attest to your completion. You will not be able to submit this form without this completed. * must provide value	
Date	Today M-D-Y
Provide Signature:	
Submit	

Figure 3: Representation of Workflow for Protocol Training



When this training system was implemented, it was with the knowledge that there would be a learning curve and that turnaround for completion was going to be less than satisfactory. Numerous auto-generated reminders were necessary to get people "onboard." As team members became more familiar with the process, compliance improved dramatically.

Organization for the regulatory coordinator with multiple studies and amendments also required a system. With multiple training surveys in process at once, and most deadlines for completion in a four- week range, a tracker of active surveys was developed. Another useful tool is a master study team list. As the studies the lead author is involved in can include as many as 65 people from multiple disciplinary teams at one time, a spreadsheet listing the personnel, their e-mails, and roles comes in handy. With this, all that is needed is to copy and paste e-mail addresses into the study participant list when a survey is created. The lead author also created a document listing e-mail templates for when she sends REDCap survey invitations or reminders, and has developed e-mail templates for initial training for new studies and applicable amendment training.

Dissemination Within the Institution and to Other Institutions

Once our process was established, it was shared at the Fall 2018 COG Poster Session. The lead author has met numerous people interested in learning more about using REDCap surveys for training. Upon follow-up a year later to each inquiry, three (from the University of Florida, CancerCare Manitoba, and Dana- Farber Cancer Institute) have expressed gratitude and intend on using REDCap as the main platform for training documentation.

Within Children's Mercy, the REDCap training process is now being used within other sections of the hospital with resources on how to create the successful workflow shared with research teams that inquire. The institutional Research Quality team recommends the REDCap training system to other teams during monitoring visits and provides contact information to learn more.

Conclusion

Attributes for good documentation as described by the U.S. Food and Drug Administration are attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring, and available.{3} REDCap meets all these attributes and creates an audit trail of documentation reflecting compliance with GCP. REDCap has become the main tool used for providing and documenting training at the Children's Mercy Hospital—Oncology Section, as this effort has been very effective and user-friendly.

References

1. See ICH GCP E6(R2) at https://www.ich.org/page/efficacy-guidelines.
2. https://health.usnews.com/best-hospitals/area/mo/childrens-mercy-hospitals-and-clinics-6630340/pediatric-rankings/cancer
3. https://conductscience.com/portfolio/alcoa-c/

Carol Brooks, BHS, ACRP-CP, (cmbrooks@cmh.edu) is a Clinical Trials Coordinator (Regulatory) for oncology/bone marrow transplant studies with Children's Mercy Hospital in Kansas City, Mo.

Robin Ryan, MPH, CCRP, is Research Program Director, Division of Hematology/Oncology/Stem Cell Transplant, Children's Mercy Hospital.

Clinical Researcher—November 2021 (Volume 35, Issue 8)

SPECIAL FEATURE

Inclusion of Pregnant Participants in Clinical Research: The History, the Concerns, and the Path Forward

Tara Coffin, PhD, MEd; Sharad Adekar, MD, PhD, CIP

Clinical research facilitates medical advances, improving treatment options for a multitude of health conditions. In fact, the sole act of participating in a research study has been demonstrated to improve health outcomes for individual research participants and patients alike.{1} However, the benefits rendered from research results and participation are limited to the groups and sometimes communities that are represented in the research setting, leaving underrepresented groups less likely to benefit clinically.{2} For example, Black and Indigenous People of Color{2,3} and pregnant people{4,5} are critically underrepresented in the clinical research setting, and care options available to these groups, along with adjacent health outcomes, suffer as a result.

This discussion will focus on the inclusion of pregnant people in clinical trials.

The Problem with Underrepresentation

By excluding pregnant people from research, health professionals are effectively disregarding the fact that these patients fall ill, and that people who are sick give birth.{6} As a result, there are relatively few “on label” medications and medical devices available for pregnant people.{6,7}

For example, a pregnant person seeking treatment for gestational diabetes is often limited to “off label” treatment options—medications or medical devices that have not been formally tested in a prospective interventional study with pregnant participants. Without adequate research data, such

treatments are often not approved for use in this population. That doesn't mean they are inherently unsafe, it just means that the safety profile is unclear for pregnant individuals, simply due to the lack of data.{7} Real-world evidence may be available, but when investigations are forced out of the research setting and into the "real world," we effectively move an element of risk out of a well-controlled environment and into the clinical setting, where there may be fewer safeguards.

Why are These Groups Underrepresented?

Underrepresentation of pregnant participants, as well as persons of childbearing capacity, is frequently attributed to safety concerns about parental and fetal exposure, associated liability with risks, response from regulatory authorities, and finally preferences of the pharmaceutical industry. This may be the case even when there is possible benefit to the pregnant person and fetus/newborn. In essence, pregnant participants are treated like a vulnerable population{8} as part of a conservative approach fueled by the thalidomide tragedy.

In the late 1950s, thalidomide was touted as an anti-morning sickness drug and was widely used in Europe and the United Kingdom. It didn't take long for concerns to emerge, as parents who took thalidomide during pregnancy gave birth to children with limb differences and other medical problems. Use of thalidomide (which had never been approved for use in the United States) was severely restricted and significant changes were made to the U.S. Food and Drug Administration drug approval process in response, but the issue made a lasting impression.{9}

Animal studies which seek to describe potential teratogenicity inconsistently predict teratogenic effects in humans, leaving many researchers poised to exclude pregnant participants out of concern for unknown risks to the pregnant participant and the fetus.{10} This conservative approach also extends to lactating individuals.

Research teams may also be concerned that the inclusion of pregnant participants may confound the interpretation of study data. Pharmacokinetics may be influenced by the normal physiologic changes that take place during pregnancy, including changes to binding proteins, the increase in blood volume observed in a pregnant body, metabolic changes, changes in body weight, and other issues that impact the bioavailability and metabolism of drugs.{6,11} The physiologic

changes (and signs and symptoms) that occur with pregnancy may be difficult to distinguish from adverse events possibly related to the study interventions. Pregnancy-related tests and interventions that may need to occur to monitor and protect the health of the pregnant person and the fetus may conflict with study procedures or impact the assessment of study outcomes.

Complicating the situation further, there are ambiguous guidelines concerning the inclusion of pregnant people in clinical research.{12,13} With these concerns in mind, additional guidance and acceptance are needed to better understand when and how to include pregnant participants in research studies, addressing representation while maximizing potential benefits and minimizing risks.{7}

Improving Representation of Pregnant Persons

Currently, there are a few ways in which pregnant participants are included in research, including the following:

- Minimal risk research, when research procedures pose no additional risk (to the pregnant participant and the fetus) outside what the participant would encounter in daily life.
- In some cases, a participant of childbearing potential may become pregnant while enrolled in a research study that excludes pregnant people. Depending on the nature of the research, the investigator may determine that it is still in the participant's best interest to receive the study treatment, or the study treatment may be stopped, but the participant and infant(s) may be followed to assess outcomes.
- A pregnant participant may be enrolled in a study evaluating treatment for a condition that exclusively impacts pregnant people. Depending on the investigational treatment, inclusion of pregnant participants in this case would typically occur after safety and efficacy has been demonstrated in healthy adults.
- Finally, there may be situations when a pregnant participant is enrolled in a study evaluating a treatment for a condition that is not exclusive to pregnant people, but that may benefit the pregnant person or fetus. Even though the compassionate use programs are not considered as research studies, we have seen some change during the COVID-19 pandemic where pregnant patients received treatment under compassionate use programs. The overall representation of pregnant participants in clinical studies including vaccine studies is still low—even in the current COVID-19 pandemic.

Even in situations when there is the potential for benefit, research teams may be reluctant to include pregnant participants for many of the reasons detailed above. However, this conservative route quickly becomes a justice issue, with underrepresentation contributing to existing health disparities. The Double Effect Doctrine offers guidance for when pregnant patients may be included in research,{4} providing another view of the Belmont Report's principle of beneficence.

The Double Effect Doctrine explains that an act, such as exposure to an investigational treatment during pregnancy, 1) must have good intention, 2) must exclude any intentional harm, 3) must ensure that the benefit is a product of the treatment, rather than a product of the harm, and 4) the benefit must be desirable enough that it "makes up" for any harm experienced on the way.{4} Importantly, the research team should consider how the investigational treatment stacks up against currently available treatments. In other words, how does the risk-benefit ratio of the investigational treatment compare to the risk-benefit ratio of the standard of care pregnant patients would receive outside the study?

Such guidance may assist research teams in addressing a situation when a pregnant participant may otherwise be eligible for participation in a research study that could benefit them or the fetus, but also may pose a potential risk. From a regulatory perspective, inclusion of pregnant participants is ethically permissible, if it meets the criteria for approval under the 45 CFR 46 Subpart B of the *Code of Federal Regulations*.{14} These regulations are what the institutional review board will adhere to and capture in the careful risk-benefit analysis.

Delivering the Data

While the above considerations offer guidance for when it is ethical to include pregnant participants, what about the practical consideration of data interpretation? As mentioned earlier, pregnancy introduces biological changes that may confound research results.

With this issue in mind, research teams may consider including pregnant participants as a separate cohort when the risk-benefit ratio is favorable. Interpretation of these data would take into account the physiological changes that take place during pregnancy. This will also facilitate

additional pregnancy-specific safeguards unique to the research setting. These accommodations could be built into a protocol and drive enrollment.

Alternatively, these plans could be written into the protocol with the intent of creating a pregnancy-specific cohort if a participant becomes pregnant while participating in a study, and the study doctor and the patient determine that it is in the patient's best interest to continue receiving the investigational treatment. Small cohorts of this sort would likely lack statistical power, but could generate hypotheses and help build upon existing safety profiles.

Conclusion

Safety will always be paramount, but as long as pregnant people get sick (and sick people get pregnant), there will be situations where healthcare can be improved by including pregnant participants in the clinical research setting. By including pregnant participants when the risk-benefit ratio is favorable, researchers create opportunities to improve resources for on-label treatment options for pregnant people, but also effectively move the "risk" associated with using new therapies out of the clinical setting and into the research setting.

With appropriate safeguards in place and with a critical look at the risk-benefit ratio, pregnant participants can be included in the research setting, without facing another thalidomide disaster. In essence, if safety is truly at the heart of this issue, there are times when the safest option may be to include pregnant people in research.

References

1. https://obgyn.onlinelibrary.wiley.com/doi/full/10.1111/1471-0528.14528
2. https://www.frontiersin.org/articles/10.3389/fcell.2019.00074/full
3. https://extramural-diversity.nih.gov/diversity-matters/underrepresented-groups
4. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4303058/
5. https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-017-2402-9
6. http://www.gfbr.global/wp-content/uploads/2017/04/GFBR-2016-report-ethics-of-research-in-pregnancy-FINAL.pdf
7. https://peh-med.biomedcentral.com/articles/10.1186/s13010-019-0081-8

8. https://link.springer.com/chapter/10.1007/978-3-319-26512-4_3
9. https://www.sciencemuseum.org.uk/objects-and-stories/medicine/thalidomide
10. https://www.jacc.org/doi/full/10.1016/j.jacbts.2019.10.008
11. https://muse.jhu.edu/article/245708
12. https://obgyn.onlinelibrary.wiley.com/doi/10.1111/jog.13899
13. https://care.diabetesjournals.org/content/39/6/1004
14. https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/common-rule-subpart-b/index.html

Tara Coffin, PhD, MEd, is IRB Chair/Vice Chair at WCG IRB, which conducts ethical reviews of clinical research protocols and studies and has more than 200 members on boards accredited by the Association for the Accreditation of Human Research Protection Programs, Inc.

Sharad Adekar, MD, PhD, CIP, is Medical Chair at WCG IRB.

Clinical Researcher—November 2021 (Volume 35, Issue 8)

OPINION

Are “Siteless Trials” a Paradox or Oxymoron in Modern Clinical Research?

Mary Costello

Everyone’s familiar with paradoxes that seem contradictory, but still true—for example, “less is more”—and oxymorons that combine contradictory words but are contextually logical, such as “jumbo shrimp.” However, there’s one phrase dominating recent clinical headlines that makes little sense no matter its label—“siteless trials”—an oxymoron disguised as a paradox. How can decentralized clinical trials (DCTs) be compared to trials that bypass sites completely?

It’s too big of a leap, a contradiction of terms, a wolf in DCT’s clothing.

Sites are the center of clinical research, even in a decentralized trial, and are crucial for success and health outcomes. This is especially true for companies seeking to expand access to clinical research opportunities to underserved communities where trust remains a barrier.

“Given our medical establishment’s history of mistreatment, there’s a deep distrust and negative perception of clinical research by many black Americans and other minority groups,” said Melissa Opraseuth, COO of par 80, which provides care coordination services and technology to more than 11 million patients and recently launched a network to improve health equity and access to research among health center patients.

Opraseuth, who is a member of Medable's new Site Network Council, continued, "Local sites are a lynchpin to overcoming some of these sensitive barriers because they foster a more intimate and ongoing personal connection with patients. Principal investigators don't just do blood draws; they do community outreach and educate patients. There's familiarity."

How Did We Get Here?

Clinical trial designs today span a wide continuum, ranging from 100% site-based trials, where all interactions with study participants occur at the site, to 100% decentralized trials, where all interactions are remote and leverage wearable technologies supplemented by occasional visits by trial nurses to the participants' homes. The latter are often referred to as "siteless," but the vast majority are hybrid. This is true even as decentralization, accelerated by the COVID-19 pandemic, jumped to a 77% CAGR between the second halves of 2019 and 2020, according to data from more than 1,000 trials.{1}

Even so, "siteless" trials are not optimal. The site, together with trial coordinators, should remain a key part of the trial ecosystem, whether the trial leverages a single site or a network of coordinated sites, local pharmacies, community clinics, and home health aids supported by wearable devices and platform solutions. Technology simply cannot replace people.

Recent industry experience offers a relevant analogy. Between 2005 and 2015, many pharmaceutical companies rapidly adopted salesforce automation tools for their sales representatives while cutting sales jobs at the same time. From its height at 101,000 sales reps in 2005, the number of reps in the U.S. market dipped to 76,000 by 2010 and hit its lowest level of just 66,000 in 2012.{2} Accenture research showed that one in four pharmaceutical sales rep interactions was replaced by digital alternatives, but it did not achieve the intended effect of improved profitability.{3} The strategy backfired and sales dipped. Now, there are more than 100,000 pharma sales reps in the U.S., according to various estimates, and overall revenues have been setting records year over year.{4} The ship has righted itself.

Today, we are on the doorstep of a similar technology revolution, largely accelerated by COVID-19 when clinical researchers had no choice but to leverage innovative digital technologies to continue their work. Now, the excitement around technology's potential is soaring again. The

innovative technologies enabling remote or decentralized trials have the potential to dramatically reduce the burden for patient participation in research and for sites hosting studies.

Recent data back this claim, with at least half of the respondents to a recent Signant Health survey described in *Clinical Researcher* anticipating "strong" use of eConsent (63%), eSource (56%), remote monitoring (55%), and wearables (50%) post pandemic.{5} Further, a recent Oracle survey found 76% of respondents have recently accelerated their adoption of decentralized clinical trial methods.{6} Decentralized trials are here to stay just as a new generation of sites are, too.

Caution: Watch What You Say

Industrywide, there is confusion over terms like "virtual," "remote," and "siteless" when applied to trials. A review of current literature on DCTs will demonstrate phrases like "decentralized" and "hybrid" blur the distinction between trials with or without patient site visits. The DCT concept traces back to a 2018 Clinical Trials Transformation Initiative white paper that specifies that "DCTs can be conducted as 100% decentralized or as a hybrid study in which the DCT offers the additional flexibility of incorporating both in-person visits and virtual visits into the study as appropriate."{7} Although the intent was to standardize terminologies, this definition proposes that "decentralized" and "hybrid" are synonymous.

The COVID-19 pandemic has changed industry perspectives on the meaning of "siteless" or fully virtual trials versus hybrid DCTs. A July 2020 Society for Clinical Research Sites (SCRS) survey found that a mere 3% of clinicians "had participated in a completely virtual trial, where all visits are conducted remotely."{8} However, a December 2020 SCRS white paper (downloadable by visitors who supply demographic information at https://myscrs.org/learning-campus/white-papers/), based on a May-to-July survey, found that use of "the fully virtual approach" had risen to 15.46%. More recent data from Avoca found that 22% of respondents conducted "siteless" trials pre-pandemic; 17% had done so during the pandemic "but not because of it"; and 12% had done so "because of COVID-19."{9}

The clinical trial lexicon will continue to evolve, but "siteless" should not receive a dictionary reference.

The Future is NOT All or Nothing

For the near future, most research sponsors will leverage the hybrid approach and adopt some elements of decentralization in trial design. For example, a trial protocol may require initial in-person site visits prior to patient enrollment and then leverage remote tools to maintain communication and data collection.

Hybrid protocols are highly beneficial for trials involving rare and ultra-rare diseases, which often require patients to receive specialized and invasive treatments at designated sites. Routine lab tests and follow-up appointments, however, can be handled in a decentralized manner at local healthcare facilities, community health clinics, pharmacies, or through telehealth to reduce the burden of participation for both patients and their caregivers. In this example, patients appreciate the comfort of a familiar face on a more regular basis but under circumstances that create less stress or take less time.

According to Opraseuth, “Technology is changing the traditional site-research model, but to make research better. It’s a balance. Sites will look very different in five or 10 years, but they will still be here. In fact, I hope we will have more clinical research site locations, even if they look differently than they do now, so they can be embedded in the communities where patients live, work, and play. It’s the best way to familiarize and educate patients so they will be more comfortable participating in research.”

Rather than a “siteless” trial, the better approach is to build fit-for-purpose clinical research with a next-generation site at its center. Some trials might be, in fact, wholly decentralized, but even those should incorporate a site whose role may be a different iteration of what a traditional site looks like today. The best-performing trials will continue to have human interactions between physicians and patients. They will not be without sites—rather, they will be enabled with the technologies needed to reduce burdens and improve efficiency. That is what well-designed technology should do—both for patients and for trial administrators.

Community Site Connection Drives Diverse Participation

Among other benefits, DCTs promise to improve the recruitment and retention of trial participants and increase diversity in trials, thereby improving the efficacy of approved therapeutics for all.

Given that only seven of 100 enrolled patients complete trials,{10} ensuring patient retention through all means is vital to trial execution and research efficiency. Frequent interactions with trial physicians, care coordinators, and staff are vital to these goals—and while technology can supplement in-person interactions to increase those touches, it cannot completely replace the human connection.

"Compassion and inclusivity combined with a community-based approach to patient recruitment is essential," noted Opraseuth. "As more people within a community become comfortable with clinical research and have a positive experience, they are more likely to become evangelists. Others will listen to familiar faces, and patient recruitment will not be the barrier to research that it is now."

The proof is in the people—31 cancer drugs have been approved since 2015, yet 24 of the trials for them included fewer than 5% African Americans, despite Blacks making up 13.4% of the U.S. population. Asians account for about 6% of the U.S. population but account for less than 2% of clinical trial participants; and Native Americans and Alaska Natives account for 2% of the U.S. population but were not represented at all in two-thirds of drug trials.{11}

People of all ethnicities are foundational to clinical research, and the physician/patient relationship is the building block for long-term participation in a trial. It also builds trust, something that is especially critical today as public confidence among minority communities has eroded dramatically since the start of the pandemic. Patients develop close relationships with their study coordinators, who spend time engaging on a very personal level and deliver tender care. Coordinators and site staff give hugs, call patients by their first names, and nurture the relationship. In fact, this is the number one determinant of a patient's completion of a trial. A "siteless" experience takes this away.

DCT technology should assist site administrators in fostering a trusted patient relationship, while at the same time provide improvements in data quality, data collection, study startup speed, informed consent, regulatory compliance, and all the other goals of a well-run trial. In the aforementioned Avoca report from 2020,{9} respondents indicated the two most substantial benefits of DCT technologies are retention of study participants (with a mean score of 4.2 on a 1–5 scale) and diversity of study participants (3.9). Technology along with real-life patient engagement are the one-two punch to overcoming two of our greatest trial obstacles.

Besides the obvious obstacle to better patient recruitment and retention of travel to and from trial sites, patients can also suffer from limitations in handling modern technologies, ranging from lack of familiarity with smartphones to poor WiFi connections in their homes. In these cases, site-driven, hands-on guidance is paramount to the success of a DCT—and is another instance where the personal touch provided by the staff at a high-quality trial site is important.

The Role of Sites Will Evolve, Not Fade

While technology can make onboarding patients into trials easier thanks to eSource, eConsent, and remote monitoring tools, there's a misconception that these technologies eliminate the need for sites. On the contrary, new DCT technologies open the door for growth and new expertise, including more tech support, but do not change the fact that there needs to be a centralized location for research and the back-end aspects of a well-executed trial.

The life sciences industry is having the wrong conversation. Rather than focusing on cutting sites out of research, we need to discuss how to better support sites. Technology companies and site managers should not be at odds with each other. Instead, they should be collaborators in providing the best patient experience and enabling successful trials.

References

1. https://www.appliedclinicaltrialsonline.com/view/why-decentralized-clinical-trials-are-the-way-of-the-future
2. https://www.biopharmadive.com/news/spotlight-trends-pharma-sales-force-digital-marketing/504949/
3. https://www.pharmavoice.com/article/2016-01-salesforce/

4. https://insights.axtria.com/blog/measuring-the-value-of-providing-call-plans-to-the-field-sales-teams
5. https://acrpnet.org/2020/01/14/delving-into-econsent-industry-survey-reinforces-patient-centricity/
6. https://www.oracle.com/news/announcement/covid-19-the-tipping-point-decentralized-clinical-trials-111820.html
7. https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwiupur5q9zzAhXrj3IEHVAgCgsQFnoECCYQAQ&url=https%3A%2F%2Fctti-clinicaltrials.org%2Fwp-content%2Fuploads%2F2021%2F06%2FCTTI_DCT_Recs.pdf&usg=AOvVaw214PvI43tbWTf27pRJal_S
8. https://myscrs.org/learning-campus/white-papers/
9. https://www.theavocagroup.com/wp-content/uploads/2021/06/2020-Avoca-Industry-Survey-Report-Innovation-and-Diversity.pdf
10. https://www.advarra.com/resource-library/retention-in-clinical-trials-keeping-patients-on-protocols/
11. https://www.statnews.com/2018/09/19/black-patients-cancer-clinical-trials/

Mary Costello (mary.costello@medable.com) is Head of the Site and Investigator Network for Medable. She has spent more than 30 years in the healthcare and clinical research fields, working in commercial leadership roles with such large organizations as Covance and Thermo Fisher and, more recently, supporting the growth and expansion of eClinical Solutions and Elligo Health Research. She also has served on several industry advisory groups and is a founder and board member of BioAustin.

Clinical Researcher—November 2021 (Volume 35, Issue 8)

SITES & SPONSORS

Advanced Therapies: Strategies for Success in Clinical Development

Jessica Merryfield

Advanced therapy medicinal product (ATMP) development is on the rise. According to the American Society of Gene + Cell Therapy, there were 1,745 gene therapies in development in May 2021, 70% of which were in preclinical studies, and more than 1,300 of these candidates were in development for oncology, the most active therapeutic area.{1}

Given that ATMPs—and the patient journeys associated with them—are fundamentally different from traditional biopharmaceuticals, designing and conducting trials of these novel therapeutics involves unique regulatory and clinical considerations. In this article, we explore strategies for successful start-up and execution of ATMP studies.

Engaging with Regulators

As the regulatory framework for ATMP development can be complicated, early and proactive engagement with regulators is essential. Requesting feedback on data and biomarker requirements, the need for long-term follow-up (LTFU), and opportunities for expedited review and approval will help sponsors shape their clinical development programs. In the U.S., for example, the regenerative medicine advanced therapy (RMAT) designation offers a streamlined approval pathway for ATMPs that address unmet medical needs for serious or life-threatening conditions.

The European Union (EU) regulatory landscape is a patchwork of European Medicines Agency (EMA) and individual member-state legislation. While the EMA has separate legislation for ATMPs and genetically modified organisms (GMOs), this distinction may not exist at the member-state level, and non-GMO ATMPs may still be subject to GMO legislation that requires additional approvals.

Understanding Stakeholder Priorities

ATMPs are typically costly and complex treatments. Understanding the needs of patients and families, providers, and payers is critical for clinical and commercial success. Involving patients and families in protocol design is useful because their preferences may influence study feasibility, and regulators may require patient experience data. Additionally, early engagement with patients, families, and advocacy groups can help to create enthusiasm and increase awareness about the study.

Conversing with healthcare providers and key opinion leaders can help sponsors understand standard of care and validate proposed assessments and outcome measures. It also can be valuable for identifying clinical champions and collaborators who have access to the target patient population.

From a payer perspective, the long-term value of ATMPs is not yet known, as their durability is still unproven. The high upfront costs of what can often be one-time treatments may require new payment models to increase payer acceptance and patient access. Understanding payer priorities and limitations can help sponsors define their target product profiles and the data needed to support reimbursement for their ATMPs.

Evaluating Sites

Selecting qualified study sites is essential to the development program’s success. Sites should be familiar with the therapeutic area and have experience handling and administering the ATMP under investigation. Key criteria for qualifying sites include:

- Past performance in similar studies
- Proven access to the target patient population
- Existence of GMO-specific standard operating processes and best practices, if the ATMP is a GMO
- Experience with the mode of administration, especially if the study involves intracranial delivery or other specialized procedures

To limit site burden, it may be useful to try to align study protocol requirements with standard institutional policies and workflows. Developing a rigorous training program and site-specific execution map can help reduce operational complexity and enhance site performance.

Certain types of ATMPs may require additional site certifications or approval. In the U.S., human gene transfer products require approval from an institutional biosafety committee. In the EU, the regulatory environment may be less straightforward. Study start-up activities for gene therapy products may vary depending on the regulatory pathway and the requirements of individual member states.

Considering Lesser-Known Sites

Established sites with proven track records in ATMP studies are highly sought after and may have long wait lists. In an increasingly crowded space, sponsors seeking sites will compete against both investigator-initiated projects and other ATMP programs for attention at these go-to centers. Sponsors may find it useful to widen their search to include other leading, but lesser-known, academic medical centers and community-based hospital systems that have the necessary accreditations and facilities to administer ATMPs.

As of September 15, 2021, 295 U.S. centers have been accredited by the Foundation for Accreditation of Cellular Therapy.{2} In the EU, 284 centers have been accredited by the Joint Accreditation Committee ISCT-Europe & EBMT, with an additional 138 centers in process as of August 31, 2021.{3} Working with lesser-known sites also may broaden access to patients who might otherwise not be interested in—or eligible for—clinical trial participation due to travel limitations.

Enhancing Study Participation

As the number of ATMP clinical trials increases, so does the challenge of recruitment. Sponsors are tasked with making study participation as easy as possible—not just for patients and families, but also for sites and study staff. For rare diseases trials with small and geographically dispersed study populations, sponsors may need to take extraordinary measures—such as relocating families for prolonged periods—to enable study participation. For some ATMPs, it may be feasible to centralize therapeutic administration and then coordinate local follow-up. Sponsors should consider the costs of travel, lodging, and other study amenities that maximize convenience and minimize burden for participants and their families.

Enabling Cross-Border Enrollment

Cross-border enrollment, in combination with remote data collection for studies that require LTFU, offers the potential to increase patient access to investigational ATMPs. With cross-border enrollment, patients enroll in clinical trials at sites outside their countries of residence. Depending on the ATMP, the patients may return to their home countries or be required to remain in proximity to the sites for some period of time.

Cross-border enrollment may be suitable for studies of ATMPs targeting rare and ultra-rare diseases, due to low prevalence and the need for specialized site facilities. Cross-border trials do, however, come with additional regulatory and operational considerations. For example, all patient-facing documents need to be translated into the language of the patient and submitted to the ethics committee (EC) or institutional review board (IRB) in the host country. If screening or pre-screening activities will be conducted in the patient's country of residence, additional regulatory authority and EC/IRB notifications or approvals may be required. Moreover, in most countries, sharing of medical records is governed by data protection legislation, so any records provided by local healthcare providers need to be anonymized prior to translation.

Sponsors considering cross-border enrollment for ATMP studies will also need to plan for:

- Travel arrangements, including special accommodations that may be needed to ensure the safety and comfort of the patient

- Contingencies if disease progression affects travel capability and protocol-specific assessment timings
- Maintenance of standard of care, including shipping of country-specific drugs to avoid discontinuation of treatment
- Cultural or social connectivity opportunities, especially for extended stays

Supporting Site Success

ATMP administration generally requires tight coordination among sites, laboratories, hospitals, and sponsors. To support site success, sponsors should consider developing a site onboarding and training program that includes detailed product manuals and checklists to help ensure that all study procedures are performed on time and according to the protocol for every patient. It also may be helpful to provide sites with coding and billing guides, adverse-event management sheets, and other product-specific resources. Performing practice runs of the entire protocol is useful for identifying and mitigating potential risks and increasing confidence among site staff.

Planning for Long-Term Follow-Up

Historically, the 15-year LTFU period has been reserved for lentiviral vectors. With the increasing use of gene editing technology, however, it is likely that the number of investigative therapies subject to the LTFU requirement will increase. When LTFU is required, retention becomes even more challenging. Patients may relocate or transition from pediatric to adult care, and sponsors may need to add new sites using investigators or local healthcare providers who were not affiliated with the initial study.

mHealth and offsite or home nursing visits can be helpful options for reducing patient burden and cost during the follow-up period. These options allow certain clinical trial obligations or study-related assessments and data collection to be completed in the comfort of the home and at the convenience of patients and their caregivers. By bringing the trial to the patients, sponsors also may benefit from increased study engagement.

Technologies such as eSource and eConsent also may be useful tools for facilitating LTFU due to the following considerations:

- eSource enables flexible direct data capture and instant data validation, with an audit trail for each datapoint containing the full lifecycle of the data.
- eConsent helps simplify the consenting process, particularly for complex, highly technical studies, by converting paper forms into an electronic format that may include multimedia components to facilitate patient understanding and education. There are also teleconsent options that can be completed from any remote location, eliminating the need to travel to the site.

Sponsors also may consider the use of satellite or community sites, which enable local follow-up during the LTFU period.

Conclusion

With their life-changing potential, ATMPs are a harbinger of hope for patients with unmet medical needs and their families. Research in this field is robust, and the clinical trial landscape is growing increasingly competitive. To succeed, sponsors must stay abreast of evolving regulations, involve patients and families in the process, and focus on optimizing study operations and execution at the outset of clinical trial development planning.

References

1. https://pharmaintelligence.informa.com/resources/product-content/asgct-pharma-intelligence-quarterly-report-q2-2021
2. https://accredited.factwebsite.org/
3. https://www.ebmt.org/jacie-accredited-centres

Jessica Merryfield is Senior Director for Program Delivery with Premier Research. She has more than 20 years of pharmaceutical industry experience at overseeing activities for early regulatory authority engagement through approvals.

Clinical Researcher—November 2021 (Volume 35, Issue 8)

RECRUITMENT & RETENTION

Overcoming the Logistics Challenges of Global Studies

Scott Gray

Although the United States contributes more than two-thirds of global trial participants, according to recent statistics published by ClinicalTrials.gov, only 32% of registered trials occur solely within U.S. borders.{1}

Cross-border travel creates significant complexity for trial sponsors and clinical research organizations (CROs), who must contend with complicated travel logistics, participant and family unease, international regulatory compliance, and more. Although many of these challenges have been brought to light in recent years, COVID-19-era travel restrictions have only exacerbated these issues.

Meanwhile, challenges with participant retention delay 80% of clinical trials by at least one month, with potential losses of $600,000 to as much as $8 million per day.{2}

Most CROs who partner with pharmaceutical companies do not have the network or resources necessary to manage highly sophisticated and diverse logistics requirements. Organizations that understand these limitations can engage companies focused on patient support services, providing personalized and comprehensive logistical support to help patients reach distant trial sites.

Patient support services are an investment in trial performance. They help reduce the burden placed on patients, caregivers, and site coordinators while improving trial retention rates and accelerating the commercialization of new treatments.

Navigating Border and Travel Issues

Navigating international travel, particularly for extended periods, requires logistics expertise, a global network, and ample time and persistence. In addition to travel coordination, documentation (passports, visas, pandemic-era forms, etc.) and health requirements (immunizations, timed COVID-19 testing, etc.) must be accounted for and arranged.

Engaging support services to navigate these issues is even more critical for clinical trials in the rare and ultra-rare disease space. For these studies, sponsors must cast a much wider geographic net and increasingly compete for the attention of a limited number of eligible participants to satisfy recruitment and maintain retention.

Rare and ultra-rare disease trial participants often have complex needs when traveling. They may require medical equipment or medical services between their origin and destination, and site visits often involve the patient and a caregiver, as well as family members. With both governments and private industry increasingly incentivizing and launching trials for rare and ultra-rare diseases,{3} the need for patient support services continues to grow.

It takes a team of patient coordinators around the globe to help manage these unique challenges. Recently, a coordinator helped a patient navigate the logistical challenges associated with traveling to Russia, a country with relatively few domestic airports or rail stations compared to other regions of a similar size. The coordinator's local understanding of ground transportation options and travel routes was essential in getting the patient to the trial site quickly and safely.

In another case, a Venezuelan couple had to prove their need for access to urgent medical treatment. Patient coordinators helped them obtain special humanitarian permissions to relocate across borders to participate in a long-term trial. After several years living abroad, a coordinator helped repatriate them back home.

Reducing Financial and Emotional Burdens

Dealing with a chronic or serious health issue while preparing to participate in a clinical trial is extremely stressful for patients and their caregivers. The financial burden can be intense,

particularly for families traveling to countries with higher costs of living. Patient coordinators manage prepayments and expedite reimbursements and stipends on behalf of trial sponsors and CROs, making it easier for patients to commit, participate, and remain in their clinical trials.

When traveling for extended periods, it is not unusual for families to contend with sudden changes in currency value, resulting in unexpected cost increases and unplanned expenses. In Argentina, for example, inflation can cause travel and lodging costs to double in only a matter of months. A patient support coordinator can help sponsors, CROs, and families anticipate and manage these challenges in real-time. A coordinator currently working with patients in Brazil is in regular contact with Banco de Brasil and Caixa Bank to facilitate the prompt release of participant reimbursement funds, as these transfers are often flagged and frozen as potential money laundering.

Several studies, including a 2019 National Institutes of Health survey on trial retention among military service members,{4} have demonstrated a high correlation between timely patient reimbursement and trial retention. These studies underscore the importance for sponsors and CROs to have expert, compliant advisors overseeing the financial complexities of trial participants.

In addition to addressing financial burdens, coordinators help reduce emotional, psychological, and safety barriers to trial participation. One patient coordinator shared, “I look for nice hotel rooms with amenities for families, so the children feel like they’re on vacation and are less likely to focus on or fear going to the trial site.”

Another coordinator recently shared a story about a patient traveling to an appointment in Rio de Janeiro. His car got caught in the crossfire between the army and members of a local gang. The patient, his caregiver, and their driver hid underneath the car until the shooting stopped. Since that experience, the patient coordinator now plans routes that avoid known conflict areas and arranges armored vehicles to transport patients in regions prone to violence.

Providing Linguistic and Cultural Assistance

Patients traveling abroad often need interpreters to explain study requirements and patient obligations during treatment at the trial site. Coordinators from patient support service providers

who speak the participant's native language can assist them from recruitment to patient consent through study completion.

Translation services can mean the difference between life and death for some trial patients. In one example, the family of a pediatric patient living in Israel received special permission from Israel's Minister of Health to import life-saving medication. The family did not speak the native language of Hebrew, which made obtaining treatment difficult. A tri-lingual patient coordinator who spoke the family's native language and Hebrew and English could explain the severe condition of the patient and their urgent medical needs to authorities and help find medical personnel to administer the drug safely.

Often being from the same country is not enough; the coordinators need to be local to the patient. The country of Spain, for example, has four official languages—Spanish, Catalan, Basque, and Galician. One coordinator shared, "When participants know their coordinator is local, it makes the connection stronger." However, building solid connections extends far beyond language proficiency. Studies also suggest that among other trust-based factors, "understanding cultural and social dynamics of the population under study prior to investigation" increases trial retention.{5}

Anticipating the medical needs of patients and helping them navigate the dynamics of the healthcare market are also essential for trial participants around the world. A patient from Ukraine living in Poland needed a specific treatment typically offered free for Polish citizens, meaning there was little to no market for private payers. A patient coordinator called healthcare facilities throughout the country to track down a provider willing and able to provide the necessary treatment.

Guiding Patients Through Pandemic-Related Restrictions

At the height of the COVID-19 pandemic, travel restrictions changed rapidly and varied greatly between countries. Many sponsors and CROs found themselves unprepared to conduct global clinical trials amid the fluctuating restrictions. Investing in additional resources such as patient support services helped them retain study participants while maintaining trial integrity.

Patient coordinators prepared trial participants and families for potential travel issues and managed daily changes in guidelines impacting travel, lodging, visitor policies, and vaccination recommendations. One European patient planned to fly to Spain for a study visit, but air travel and public transportation were not viable due to COVID-19. To ensure she made it to her visits, her patient coordinator scheduled two extended private car trips and arranged overnight accommodations for both the patient and driver.

These examples represent a glimpse into the challenges presented by cross-border travel. Understanding and proactively managing financial, emotional, linguistic, cultural, and pandemic-era barriers allow participants of all income levels, ages, and locations to participate in clinical trials. This assistance, in turn, enables trial sponsors and CROs to boost recruitment, retention, and population diversity. As trials increase the need for cross-border travel, patient support services will play an increasingly central role in successful clinical trial outcomes.

References

1. https://www.fda.gov/files/drugs/published/2015---2016-Global-Clinical-Trials-Report.pdf
2. Clinical trials and their patients: The rising costs and how to stem the loss | Pharmafile
3. https://credevo.com/articles/2019/12/15/rare-diseases-regulatory-incentives-for-development-of-orphan-drugs-us-europe/
4. https://doi.org/10.1016/j.conctc.2019.100353
5. https://doi.org/10.1093/her/cyl095

Scott Gray is co-founder and CEO of Clincierge, a provider of patient support services for clinical trials. Since 2015, the company's patient coordinators have managed travel and reimbursements in more than 140 clinical trials around the world.

Clinical Researcher—November 2021 (Volume 35, Issue 8)

GOOD MANAGEMENT PRACTICE

Why Public Sector Biobanks Must Support Biotech Companies

Robert Hewitt, MB BS, PhD

Biotech companies play a key role in developing new drugs, diagnostics, and vaccines. They are the risk-takers and innovators on which big pharma often depends for new opportunities. They translate promising ideas generated in academia into potential therapies, vaccines, and diagnostics that can be evaluated by the pharma industry.

Biotech companies around the world need reliable patient samples to do their important work, but often have great difficulty accessing such samples. A large part of this unfortunate problem is that patient samples generally originate in public sector healthcare facilities. Being in the private sector, biotechs have limited access to public sector resources.

Clinical research professionals may be involved in the oversight and management of hospital biobanks. For example, they may be members of biobank access committees. This makes it vitally important that they are aware of the difficulties that biotech companies have in gaining access to high-quality samples.

About Hospital Biobanks

Hospital biobanks generally exist in teaching hospitals and academic centers; they are publicly funded and are established for the purpose of supporting research in associated universities and institutes. They require dedicated staff and expensive equipment like liquid nitrogen freezers, so the start-up and maintenance costs are considerable. The start-up phase may be funded by research grants, but it is harder to obtain research funding for the ongoing maintenance costs of these unglamorous yet essential core facilities.

Thus, many biobanks survive on funding provided by their own institution. A typical hospital biobank may have two or three staff working extremely hard on a shoestring budget to provide professionally curated clinical samples for in-house researchers.

One way in which biobanks can develop an independent income stream is to charge a fee for the provision of patient samples. This must be approached with caution, because it is unethical and illegal in many countries to make a profit from the sale of human tissue. However, biobanks are allowed to charge a carefully calculated cost-recovery fee.

Access to a biobank's samples is decided by scientific and ethical committees that are populated by various institutional members (e.g., scientists, clinicians, administrators, ethicists) with the frequent addition of a patient representative. These committees judge the merits of each application for samples and operate according to institutional policies.

One issue that sometimes reduces the likelihood that samples will be provided to industry is the concern that some patients may not want their samples to be used by commercial organizations standing to make a profit from them. Whether patients react in this way is very much dependent on how matters are presented to them and how the societal value of industry research is emphasized, if at all.

In many cases, these biobanks are open to applications from industry—in theory, at least. Biobanks of different specialties can be found in various national and regional biobank directories, but unfortunately their level of interest in working with industry is often obscure and this can make useful biobanks hard to find.

Why Small Biotechs and Big Pharma Are Very Different

Sample access problems are a bigger for biotech companies, which are generally smaller and younger organizations, than for established pharma companies. For one thing, these pharma companies will have had many years to develop networks of hospital suppliers of samples. For another, the fact that pharma companies sponsor clinical trials gives them access to hospitals, doctors, and patients. Many large pharma companies have teams of dedicated clinical sample procurement staff and their own in-house biobanks, which often dwarf the biobanks found in typical hospital biobanks.

In contrast, a small biotech company, particularly a start-up, has none of these advantages and certainly cannot afford to have staff dedicated to sample procurement.

The Commercial Broker

In general, the easiest way for biotech companies to obtain samples is to get them from a commercial broker. These companies have the sole focus of providing clinical samples for industry, and naturally they are driven by the need to make a profit.

Brokers generally find it difficult to obtain their samples from hospitals and biobanks in western Europe, where ethical concerns about the sale of human tissue are prevalent. Some countries in Eastern Europe and parts of Asia provide a more important source. The United States is one industrialized country where brokers are much better accepted. Many U.S. hospital biobanks are willing to supply brokers. The majority of brokers are based in the U.S., and many have sample procurement operations that extend across global networks.

Scientifically speaking, the main disadvantage of using a broker is that sample provenance may be lacking (brokers tend not to reveal their sources for business reasons). Along with this, there may be uncertainty about the quality of the samples and hence the reliability of resulting research.{1}

Better Solutions

So, what can be done to provide industry, and particularly small biotech companies, with high-quality, reliable samples? This is important because all of us as patients (past, present, or future), depend on the drugs, diagnostics, and vaccines that biotech companies make possible. The answer is that some practices that need to be encouraged, while others need to be discouraged.

Encouraging Best Practice

It must surely be best practice for researchers to obtain biosamples direct from source—that is to say, directly from the hospital biobank that collected the sample from the patient. In this way, they can have the most confidence that samples and their related data have been collected professionally.

To encourage this, we need to make it easier for biotechs and hospital biobanks to find each other. Biotechs can search a number of biobank directories to find suitable partners, but this is often a difficult approach. Many of the biobanks listed may not be open to working with industry or may give companies a low priority. Use of biobank directories often results in a lot of disappointing false leads.

One initiative that offers a solution to this problem is an online platform called Biosample Hub, which is dedicated to bringing biotechs and academic/hospital biobanks together and restricts its use to these two groups. It includes a directory of biobank members, a directory of biotech members, a directory of sample requests, and social networking features. The only reason for biobanks to be on the platform is to supply industry, so the problem of false leads is minimized. One other key aspect of the platform is that it is a not-for-profit entity, so this overcomes the aforementioned profit-seeking ethical concerns related to some biobanks.

Another way to encourage this is to make it more attractive for hospital biobanks to work with industry. In other words, there need to be more and bigger incentives. The problem is that, for many hospital biobanks, local academic researchers get top priority, other academic researchers get second priority, and industry gets third priority, if at all. This is natural, because these biobanks are established as institutional initiatives, with the purpose of serving their own institution. The focus of academic biobanks is very much on research productivity as measured by publication impact, and unfortunately industry is restricted in when and how much work it can publish for reasons of intellectual property.

The incentive of funding is certainly the most viable option for getting hospital biobanks to work with industry. Biobanks need funding and often operate on very limited budgets. Much has been written about biobank sustainability, especially in terms of financial sustainability. One approach is for biobanks to charge industry both a cost-recovery fee for its samples and a fee for additional sample processing services like cutting sections and extracting DNA. This approach seems to be especially well understood by French biobanks, which apply the term “valorization” to the process of adding value to and yielding value from their samples.

Almost half of the biobanks that have joined Biosample Hub are French and most offer additional sample processing services. All French hospital biobanks are certified according to the French norm NF S96-900, which must also make them more attractive to industry.

Another approach is to make external grant funding of biobanks conditional on service to industry. This could be aided by making it mandatory for funded biobanks to make their sample access policies public, by requiring annual reports on sample distribution, and perhaps even by having industry representatives on sample access committees. Patient representatives are well accepted, so why not industry representatives?

An example of the kind of support needed is provided by the following statement from the UK Medical Research Council (MRC): *"The development of new drug therapies, and diagnostic and screening tests, to the point where they can be made sufficiently widely available to benefit human health, is crucially dependent on commercial involvement. Therefore access by the commercial sector to samples of human material collected in the course of MRC-funded research should be facilitated, where this is consistent with our mission."*{2}

Discouraging the Use of Samples That Lack Provenance

New regulations are likely to have a major impact on how biotech companies source clinical samples. An example is provided by the new European regulation governing manufacture of *in vitro* diagnostic devices (IVDs), which comes into force on May 26, 2022. To demonstrate conformity, makers of IVDs must show that the biospecimens used to validate their devices have undergone acceptable pre-analytic processing. This will require the sourcing of samples from biobanks that are certified to meet specific quality management standards.

As a result, diagnostics companies will need to obtain samples from known sources that provide full provenance information. This need for provenance information will put pressure on commercial brokers to change their business practices and reveal the source of their samples. One way for brokers to manage this is to avoid their own circumvention by use of binding contracts with both the provider and the requestor of samples, thus preventing them from interacting independently of the broker. Of course, not all companies or biobanks will be comfortable with such restrictions.

There are technological solutions that can be used to ensure the reliability of provenance information of samples, and use of these will be beneficial. The use of blockchain is one example; this digital technology allows tracking of the transfer of biospecimens from the patient donor to the researcher in a secure, transparent, and ethical manner, with all transactions documented in an incorruptible, shared digital ledger.

What Do Patients Want?

The time seems ripe for a major change in the way clinical samples are sourced by industry and by smaller biotech companies, in particular. Now more than ever, the general public understands the importance of biotech and pharma companies. As a result of the pandemic, we all understand why supporting these companies is important.

Thus, the question is: Do we want to allow biotech companies to have access to the best quality patient samples, in order to speed up development of new therapies, diagnostics, and vaccines? Or do we want this access to be blocked for a variety of possibly short-sighted reasons? As patients (past, present, and future), we need to deliberate and decide—then, perhaps, patient advocacy organizations will act on our behalf.

References

1. https://www.appliedclinicaltrialsonline.com/view/point-view-traceability-and-transparency-should-be-mandatory-all-human-biospecimens
2. https://www.ahspartnership.org.uk/images/cmsimages/TCTU/Human_Tissue_and_Biological_Samples_for_use_in_Research_-_Operational_and_Ethical_guidelines%5b1%5d.pdf

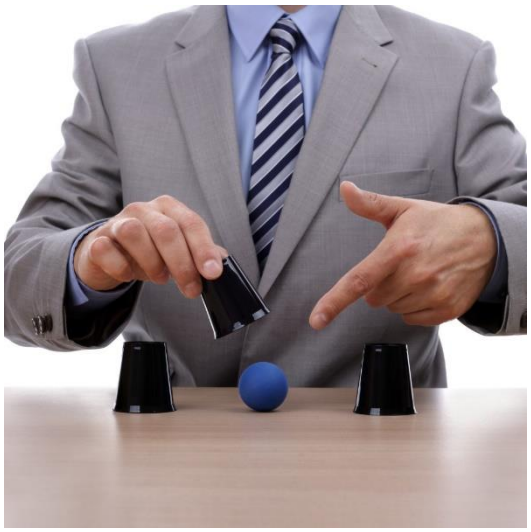
Robert Hewitt, MB BS, PhD, is the founder of Biosample Hub, an international, not-for-profit platform connecting biotech companies looking for samples with biobanks that have ethically sourced samples available.

Clinical Researcher—November 2021 (Volume 35, Issue 8)

PRESCRIPTIONS FOR BUSINESS

The Funding Disparity in Clinical Trials for CKD: Why What You See is Not What You Get

Kurt Mussina, MBA



There's no disputing that chronic kidney disease (CKD) is a public health crisis. In the U.S. alone, CKD affects approximately 15% of the population and is a leading cause of death.{1} Internationally, the global estimated prevalence of CKD is 13.4% and the disease "directly affects the global burden of morbidity and mortality worldwide,"{2} according to a 2019 study published in *Advances in Experimental Medicine and Biology*.

One would expect that with this vast impact on populations, clinical research trials would be in lockstep with prevalence. However, this is not the case. On the contrary: the funding for, and the number of, clinical research trials for CKD lag significantly behind its incidence and behind other diseases. For example, in Q2 2019, there was only one late-stage nephrology study for every 39 cancer studies. As for the funding disparity, the National Institutes of Health (NIH) provided 10 times more funding for cancer than for kidney disease.{3} In fact, it has been noted that nephrology has lagged behind its disease prevalence in the annual percentage of randomized control trials performed globally since records have been kept—more than 50 years.

The number of clinical trials dedicated to kidney disease is striking in how far it lags other therapeutic areas. Unexpectedly, it is not anywhere near commensurate with its prevalence. For instance, between 2016 and 2020, there were 22,486 clinical trials for cancer while there were less than 10% of that amount—only 2,227 clinical trials—for kidney diseases. This has been noted as a growing public health issue (see The Underrecognized Epidemic of Chronic Kidney Disease).

As stated definitively in one study on federal funding for kidney disease research "NIH funding for kidney disease research is inadequate."{4} As such, it is critically important that this oversight be recognized and addressed immediately to help meet the needs of the 37 million people currently living with CKD in the United States alone.

Research investment often correlates with advances in treatment, which can be clearly seen in cancer and HIV care. According to one source, the American Society of Nephrology's Research Advocacy Committee "estimated that the [NIH] spent only $30 on research annually for each [CKD)] patient in the [United States] while it spent over $500 for every patient with cancer and over $2,500 per individual with HIV infection. It is therefore not surprising that the cancer and HIV areas have experienced the greatest technological healthcare advances over the last few decades."{5}

Understanding the Divide

Why does this divide occur? For many, the funding-to-disease ratio may seem obvious: diseases with the heaviest impact on human suffering and/or mortality receive the most funding to advance treatment options. However, this is not necessarily the case—and the reasons for it can be confounding.

An article in *The Washington Post* offers a thoughtful summary of the, at times, seemingly random allocation of funding: "The differences are an illustration of just how complex—and sometimes surprising—national decisions are about how to allocate research money. It might seem that research dollars should follow public health impact, with the diseases that cause the most harm attracting the most money. Overall, most diseases do follow that general pattern. But the outliers can be significant—HIV currently gets 10% of the NIH budget—and highlight just how complex and baffling this process can be, influenced by factors that range from the amount of scientific opportunity to make progress to the level of human suffering."{6}

Focusing On the Ethics

If treating all people equitably is one of the fundamentals of medicine, then we must look at the ethics as they pertain to funding and research opportunities. According to an article in the

American Journal of Public Health published by researchers from Harvard Medical School, "Kidney disease is an underrecognized but common public health issue that is expensive to treat and disproportionately affects vulnerable populations. As physicians and public policy professionals involved in the treatment and research of kidney disease [we must recognize that] increased research investments are a critical step to reduce the public health burden of kidney disease."{4}

As with many diseases, the cost of CKD is intense regarding human suffering and from a monetary perspective. Caused primarily by diabetes and high blood pressure, people living with advanced CKD may deal with a plethora of symptoms including lethargy, poor appetite, and poor sleep quality. The statistics on mortality are even more sobering. Using United States Renal Data System (USRDS) data, even when the numbers are adjusted for age, gender, race, comorbidity, and prior hospitalizations, patients with CKD have a 2.3 times higher mortality rate than those without the disease. For those with more advanced CKD (stages 4 or 5), that adjusted mortality rate increases to a 400% increase over patients without CKD.{7} Therefore, males between 40 and 44 with ESRD can expect to live for 10.9 years longer, compared to 36.5 more years for men in the U.S. general population.{8} Notably, the USRDS data use the information from Medicare beneficiaries, which is not a perfect representation of CKD at the population level, but this does highlight issues with this more vulnerable subgroup.

Questions remain regarding the underrepresentation of nephrology when it comes to investment in clinical trials. These are difficult but important questions that deserve exploration, including:

- Does the pharma industry benefit more from conducting research in other areas such as oncology?
- Where do the National Kidney Foundation and American Society of Nephrology fit in addressing this disparity?
- Is it that there simply are no appropriate drug targets in renal disease currently?
- Are the commonly used endpoints the most valuable? How can they be refined, accelerated, or otherwise improved?
- Where is precision medicine in nephrology and why is its development lagging behind other therapeutic areas? What can we do to advance in this area?

Education and Advocacy

There is a great need to better promote current renal disease clinical trials to nephrologists. Beyond the specialists, we need to deliver more wide-reaching education about kidney diseases to the public and to healthcare providers. Improving CKD will rely on a "call to action" advocating for the unique needs of this patient population. We must continue to press for more clinical research trials for the millions of people across all demographics who are living with CKD.

The impact of advocacy will be crucial to engaging patients directly with their kidney health and understanding the impact of CKD. The advantages of early diagnosis and treatment of CKD cannot be overstated. Patients who are diagnosed in the early stages of kidney disease have the chance to make lifestyle changes, learn how to manage their disease, and live longer. We need to convince and recruit these patients for CKD clinical trials. With their help as partners, we can work quickly to uncover innovations for treatment and prevention.

By raising awareness about CKD for scientists, physicians, patients, and funders, we can meaningfully increase the amount of research attention CKD receives. Together, we can move toward a future where CKD has the appropriate amount of clinical study support, relative to its prevalence, needed to reduce its impact. Only by supporting this foundational clinical research can we understand kidney disease and decrease the suffering of those impacted by it.

References

1. Centers for Disease Control and Prevention. Kidney Basics. https://www.cdc.gov/kidneydisease/basics.html
2. Lv JC, Zhang LX. 2019. Prevalence and Disease Burden of Chronic Kidney Disease. In: Liu BC, Lan HY, Lv LL (eds.). Renal Fibrosis: Mechanisms and Therapies. *Advances in Experimental Medicine and Biology* 1165. Springer, Singapore. https://doi.org/10.1007/978-981-13-8871-2_1
3. Building a Global Research Network: Chronic Kidney Disease as a Public Health Crisis. 2019. Frenova.
4. Mendu ML. Federal Funding for Kidney Disease Research: A Missed Opportunity. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4815960/
5. Impact of Recent Clinical Trials on Nephrology Practice: Are We in a Stagnant Era? https://www.karger.com/Article/Fulltext/495139

6. *The Washington Post*. Why the Diseases That Cause the Most Harm Don't Always Get the Most Research Money. https://www.washingtonpost.com/news/wonk/wp/2015/07/17/why-the-diseases-that-cause-the-most-harm-dont-always-get-the-most-research-money/
7. United States Renal Data System. 2020. *USRDS Annual Data Report: Epidemiology of kidney disease in the United States.* National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. https://adr.usrds.org/2020/chronic-kidney-disease/3-mobidity-and-mortality-in-patients-with-ckd
8. Gulati S, et al. 2020. Chronic Kidney Disease in Children. https://emedicine.medscape.com/article/984358-overview

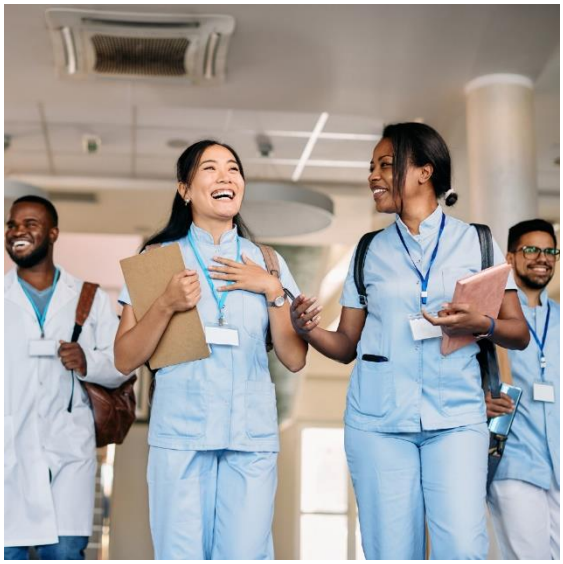
Kurt Mussina, MBA, is President, Frenova Renal Research, and Senior Vice President, Global Medical Office, FMC.

Clinical Researcher—November 2021 (Volume 35, Issue 8)

OVER THE TRANSOM

Sticking to the Agenda

Gary W. Cramer



In addition to education, an integral part of any academic medical center's mission is its research agenda. While recognizing the value of teaching, academics requires asking questions. It is vital to understand the mechanisms of health and illness, how to treat patients and their diseases more effectively, and how to provide healthcare to a community more effectively.

The sentiments above come from the introduction to a 2000 article in *The Ochsner Journal* on "The Roles of Research in an Academic Medical Center." The author goes on to indicate that the "end product of clinical research is the knowledge that allows us to understand disease processes and the prevention and treatment of these diseases. Clinical research is vital to achieving our ultimate goal of promoting health." He also notes how the Association of American Medical Colleges had "emphasized the need for teaching hospitals and medical schools to reaffirm that clinical research is part of their fundamental mission."

It's obvious that many institutions have taken this message to heart. For example, a webpage on "What it Means to be an Academic Medical Center" from the University of Pennsylvania's Penn

Medicine notes that, “With physicians, nurses, researchers, and teachers all working in unison, patients have better access to the latest medical breakthroughs and clinical trials that aren’t available at other hospitals.” Further, one can point to how nearly 20% of ACRP members report themselves as working in academic/university settings to highlight the importance of this segment of the clinical research enterprise in the scheme of research and development for drugs, devices, diagnostics, surgical techniques, and other forms of therapy.

With all of this in mind, this column delivers recent news from a variety of academic medical centers that are sticking to the agenda of clinical research activities vital to the advancement of scientific understanding for healthcare improvements and breakthroughs (no endorsements implied).

$31.7 Million Award Aims to Harmonize Alzheimer’s Research Data

Vanderbilt University Medical Center has been awarded a five-year, $31.7 million grant by the National Institute on Aging, part of the National Institutes of Health (NIH), to harmonize research data gathered on human subjects in scores of disparate studies of Alzheimer’s disease and related dementias (ADRD).

ADRD is studied from various angles, and from one human research cohort to the next the data are collected in different ways and at different scales, with many datapoints conforming to *ad hoc* definitions. Starting with data from more than 30 research cohorts, the new project will pool these data using data harmonization principles that are well established. This will produce a large-scale, racially diverse, standardized set of transparently defined data that will support machine learning and open new windows into the genetic basis of ADRD and Alzheimer’s resiliency. The goal: stimulation of new drug development.

Research data types encompassed by the project range from clinical information to genomics, cognitive performance, neuroimaging, biomarker data (currently derived from cerebrospinal fluid analysis), and autopsy neuropathology data. Per NIH data-sharing policies, the harmonized data will be available to qualified researchers from far and wide, primarily via established, secure computing resources supported by the National Institute on Aging.

$25 Million Award Seeks to Enhance Medical Research, Human Health

Expanded partnerships, access to clinical trials, and new medical and behavioral treatments and interventions reaching individuals more quickly will benefit communities in Pennsylvania and beyond thanks to the renewal of Penn State's Clinical and Translational Science Award (CTSA) funded by the NIH. The NIH's National Center for Advancing Translational Sciences awarded Penn State more than $25 million to provide critical clinical and translational research infrastructure and continue building collaborations across the university's campuses and with communities around the state.

The CTSA Program develops innovative solutions to improve processes for turning laboratory, clinical, and community research into health knowledge, interventions, and treatments. CTSA institutions partner to advance biomedical and health research and share best practices and tools. Penn State is one of 64 funded CTSA organizations nationally and is among the few that serve primarily rural communities.

The institute's involvement in the CTSA Program Trial Innovation Network gives Pennsylvania residents opportunities to become involved in both large national, and smaller local, clinical trials. It has supported several trials involving diagnostics and treatments, including for COVID-19, at Penn State Health Milton S. Hershey Medical Center through its Clinical Research Center. Clinical Research Centers, located at both the Hershey and University Park campuses, provide dedicated space and research staff for study visits. Studyfinder is the university's searchable website of actively recruiting research studies.

$5 Million Award Goes to Training of Diverse Researchers

The University of California, Irvine (UCI) has received a five-year, $5 million award from the California Institute for Regenerative Medicine (CIRM) to support a comprehensive doctoral, postdoctoral, and clinical researcher training program to prepare the current and next generation of leaders in stem cell biology, gene therapy, and regenerative medicine.

With an emphasis on basic and translational research, the award will support 12 fellows and be administered through the Sue & Bill Gross Stem Cell Research Center. This funding will expand

and extend the successful track record of the center's previous CIRM grants, which enabled the training of 73 scientists in 40 labs at UCI between 2005 and 2015.

A major goal of the CIRM training program is to increase diversity in stem cell research and help shape California's regenerative medicine workforce into one more representative of the state's population. Federally designated as an Asian American and Native American Pacific Islander-Serving Institution and a Hispanic-Serving Institution, UCI facilitates the recruitment of a diverse cohort.

Medical Center and Foundation Collaborate on Treatments for Rare Cancers

The University of Texas MD Anderson Cancer Center and the Rare Cancer Research Foundation have announced the launch of a collaboration designed to accelerate the development of new treatments for rare cancers by empowering all patients in the United States to contribute tumor samples directly to MD Anderson for translational research efforts.

This initiative is designed to overcome a major obstacle that has long prevented significant progress in rare cancer research—the lack of available samples. The Rare Cancer Research Foundation will use its Pattern.org online engagement platform to enable patients to donate tumor biopsies and surgical samples for research purposes.

With these samples, MD Anderson researchers will perform comprehensive analyses and will work to develop laboratory models that can be used to pursue new therapeutic strategies for rare cancers. New discoveries then can be used to design and launch clinical trials to evaluate these strategies for patients in need.

Rare cancers are defined as those with fewer than 40,000 new cases diagnosed annually in the U.S. Taken together, rare cancers represent roughly 25% of all cancer cases and are the leading cause of cancer-related deaths. The initiative aims to fully characterize more than 60 rare cancer samples and develop 20 laboratory models. These data and models will be made available to the research community, allowing scientists worldwide to contribute breakthroughs to the field.

Gary W. Cramer (gcramer@acrpnet.org) is Managing Editor for ACRP.