

Clinical Researcher

The Authority in Ethical, Responsible Clinical Research

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Gears in Motion

(Elevating People and Processes in Inclusive Clinical Research Arenas)

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Table of Contents

PEER REVIEWED

4 Building an Institutional Clinical Research Professionals Group at an Academic Institution: Evidence of Need and Initial Structure
Demi Beckford, MHS; Kelly Boone, MA, CCRP; Jessica Fritter, MACPR, ACRP-CP;
Grace Wentzel, CCRP, CHRC

12 Strategies for Selecting Appropriate Satellite Sites for Clinical Research
Esther Mahillo, PhD, MBA

18 Deprogramming and Desegregating Racial Inequities in Healthcare
Preethi Sriram, DHSc, MSN, BSN

DCT CENTRAL

28 Chair’s Message—What’s Missing in the Discussion About DCTs: A PI’s Perspective
David J. Morin, MD, FACP, CPI, FACRP

31 Recruitment & Retention—How to Make Clinical Trials More Diverse and Inclusive
Contributed by Florence HealthCare

37 Over the Transom—Gears in Motion: Elevating DCTs and the Professionals Who Run Them
Gary W. Cramer

FEATURED COLUMNS

40 Data-Tech Connect—Technology Considerations When Onboarding and Offboarding Clinical Research Staff
Mollie Maggied, MSN, MHA, RN, AT-C, CPN; Paula Smailes, DNP, RN, CCRP

45 Good Management Practice—Disruption and Bravery: How You Can Make a Difference in Clinical Research
A Q&A with Tina Barton, PhD, MBA

50 IRBs in Focus—Carving Out a Career in Ethical Review
Contributed by WCG IRB

55 On the Job—Stop Struggling to Manage the Complexity of Your Studies
Debbie Taylor, MBA

58 Sites & Sponsors—Blazing Clinical Pathways for Phage Therapy
Paul Kim, PhD, MBA

65 Trials & Technology—Effective Data Analysis for Nontraditional Study Designs
Dejun (DJ) Tang, PhD

ACRP Celebrates 2022 Class of Fellows Representing the Clinical Research Profession
(Online Only)

PEER REVIEWED

Building an Institutional Clinical Research Professionals Group at an Academic Institution: Evidence of Need and Initial Structure

Demi Beckford, MHS; Kelly Boone, MA, CCRP; Jessica Fritter, MACPR, ACRP-CP; Grace Wentzel, CCRP, CHRC



Nationwide Children’s Hospital has an expansive clinical research portfolio that has continued to increase in number and complexity over the last five to seven years. As this has occurred, the number of clinical research staff being hired across the organization has steadily increased to approximately 2,100 in the last five years. With such a large group of clinical research professionals, a program to serve as a central point for staff to connect and obtain resources

became essential. This led to the creation of Bloom: Clinical Research Professionals Group (Bloom).

Bloom is one of two initiatives under the hospital’s Research Matters committee, which is managed in the Abigail Wexner Research Institute and is overseen by the Director of Safety and Training. The mission of Research Matters is to serve as a resource to the hospital and research institute community, including patients and families, on issues related to both basic science and clinical research activities.

The other initiative under Research Matters is the Research Institute Diversity Enrichment (RIDE), with a mission to engage the research community through education, celebration, and promotion of diversity. Bloom and RIDE work in tandem across the organization.

Bloom was established in 2020 with the purpose of building a network of clinical research professionals and providing a space to collaborate, receive education and training, and find mentors/mentees within a large pediatric academic medical institution that integrates both a free-standing pediatric hospital and a dedicated research institute. Bloom is overseen by the Director of Clinical Research Services. Bloom does not have an operating budget; however, there are some internal funds that Bloom can utilize.

Bloom leadership consists of research-affiliated departments across the hospital, including Hematology/Oncology/Blood and Marrow Transplant, Clinical Research Services, and the Behavioral Trials Office. There are three main positions within the Bloom steering committee: Program Chair, Education and Activities Coordinator, and Administrative Coordinator. The steering committee has a rolling membership of two years for leadership roles within the program.

The leadership aims to strengthen and enhance the clinical research community by connecting its professionals and providing them with resources and opportunities to discuss timely topics, address knowledge gaps, and expand the community. The goal of Bloom is to create a sense of belonging within the organization and foster retention. Currently, there are very few instances in the literature discussing how and why to build and maintain a group for institutional research professionals like Bloom.

Our objective in this article is to describe the baseline characteristics and needs of members as well as the structure of Bloom. We discuss the benefits of the group and conclude with how an institutional group for clinical research professionals can develop, enhance, and strengthen an institution's clinical research community.

Methods

In collaboration with our project managers, the authors designed two surveys (a baseline/interest survey and the first annual member survey for the conclusion of Bloom's first year of activity) to distribute among clinical research employees.

The baseline survey included 12 items and was distributed through multiple channels, such as employee engagement e-mail lists and employee news e-mail lists. The baseline survey asked for employment (e.g., years in clinical research, job title) and demographic (e.g., education level, clinical research certification) information. It also asked what educational topics, speakers, and/or service opportunities members would like to see facilitated through Bloom.

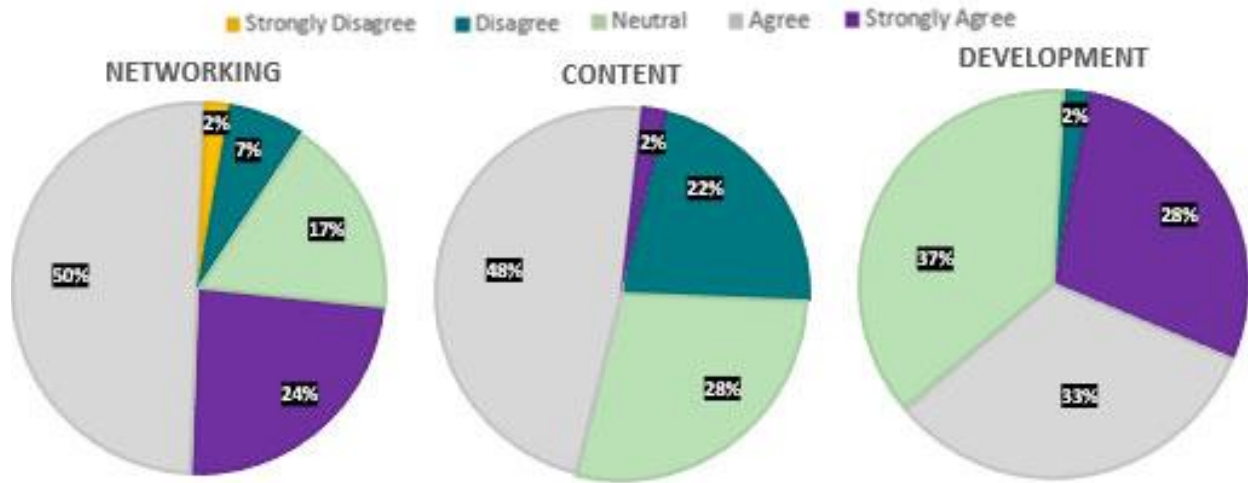
In addition to gathering baseline data, the survey obtained e-mails, and thus prompted an e-mail list that enabled efficient and timely distribution of information on Bloom events and research-related policies (e.g., COVID updates). Summary statistics describing employment and demographic characteristics and broad themes were identified to summarize engagement opportunities of interest to members ([see Appendix A](#)).

Those who completed the baseline survey and became members of Bloom were then given a 16-item survey which was distributed via e-mail one year after the inception of the group ([see Appendix B](#)). This consisted of questions regarding professional certification and job promotion status within the previous year. There was a section for open comments to facilitate suggestions for group resources and networking opportunities.

The survey tool used was Research Electronic Data Capture (REDCap) software. Under 45 CFR 46.101 in the *Code of Federal Regulations*, the Nationwide Children's Hospital Institutional Review Board was able to exempt the survey tool. The survey was live for five weeks and results were downloaded from REDCap for analyses. Data were analyzed using summary statistics.

The first annual member survey was distributed to clinical research staff who were members of Bloom during the winter of 2021. Group members consist of research professionals from three categories: Abigail Wexner Research Institute at Nationwide Children's Hospital, other areas of Nationwide Children's Hospital, and The Ohio State University Medical Center. The questions focused on demographics, site-specific training, job titles, research professional certification, promotions, content of meetings, skill level, and open comments/suggestions. Using a five-point Likert scale, participants were asked to rate the competencies obtained during Bloom sessions from "strongly disagree" to "strongly agree" (see Figure 1).

Figure 1: Likert Scale One-Year Survey Responses



Results

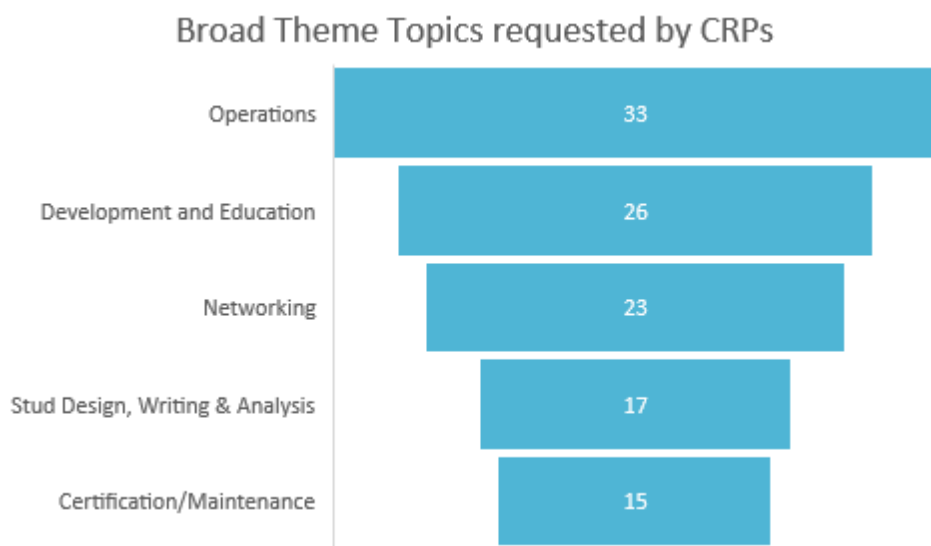
The baseline/interest survey had 172 respondents across a variety of clinical research roles: 72% Clinical Research Coordinators (CRCs), 9% Research Managers, 8% Investigators, 3% Research Assistants, 5% Research Administration, and 3% Data Analysts/Managers (see Figure 2). The median length of time engaged in clinical research was three years (with a maximum of 37 years), with 26% of respondents starting employment at the institution within the past year. More than half (52%) of respondents were research institute (vs. hospital) employees. Five percent had an associate degree or lower, 56% had a bachelor’s degree, 22% had a master’s degree, and 17% had an MD or PhD. At baseline, only 17% of respondents had a clinical research certification, but 83% of those who did not have this credential were interested in pursuing a certification.

Figure 2: Group Membership Role Breakdown



Broad themes that emerged in terms of what members would like to gain from involvement in the group include topics related to clinical research operations (33%); professional development and education (26%); professional networking opportunities (23%); study design, writing, and analysis (17%); and clinical research certification and maintenance (15%) (see Figure 3). Topics of interest were not associated with years in clinical research.

Figure 3: Broad Theme Topics



For the first annual member survey, 47 of 172 recipients responded (27%). Within one year from the creation of the program, Bloom supported fees associated with obtaining a clinical research certification for five members. Two members were promoted (Research Regulatory Coordinator to Research Regulatory Specialist; CRC I to CRC II). Almost three-quarters (74%) of respondents indicated that Bloom provided networking opportunities and 70% thought that the content of the meetings/seminars were useful. Sixty-one percent indicated that the group enhanced their professional development.

Discussion

At its conception, Bloom was structured to host a monthly meeting with themes relating to researcher spotlights, educational topics (continuing education credits provided), and networking and service opportunities. Sub-groups were also created called People Like Me groups, which

consisted of research professionals with similar titles and responsibilities. The purpose of these groups was to engage, support, and provide resources to members by holding quarterly meetings to enable networking within the organization.

Bloom meetings began in May of 2020 during the early days of the COVID-19 pandemic. This affected the structure of the group and its ability to host in-person networking functions. All in-person meetings and events were reformatted to virtual, with the highest attendance rate being 74% and an average attendance rate of 52%. As a result of no in-person meetings or events, we measured the group's effectiveness by relying heavily on virtual meeting interactions and survey responses.

We used feedback received in the first annual member survey to determine the 2022 schedule. This includes more in-person networking opportunities (as COVID-19 allows), a clinical research speaker series, and more in-depth discussions surrounding grant management, diversity/inclusion trainings, and other appropriate topics. A monthly newsletter will also be implemented to further integrate different areas of research. This newsletter will include current research job openings, relevant research trainings and seminars from other organizations, as well as departmental spotlights to increase collaboration.

Initiatives offered through this group benefit the clinical research community by facilitating interdisciplinary collaboration, with the aims of achieving optimal results and increasing organizational efficiency and compliance.

Limitations

One limitation to this study is that the outcomes rely on self-report. In addition, although this survey captured respondents from three different categories of employment, our results may not be generalizable because only 27% of members responded. Another limitation is due to the COVID-19 pandemic guidelines; these guidelines prohibited the group from conducting some 2020 and 2021 agenda items that were set prior to COVID-19. These events included meeting in person to provide further networking/hands-on learning opportunities, which may have affected the survey responses.

Conclusion

Clinical research professionals at a large pediatric academic medical center are eager to find a space to connect with their colleagues across the institution, regardless of years in the profession. To fill this gap, we created a group that offers regular steering committee meetings, speaking engagements, and educational sessions, it also provides various networking opportunities and financial and educational support to obtain/maintain a clinical research certification. Collectively, initiatives offered through this group benefit the clinical research community by facilitating cross-cutting collaboration, with the aims of achieving optimal results and increasing organizational efficiency and compliance. This group will continue to develop by enlisting new members and conducting routine follow-up surveys to gauge the relevance of provided sessions, as well as to identify needs of members.

Acknowledgement

The authors wish to thank Katie Campbell for her continued support of the Bloom: Clinical Research Professionals Group.

Editor's Note: In between the acceptance of this article for publication and its appearance online, Bloom was rebranded as Children's Hospital Clinical Research Professionals (CHIRP).

References

1. U.S. Department of Health and Human Services. 45 CFR 46.
<http://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/>
2. Wentzel G, Fritter J. 2021. ACRPtv Spotlight On... The Benefits of an Institutional Clinical Research Professionals Group. <https://acrpnet.org/2021/03/02/acrpvtv-spotlight-on-the-benefits-of-an-institutional-clinical-research-professionals-group/>
3. Jones C, Kesling B, Fritter J, Neidecker M. 2020. How to Begin a Career as a Clinical Research Professional. *Clinical Researcher* 34(6).
<https://acrpnet.org/2020/06/09/navigating-a-career-as-a-clinical-research-professional-where-to-begin/>



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PEER REVIEWED

Strategies for Selecting Appropriate Satellite Sites for Clinical Research

Esther Mahillo, PhD, MBA



Today, there are more than 15,000 open or planned clinical trials in the United States, approximately 5,500 of which are for oncology therapies. With large cancer centers like MD Anderson and Memorial Sloan Kettering managing an estimated 1,100 and 700 clinical trials, respectively—and with the number of studies expected to expand at a compound annual growth rate of 5.7% from 2021 to 2028—there exists a tremendous opportunity for satellite sites to support the expansion of this \$44 billion dollar industry. { 1 }

Investigator satellite sites are an important and underutilized strategic resource, and some in the industry even see them as the [next rising star in clinical research](#). The term “satellite site,” as it relates to clinical trials, has been used in various contexts throughout the years. For the purposes of this article, the term covers independently operated study sites based within private physician practices, standalone hospitals, and other small, typically community-based, sites which large academic medical centers (AMCs) can turn to for help with certain trials on a case-by-case basis. It does not include sites that are run directly by sponsor organizations or as members of site management organizations, research consortia, or other forms of large research networks.

Due to historic misconceptions about their capabilities, resources, and output, satellite sites are often overlooked in clinical research. Today, however, these sites may be fully equipped with modern infrastructures and feature practitioners trained at prominent cancer centers of excellence who have vast clinical trial experience. The potential of these sites to add value in oncology clinical trials, as discussed further below, is tremendous, in that they often feature well-trained

staff who can be dedicated to research projects, have experience with lab sampling, and understand the complexities of handling investigational products (IPs).

When added on an as-needed (temporary) basis to an existing AMC network of sites to contribute to the conduct of complex, multisite trials, satellite sites often already have all the necessary equipment to run such studies, and can quickly come up to speed with the robust compliance protocols and established standard operating procedures (SOPs) necessary for IP transfers from the primary site to the satellite. Some AMCs even make it easier for satellite sites to participate by using centralized institutional review board (IRB) approvals and employing uniform methods for capturing electronic delegation of authority logs. The symbiotic relationship between satellites and the primary site adds a new dimension to clinical trial conduct.

The Advantages of Satellite Sites for Oncology Trials

For people with cancer, satellite involvement can make clinical trial participation more appealing. Patients who seek inclusion in clinical research are likely to have a well-established relationship with their local oncologist, often preferring to stay with their doctor versus being transferred to a new oncologist at a larger research center further from their home. By virtue of their location, satellite sites enable clinical trial participants to stay within more familiar territory, eliminating the need to travel unnecessarily and lowering the barrier to entry for those who cannot accommodate the rigorous demands of study participation—often members of underprivileged groups, the exclusion of which results in skewed population metrics for trials.

Extracting the most benefit from the partnership between satellite and primary sites means sponsors must understand the varying degrees of maturity and centralization across the affiliate networks. These are just some of the considerations that can drive the selection of a satellite network partnership:

Capability: Satellite sites come in all different shapes and sizes. It is crucial to match a study's protocol requirements with those of the AMC network and satellite sites being considered. Centralized training conducted by a primary academic site, along with oversight of start-up processes, is a common practice to ensure an on-time study start.

Capacity and Patient Match: Satellite sites are likely to have less competition for certain patient groups than large cancer centers. Additionally, by bringing trials out into more suburban areas, the enrollment area can expand to a broader and more diverse population.

Researching these criteria will be challenging for sponsors, but partnering with a qualified primary clinical trial site that has a well-established roster of satellite sites that may be relied on when the need arises eliminates hurdles regarding obtaining information on where suitable patients are located and where they are in their treatment journey.

Other Keys to Success with Satellite Sites

The primary academic site understands each of its satellite sites' capabilities and can identify those that make sense for a specific trial.

Some sites excel at investigational trial work, others at biospecimen collections. AMCs with satellite site networks ([Roswell Park](#), for example) have intimate knowledge of their collective sites' strengths and patient populations. This enables sponsors to find the right investigators for their trial and generate higher quality data from the harmonized processes across this network.

Many organizations have invested heavily in SOPs, data platforms, and administrative services to create tremendous efficiencies and bring the capabilities of large sites to satellite locations.

This helps them to:

- Ensure proper training, oversight, and infrastructure, potentially eliminating the need for site qualification visits at satellite sites.
- Provide contractual harmonization for most legal language and budgetary items—only small nuances reflect individual site capabilities and needs.
- Enable centralized, streamlined start-up activities, combined training activities, and potentially minimized delays in IRB approvals and navigation through other administrative red tape.

Many satellite site networks have uniform systems that centralize information on patient locations and diagnoses.

Targeting specific patient populations can be a daunting challenge. With standardized electronic medical record (EMR) systems, data collection can be streamlined to create more uniform treatment pathways and drive more consistent patient tracking and care.

Centralized and uniformed access to patient information simplifies the identification of potential trial participants and provides other value-added benefits to a study, including:

- SOPs and shared trial management platforms can drive consistency across a study to establish a strong baseline.
- Data from the EMR is uniform and always accessible, which eliminates the need to establish baseline using expensive claims data.

Satellite locations make a local presence possible, bringing science closer to patients.

Study participation will always pose some degree of burden, but with the COVID-19 pandemic, the paradigm shifted. The influx of patients to large academic sites made local community centers step up to handle the overflow of trial work. Despite this unplanned involvement, studies continued to run successfully, demonstrating the abilities of select sites to support oncology clinical trials and marking an important step forward toward more patient-friendly study practices.

Finding other ways to minimize the burden of participation on patients will be key to supporting them in their time of need, as well as for making studies more attractive—an important consideration for patient enrollment and an on-time study start. The challenges in this area include:

- The difficulties of travel—driving to metropolitan areas, parking, and time off work—make enrollment burdensome, discouraging people from participating in a trial. Having a trial accessible at a satellite location greatly reduce the hassle of commuting.
- Patient comfort is an important factor to reduce anxiety. This can include wanting to stay with their regular physician whom they trust (potentially avoiding loss of knowledge regarding the patient’s condition).

- Improving representation is an ongoing challenge; however, suburban sites may be more accessible to certain groups who do not have the ability to take extended time off from work or the means to travel long distances.

The inclusion of satellite sites in a clinical trial can be a competitive differentiator for sponsors.

Growing competition and other enrollment challenges amplify the importance of easier trial participation experiences. Patient-centric considerations, together with network-enabled patient insights, make selecting satellite sites a far more digestible option.

By successfully pairing the right sites with the right studies, sponsors can improve the breadth and quality of data, drive enrollment more representative of real-world populations, and create better experiences by bringing the science closer to the patient. As the industry continues its shift toward decentralization, satellite sites will continue to play a key role in realization of patient-centric clinical trials.

As the numbers of trials continue to grow, sponsors who partner with academic sites with mature site networks to implement [decentralized clinical trial strategies](#) will benefit from the added capacity of highly skilled and motivated staff and faster enrollment from a broader patient reach, while continuing to maintain data quality. However, the most important driver of satellite site involvement lies beyond the dollars and cents.

Conclusion

Cancer can strike any person at any time and the impact spreads extends far beyond the patient, affecting families, caregivers, friends, neighbors, and coworkers. Today's reality is that many clinical trials are not accessible to the people who need them the most due to the high demands of study participation. This does not have to be the case. As various AMCs have already demonstrated, by implementing standardized processes and procedures, with centralized training and oversight by the primary site, they are able to bring the trials to the ones who matter the most—the patients.

Reference

1. Grand View Research. 2021. Clinical Trials Market Size, Share, and Trends Analysis Report by Phase (Phase I, Phase II, Phase III, Phase IV), by Study Design (Interventional, Observational, Expanded Access), by Indication, by Region, and Segment Forecasts 2021–2028.



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PEER REVIEWED

Deprogramming and Desegregating Racial Inequities in Healthcare

Preethi Sriram, DHSc, MSN, BSN



Many aspects of the current state of public education and healthcare in America reflect upon the dark history of race relations in the country, in that lingering practices in these arenas have been constructed from a time of apartheid and discrimination that carries its impacts into the modern day. {1} Some of the tragedies found in the history of race relations as it pertains to medical research and healthcare are well known, such as the government-backed Tuskegee syphilis studies focused on the long-term effects of syphilis on Black

American men even after an effective cure, penicillin, became available. {2} From this notorious study came about the Belmont Report principles of respect for persons, beneficence, and justice that form the ethical backbone of the modern-day clinical research guidelines. {3}

While the Tuskegee syphilis study and other egregious examples of unethical medical experimentation are often cited as reasons for minority distrust of the medical community, there are less well-known incidences of concepts that have been created in the past 150 years that are still being utilized in healthcare for diagnoses and treatment within a present-day context that need to be reexamined. This paper will explore these concepts with special attention paid to the topics of body mass index (BMI), acute kidney injury (AKI), the spirometer medical device, and the advent of therapies targeted toward specific racial groups.

Body Mass Index (BMI)

Achea Redd, a Black woman, noted that when she would attend her yearly checkups and discuss her fear that she may have an eating disorder, the physicians dismissed her worries, as her BMI

did not reflect this possibility. She was later diagnosed by her therapist as having atypical anorexia, yet her insurance would not cover her treatment because of her BMI, and she paid \$800 monthly out of pocket to get the specific healthcare guidance she needed. {4}

The concept of BMI is well known by name in healthcare and amongst laymen. This is an index that can be utilized as a benchmark for determining risk for other health conditions. The BMI is calculated using the individual’s height and weight to give an estimate of body fat for both genders and all ages. {5} Figure 1 shows how this is calculated per the height and weight of any given adult individual to reach a categorization of Normal, Overweight, Obese, or Extreme Obesity. This is often used in clinical trials to exclude a patient, as it could imply other underlying health conditions.

Figure 1: Body Mass Index Table

Body Mass Index Table																																																						
	Normal										Overweight					Obese										Extreme Obesity																												
BMI	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54																		
Height (inches)	Body Weight (pounds)																																																					
58	91	96	100	105	110	115	119	124	129	134	138	143	148	153	158	162	167	172	177	181	186	191	196	201	205	210	215	220	224	229	234	239	244	248	253	258																		
59	94	99	104	109	114	119	124	128	133	138	143	148	153	158	163	168	173	178	183	188	193	198	203	208	212	217	222	227	232	237	242	247	252	257	262	267																		
60	97	102	107	112	118	123	128	133	138	143	148	153	158	163	168	174	179	184	189	194	199	204	209	215	220	225	230	235	240	245	250	255	261	266	271	276																		
61	100	106	111	116	122	127	132	137	143	148	153	158	164	169	174	180	185	190	195	201	206	211	217	222	227	232	238	243	248	254	259	264	269	275	280	285																		
62	104	109	115	120	126	131	136	142	147	153	158	164	169	175	180	186	191	196	202	207	213	218	224	229	235	240	246	251	256	262	267	273	278	284	289	295																		
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Source: Adapted from Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report.

Source: https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmi_tbl.pdf

Many though are not aware of the origins of the BMI index, and that it was created in the 1830s by a Belgian man, Lambert Adolphe Jacques Quetelet.^{6} This index was created using European men to measure weight and Quetelet noted that it was not supposed to be applied on an individual basis, but as a population level tool. This Quetelet Index was introduced after nearly 140 years in 1972 by a physiologist, Ancel Keys. Sabrina String, an assistant professor at University of California, Irvine, notes that it was created using mostly white males, and that females and other groups had not been included in the analysis when creating the index; accordingly, is not a tool that should be utilized in health outcomes.^{7} Thus, the tool is flawed as it does not take gender and other backgrounds into account, nor does into take age into account.

While BMI is not the only marker for health, and there are many different variables that need to be considered when working with an individual, when this index is still utilized inappropriately or in a flawed way, it has consequences—as with the case of Achea Redd. Redd’s healthcare treatment was delayed by her provider as the index was not reflecting the reality that she was suffering from an eating disorder, and even when later diagnosed, insurance would not cover her treatment since she did not meet the predetermined numbers.^{4}

Acute Kidney Injury (AKI)

Cases of chronic kidney disease (CKD) and end-stage kidney disease (ESKD) are noted as dramatic examples of race-based health disparities in the U.S. Laster, et al. cite that African Americans experience some of the highest rates of ESKD compared to other ethnic groups.^{8} With this information, it would thus seem intuitive that diagnoses and treatment should occur earlier, and the healthcare providers would be vigilant with regards to these data, yet ironically, it seems the opposite when looking from the angle of the formula for diagnosing acute kidney injury (AKI).

AKI is common amongst critically ill patients and can foreshadow a significant impact to CKD, cardiovascular disease, and overall mortality.^{9} With regards to AKI, as it is difficult to measure the function of the kidney directly, equations were developed by researchers to

determine the estimated glomerular filtration rate (eGFR) using the serum creatinine level. {10}
 Table 1 shows the normal creatinine levels with categories by age, race, and gender.

Table 1: Estimated Baseline Creatinine

Age (Years)	Black Males (mg/dl) (mmol/L)	Other Males (mg/dl) (mmol/L)	Black females (mg/dl) (mmol/L)	Other Females (mg/dl) (mmol/L)
20-24	1.5 (133)	1.3 (115)	1.2 (106)	1.0 (88)
25-29	1.5 (133)	1.2 (106)	1.1 (97)	1.0 (88)
30-39	1.4 (124)	1.2 (106)	1.1 (97)	0.9 (80)
40-54	1.3 (115)	1.1 (97)	1.0 (88)	0.9 (80)
55-65	1.3 (115)	1.1 (97)	1.0 (88)	0.8 (71)
>65	1.2 (106)	1.0 (88)	0.9 (80)	0.8 (71)

Source: Bellomo R, Ronco C, Kellum, JA, Mehta RL, Palevsky P. 2004. Acute renal failure—definition, outcome measures, animal models, fluid therapy, and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Critical Care* 8(4):R204–12. <https://doi.org/10.1186/cc2872>

The normal levels used as a reference for diagnosing AKI results in higher reported values in anyone identified as Black, and the justification given by the developers of the measurement is that there is a higher serum creatinine amongst Black people versus White people. {10}

While the measure of creatinine may not be the only criteria with regards to determining AKI, it is one of the parameters that is relatively easy when taking into consideration that creatinine values can be determined from blood work when the individual is in the clinic, and thus, the value of creatinine can be very misleading, especially if it is only looked at by itself. Someone with a creatinine value that may be “normal” due to being categorized by a certain race, may actually be overlooked for further care because the value itself may not “flag” during a routine visit. Vyas, et al. cite that the adjustments in the formula with consideration to race may impact

the care that those identified as Black patients may receive, may delay counsel for specialist care, and may lead to worse outcomes.{ 10 }

The equation itself seems outdated in that it splits the population between Black and non-Black, though the concept of being Black has more of a social role than a biological one. Bichell and Anthony show just how regressive the concept of using a Black/non-Black equation is with the case where Glenda V. Roberts, whose genetic ancestry shows at least 48% from non-African countries and 25% Native American, could be identified as Black due to social impacts of American culture. The authors note that the race factor does not work as well for Black Europeans or those in West Africa, and that Australian researchers found that the measure also led them overestimate the function of the kidney in native Australians.{ 11 }

Thus, depending on self-identification, as well as judgement/stereotyping of the healthcare provider to categorize the individual as Black or non-Black, an individual is likely to receive different answers about his or her staging of AKI. The type of treatment and care given may be lacking if it is estimated that persons are healthier than they really are and, in fact, are sicker than the formula reflects.

Spirometer

In the past century, the use of spirometers has spread worldwide for the identification and treatment of various respiratory diseases, in both primary care and specialist settings. The spirometer has a correction factor for race—as self-identified by the patient or determined by the judgement of the healthcare provider—programmed by the manufacturer and difficult to deactivate.{ 12 } Figure 2 shows a calculator from the National Institute for Occupational Safety and Health that considers the race of the individual when calculating the spirometry reference.

Interestingly, the race correction that is utilized today has roots in a very racist period of history in America of the 1800s, when Samuel Cartwright, a physician and slaveholder, deemed that enslaved Blacks had lower pulmonary function than Whites and utilized this “finding” to promote the idea that forced labor was good for them.{ 13 } This philosophy was utilized to justify slavery as beneficial—even necessary—in terms of helping the physical condition of enslaved Blacks, yet it did not look into social reasons as to why they may have had lower

pulmonary function (i.e., working in environments that may have impacted the lungs, the strains of forced labor, undiagnosed conditions, etc.).

Figure 2: Spirometry Reference Value Calculator

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Spirometry Reference Value Calculator

Reference Value Calculator

Enter Age, Height, Gender and Race. To see Percent Predicted, you must enter observed FVC, FEV1, and FEF25-75% values in the appropriate boxes. Click Calculate to calculate the predicted values.

Reference Source: Gender:

Race: (Dropdown menu open showing: Caucasian, Black, Hispanic)

Age: Height: in

Optional Observed Values Below - Enter to calculate Percent Predicted

FVC (L):

FEV1 (L):

FEF25-75% (L/s):

FEV1/FVC%:

Calculated Values

	FVC (L)*	FEV1 (L)*	FEV1/FVC%	FEF25-75% (L/s)*
Predicted	Blank	Blank	Blank	Blank
Percent Predicted	Blank	Blank	Blank	Blank
Lower Limit of Normal	Blank	Blank	Blank	Blank

* - Predicted values are for race selected above.

Disclaimer: This calculator is intended for use with the NIOSH Spirometry Workbook exercises and has NOT been approved by the FDA for clinical use.

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Source: <https://www.cdc.gov/niosh/topics/spirometry/refcalculator.html>

Healthcare providers may not even be aware of these race corrections programmed into the modern-day spirometer, nor aware of its history, and this ignorance can lead to real consequences. For instance, providers may miss a diagnosis if lower limits are considered normal for the reference population. The spirometer is used to measure forced expiratory volume and this can influence the treatment plans. For example, patients with COVID-19 pneumonia resulting in pulmonary fibrosis may require pulmonary rehabilitation, including breathing exercises and continual monitoring, but this might not be undertaken if the adjustment factor is race programmed and thus leads to an incorrect diagnosis. { 14 }

This is the reason behind Anderson, et al. urging healthcare providers to be aware of the disparities that may be intensified amongst the racial groups by using a correction for race, and in recent times, particularly considering the pandemic.

Race, Genetics, and the New Frontier

“Race” can have various meanings, but starting in the 18th century, the concept of race was conceived as a biological construct and the archaic categorizations no longer holds scientific merit. Race is currently seen as a social construct—at least, from a scientific viewpoint. {15} Yet, the concepts of race and ethnicity are still being included in medicine and treatment and have very real implications in medicine and healthcare.

Washington notes a certain drug—developed in the late 1990s and originally targeting the general population—was first rejected by the U.S Food and Drug Administration (FDA). This drug was not approved until 2005, only after its developer said that, based on a retrospective data analysis, the drug’s mechanism of action was potentially of benefit against a genetic anomaly that makes African Americans susceptible to congestive heart failure. Although the company had created a perception that the drug worked distinctly in African Americans, this relied on outdated data regarding how many African Americans in a certain age range died from the condition versus Whites—and discounted a variety of nongenetic factors at play in the difference in death rates between the races. In any event, marketing for the product notes it as the only drug indicated for heart failure for those who self-identify as African American, making it seem that there is a distinctive pathophysiological difference between African Americans and other populations with regard to presentation of congestive heart failure. The validity of that claim is spurious, given the data used. {2}

Further, “scientific” terminology used to define who is African American versus White has changed throughout American history. There may be people who are of mixed ancestry, or adopted, or who may appear at first to fall under the societal construct of one paradigm for a certain race, yet in truth fall outside it. If a drug can only be prescribed based on self-identification of one’s race, this raises social quandaries about who is “allowed” to self-identify

as belonging to one group or another. For example, should individuals be required to take a genetic test to back up any claims of self-identification for a particular race?

The genetic frontier of personalized ancestry testing is here and brings with it more recent ethical questions. While there are those who recommend using personalized genetic testing to help bridge the gap between healthcare and genetics,{16} the very science of testing ancestry seems to be somewhat murky in that the baseline set of samples is created from a sample population of modern individuals selected with the idea that they are “pure,” or not mixed. Blell and Hunter cite how the concept of a population of people being pure begins with researchers adopting categories of ethnicity and race and then labelling these categories per the sample sets.{17} However, as noted earlier, the definition of race has changed over time. This is a subject that appears to be far from settled in the U.S., let alone globally, regardless the damage it can do in healthcare.

Conclusion

Though, from a biological perspective, race is now being acknowledged as a social construct, the perceived notion of race still carries with it impacts from a racist past to the present day in terms of healthcare equity.

A formula from nearly 200 years ago is still used for measuring BMI, though its own creator noted that it should not be utilized on an individual basis. Another formula with its inception in the times of slavery—and utilized nefariously to justify slavery—is now insidiously programmed into the spirometer. The formula for diagnosing AKI segregates Black from non-Black.

The very essences of the medical uses of BMI, AKI, and the spirometer are flawed in application. This has real consequences for clinical research, such as poorly designed clinical study protocols that use formulas for BMI or AKI to exclude would-be participants from trials for which they would otherwise be qualified. In the healthcare setting, the real consequences can be with diagnosis and treatment; a formula may deliver a false negative, in that the individual may be sicker than the formula shows, especially in cases of AKI and spirometer usage.

With the examples provided in this review, it is important that those within healthcare and clinical research be vigilant to how the tenants of equitable treatment must be re-evaluated regarding the social realities of race and how to mitigate the disparities that are created from misapplication of outdated concepts tied to race. Further, educators should be aware that strains of racism are still present and embedded in the fabric of healthcare. Healthcare curricula in our educational institutions at all levels need to reflect the most updated concepts regarding what exactly race is, and to teach it as a social construct that impacts the lives of various groups.

It is important that the individual patient be seen as an individual, and not “stereotyped” into a group when it comes to healthcare. Educators should address in class how healthcare disparities arise when different groups are treated differently and homogenously, and how the environments individual patients grow up in account for far more in their health journeys than any superficial difference of “race.” Continuing education is also needed for established professionals to learn about new models for addressing disparities in healthcare and research settings.

To truly bring about change and equity, the formulas and paradigms that have been held for the past 200 years must be deprogrammed, and it is time for healthcare and clinical research to evolve away from stereotyping groups and toward elevating care for individuals.

References

1. Daher Y, Austin E, Munter B, Murphy L, Gray K. 2021. The History of Medical Education: A Commentary on Race. *Journal of Osteopathic Medicine* 121(2):163–70. <https://doi.org/10.1515/jom-2020-0212>
2. Washington HA. 2006. *Medical Apartheid: The Dark History of Medical Experimentation on Black Americans from Colonial Times to the Present*. <https://www.penguinrandomhouse.com/books/185986/medical-apartheid-by-harriet-a-washington/>
3. Emanuel EJ, et al. (editors). 2003. *Ethical and Regulatory Aspects of Clinical Research: Readings and Commentary*. Baltimore: Johns Hopkins University Press. <https://www.amazon.com/Ethical-Regulatory-Aspects-Clinical-Research/dp/0801878136>
4. Stern C. 2021. Why BMI is a Flawed Health Standard, Especially for People of Color. *The Washington Post*. https://www.washingtonpost.com/lifestyle/wellness/healthy-bmi-obesity-race-/2021/05/04/655390f0-ad0d-11eb-acd3-24b44a57093a_story.html
5. Weir CB, Jan A. 2019. BMI Classification Percentile and Cut Off Points. *StatPearls*. <https://pubmed.ncbi.nlm.nih.gov/31082114/>
6. Brazier Y. 2021. How Useful is Body Mass Index (BMI)? *Medical News Today*. <https://www.medicalnewstoday.com/articles/255712>

7. Christine B. 2020. The BMI is Racist and Useless. Here's How to Measure Health Instead. *HuffPost*. https://www.huffpost.com/entry/bmi-scale-racist-health_1_5f15a8a8c5b6d14c336a43b0
8. Laster M, Shen JI, Norris KC. 2018. Kidney Disease Among African Americans: A Population Perspective. *American Journal of Kidney Diseases* 72(5):S3–7. <https://pubmed.ncbi.nlm.nih.gov/30343720/>
9. Teo SH, Endre ZH. 2017. Biomarkers in Acute Kidney Injury (AKI). *Best Practice & Research Clinical Anaesthesiology* 31(3):331–44. <https://pubmed.ncbi.nlm.nih.gov/29248140/>
10. Vyas DA, Eisenstein LG, Jones DS. 2020. Hidden in Plain Sight—Reconsidering the Use of Race Correction in Clinical Algorithms. *New England Journal of Medicine* 383(9):874–82. <https://pubmed.ncbi.nlm.nih.gov/32853499/>
11. Bichell RE, Anthony C. 2021. *Kaiser Health News*. <https://khn.org/news/article/black-kidney-patients-racial-health-disparities/>
12. Braun L. 2015. Race, Ethnicity, and Lung Function: A Brief History. *Canadian Journal of Respiratory Therapy* 51(4):99–101. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4631137/>
13. Lujan HL, DiCarlo SE. 2018. Science Reflects History as Society Influences Science: Brief History of “Race,” “Race Correction,” and the Spirometer. *Advances in Physiology Education*. <https://pubmed.ncbi.nlm.nih.gov/29616572/>
14. Anderson MA, Malhotra A, Non AL. 2021. Could Routine Race-Adjustment of Spirometers Exacerbate Racial Disparities in COVID-19 Recovery? *The Lancet Respiratory Medicine* 9(2):124–5. [https://www.thelancet.com/journals/lanres/article/PIIS2213-2600\(20\)30571-3/fulltext](https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30571-3/fulltext)
15. Witzig R. 1996. The Medicalization of Race: Scientific Legitimization of a Flawed Social Construct. *Annals of Internal Medicine* 125(8):675–9. <https://pubmed.ncbi.nlm.nih.gov/8849153/>
16. Smart A, Bolnick DA, Tutton R. 2017. Health and Genetic Ancestry Testing: Time to Bridge the Gap. *BMC Medical Genomics* 10(1):1–9. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5223458/>
17. Blell M, Hunter MA. 2019. Direct-to-Consumer Genetic Testing's Red Herring: “Genetic Ancestry” and Personalized Medicine. *Frontiers in Medicine* 6(48). <https://www.frontiersin.org/articles/10.3389/fmed.2019.00048/full>



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CHAIR'S MESSAGE

What's Missing in the Discussion About DCTs: A PI's Perspective

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The definition of decentralized clinical trials (DCTs) varies from source to source, but a central theme involves processes that move data collection and investigational product (IP) administration closer to the study participant and farther from the site as the center of activity. DCTs are a natural evolution of research accelerated by the pandemic, and can provide novel datasets via mobile technology from “real-world” settings and virtual and offsite

interactions. They can also broaden participation in research by enhancing researchers’ access to more diverse populations, resulting in a more accurate scientific understanding of future therapeutics.

DCTs, once resisted by many professionals but long preferred by many patients, [are here to stay](#), and site processes and personnel must adapt to new operating procedures while maintaining traditional site-centric methods, which are critical in onsite/offsite hybrid models for conducting trials.

PIs and DCTs: A Healthy Combination?

With the rapid rise of DCTs to such levels of prominence as they are currently enjoying, we find ourselves embarking on an unprecedented experiment with the research process itself—one requiring us to tread thoughtfully in regards to how all stakeholders are affected, lest we run into

the law of unintended consequences. Unfortunately, mostly left out of this discussion is how this affects the abilities and willingness of site staff and principal investigators (PIs) to perform the new duties and responsibilities entailed in DCTs.

In the conventional, site-centric model, coordinators and supporting personnel perform most protocol-related tasks under the supervision of the PI. The latter accepts responsibility for the conduct of the study and the safety of participants. When a study participant visits a site as directed by the protocol, all resources are available to complete the requirements and monitor safety. Trust is the main attribute behind the Delegation of Authority by the PI for those deemed qualified by training, education, and experience.

Pending the release of updated U.S. Food and Drug Administration (FDA) guidance on DCTs, the regulatory requirements are the same for DCTs as site-centric studies. In 2009, the FDA released the “Final Guidance Document” on “Investigator Responsibilities.” The document confirmed the PI’s responsibility for study staff directly involved in the conduct of the study, even when they are not under the PI’s employ—in effect, anyone to whom the PI has delegated study duties for which they are qualified.

However, the sponsor is held responsible for “critical aspects of a study performed by parties not involved directly in patient care or contact and not under the direct control of the clinical investigator.” An example provided in the guidance is clinical chemistry testing “commonly done by a central independent facility retained by the sponsor.” It seems, then, that the difference in determining if the PI or sponsor is responsible is whether the individual or party in question is directly involved with “patient” care and has “direct control.”

Who’s On First?

All of this raises the question: Should the PI be held responsible for activities that directly involve “patient” care per the protocol, but in situations under which they have no “direct control”? An example would be an offsite protocol visit conducted by a home healthcare nurse employed by the sponsor. Another would be when an IP is sent directly by the sponsor to the patient’s physician to administer.

In these cases, a regulatory decision to make PIs responsible may affect their willingness to accept a study. DCTs may also require site staff to conduct home visits that raise logistical issues involving time, travel distance, personal safety, IP transport, lab collection, and safety assessments. These will require updates to regulations, oversight, standard operating procedures, budgets, recruitment strategies, training, and organization structure.

Ongoing reviews of how DCTs affect the main goals of broadening study participation, increasing patient diversity, and improving study implementation, as well as their effects on the clinical research workforce itself, are needed. Much of this depends on how regulatory authorities define the roles and responsibilities of sponsors, study teams, investigators, and other new stakeholders. For more background on DCTs, you can visit the ACRP website to download the recent whitepaper on [*Decentralized Clinical Trials: Perspectives for Clinical Research Professionals*](#) developed by expert members of the ACRP Fellows.

In addition to his volunteer duties with ACRP, Morin provides patient care and serves as the Director of Research at Holston Medical Group, a multispecialty practice in Tennessee, Virginia, and North Carolina, and is Director of the High-Risk Disease Prevention program for a Fortune 100 company.



RECRUITMENT & RETENTION

How to Make Clinical Trials More Diverse and Inclusive

Contributed by Florence HealthCare



Many medical professionals worry about a lack of representation in clinical trials, and this lack can have medical consequences. A [2014 study](#) showed that around 20% of new drugs approved between 2008 and 2013 had different effects depending on a person's race or ethnicity.

In spite of this, many clinical trials in the U.S. still don't have participant pools that accurately reflect the demographics of the people who will use the drug.

If clinical trials truly wish to be patient-centered, they must include all patients; but how can organizations in the clinical research industry increase the diversity of their trial participants? Further, will the move toward decentralized trials increase diversity or make health disparities worse?

We believe that [decentralized trials](#) play an important role—but not the only role—in increasing diversity and inclusion. Research sites, contract research organizations (CROs), and sponsors must combine decentralized technology with an understanding of historical inequities and community outreach if they truly want to increase the diversity of their clinical trials.

Underrepresentation and Patient Recruitment in the U.S.

Recruiting enough patients often presents a problem for clinical trials in the United States. [Joseph Munda of First Analysis](#) notes that around 50% of research sites have to extend their recruitment periods, and 37% of sites fail to meet their recruitment targets.

Even when clinical trials succeed in finding enough participants, those participants often don't reflect the population the research is meant to serve. A [special feature](#) in a 2020 issue of ACRP's *Clinical Researcher* journal mentions that 13.4% of the U.S. population is Black versus only 5% of trial participants. The disparity is worse for Latinx people, who make up 18% of the population and 1% of trial participants.

In 2021, [JAMA](#) published an article on the demographics of vaccine clinical trials from [July 2011 to June 2020](#). This chart shows how the demographics of those vaccine trials compare to the demographics of the U.S. as a whole:

Race/Ethnicity	Percentage of U.S. population (approx.)	Percentage in vaccine clinical trials (approx.)
White (not Hispanic or Latinx)	60.1%	77.9%
Hispanic/Latinx	18.5%	11.6%
Black/African American	13.4%	10.6%
Asian	5.9%	5.7%
American Indian/Native American	1.3%	0.4%
Biracial	2.8%	Included in the numbers above

These numbers show that White people were vastly overrepresented in vaccine clinical trials, while Asian people were almost accurately represented. Black, Hispanic, and Indigenous people were underrepresented, and the disparity was most severe for the Black and Hispanic communities.

Other vulnerable groups are underrepresented in clinical trials as well. Clinical trials often don't track whether they're including [LGBTQ+ people](#), and [people 65 and older were underrepresented in COVID-19 vaccine trials](#), even though that population was especially vulnerable to the disease.

For vaccines to be effective, they need to be tested on people of many ages, gender identities, races, and ethnicities. However, vaccine clinical trials, like clinical trials in general, do not yet accurately reflect the U.S. population.

How to Improve Representation

Genetics, race, age, gender, weight, and geographic location [can all influence](#) whether medical treatments are effective for a specific person. The rise of precision medicine—therapies designed to target specific genes—makes including diverse participants even more important.

So how do we make clinical trials more representative of the population they're meant to serve?

Dr. Yella Hewings-Martin suggests in her article for [Medical News Today](#) that the lack of diverse participants in trials has many causes, from preexisting health inequities to limited access and distrust of medical research. The [U.S. Food and Drug Administration](#) (FDA) has also discussed how inclusion/exclusion criteria and difficulty reaching research sites can cause a lack of diversity.

It's hard to list every factor that could lead to clinical trials not being diverse enough, but we've compiled four that we believe have solutions: lack of access to sites, insufficient time and money to participate in studies, overly stringent study inclusion criteria, and patients not feeling represented by the researchers conducting the trial.

As discussed in the sections to follow, some of these problems can be solved by technology, while others require a more comprehensive approach.

Increase Access

[Decentralized technology](#) can help a wider range of people take part in clinical trials. According to [Dr. Pamela Tenaerts](#), Chief Scientific Officer for Medable, 70% of people live more than two hours from a major research site. Sean Lynch, Director of Study Operations at TrialSpark, claims that [“50% of FDA trials in the U.S. are conducted in only 1% to 2% of ZIP codes.”](#)

Patients who live in rural or underserved areas may be left out of clinical trials because the research site doesn't reach out to them or because they can't drive to the site. This leads to a less diverse patient population from which researchers can recruit.

[Decentralized clinical trials](#) (DCTs) can help with this problem, since they can take place anywhere. Some DCTs let patients visit clinics and pharmacies close to where they live, while others let patients submit all their data remotely through apps, telehealth visits, or wearable devices. [Amir Lahav advocates for this type of remote trial technology](#) on an episode of our podcast.

Michelle Shogren, Senior Director of Innovation at Bayer, also emphasizes the importance of [“choose-your-own-adventure” clinical trials](#) personalized to the patient. “Somebody who might have a hard time getting away from work or who lives a long distance from the site might say ‘I would like to have more video visits and home nursing instead of having to come here all the time,’” she points out.

Still, decentralized technology alone won’t guarantee diversity. Research sites, sponsors, and CROs need to consider other factors as well.

Account for Socioeconomic Factors

Distance isn’t the only reason people don’t sign up for clinical trials. Some people can’t pay the [associated healthcare costs](#), and others can’t take time off work or pay for childcare.

For clinical trials to be truly inclusive, they need to be affordable. Technology vendors and research sites don’t have the ability to offset all costs for patients, but they do have the ability to help hourly workers and parents. More people can participate in clinical trials if they can check in on their phone or computer while they’re at work or at home.

Allowing check-ins at local doctor’s offices or pharmacies can also help patients in low-income or rural areas. Michelle Shogren notes that technology can help doctors in these communities serve their patients better by quickly looking up clinical trials [for patients who may not have realized trials are available](#).

However, as Leslie Byatt, Clinical Research Manager for the New Mexico Cancer Care Alliance and University of New Mexico Comprehensive Cancer Center, pointed out [when she joined us on our podcast](#), not every patient has access to WiFi, a computer, or a phone. Patients who can’t

afford the Internet may not be able to afford a car either, so they need to receive treatment at places they can reach on foot or by public transport, like the doctors' offices that Shogren mentioned.

Rethink Trial Exclusion and Inclusion Criteria

Investigators must set inclusion and exclusion criteria to run safe, effective clinical trials. However, [the FDA has urged](#) research sites, CROs, and sponsors to think carefully about how they set inclusion criteria to make sure they aren't excluding potential participants for the wrong reasons.

The FDA has observed that the elderly, people who are overweight, and people who have disabilities or chronic illnesses are sometimes excluded from Phase III or Phase IV trials when they could provide valuable insight into how the drug works for people like them. The investigator must use his or her professional judgment to decide when inclusion criteria can and can't be expanded, but loosening overly strict criteria may make trials more diverse.

The FDA also notes that people can be unintentionally excluded because they need accommodations to participate in a trial. For example, the 2016 census showed that roughly [13% of the U.S. population spoke Spanish at home](#), and that number keeps growing. Research sites may be able to recruit more Latinx trial participants if they employ Spanish speakers and offer informed consent forms in Spanish.

Make Participants Feel Represented and Welcome

Some diverse patients might not want to participate in clinical trials because they don't trust [the medical research industry](#). DCTs can alleviate this feeling by letting participants visit local doctors and pharmacists they already trust.

In the meantime, what if patients don't have a healthcare provider or need to interact with clinical research staff? Research sites can build trust between participants and their staff by ensuring they have a [diverse workforce](#). Patients may be more likely to participate in clinical research if they see themselves represented among the people running the trial.

[Community outreach](#) can also help patients feel like their needs and wants are being considered. Some research sites have started reaching out to patients by speaking at local community centers or houses of worship. Programs like these can show that researchers care about patients' questions and concerns.

Conclusion

To ensure patients receive the safest, most effective treatments, clinical trials in the U.S. need to recruit diverse participants who accurately represent the population. This can mean using decentralized trials to work with patients in the areas where they live, but it can also mean rethinking exclusion criteria, building a diverse workforce, and establishing trust between research professionals and participants.

To learn more about enhancing representation in clinical trials, check out our [eBook on DCTs for research sites](#) and [our CEO's article for the Forbes Tech Council](#) about representation, equity, and inclusion.



OVER THE TRANSOM

Gears in Motion: Elevating DCTs and the Professionals Who Run Them

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



It's no secret that some of we few, we happy few, on the ACRP staff have been spending quality time lately collaborating with ACRP Fellows and other experts from beyond the Association to hone our understanding of what decentralized clinical trials (DCTs) are, to appreciate how they function ideally, and to share [what stakeholders in the clinical research enterprise need to know](#) about them as they evolve beyond their utility in pandemic conditions into what looks to be an ongoing and potentially game-

changing presence in the clinical trials arena.

For this installment of our humble column on news from the wonderful world of press release services and public relations offices, we offer glimpses of how various organizations (no endorsements implied) are tapping into the gearworks of DCTs to see for themselves if the payoff lives up to the hype.

U.S. Leading the Way in Virtual Trial Adoption

The term DCT (they are also known as remote/virtual trials) refers to digitally empowered clinical trial processes. The market growth is driven by growing adoption of virtual trials following the outbreak of the COVID-19 pandemic. Medi-Tech Insights in March [reported](#) that the global virtual clinical trials market is estimated at close to \$8 billion as of 2020, and is growing above a 10% compound annual growth rate. Key players in the virtual clinical trials market are ICON, Parexel, IQVIA, Covance, Thermo Fisher, LEO Innovation Lab, Huma, Medidata, Oracle, CRF Health, Medable, Signant Health, and Clinical Ink.

The number of venture capital funding deals involving DCTs has increased post-COVID-19, the consulting service adds. There were six deals in 2018 which increased to 18 in 2020. Most venture capital funding occurred in Q3 2020 (10 deals). Notably, Medable—one of the fastest growing DCT platform providers—raised \$524 million from various rounds since 2020. One of the biggest rounds occurred in October 2021, when the company received \$304 million in Series D funding. Growing venture capital funding will enable companies to make technological advancements and increase their customer and geographic reach, Medi-Tech Insights predicts.

Meanwhile, comprehensive regional assessment of the virtual clinical trials market suggests that the U.S. is currently the largest such market. On the other hand, European life science/medical device companies have not moved as rapidly to adopt virtual trials as the U.S. However, there have been developments taking place in the European Union that are expected to propel the adoption steadily, the consulting firm notes.

Bringing Artificial Intelligence to Bear

THREAD, a technology and consulting service provider from North Carolina enabling electronic clinical outcome assessments and DCTs, [announced](#) in late March that it is collaborating with Amazon Web Services, Inc. (AWS) to launch enhancements to the THREAD platform powered by enterprise-scale automation and built-in artificial intelligence (AI)-driven technologies. The company says that these next-generation DCT technology features will serve as the backbone for modern clinical research by enabling faster, more efficient clinical trials while improving access for research participants with higher quality data capture across the life cycle of a study.

THREAD is working with AWS Professional Services experts to design an advanced machine learning architecture and AI models to automate processes for customers. THREAD's hope is that its new cloud-enabled platform features will accelerate clinical research by reducing inefficiencies in real-time data capture, auto-populating data workflows that are completed manually today, and more.

Accelerating Adoption, Increasing Access

Also in late March, ActiGraph, a Florida-based provider of wearable, technology-enabled scientific solutions for clinical trials and academic research, [announced](#) it has joined the [Decentralized Trials & Research Alliance \(DTRA\)](#). By enabling collaboration between stakeholders, the DTRA accelerates the adoption of patient-focused DCTs and research within life sciences and healthcare through education and research.

“Now is the time to share ideas and insights that will chart the future course of clinical trials, accelerating drug development and saving lives—and by taking part in the DTRA, ActiGraph is joining the many entities that are contributing to this mission,” said Craig Lipset, DTRA co-chair. “We have a responsibility to advance the health of people with unmet medical needs, and by convening stakeholders, we can remove remaining barriers to adoption and impact patients today.”

Meeting the Needs of Growth and Expansion

Last but not least, CCT Research in Arizona has [announced](#) the addition of a new DCT-focused team dedicated to supporting a positive subject experience and delivering exceptional quality data as the company continues to grow and expand. The company notes that this team, made up of experienced and remote clinical research coordinators (CRCs), “will be pivotal...to expand [our] reach and management of clinical trials by providing expert support to all subjects and sites within the network.” CCT adds that the team “will operate in a hybrid environment that will blend traditional clinical research and current technology to provide a contemporary definition to the CRC role.”



DATA-TECH CONNECT

Technology Considerations When Onboarding and Offboarding Clinical Research Staff

Mollie Maggied, MSN, MHA, RN, AT-C, CPN; Paula Smailes, DNP, RN, CCRP



While technology is known to help with efficiency and productivity for clinical researchers, it can also be accused of leading to feelings of stress, burnout, and being generally overwhelmed. {1,2} Increased work volumes thanks to electronic workflows can be to blame, but staffing crises may also be at fault. Meanwhile, there exists a smaller number of experienced applicants being considered for open research positions across the drug and device research and development industry. {3,4}

That said, when the perfect applicant is hired, there may be a tendency to expedite onboarding. From the site perspective, there are obvious considerations with onboarding, such as adding new hires as staff on institutional review board (IRB)–approved research and providing training on the protection of human subjects.

Adding to that, the technology needs for today’s clinical research staff are equally essential. When new hires onboard, access to technology becomes critical to perform daily workflows. Central to that are communication, such as e-mail, and data sharing (e.g., via electronic case report forms). While technology considerations are important to onboarding, they are crucial throughout the duration of employment to offboarding. Even internal transfers may have technology changes as they move from one position to another.

Onboarding

The [Joint Task Force for Clinical Trial Competency](#) (a collaborative effort of representatives from many organizations, including ACRP, managed by the Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard) has identified data management and informatics as key skills that clinical research staff should possess. {5} When applying this philosophy to new staff who are onboarding, access to technology should be one of the most important considerations. Given the needs and complications of standard operating procedures for using company e-mail and shared drives, electronic case report forms (eCRF), IRB portals, virtual meeting platforms like Microsoft Teams, Zoom, and WebEx, plus the electronic medical record (EMR) system, access becomes crucial to daily operations.

Consider the revenue cycle aspect of conducting research. Are billing systems available for sponsor or patient payments when access becomes critical? Is scheduling software ready for patient appointment-related tasks?

For some systems, such as those tied to eCRFs and EMRs, training also becomes a priority. Ideally, training will occur close to the beginning of the end-user's first official use of a system, so as to not leave him or her forgetting the system features that were taught. If the system is complex, use of a playground environment, if possible, can increase confidence until access to the live system becomes possible.

Meanwhile, since the onset of the pandemic, the use of telehealth has skyrocketed, including in clinical trial situations. Telehealth has become a much more widely used means to conduct clinical research visits and another system to which new hires require orientation. {6}

Consider the use of a checklist that includes both the technologies that the new hire needs oriented to, but also a competency checklist, to ensure that new hires have a basic understanding of both how to use the systems and how to apply any efficiency tools that may exist.

Offboarding

Why is this important if the research staff are transitioning into a new role in the organization or leaving it altogether? The answer lies with the consequences that may exist without a properly executed exit plan. There needs to be assurance that nothing is left undone, and while technology access has stopped, communication channels must continue. The following tasks, explained in more detail afterward, should be considered when an employee is leaving an organization or is an internal transfer leaving a research role:

- Remove research staff from being listed in research protocols when there are system impacts, from inclusion in organizational drives and e-mail systems, and from access to sponsor systems.
- If electronic documentation was used, ensure that any final research notes and encounters are signed.
- Place an “out of contact” message in e-mail and the EMR communication tools for staff who are leaving, along with guidance for whom should be contacted for future operations.
- Perform a messaging system “cleanup,” including e-mail and EMR systems.

Removing Staff

If the EMR has research notifications based on protocols, there can be concern if staff members are not removed from studies upon leaving the organization or transitioning to new roles. If staff become internal transfers, alert notifications may continue to fire to them for patients on studies for which they are no longer covering. This could lead to Health Insurance Portability and Accountability Act (HIPAA) violations if study staff are no longer involved in patient care per protocol.

Staff who leave will need to have their replacements added as soon as possible to ensure communication continues for the study, regardless of technology medium. It is imperative these steps are taken to avoid issues.

Unfinished Notes and Encounters

Another possibility from research staff departure exists when notes are not signed by the research staff if the documentation method is electronic. This could result in incomplete notes being

placed in a pending status that eliminates the possibility of other staff members being able to view unfinished work. Open notes could lead to open encounters in EMR systems, which could inevitably result in incomplete data for the research study. Given this consideration, protocol deviations or violations may be the ultimate negative outcome.

Messaging

Ongoing communication about coverage is important in that it allows people to know who is covering upon any departures of staff. Thinking of the multiple systems that clinical researchers use, how many have a built-in messaging feature? For EMRs, an internal messaging system allow users to message other system users, keeping the dialogue secure within it. However, e-mail is just as important. Setting up an away message for the end-user who is leaving will allow others to contact the correct person if there are questions. It also ensures continuity of research-provided care. If the system allows, providing a start and end date can facilitate staff coverage. This process allows for a coworker to continually monitor incoming communication that are sent to the departing research staff.

Related to system messaging, it is important that the departing staff member have all messages acknowledged and reconciled. This ensures there are no outstanding issues requiring their attention. This also allows for the covering coworker to not be inundated with old messages that still may need attention after a staff mate's departure. Having the researcher clean up and handle messages and tasks within the system prior to his or her departure is in the best interest for all users of the system.

Conclusion

Technology has evolved into the backbone of clinical research operations. As we grow accustomed to electronic systems to execute daily workflows, how staff are properly oriented to systems will lead to faster functioning in their assigned roles. Offboarding is just as important to assure that there is no unfinished work and ensures a continuous flow of operations and smooth transitions when staff depart. If your organization has an informatics department, consider soliciting its help to facilitate and support staff during these times.

References

1. Harper B. 2020. Capacity and Competency of the Clinical Research Workforce: Today and Tomorrow. *Clinical Leader*. <https://www.clinicalleader.com/doc/capacity-competency-of-the-clinical-research-workforce-today-tomorrow-0001>
2. Causey M. 2021. Burnout Threatens to Undermine Clinical Trial Workforce Productivity. <https://acrpnet.org/2021/09/13/burnout-threatens-to-undermine-clinical-trial-workforce-productivity/>
3. Aerotek. 2018. The Staffing Crisis in Clinical Trials and the Drive for Permanent Staff. <https://www.aerotek.com/en-gb/insights/the-staffing-crisis-in-clinical-trials-and-the-drive-for-permanent-staff>
4. Kremides J. 2017. A Turning Point: Examining the Clinical Research Workforce in 2018. <https://www.outsourcing-pharma.com/Article/2017/12/21/A-turning-point-Examining-the-clinical-research-workforce-in-2018>
5. Sonstein S, Jones C. 2018. Joint Task Force for Clinical Trial Competency and Clinical Research Professional Workforce Development. *Frontiers in Pharmacology* 9:1148. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6198073/>
6. Lorusso D, Ray-Coquard I, Oaknin A, Baberjee S. 2020. Clinical Research Disruption in the Post-COVID Era: Will the Pandemic Lead to Change? *ESMO Open Cancer Horizons* 5:5. [https://www.esmooopen.com/article/S2059-7029\(20\)32718-6/fulltext](https://www.esmooopen.com/article/S2059-7029(20)32718-6/fulltext)



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GOOD MANAGEMENT PRACTICE

Disruption and Bravery: How You Can Make a Difference in Clinical Research

A Q&A with Tina Barton, PhD, MBA



Dr. Tina Barton, chief operating officer of eMQT in Milton Keynes, England, United Kingdom, is a drug development specialist with more than 40 years of experience driving growth, managing teams, and training for the future in settings that range from large global organizations to small start-up enterprises. She has been a champion for the inclusion of Central Eastern European countries in clinical development projects, and now is focused on Sub-Saharan Africa for the same purposes.

*She also is the 2021 winner of the Christine Pierre Clinical Trials Lifetime Achievement Award, named [in memory](#) of the late founder and CEO of RxTrials Inc. and the Site Solutions Summit, founder and president of the Society for Clinical Research Sites (SCRS), and 2007 chair of the Association Board of Trustees for ACRP. Managed by **mdgroup** since 2015 and presented annually at Clinical Trials Europe, [the award](#) celebrates the groundbreaking work and contributions of individuals across the field of clinical research.*

*This Q&A is excerpted from Barton’s talk with **mdgroup** about winning the award, why clinical research is the “most incredible” global industry to work in, and the importance of diverse skill sets for professionals on clinical trials teams.*

Q: Supporting the patient at every stage of his or her clinical trial journey is of benefit to the whole ecosystem. Why are you passionate about working in clinical research?

A: I have spent more than 40 years in this business, and I love it. I'm passionate about it. I have had the time of my life, but I never thought when I left university and got a job in a hospital laboratory that I would end up doing what I have.

Working in clinical research means being able to make a difference to people's lives. Even though sometimes it might seem small, every contribution is important. One of the positives to come out of the COVID-19 pandemic is that pharma is no longer seen as the "Big Bad Wolf." For most of my career, publicity mainly portrayed our industry negatively, but I think there is a much bigger population now that understands this industry can really bring value and do good, which is a real asset.

To maintain that positivity, we should always be looking at how we can improve the way we work and attract the very best people to work in our industry. We need to embrace the challenges that creating truly diverse, patient-focused clinical trials brings. As my grandmother used to say to me, there is no such thing as "can't"—we just haven't found a way to do it yet.

Q: You mentioned the need to maintain the positive momentum we have built up as an industry over the past two years. How can individuals working in clinical research contribute to this?

A: I am quite disruptive, and I would encourage others to think that way too. I think that, as an industry, we are very slow to change.

Another positive to come out of COVID-19 is we have learned to work differently. Finally, we are changing faster. I really hope that, once this pandemic is deemed to be over, we do not go back into our old ways of being slow to implement change.

Earlier in my career, I was more hesitant about being disruptive, but over the years I have learned that someone has to be first and I am more than happy to be that first person. As an

industry, we should focus on what is difficult—whether that is diversifying clinical trials or reaching patients without access to the latest technology.

That is why, for example, I push for Africa to be included in clinical trials. Yes, there are challenges, but just as we adapted to cultural differences and logistical difficulties when we first ran trials in China, or Hungary, or Brazil, we can learn to embrace and accommodate different cultures and work with them in Africa.

It is also important to remember that including African sites in a global programme of clinical trials brings huge benefits for all.

Q: Looking at new markets like Africa, is there any potential for established markets to learn from what is happening there? Can we find new ways of combining human interaction with technological advancement? Can we make both protocols and staff more responsive?

A: Absolutely! Working with sites in African nations brings new insight into long established methods of training and highlights how quickly we can adapt.

In Africa, they are so hungry to learn. The healthcare professionals go above and beyond and really give you their time. This kind of involvement can be much harder to come by in some of the more traditional sites, particularly with senior team members. In Africa they want to learn—they want to be involved in improving trial outcomes and adapting to patient needs.

Many of the professionals we deal with in Africa had their original training in the western world and are now running hospitals and clinics in their own countries. Having seen what is open to colleagues, they are rightly asking how they can be involved in the next stages of the development of new medicines, how they can get the best possible treatments for their patients, and how they can be accepted as clinical trial sites.

It is not a big ask to make these changes happen. Where there is a will, there is a way, and they are certainly very willing and more than happy to go the extra mile.

As an example, there was a site in Nigeria where the sponsor required them to have a separate lockable room for documents, consents, and seeing patients, so they found a room and equipped it. They are willing to do whatever it takes because they want to be included. The size of the workforce is not an issue. The issue is more about an appropriately trained workforce. If you are prepared to help them with that training and learning, then anything is possible.

At another site, there was an outbreak of chikungunya about four hours' drive from the main centre where the project was under way. Two doctors, a nurse, and our clinical trial coordinator took a three-day field trip to collect samples and work with the patients who were suffering there. That would not happen in most other countries I have worked in. Their ethos was, if the patient cannot come to the site, we will go to the patients.

This willingness to engage with learning, quickly problem solve, and adapt to changing patient needs is something which could benefit the profession globally, not just at new sites.

Q: How do you think awards like those presented at [Clinical Trials Europe](#) help both individual career advancement and the wider industry?

A: If we are going to attract the best and brightest to clinical research and encourage them to develop new and improved ways of working, we need to recognize those currently pushing the boundaries and innovating.

For me personally, it was amazing to get the recognition of my peers from around the world when I received the Christine Pierre Lifetime Achievement Award. However, the award also meant recognition for the people and sites I work with.

For companies like **mdgroup**, these awards are a chance to demonstrate they believe in people who make a difference.

Awards can also add value by highlighting how our industry has already changed for the better. For example, at Clinical Trials Europe it was great to see this industry is now full of women in the more senior positions. When I started, there was a glass ceiling and it was pretty low. You did not see many women around the board table.

While that has changed, the message still needs to get out there. Women can have long and very successful careers in this industry in whatever they do.

Q: Beyond gender diversity, what are the needs for diverse skills in areas of our industry that people might not think of as representing traditional research roles?

A: It is important to remember clinical research extends far beyond the boundaries of the laboratory, and our required skill sets reflect that.

We need graphic designers to produce amazing materials to reach and inform patients. We need marketers who can raise awareness of trials. We need engagement experts who can understand cultural sensitivities and ensure a positive patient experience. We need such a huge range of skill sets to get the best possible outcomes—both for patients and trial sponsors.

If you are in the early stages of your career, or are thinking about making a lateral move into the clinical trial research industry, just do it. It is the most incredible business to be in. You can meet amazing people and, at the end of the day, it is all in the name of helping patients. There is room for everyone and so much fun to be had.

Be disruptive, be prepared to work differently, and be brave. That way you can make a difference.



IRBs IN FOCUS

Carving Out a Career in Ethical Review

Contributed by WCG IRB

When people consider a career in ethical review at an institutional review board (IRB), they tend to imagine themselves sitting in board meetings evaluating clinical research protocols and informed consent forms. However, the range of positions at an IRB is much broader and far more diverse. This column features three employees in very different roles at [WCG IRB](#) describing their current duties and the competencies required to excel at what they do for the clinical research enterprise.

Heather Kim, MS, RAC, CIP

Manager, Quality Assurance (QA)



I joined WCG IRB as an intern and am now QA Manager on the IRB’s Compliance team.

I was originally interested in regulatory affairs, which is on the sponsor side of the industry, preparing and submitting Investigational New Drug and New Drug Applications to the U.S. Food and Drug Administration (FDA). I had studied for the Regulatory Affairs Certification Exam and obtained my master’s in Regulatory Affairs. During my studies, there was perhaps one chapter on IRBs, so I knew the basic purpose of an IRB, but not much else.

Copernicus Group IRB [now part of WCG IRB] had an internship program, and I thought that would be a great way to get started in the regulatory field. Once I started the internship, I discovered a completely different, fascinating regulatory field—one in which the IRB interacts with both the FDA and investigators. I was attracted to the role, knowledge, and specialization it gave me, but also to the people; I really fell in love with the company. I had a great team and a great boss, and that really helped me to develop as a young professional.

In my current role, every day is different and my workload shifts constantly. It's a challenge, and that's what I love about it! There are eight members of the Compliance team, and we are based throughout the U.S. My responsibilities have really run the gamut. They include managing standard operating procedures; overseeing the document workflow; investigating site noncompliance; providing regulatory support for the IRB staff and the IRB chairs; answering questions from sponsors, clinical research organizations (CROs), and sites; developing corrective and preventive actions (CAPAs); hosting FDA inspections; and helping to respond to any questions or concerns during an audit. I also manage clinical trial participant calls, since the IRB is listed as a contact.

This position requires diplomacy and strong interpersonal and communication skills. You are dealing with a wide variety of situations—from internal discussions regarding errors, to handling auditor findings, to speaking with upset clinical trial participants. I really enjoy the problem-solving aspect of the job and working toward solutions in a collaborative way.

I am also a Type A personality; if you are in quality or compliance, you need that type of personality. There is room for some flexibility, but you must be detail oriented and always dot your i's and cross your t's. If you are in the Quality department, it's expected that things be done right the first time.

WCG IRB's mission to protect the rights and welfare of human participants and advance clinical research is very important to me. The company has been at the forefront of the IRB industry for many years and paved the way for the establishment of the central IRB model.

To this day, we continue to work with large academic medical centers, pharmaceutical companies, CROs, and independent research sites to assist in ethical review oversight, streamlining study start-up efficiencies, and aligning with our partners on operational processes related to their trials. It has been very exciting to be part of advancements in the industry.

Marcus Lias

Lead, Client Care Center



As the Lead in the Client Care Center, I respond to clients directly regarding any of their clinical study review questions. I will communicate via phone calls, chats, and e-mails with sponsors, CROs, sites, and clinical trial participants. I also help manage the training for any new staff members who join our department.

There are many client care specialists in our team, and we manage calls predominantly from the U.S. and Canada. Since we

are a global company, we have teammates in other countries, too. While we do not work directly with participants like a site does, participants do contact us when they have questions about a study. For example, we will go over an informed consent form with a participant, making sure that's clear. If there is an issue that we can't help to resolve, we refer it to a Participant Protection Liaison, such as Heather Kim, who will address their concern promptly with the site.

We also work with sponsors. We understand what they are going through trying to meet their goals and time frames to get studies off the ground and patients enrolled. We also help sites and principal investigators at their institutions. As members of the Client Care team, it's integral that we understand what our clients need, which is always changing, so we are always learning. I have worked at WCG IRB for nearly seven years, and I still learn things every single day. It's great!

This role requires a good customer service background, strong communication and problem-solving skills, and the ability to think quickly on your feet. You also need empathy, to understand how people are feeling. I have been in customer service for about 20 years, so I know how to respond to people. Customer service is not for everybody, but it is definitely for me.

I enjoy being involved, being able to help participants, and knowing that the clinical studies our company reviews and approves help people either in the future or currently for Compassionate Use cases [formally known as [Expanded Access](#) cases by the FDA].

At the start of the pandemic, we were triaging issues that nobody in the industry had faced before. There were lots of questions from our clients and lots of changes to the way studies were being conducted. Everybody was going remote with their site visits and not having participants come into a location anymore, and we had to know how that works and how to get the appropriate approvals. We are trained on how processes work as an IRB, so we know what they can do. We are also constantly getting updates from our board panel members on different review types and changes to the regulations. Then I must train my team on how we're handling those changes.

I like knowing that we are helping people to get healthy and be the best that they can be. It feels good to hear about projects that we have worked on in the news. We had a client that helped the White House to get COVID-19 tests in homes. We were involved directly, e-mailing back and forth all the time, trying to get it done and processed as soon as possible because we knew the need for it. We put our heart into what we're doing. It's not about money. It's about helping people. We're all about the human participants and making sure that they're taken care of. There have been Compassionate Use cases where a physician was trying to get access to a therapy to treat one of their patients, and we helped them get approval as soon as we could, and that saved somebody's life. It's a cheering moment for the entire team!

Michele Baptista

Director, Business Development



I joined WCG IRB on June 1, 2014, when it acquired Aspire IRB. I cofounded Aspire, which was the first female- and minority-led independent IRB.

Originally, I did not set out to join the Business Development (BD) team. However, the WCG leadership team recognized that I had the requisite skillset and thought I would be good at it, so I decided to give it a try for a couple of years. That was almost eight years ago. I am very grateful to them for seeing my potential. I have 30-plus years of IRB experience, I am honest and trustworthy, and I connect with people well. It turns out that I fit into the BD world well, and I love it!

As a small business owner, I wore many hats and was constantly pulled in a lot of directions. In my new role, it is great to be able to focus on one area and really excel. As Director of BD for the WCG IRB and institutional biosafety committee (IBC) sponsor/CRO team, I partner with current clients and research new companies that may need an IRB for their upcoming trial or portfolio of trials. I focus on small- to medium-size biotechnology, medical device, diagnostic, and biologic companies in the U.S., Canada, and Puerto Rico. Some of them have preclinical products and will not need an IRB until their first-in-human studies.

That said, advance planning is important to expedite the study start-up process, especially for gene therapy trials, which require both IRB and IBC reviews. I also work with the smaller, niche CROs and independent Phase I clinical research sites. Due to the nature of my work, I partner regularly with experts in our gene therapy, biotechnology, and scientific and regulatory divisions.

One of the most rewarding aspects of my job is helping people who feel a little lost regarding the IRB process. I have met engineers at some of the medical device companies that I work with who say, “I have this device and I need an IRB.” They don’t have a protocol; they don’t have a plan or a pathway through the FDA to get approval. They just have an idea and their device, and someone told them they needed an IRB. It is fun to lead them through a process that sounds very complicated and make it simple.

I am inspired by collaboration and human interaction, so staying focused while working from home during the pandemic was a challenge. I participated in a lot of videoconferencing and

FaceTime calls with my teammates, discussing what we were working on, and helping each other stay motivated.

I also started the external Coffee Klatch Networking Group, which met once a month via Zoom. WCG was hosting a series of solution-oriented weekly webinars on pandemic-related topics. [It ultimately held 40 webinars, which were attended by 70,000 industry professionals]. At the Coffee Klatch, we took turns talking about what we learned from the webinars and discussing our personal experiences. Whether a member was a vice president of clinical operations at a biotech company, a project manager at a CRO, or a study coordinator at a site, we were all trying to navigate this new reality together. We had 10 to 15 people on every call, and it was great.

Prior to the pandemic, our team probably spent 80% of the time on the road. So, when offices across the country started to close, the first challenge was figuring out how to do our jobs from home when we could not be out talking to people. At the time, that was a huge shift—like a train hitting a wall! However, we all quickly discovered new ways of working together, and it will be interesting to see what the future holds as businesses start to open back up. I doubt that we will return to 80% travel; it will likely be a hybrid model with a mix of in-person and at-home/Zoom meetings. There is certainly value in having in-person interactions with clients, but reduced travel time has enabled us to be more productive and devote longer periods of time connecting to one another.

I am proud to say that the career experience at our company is unparalleled. I have a long history in the IRB business, and WCG is the “who’s who” of the industry. The people that I used to take classes from at the PRIM&R Annual Conference are now my coworkers. It’s like growing up wanting to be an NFL player and then being on an NFL team.

WCG IRB puts a lot of effort into regulatory intelligence, quality control, quality assurance, and continuous improvement. People look to us to tell them how to apply the regulations during the pandemic. I wouldn’t feel comfortable working anywhere else.

Conclusion

As the experiences of this trio illustrate, there are many varied, but equally rewarding, roles available for clinical research professionals who would like to pursue a career at an IRB.



ON THE JOB

Stop Struggling to Manage the Complexity of Your Studies

Debbie Taylor, MBA



Once you've secured an industry-sponsored clinical trial for your site, how can you make sure that the study runs smoothly and you are capturing all the revenue that your site is due?

Documentation is key to keeping track of key dates and collecting all payments due. In order to know the financial status of your study, you need to see how those collections impact forecasted budgets in real time. Payment terms are often complex and protocols often change, leaving many sites with payment delays and unrecognized revenue. Tracking this information in an online database simplifies life for research coordinators, while allowing the finance team to see the “big picture” status of your site's trials.

Here are nine tips to help keep your financials on the straight and narrow from study start-up to closeout:

1. **Budgets:** Create an internal budget to link revenue and costs to the appropriate timelines. Include all expected payments from the coverage analysis (CA) billing grid into your budget as well as administrative costs (e.g., study start-up and institutional review board [IRB] fees). Rather than simply using an Excel spreadsheet, it is preferable for principal investigators (PIs) to upload the CA to a database to create an internal budget.
2. **Dates:** Make sure payment terms and specified payment triggers and timelines (e.g., IRB deadlines, goal dates, and signatory schedules) are integrated into calendars and reminders to ensure the study stays on track.

3. **Enrollment:** Keeping track of metrics on enrollments is key to making sure your site is meeting specified targets. Make it easy to ensure that payments triggered by reaching certain enrollment targets are collected. Keep enrollment and payment data and key dates in one integrated system that automates calendar reminders.
4. **Finance:** Make sure that accounting keeps invoices organized to avoid billing errors and misallocating payments. Manually scanning copies of invoices and checks and storing them in computer folders with naming conventions is a cumbersome and error-prone process. It's even more difficult to do when sites, running different trials for the same sponsor or contract research organization (CRO), get a lump sum payment. Invoicing integrated with accounting systems like QuickBooks can be a game changer.
5. **Monitoring Visits:** Payment terms that rely on data monitoring often cause significant payment delays. Keeping tabs on key data monitoring dates is easier when those dates are visible in the same place as payment data. A database with automated workflows can populate calendars and send reminders.
6. **Holdbacks:** After all their hard work, sites often neglect to collect holdback payments and closeout costs once a study is complete. Carefully track and manage accounting of holdbacks to make sure that all revenue that your site earned gets collected. This can require follow up for months or even years after a study ends.
7. **Completed Line Items:** Payments terms are complicated and depend on scheduled dates and key targets. It is hard for PIs to wrap their heads around what receivables might still be outstanding. See all the completed line items in one place so you can narrow down what payments may need to be followed up on.
8. **Forecasts:** Accounting entries made in siloed invoicing spreadsheets will not be reflected in real-time status of actual budget numbers vs. forecasts. Having an integrated system that automatically updates forecasts when payments are made or delayed allows the finance team to see the status of your study in real time.
9. **Metrics:** A system that tracks all of your studies has the added benefit of automatically providing marketing metrics on your site's overall success across all of your trials. Know how long your site takes to enroll the first patient, execute a contract or budget, and whether you meet sponsor/CRO timelines. Having these metrics readily available is key to standing out among other research sites and getting selected for the next study.

Conclusion

Don't reinvent the wheel trying to manage complex studies. Technology can ease the burden. Systems built in collaboration with industry experts often better fit sites' needs than a huge, expensive clinical trial management system.



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SITES & SPONSORS

Blazing Clinical Pathways for Phage Therapy

Paul Kim, PhD, MBA



In 1747, Dr. James Lind, a Royal Navy surgeon aboard the *HMS Salisbury*, noted high mortality rates among sailors suffering from scurvy—a condition caused by severe vitamin C deficiency that is often affiliated with seafarers due to the absence of fresh fruit on long voyages. In his mission to cure them, he divided 12 patients into groups of two and ordered each group to incorporate cyder, elixir vitriol, vinegar, seawater, fruit, or an electuary into their diet. By the end of what some consider history’s first clinical trial, Dr. Lind identified

oranges and lemons as the optimal remedy for this disease. This research would go on to support the evolution of naval treatment of vitamin deficiency and contributed to the future structure of controlled clinical trials. { 1 }

Since the famous scurvy trial, clinical research—particularly the use of randomized controlled clinical trials—has become a cornerstone for how modern medicine advances. Today, we use clinical trials to improve how we prevent, detect, diagnose, and treat diseases with various phases testing for safety and efficacy. From concept to commercialization, standard drug development programs typically take more than a decade to reach consumers. However, the COVID-19 pandemic and the phenomenal success of the COVID-19 vaccines has shown a spotlight on the critical need and potential for rapid innovation and accelerated clinical trial processes in infectious diseases.

In recent years, phage therapy, which gained popularity in the early 1900s before losing traction due to the development of cheap and widely accessible antibiotics, has reemerged as having the potential to be a powerful solution to combat bacterial infections. In particular, treatment of antibiotic resistant strains of pathogens like *E. coli*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, and *P. aeruginosa*, which cause the largest numbers of global deaths, are poised to benefit from this innovative approach.^{2} As multiple groups advance into the clinic to deliver phage therapies to patients and combat the emerging pandemic of antibiotic resistance, it is more important than ever to understand the intricacies of the clinical and regulatory pathways for these life-saving medicines.

Design and Conduct of Bacteriophage Clinical Trials

The overall structure and administration of bacteriophage clinical development programs are similar to other drug development programs within a given indication. However, bacteriophages have unique nuances which must be accounted for in preparing preclinical and clinical development plans.

Perhaps the most prominent distinction is their pharmacokinetic (PK) characteristics—or how a drug is absorbed and transported inside and outside the body. Bacteriophages replicate within target bacterial cells, so the effective dose at the site of infection may be many times greater than the input dose, unlike most other drugs in which drug concentrations go down over time. This also creates other challenges such as optimizing delivery, accounting for predator/prey dynamics (which impact sample timing and quantification), specimen acquisition and stability, methods of quantification, and PK modeling.

For example, the gold standard for bacteriophage quantification is the plaque titer assay. This method involves skilled technical support and sometimes multiday processing before results can be interpreted. Because bacteriophages must remain viable through the process, care and consistency must be applied from collection, through shipment and storage, to final assay conduct. Methods for maintaining phages in good condition is also impacted by specimen type, which varies by indication.

The bacteriophage's predatory relationship with bacteria, as well as its inherent desire to maintain a homeostasis with bacteria, must also be considered within the clinical program as the location, quantity, and lifestyle of these bacteria can directly influence resulting phage quantification. Fully understanding these dynamics requires sophisticated sampling and modeling techniques, many of which must be developed alongside the study, given that most PK modeling and reporting groups are unfamiliar with bacteriophage biology. Due to these complexities, few commercially available reference laboratories are capable of reliably performing plaque titer assays.

Two other major distinctions to note are:

- The specificity of this type of targeted therapy, in terms of how it spares the rest of the microbiome and theoretically prevents comorbidities like *C. difficile* infection.
- The unique mechanism of action, which is why everyone is so interested in developing phage therapies because they have potential to address antimicrobial resistance.{2}

Because of these considerations, early-phase investigations of bacteriophage products require special care for development of analytical methods and trial logistics to enable effective interpretation of the results.

Challenges of Selecting Human Subjects for Bacteriophage Trials

Bacterial pathogens causing a patient's infection are typically identified via culture and susceptibility testing at a local or central laboratory, which can take several days. As a result, conventional modern medical practices typically start by empirically treating patients with broad spectrum antibiotics while waiting for the culture to identify the pathogen—a practice that contributes to the emergence of multidrug resistant bacteria. For a precision therapeutic such as bacteriophage, which targets a particular bacterial species, this conventional dynamic creates a challenge for identification and enrollment of the patient population most likely to benefit from the experimental therapeutic.

The most straightforward approach to counter these challenges is use of a bedside or other rapid diagnostic. However, there are still relatively few rapid clinical diagnostics available and even fewer that provide truly “rapid” results (e.g., less than two hours) that could be used to identify and enroll a patient with an acute infection into a clinical trial.

The next best option is to rely on a patient’s clinical symptoms and medical history. In urinary tract infections, for example, more than 80% of all infections are caused by *E. coli*. Likewise, most recurrent patients return with urinary tract infections caused by the same bacteria as the prior infection, meaning that patients’ medical histories can be used as an enrichment strategy when creating study eligibility criteria. Therefore, strategically selecting indications driven by pathogens with high prevalence and targeting patients through their medical histories and eligibility criteria can reach the populations most likely to benefit from participating in precision medicine clinical trials such as those conducted with phage therapies.

In less well-understood diseases such as those with chronic inflammatory indications (e.g., Crohn’s disease or ulcerative colitis), where bacteria seem to play a role in the underlying disease pathology, understanding the perturbations in the patient’s microbiome may help to identify specific subsets of patients where modifying their microbiome in a targeted way may improve their clinical outcome. In these cases, basic bacterial identification techniques are not enough to determine if patients could benefit from precision therapies; rather, patient identification would require advanced culture techniques to isolate individual strains and genetic deep sequencing technologies to sort through complex microbiome data. This is necessary not only to evaluate the relative levels of different types of bacteria, but also what molecules these bacteria are ultimately expressing.

In both cases described above, identification of patients who may benefit from a clinical trial involving bacteriophages requires a deep understanding of the disease, identification of the clinical sites and physicians seemingly best suited to enroll and manage these patients, and sophisticated laboratory logistics and testing programs.

Site and Principal Investigator Selection for Phage Clinical Trials

Identification of study sites with teams experienced in the target indication or patient population is critical for success of any clinical trial. Bacteriophage therapeutics being a new modality, especially in the United States, requires good sites, sponsors, and contract research organization (CRO) engagement to plan and execute these types of trials effectively.

Additionally, clinical sample testing labs as well as clinical sites and their staff must be trained in the handling of specimens, given that both the therapeutic target (bacteria) and therapeutic agent (bacteriophages) are living systems. Extra care must be taken to prevent cross contamination of samples and knowledge of the storage conditions required across multiple sample and assay types must be added to the clinical protocol. Collectively, this requires advanced site training from sponsors and partner CROs on the nuances of patient management and sample handling procedures, cleaning protocols, and coordinated sample logistics to ensure that samples provide accurate and reliable results.

Clinical Data and Institutional Review Board (IRB) Reviews

In general, bacteriophage therapeutics are considered intrinsically safe. Bacteriophages are ubiquitous in the environment—meaning that humans are constantly exposed to bacteriophages without any ill effects. Additionally, though not broadly used in the U.S. and other parts of the world, bacteriophages as a therapeutic modality have been safely used in Central and Eastern Europe for more than 100 years. Highlighting these points to IRBs—especially in regions where bacteriophages are not commonly employed—is an important first step to ensuring that these groups have the necessary information to accurately review proposals for new clinical programs designed to test phage therapies.

Bacteriophage programs are reviewed by IRBs just like any other therapeutic, meaning that nonclinical *in vitro* and *in vivo* testing, as well as information related to the drug properties and any prior clinical data, must be provided and summarized. In addition, the IRBs review elements of the clinical trial, including the protocol, informed consent form, and risk/benefit profile, just like for any clinical program.

Important Regulatory Considerations

Currently, there are no bacteriophage-specific U.S. Food and Drug Administration (FDA) regulations or guidance documents. The field at large is rapidly developing and becoming more sophisticated as more potential bacteriophage products approach and enter the clinic.

In 2017, the FDA held the Bacteriophage Therapy: Scientific and Regulatory Issues Public Workshop.^{3} This workshop clearly defined bacteriophage therapies as biological drugs for which all clinical research must be conducted under Investigational New Drug (IND) regulations. Hence, for phage therapeutic products to be licensed for use in the U.S., safety and efficacy in the target population must be demonstrated, as well as key attributes of the drug must be defined, such as purity, potency, and consistency of manufacture.

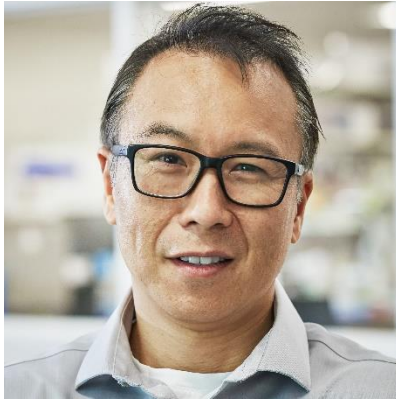
With any clinical development program, the clinical trials must demonstrate statistically significant efficacy within a specific patient population. In this way, the steps involved in clinical development, and the pathways to regulatory approval for bacteriophage therapy, share some similarities with those for any other therapeutic product. However, the intrinsic safety of phages, their unique mechanism of action, and their ability to be genetically enhanced have opened up a window of opportunity to address a variety of infectious diseases as well as other diseases that have strong bacterial associations.

Despite the current lack of regulations which specifically encompass phage therapies, the FDA has been very supportive of testing phage in controlled clinical trials and the use of innovative study designs for this modality—including multistage and adaptive trial methodologies—to help to advance these important precision medicines.

As companies continue to progress phage therapies towards commercialization, clinical trial sponsors can play a key role in working with the FDA in the creation and evolution of bacteriophage-specific regulations and guidance documents. If these efforts go well, the future looks bright for the biopharmaceutical industry and global regulatory bodies to apply phage products to the increasing need for novel therapies that can potentially combat the “silent pandemic” of antibiotic resistance.

References

1. [Evolution of Clinical Research: A History Before and Beyond James Lind \(nih.gov\)](#)
2. [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(21\)02724-0/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02724-0/fulltext)
3. <https://www.fda.gov/vaccines-blood-biologics/workshops-meetings-conferences-biologics/bacteriophage-therapy-scientific-and-regulatory-issues-public-workshop-07092017-07102017>



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Effective Data Analysis for Nontraditional Study Designs

Dejun (DJ) Tang, PhD



The nice-to-have advantages of nontraditional study designs have become must-haves as the need for innovative approaches to clinical trials has gained critical mass. The scientific community has always embraced a conservative acceptance of unconventional design to tackle specific challenges like those in rare disease research. The rise of big data, passage of the 21st Century Cures Act in 2016, and the novel coronavirus crisis have all accelerated the need to more broadly systematize a framework for putting innovative designs and methodologies into practice and reaping the benefits.

For traditional, relatively straightforward studies, the study designs and statistical analysis methods may have been developed and standardized to a degree and included in the protocol by rote. Decentralized, adaptive, and complex innovative trial designs (CID), however, require biometrics teams to push the boundaries and approach planning, execution, and analysis with feasibility and meaningful interpretation in mind.

This article will discuss the differences between traditional study designs (including those listed in ICH E9 from the International Council for Harmonization and other common ones) and nontraditional study designs, and then explain how biometrics teams can successfully navigate the changing approaches, including through:

- examples of nontraditional study designs (for example, enrichment designs and event-driven designs);
- advanced data analysis tools for unconventional data;
- the application of digital technologies to increase flexibility while preserving integrity; and
- future development of biostatistical methods for nontraditional designs.

Downstream Impacts of Nontraditional Study Designs

Nontraditional studies require more careful considerations of many design elements. Following are some of the more familiar unconventional approaches and how each impacts data analysis.

Adaptive

The term “adaptive design” in clinical trials covers a very broad area with different types of adaptations. In general, any preplanned changes in the middle of trials based on the results of one or more interim analysis can be categorized as adaptive design.

Some specific adaptive designs have been studied and developed for more than a decade and the study designs and analysis methods are relatively mature (e.g., Phase II/III seamless design with the group sequential method). However, many other types of adaptive designs are still considered nontraditional, under development, or controversial (e.g., unblinded sample size reassessment to increase the sample size of a clinical trial).

One of the key components for the adaptive design is to control the familywise type-I error rate while maintaining the study power. In many cases, this proves challenging, and we often need to develop special approaches for the analysis. For example, an adaptive design needs to set up the go/no-go criteria for the interim analysis. When the criteria are based on multiple endpoints, it is not a straightforward matter to determine the distribution of the alpha-spending among different endpoints at the time of the interim analysis. A special method to control the alpha-spending needs to be developed to tailor that situation.

Enrichment

Enrichment study design is usually employed for the purpose of selecting more efficacious patient population or populations for the investigational medicines under study. It can be applied to some medical products that may not show effectiveness in the general patient population, but which have good treatment effects for a very specific patient population.

The main challenge is how to predefine the criteria to select the suitable candidate populations. When sufficient data are available for different populations, it may not be a difficult task to identify the efficacious patient populations; in this case, however, the enrichment design may not help too much.

When designing a study with an enrichment setting, it means that we do not have much information and we need to rely on the early stage of the study to collect the data and then to determine the appropriate populations. Setting the predefined criteria won't be an easy task due to lack of sufficient information.

Event-Driven

Many clinical studies define time-to-event variables as key efficacy measurements; this is especially common in oncology trials. These types of studies could last the treatment duration for each patient, which means the study doesn't end until the last patient completes the last assessment visit. This study design maximizes the treatment time for all patients, which will increase the opportunities to observe the predefined events since the number of events is the major contributor to the study power.

With event-driven studies, biometrics teams need to manage for the possibility of operational biases as the enrollment duration for these studies can be relatively long. Changes to the participant pool and even investigator behavior can shift over time, leading to variability in the data. During the analysis stage, some sensitivity analysis should be planned carefully to evaluate the existence and impact of possible operational biases.

Noninterventional

In a noninterventional study, patients are prescribed the marketed medicine according to the label. The study investigators plan to have as little influence as possible on the patients' condition. In general, noninterventional studies allow researchers to study a drug's efficacy and safety in real-life settings. Usually, the studies are not as restrictively controlled as clinical studies in Phases I–IV.

Due to the “uncontrolled” nature of noninterventional studies, many operational or statistical biases may be introduced during the studies. Many realized or unrealized confounding factors may exist among studies endpoints, which will compromise the assumptions for many statistical analysis methods. The statistical analysis should be carefully planned to account for such factors.

Master Protocol

Master protocol studies, whereby a group of individual clinical studies are governed by a common document, can save much of the time and effort inherent in conducting multiple clinical studies with similar or relevant objectives.

The concept of master protocol can be applicable to many areas, from key efficacy and safety assessments to similar types of clinical studies, and the challenges for statistical evaluation are many. The methodologies selected need to appropriately serve each individual study as well as to work in concert. Any contradictory needs require a thorough evaluation and often more complex and layered statistical approaches.

Preserving Integrity with Innovative Approaches to Data

Preserving scientific integrity is the core challenge for data and biostatistics teams when involved in a nontraditional study, and the concerns can be sorted into three broad categories: data source, data collection, and data analysis.

In traditional clinical trials, the data are almost always randomized. To use real-world evidence, or alternative sources, we need to apply new statistical methodologies for handling the nonrandomization as well as for combining these sources of data in a consistent and accurate

manner. When there is new incoming information, we need to invent corresponding statistical models to correctly process that information.

For example, vital signs come in the case report form, blood draw data go to a central or local lab and are analyzed by machine, and X-ray or MRI imagery must be read by a physician or radiologist who writes up a report or fills out a data collection form for the clinical trial.

Biostatistics teams have to appropriately incorporate human-entered data from the site, machine-read data from the analytical lab, and imagery reports which are often in narrative form. In Phase II or III studies, any data sources from the earlier phases or even preclinical can also be included in analysis. Further, all that historical information has to be translated into quantitative numbers to add to the analysis.

Big Data and Clinical Trials

Despite the conservative nature of the clinical trial research community, big data are almost certainly part of our future. The right mix of statistics, computer modeling, data mining, and machine learning can enable a deeper level of understanding resulting in new insights faster and with fewer risk.

The digital technologies for utilizing and applying big data are not currently mature enough to pass a risk management assessment for participant safety, but the frameworks are being tested and perfected in other industries. A close example of this concept is the auto-pilot tool in Tesla automobiles. When using the tool, real-time data on the road need to be collected and analyzed to help the driving decisions—a technological feat in and of itself.

The situation in clinical studies, however, is even more complicated than driving on the highway. Unlike highways, which are relatively static features, clinical trials have few if any similar guiderails. It is not practical to preload what is ahead to guide a particular clinical study. Yet.

However nascent, the work *has* begun. Several universities, including Stanford and Oxford, have established research institutes to study the applications of digital technologies in clinical

research. While many challenges can make the progress feel painstakingly slow, the fundamental potential is heady.

Conclusion

As the exploratory work progresses on the application of big data to various currently unsolvable challenges, heads of biostatistics and trial teams can continue to stretch our innovation muscles. Our ability to approach data analysis for nontraditional studies with flexibility, creativity, and integrity today will become the foundation for growth in a big data tomorrow.



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