Clinical Researcher™

The Authority in Ethical, Responsible Clinical Research

August 2018

Volume 32, Issue 7

Clinical Researcher—August 2018 (Volume 32, Issue 7)

EXECUTIVE DIRECTOR'S MESSAGE

A Call for Connectivity

Jim Kremidas

From beginning to end, a clinical trial is about people. It begins and ends with the patients, of course. However, as a clinical professional, you are the engine that drives innovation and steers the day-to-day efforts that make clinical trials run smoothly.

Put it another way: Clinical trials could not happen without you, the members of ACRP.

Now it's time for the clinical trial industry to give back. Entrants to the profession deserve state-of-the-art, codified standards and certifications to ensure employees hit the ground running with a good chance to thrive in their new career. For existing clinical trial practitioners, you deserve a defined career path to best harness your skills and inspire personal and professional growth.

A Commitment to Quality

As a member of ACRP, you've already demonstrated a commitment to raising the quality of clinical trials. You are part of a deep knowledge pool with the means to share best practices, learn about new tools and tactics, and remain connected with your brethren.

That last item is particularly important, I believe, because so many of you are on the road or flying the friendly skies with such frequency and for such long stretches of time. There's no replacement for meaningful, face-to-face interaction. Whether at our annual conference, where thousands will gather next year in Nashville, at training events customized for cutting-edge clinical trial sponsors and site networks, or at one of our lively chapter meetings in locations all over the country and world, ACRP offers unique opportunies to connect.

Together, we also need to make the case to employers that quality training brings out the optimum skills in coordinators, monitors, principal investigators, data managers, patient recruiters, training and development specialists, institutional review board members and managers, regulatory affairs officers, and all other members of the clinical research team like you. This must be part of an ongoing effort to help attract the "best and the brightest" to join our exciting industry.

Trials will become more efficient, driving down cost and waste, while promoting morale, reducing expensive and disruptive turnover, and delivering higher quality care to patients. Isn't that what it's all about?

For Learning, for Listening, for Life

Thank you for everything you do. At ACRP, we're excited to be a partner in your professional journey. We're here to be a resource to help you do your important work better every day.

Clinical trials are about people. It's time we as an industry invested more in the professionals like you who are helping others live longer, healthier lives.

As always, I'd love to hear from you with comments and questions.

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

Clinical Researcher—August 2018 (Volume 32, Issue 7)

MANAGING EDITOR'S MESSAGE

New Perspectives on Recruitment and Retention

Gary W. Cramer

It hasn't been so very long since the last time an issue of *Clinical Researcher* focused on the challenges of recruiting and retaining participants in clinical trials. For reasons that are all too obvious to belabor here, as themes go, it's right up there in popularity with our occasional issues devoted to regulatory matters and career development tactics.

Each of our three main articles in this issue deal with the "R&R" theme directly or tangentially, though each came about in a starkly different way:

- Stephanie Williams' peer-reviewed article is an outgrowth of her earlier presentation on the same topic at the ACRP 2018 meeting in late April. We encourage speakers at our annual gatherings to consider adapting their work into articles so that more people may benefit from their expertise. We also invite those of you who have proposed presentations that were not selected for recent conferences (ACRP or otherwise) to think of this journal as an option for reaching your audience. Look for the "Submit an Article" details at https://www.acrpnet.org/resources/clinical-researcher/ or feel free to contact me at the e-mail address below.
- The peer-reviewed contribution from Karen Lane, et al., arrived for review "out of the blue," as many of our articles and columns do, and it represents a trend that sees ACRP publishing more articles about "lessons learned" from major real-world trials. We are pleased to consider submissions from solo authors, pairings of experts, or entire teams on any relevant clinical research topics at any time of the year. With 10 issues per year to fill in our recently launched all-digital format, we can surely find a place for any article that is accepted through our peer-review process, even if it's as a "miscellaneous" article in an

issue otherwise already planned to be themed on some other topic. (However, in the case of this issue, it was the serendipitous arrival of several articles on similar topics that generated the theme.)

- The wisdom on the qualities to look for and nourish in great clinical research coordinators (CRCs) received from Cyenthia Willis, et al., in our special feature provides welcome insights from the Veterans Health Administration. This was another article that came somewhat unexpectedly, and like more such features that we have been publishing lately, it did not go through peer review, but was considered of significant value to include here. It is especially appropriate for this issue, as the responsibility for subject recruitment and retention falls frequently on the CRC(s) at a site, whether or not they are fully prepared for such duties.

Here, There, Everywhere

I'll leave you with the following links to a handful of other articles to check out on this ever-evolving and ever-important aspect of clinical trials—some from the *ACRP Blog* and others from the "outside world." It goes to show just how big the well of topics tied to R&R is once you begin to tap into it. In the meantime, we look forward to your feedback on how *Clinical Researcher* is doing so far in its new format, and as always, we welcome your ideas for articles to educate and enlighten your colleagues in the clinical research enterprise.

Arbitrary Age Parameters Can Limit Clinical Trial Efficacy (*ACRP Blog* 8/1/18)

NIH Makes Advancements in Precision Medicine Initiative Patient Recruitment (*ACRP Blog* 7/23/18)

Successful Patient Recruitment Hinges on Flexible Travel Offerings (*ACRP Blog* 7/2/18)

Orphan Indications and Clinical Trials—Recruiting (*Clinical Leader* 8/9/18)

Running Engaging Digital Enrollment Campaigns (*Applied Clinical Trials* 8/8/18)

Finding Patients Close to Home: A New Way of Recruiting for Clinical Trials (*CURE* 7/30/18)

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

Clinical Researcher—August 2018 (Volume 32, Issue 7)

PEER REVIEWED

Overcoming the Barriers to Recruitment of Underrepresented Minorities

Stephanie Lynn Williams, MS, CCRC

Racial and ethnic disparities among research subjects in clinical trials continue to persist despite the changing demographics in the United States.{1} The percentage of racial and ethnic minorities in the general population is steadily growing, but that growth is not reflected in clinical trials. There is vast literature confirming this underrepresentation, and much of it focuses on the existing barriers to subject participation.{2,3} The gold standard for clinical research continues to be randomized clinical trials, yet diversity in these trials remains extremely low and lack of representative sampling continues to be an issue.

In an attempt to correct this underrepresentation, the National Institutes of Health (NIH) mandated the inclusion of women and racial minorities with the passage of the Revitalization Act of 1993.{4} Recognizing the importance of including these groups, the Act was intended to increase the number of women and individuals from disadvantaged backgrounds, including racial and ethnic minorities, in the fields of biomedical and behavioral research and diversify research populations. The Act's intended purpose has not been fully realized, and barriers continue to impact the enrollment of many racial and ethnic minority groups. Some insight as to why the Act has been less effective than anticipated will be discussed in the sections ahead, along with some of the known barriers to recruitment and ways to address these barriers.

Importance of Minority Participation

Racial and ethnic minorities currently make up 38.7% of the U.S. population, but estimates place the rate of inclusion in research studies between 2% and 16%.{5,6} The term racial and ethnic minorities in this context refers to anyone who is not considered "white alone" for purposes of census classification. According to the U.S. Census Bureau, the country's diversity remains on

the rise, with all racial and ethnic minorities growing faster than whites from 2015 to 2016.{7} Minority residents of the U.S. are expected to comprise more than 40% of the nation's population by 2035, 47% by 2050, and 56% by 2060.{8}

The importance of minority participation in clinical trials has been garnering national attention in recent years. Countless articles and opinion pieces have been written on this topic, including a blog post from the U.S. Food and Drug Administration (FDA). As of the post, the FDA was planning a variety of activities to push for greater inclusion, including more minority participation. The author acknowledged FDA's awareness that certain groups of patients may respond differently to different therapies, and that "a wide range of people should have the opportunity to participate in trials, both for access to new therapies and to have the chance to contribute to better treatment of everyone."{9}

In his 2015 State of the Union address, President Obama announced the launch of the Precision Medicine Initiative (PMI), designed to revolutionize the approach to health improvement and disease treatment.{10} The PMI includes NIH's "All of Us" program, an effort to recruit a large research cohort to advance individualized prevention, treatment, and care for people of all backgrounds. One of the core values of the program is that participants reflect the rich diversity of the U.S.{11} National enrollment officially opened for the program on May 6, 2018. The press release announcing the enrollment date stated that "the overall aim is to enroll 1 million or more volunteers and oversample communities that have been underrepresented in research to make the program the largest, most diverse resource of its kind."{12}

There are also economic and social justice reasons for reducing these disparities. Eliminating racial and ethnic health disparities would have decreased U.S. medical costs by more than $1.2 trillion for the years 2003 to 2006. This estimate includes direct and indirect medical costs, such as loss of productivity, as well as the cost of premature death.{13} As of 2015, racial disparities continued to be associated with substantial annual economic losses nationally. Diversity in biomedical research often does not reflect the U.S. population, and in order to remain consistent with the values of our society, health-related disparities caused by this underrepresentation should be addressed.

The NIH Revitalization Act

The Revitalization Act is often referenced when discussing racial disparities and inadequate representation in clinical research. It was seen by many as a culmination of efforts to overcome the lack of representative sampling in clinical trials, and was anticipated to increase the enrollment of underrepresented groups. However, this was not the first act of legislation aimed at increasing enrollment in clinical trials, nor the first act addressing disparities in the health status of racial minorities in the U.S.

The National Research Act of 1974, enacted a mere two years after the public disclosure of the Tuskegee Syphilis Study, established ethical principles to govern clinical research and put protections in place for human subjects involved in research.{14} The Tuskegee Study is commonly perceived as the worst example of medical research exploitation in U.S. history, and was ongoing for 40 years (1932 to 1972). The U.S. government conducted the study on unknowing "subjects"—hundreds of African American men living in the Deep South who were excluded from life-saving treatment while being subjected to clinical testing so doctors could determine the natural progression of syphilis.{15} Unsurprisingly, death and disability for many men and their families resulted. Knowledge of this unethical exploitation contributes to the mistrust that some minority communities still feel today when it comes to research.

Other legislative acts followed, mostly in response to Congressional findings demonstrating a growing health disparity gap among racial minorities.{16} These disparities helped prompt the enactment of the Revitalization Act, which mandated the inclusion of racial minorities in clinical trials as a condition to receive federal funding and required that research participant characteristics be disclosed in research documentation as a way to measure inclusion.{2}

Twenty years after the implementation of the Revitalization Act, researchers assessed minority rates to see if the intended diversification had occurred in cancer clinical trials. The results showed that little progress had been made; the number of cancer trials with a primary emphasis on any racial or ethnic group was found to be less than 2%.{17} To put that in perspective, cancer is the second leading cause of death in the U.S., regardless of race or ethnicity.{18} Less

than 5% of NIH-funded respiratory research reported inclusion of racial and ethnic minorities, and similar rates are found in cardiovascular and diabetes clinical trials.{19}

One major limitation of the Revitalization Act is that NIH guidelines only apply to federally funded trials. From 2006 through 2014, newly registered NIH-funded trials steadily decreased, with a few exceptions, whereas industry-funded trials increased substantially. In 2014, pharmaceutical companies funded 6,550 trials while NIH funded 1,048 trials.{20} A majority of clinical trials leading to drug approvals are funded by pharmaceutical companies which are not held to NIH guidelines and do not require increased enrollment of racial minorities.

Known Barriers to Recruitment

Barriers to recruitment can be identified through a variety of sources. Much research has gone into determining whether minorities are reluctant to participate in clinical research and discovering other barriers. Some of this research focuses on issues of mistrust stemming from past abuses like Tuskegee and the story of Henrietta Lacks, which has seen renewed interest in recent years following the film adaptation of a book about her life and beyond.{21} A poor African American woman, Lacks went to Johns Hopkins for treatment and without her knowledge or consent, her cancer cells were used and have now become one of the most important cell lines in medical research.{22} These types of research abuses involving minorities occurred prior to the establishment of many of the ethical requirements that now govern clinical research.

The identification of barriers to recruitment can come through prescreening interviews, research participant interactions, and literature review. Prescreening interviews are valuable interactions; potential research participants call a research site to see if they qualify for a trial, and while someone may meet the initial qualifications, that person may decide not to participate for various reasons. Those reasons are barriers to participation. Similarly, through participant interactions with enrolled subjects, barriers can be identified. A participant may enroll in a study and then miss visits or discontinue the study prematurely. The reasons why a participant fails to complete a trial can sometimes be barriers to consider. The literature also explores barriers that have been identified.

From the sources mentioned above, some identified barriers include lack of awareness, logistics, mistrust, lack of diversity among the research and clinical professionals, research not being conducted in the community, disconnect between researchers and the community, limited access to specialty centers that refer patients to clinical trials, minorities not being as willing to participate in research, and fear of exploitation in clinical research. Lack of awareness can include a lack of awareness in available trials or of clinical trials as therapeutic options. Logistics can include issues surrounding costs associated with participation, transportation, and convenience. Mistrust can include not wanting to be a "guinea pig" and mistrust of the medical or research fields in general. All or some of these barriers may apply at different times and to different groups, and it is common for some of the solutions addressing these barriers to overlap.

Overcoming Known Barriers

Identifying known barriers is the first step toward addressing them. Awareness of the minority populations in the recruitment area is essential so the appropriate recruitment methods can be employed. Depending on location in the country, minority populations will differ and recruitment considerations may change depending on the population sought.

To address the lack of awareness barrier, there are a number of proposed solutions. Lack of awareness can simply mean that people are not aware of the clinical trials available to them or are unaware that clinical trials are available for numerous medical conditions. Solutions to this barrier include advertising and education. Targeted advertising, for example on public transportation or in advertising forums specific to the targeted population, can be effective. This includes going to community healthcare providers to advertise or to educate providers on available trials, rather than relying on referrals from specialty centers or other medical institutions that may not be where the target population is receiving care. Education can also occur at community health events or town hall meetings.

To address the logistics barrier, concerns such as costs associated with participation, transportation, and inconvenience must be dealt with. Possible solutions to issues concerning cost include ensuring that studies are appropriately budgeted to account for time and commitment expectations.

Another way to address this issue is by providing travel or meal vouchers that may ease the financial burden. Travel vouchers also apply to the transportation barrier along with mindfulness of where the research site is located. Knowing whether a site is along a bus route, if there is ample parking, and if a site is easy to find are all aspects of participation that can be challenging to potential participants if unclear. Some research sites are located on huge academic campuses and can be daunting to someone visiting the institution for the first time, so providing clear directions to the actual location where the trial will be conducted within the institution is also important.

When it comes to inconvenience, extending office hours outside the typical “9 to 5” can allow working participants more flexibility and potentially increase the recruitment population. The option to conduct visits over the phone or at satellite locations can make visits more convenient.

Addressing mistrust really comes down to being transparent about what is being done for a particular trial, like what is expected of the participant, what research questions are being answered, and what benefits and risks are anticipated. Education about the research process and addressing specific concerns are key. Having enough information and knowledge about commonly known research exploitations and acknowledging past abuses if they come up add credibility to the team members conducting the research, and can go a long ways toward gaining the trust of potential participants. Transparency and education are some of the best tools to combat fear of exploitation.

Further, a lack of diversity in the research team has repeatedly been reported as problematic.{23} In the fields of science, technology, engineering, and math (STEM), there is a significant underrepresentation of minority students, resulting in fewer minority scientists and physicians.{24} Efforts to increase the numbers of minorities involved in STEM fields should be made to address this problem. Minority scientists and physicians are more likely to conduct research in minority populations, may more easily be able to gain the trust of those communities, and participants may be more likely to sign up for a clinical trial if the recruiter looks like them.{23}

Ways to address the barrier of a lack of diversity in the research team include recruiting research team members from diverse backgrounds, including community advocates and student workers. Other suggestions include ensuring that language options are available for the target demographic and considering a community-research liaison.

Barriers dealing with research outside the community or disconnect between researchers and the community can be addressed by taking the research project into the community. Attending community health events where researchers can talk to members of the community about available opportunities and allow the chance for questions can be beneficial for recruitment. Setting up mobile offices or establishing satellite locations within the community can also help to overcome this barrier. Researchers who go where the participants are rather than waiting for the participants to come to them may have more success reaching populations that have historically been underserved.

Minorities being less willing to participate in clinical trials may no longer be the barrier it once was perceived to be. Recent research suggests that racial and ethnic minorities are as willing as whites to participate in clinical research.{25} Accordingly, some of the other barriers discussed should be the future focus of increasing enrollment in underrepresented groups.

Conclusion

Increased clinical trial participation by racial and ethnic groups continues to be an imperative endeavor because diseases present differently in different groups of people, certain medications have been proven to be more or less effective depending on racial or ethnic background, and increasing diversity in clinical research will help ensure that medial products are safe and effective for everyone.{26} The NIH Revitalization Act attempted to address some of the racial disparities in clinical trial populations, but limitations have rendered the Act less effective than originally anticipated. Known barriers to recruiting underrepresented groups have been identified and suggested solutions have been proffered. Discovering ways to increase the enrollment of racial and ethnic minorities continues to be an issue worthy of further exploration.

References

1. Cohn D, Caumont A. 2016. 10 demographic trends that are shaping the U.S. and the world. Pew Research Center. http://pewrsr.ch/1VUU4py
2. Geller SE, Koch A, Pellettieri B, Carnes M. 2011. Inclusion, analysis, and reporting of sex and race/ethnicity in clinical trials: have we made progress? *J Women's Health* 20:315–20.
3. Dickerson DL, Leeman RF, Mazure CM, O'Malley S. 2009. The inclusion of women and minorities in smoking cessation clinical trials: a systematic review. *Am J Addictions* 18(1):21–8.
4. U.S. Congress. National Institutes of Health Revitalization Act of 1993: An Act to Amend the Public Health Service Act to Revise and Extend the Programs of the National Institutes of Health, and for Other Purposes. *Pub Law* 1993:103–43.
5. U. S. Census Bureau. 2018. Quick Facts United States, Population estimates, July 1, 2017. https://www.census.gov/quickfacts/fact/table/US/PST045217
6. Oh SS, Galanter J, Thakur N, Pino-Yanes M, Barcelo NE, White MJ, et al. 2015. Diversity in clinical and biomedical research: a promise yet to be fulfilled. *PLoS Medicine* 12(12):e1001918. doi:10.1371/journal.pmed.1001918.
7. Chappell B. 2017. Census finds a more diverse America, as whites lag growth, *National Public Radio* https://n.pr/2sTElQ7
8. Passel JS, Cohn D. 2008. U.S. Population Projections: 2005–2050. Pew Research Center. http://pewrsr.ch/VStF8Q
9. Califf RM. 2016. 2016: The Year of Diversity in Clinical Trials. U.S. Food and Drug Administration. https://blogs.fda.gov/fdavoice/index.php/2016/01/2016-the-year-of-diversity-in-clinical-trials/
10. Precision Medicine Initiative (PMI) Working Group. 2015. The Precision Medicine Initiative Cohort Program—Building a Research Foundation for 21st Century Medicine. National Institutes of Health, U.S. Department of Health and Human Services. http://acd.od.nih. gov/reports/DRAFT-PMI-WG-Report-9-11-2015-508.pdf
11. U.S. Department of Health and Human Services, National Institutes of Health. https://allofus.nih.gov/

12. National Institutes of Health. 2018. NIH announces national enrollment date for All of Us Research Program to advance precision medicine. https://www.nih.gov/news-events/news-releases/nih-announces-national-enrollment-date-all-us-research-program-advance-precision-medicine
13. LaVeist TA, Gaskin D, Richard P. 2011. Estimating the economic burden of racial health inequalities in the United States. *Int J Health Services* 42(2):231–8.
14. National Research Act, 42 U.S.C. § 2891 (1974).
15. Jones JH. Tuskegee Institute. 1989. *Bad Blood: The Tuskegee Syphilis Experiment.* New York & London: Free Press.
16. Disadvantaged Minority Health Improvement Act, 42 U.S.C. §§300u-6 (1990).
17. Chen Jr. MS, Lara PN, Dang JH, Paterniti DA, Kelly K. 2014. Twenty years post-NIH Revitalization Act: renewing the case for enhancing minority participation in cancer clinical rials. *Cancer* 120(07):1091–6.
18. Centers for Disease Control and Prevention. 2017. Leading Causes of Death. https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm
19. Burchard EG, Oh SS, Foreman MG, Celedón JC. 2015. Moving toward *true* inclusion of racial/ethnic minorities in federally funded studies. A key step for achieving respiratory health equality in the United States. *Am J Resp Crit Care Med* 191(5):514–21. doi:10.1164/rccm.201410-1944PP.
20. Ehrhardt S, Appel LJ, Meinert CL. 2015. Trends in National Institutes of Health funding for clinical trials registered in ClinicalTrials.gov. *JAMA* 314(23):2566–7. doi:10.1001/jama.2015.12206.
21. Dean K, Wolfe GC. 2017. *The Immortal Life of Henrietta Lacks*. United States: HBO.
22. Ciaccia L. The immortal life of Henrietta Lacks. *Yale J Biol & Med* 2010;83(3):165.
23. Bole K. 2015. Diversity in medical research is a long way off, study shows. University of California San Francisco. www.ucsf.edu/news/2015/12/401156/diversity-medical-research-long-way-study-shows
24. Estrada M, Burnett M, Campbell AG, Campbell PB, Denetclaw WF, Gutierrez CG, et al. 2016. Improving underrepresented minority student persistence in STEM. *CBE Life Sci Ed* 15(3):es5. doi:10.1187/cbe.16-01-0038.

25. Wendler D, Kington R, Madans J, Wye GV, Christ-Schmidt H, Pratt LA, Brawley OW, Gross CP, Emanuel E. 2006. Are racial and ethnic minorities less willing to participate in health research? *PLoS Med* 3(2):e19. http://doi.org/10.1371/journal.pmed.0030019
26. Burchard EG, Ziv E, Coyle N, Gomes SL, Tang H, Karter AJ, et al. 2003. The importance of race and ethnic background in biomedical research and clinical practice. *NEJM* 348:0–1175.

Stephanie Lynn Williams, MS, CCRC, (stephanie.williams@cchmc.org) is a senior regulatory affairs specialist with Cincinnati Children's Hospital in Ohio.

Clinical Researcher—August 2018 (Volume 32, Issue 7)

PEER REVIEWED

African American Screening and Enrollment in the CLEAR III Trial

Karen Lane, CCRP; Maningbe Keita, BA; Radhika Avadhani, MS; Rachel Dlugash, MSPH; Steven Mayo, PD, CCRA, PMP; Richard E. Thompson, PhD; Issam A. Awad, MD, MSc, FACS, FAHA; Nichol McBee, MPH, CCRP; Wendy Ziai, MD; Daniel F. Hanley

By 2050, members of racial and ethnic minorities will represent the majority of the population in the United States.{1} While clinical trials are designed to inform the scientific workforce about the safety, efficacy, and effectiveness of medical strategies, treatments, or devices for evidence-based healthcare decision-making, the under-enrollment of minority patients reduces the generalizability of research findings.{2} Enrolling an adequate proportion of minorities into clinical trials has proven difficult in the past; however, concerted efforts must be made to overcome barriers to enrollment.{3–12} Proportional recruitment practices can provide data about health disparities and better serve the needs of minority populations.

Such is the case with hemorrhagic stroke, a devastating disease with a global mortality of 45%. Recent estimates indicate that 70,000 new hemorrhages occur in the United States each year.{13} Minority patients are disproportionally affected in incidence and severity; African Americans, particularly, have a greater risk, incidence, prevalence, and mortality compared to white Americans.{14–26} Not only does this evidence contribute to the overwhelming economic burden of sustained health disparities, it also suggests a barrier to health equity and social justice.

In 2009, the total direct and indirect cost of stroke in the United States was estimated at $68.9 billion.{17} Minority populations contribute to a significant portion of stroke costs due to higher admission rates, greater severity and mortality, increased disability-adjusted life-years, and loss of productivity from stroke incidence at younger ages.{13,16,27} Enrolling more minorities into stroke trials is an important part of any solution to alleviate the economic burden incurred

through health disparities, improve the generalizability of trial results, and raise the standard of patient-centered stroke care.

Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage III (CLEAR III) (ClinicalTrials.gov; NCT00784134), a 500-participant randomized controlled trial evaluation of alteplase in hemorrhagic stroke, presented an opportunity to assess African American (AA) trial enrollment in a hemorrhagic stroke population. As detailed in the following sections, the authors of this paper evaluated the CLEAR III screening and enrollment data to better understand if recruitment efforts provided diversity and, more importantly, to improve recruitment efforts in the future.

Methods

Trial

This Phase III randomized, double-blinded, placebo-controlled, multicenter trial was conducted at 73 sites in Brazil, Canada, Germany, Hungary, Israel, Spain, the United Kingdom, and the United States from 2009 to 2014.{28} The investigators were either neurointensive care or neurosurgical service teams. This was a first-of-a-kind trial; it combined a catheter device with up to four days of intensive care unit (ICU)–based drug treatment.

For the analysis of AA to non-AA participation, we limited the evaluation to U.S. sites. Over a five-year period, investigators across 61 U.S. hospitals screened 8,587 patients (see Figure 1) admitted to ICUs in 42 U.S. cities with stable, small non-traumatic intracerebral hemorrhage (ICH), intraventricular hemorrhage (IVH) with a clinical diagnosis of obstructive hydrocephalus, and an extraventricular drain (EVD) placed pre-trial. Participants were randomly assigned to receive alteplase (Genentech, Inc.) or normal saline (placebo) via the EVD.

Subjects

Participants were aged 18 to 80 years with known symptom onset within 24 hours of the initial CT scan. CT scans were obtained every 24 hours throughout dosing. Initial eligibility criteria required supratentorial ICH volume 30 mL or less; additional criteria included a historical

modified Rankin Scale (mRS) score of 1 or less (no disability prior to ICH), no limitations to hospital care, and no ongoing coagulopathy, suspicion of aneurysm, arteriovenous malformation, or other vascular anomaly.{28}

Consent

CLEAR III was a complex trial, with a long screening window of 72 hours. After the local principal investigator determined eligibility, the patient's family was approached and informed of relevant risks, benefits, and alternative treatments. During the study, the investigators were provided guidelines, a checklist for consent, a smartphone application with procedural bedside guidance, and training consent videos modeling best and worst consent practices, both in the general case and specific to the CLEAR III intervention.{29}

The consent training program included an annual, mandatory refresher webinar on best practices, as well as training on how to engage colleagues to refer patients into the trial. After the families were given time to consider and comprehend the elements of participation, the families of fully eligible patients were again approached, and informed consents were obtained or refused. We then compared AA and non-AA timelines for presentation, signed consent, and randomization.

Data

All data were captured electronically, and pertinent source documents were uploaded by local site personnel using a web-based electronic data capture (EDC) system (VISION, Prelude Dynamics, LLC). All participants and trial personnel, except for the local and central pharmacists and the unblinded statistician, were masked to treatment assignments. Site personnel randomly assigned patients (1:1) within 72 hours of ictus. The EDC system transmitted a treatment allocation by e-mail directly to the local, trained pharmacist.

Screening

The same EDC system was used to enter all participants screened. Study coordinators were trained to enter all admissions with a primary or secondary diagnosis of IVH in the electronic screening log. Protocol inclusion/exclusion (I/E) criteria were collected in the EDC via

prespecified selections and then categorized as either medical reasons (e.g., biologically ineligible or predetermined I/E ineligible) or nonmedical reasons (e.g., access, personal choices, mistrust).

EDC compliance was monitored, and sites were encouraged to make screening entries in real time. To limit coordinator burden, only a single exclusion factor was required for screen failures; sites were compensated for screening activities. Enrolling teams were trained to screen admissions, in person, every morning and afternoon or round with the ICU care teams. Remote screening, using electronic admission and medical records, was discouraged. Teams were trained to consider some I/E conditions as temporary and to conduct multiple screening attempts on such subjects during the 72-hour window.

Race/Ethnicity

Race was collected as part of screening data and entered locally into VISION. Investigators or study coordinators selected one or more of the following to report race: American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander, Black or African American, Asian, or White. From these categories, we grouped patients into two categories when race was listed—as either AA if Black or African American was selected (including those who chose other races in addition to AA) or non-AA if Black or African American was not selected (see Figure 1).

Analysis

We analyzed AA participation using randomization (Stage 1) and screening (Stage 2) data. Our first inspection compared trial enrollment to an National Institutes of Health aggregate report{30} and to U.S. population data from 1990, 2000, and 2010, obtained via census.gov. To inform end-of-trial comparisons, forecast projections were calculated to determine the likely AA percentage for a 2014 U.S. population.

With CLEAR III demonstrating such substantial AA participation and robust conversion rates, we stratified AA trial randomization rate by site geographic region. We then examined city census data at our CLEAR III locations, examining whether hospital location mattered. We retrieved census percentages{31} and used simple linear regression modeling to assess the

relationship between AA census in 42 cities and the AA percent screened, as well as the AA percent randomized in each city. Site and city data for CLEAR III sites that did not enroll *any* patients (regardless of race) were excluded from the analysis.

We next stratified screening data by gender and age to test for significant demographic differences. Last, we interrogated the data for AA vs. non-AA distribution among medical, nonmedical, or combination (both medical and nonmedical) reasons for screen failure. Chi-square was used to compare the proportions between AA and non-AA for each screen failure reason.

Results

Stage 1: African American vs. Non-African American Enrollment

Overall

The U.S. respective trial *enrollment* rates were: African American, 45.1%; Asian, 3.5%; American Indian/Alaskan Native, 0.3%; Native Hawaiian or Other Pacific Islander, 0.8%; White, 48.6%; remaining mixed races, 0.3%; and Unknown, 1.4%. For our analyses, we grouped the race categories into AA and non-AA. When we compared CLEAR III recruitment to other National Institute of Neurological Disorders and Stroke (NINDS) participation data and to U.S. population data during the same period as the trial, CLEAR III recruitment outperformed population expectations and that of other NINDS trials (see Table 1). AAs comprised 45.1% of total U.S. enrollments (n=370), or more than twice the 19.8% participation rate reported by NINDS in 2011{30} and triple the projected 13.9% U.S. population in 2014.

Conversion (Randomization) Rate by Geographic Region

Conversion rates for both AA and non-AA participants were calculated as total number of enrolled divided by total number screened (see Table 2). Our planned conversion rate for trial enrollment was 5%. The randomized-to-screened ratio for AAs was 8.7% vs. 3.4% non-AA ($p<0.001$). Regional analysis showed similar differentials with AA conversion rates: Northeast

(7.7% vs. 2.9%, $p<0.001$); South (8.2% vs. 4.0%, $p<0.001$); Midwest (10.3% vs. 3.6%, $p<0.01$); and West (8.9% vs. 3.8%, $p=0.02$).

Conversion (Randomization) Rate and City Census Comparisons

Trial sites were grouped by city, and their AA enrollment percentages were compared to corresponding city census data. The proportion of AAs enrolled per city ranged from 0% to 100%, with a mean of 40.4% (see Figure 2a). The AA city census ranged from 1.3% to 82.7%, with a mean of 28.0%. The enrollment mean of 40.4% robustly exceeded the census mean (28.0%). Higher AA census was associated with higher AA *enrollment* percentage ($R^2 = 0.17$, *p* value = 0.004; $\hat{\beta}$(95% CI) = 0.7 (0.25, 1.21)). The symbol $\hat{\beta}$defines the slope of the regression line. The AA percent enrolled in a city increased, on average, 0.7% for each percent increase in AA census.

Comparing enrollment timelines, only randomization was statistically significant; AAs randomized later than non-AAs, with an average difference of five hours. Time to informed consent approached significance, averaging approximately two to three hours longer.

Stage 2: African American vs. non-African American Screening

We next looked at screening to understand conversion performance, assess who was excluded, and evaluate whether reasons for exclusion related to relevant demographic and biological variables.

Screening Rate and City Census Comparisons

The proportion of AAs screened per city ranged from 0% to 63.7%, with a mean of 23.2% (see Figure 2b). Higher AA census was associated with higher AA *screening* percentage; the AA percent screened in a city increased, on average, 0.6 for each percent increase in AA census ($R^2 = 0.46$, *p* value < 0.001; $\hat{\beta}$(95% CI) = 0.62 (0.41, 0.83)). Comparing the census and screening means, CLEAR III investigators screened slightly less than the census mean (23.2% vs. 28%).

Screening by Gender and Age

We then assessed gender and age for overall U.S. screens and screen failures, where race was listed, to detect any significant demographic differences. Out of the 8,587 U.S. screens, race was reported for 7,663 participants (see Figure 1). Of the 7,663 race-listed participants, 7,298 were screen failures and 365 were enrolled; further, gender was missing on four non-AA participants, with all of these being among the screen failures.

Of the race-listed U.S. screens, AAs consisted of 918 (47.7%) females and 1,005 (52.3%) males. Equivalently, non-AAs consisted of 2,735 (47.7%) females and 3,001 (52.3%) males. Of the screen failures, AAs consisted of 839 (47.8%) females and 917 (52.2%) males. Similarly, non-AAs consisted of 2,640 (47.6%) females and 2,898 (52.3%) males. There was no statistically significant difference in gender between race-listed U.S. screens and screen failures.

For race-listed U.S. screens, the average age of AA participants was 58 years old (standard deviation 13.7), compared to an average age of 66 years for non-AA participants (standard deviation 15.6) with a p value <0.001. For the screen failure subset, similar results hold; the average age of AA participants was 58 years old (standard deviation 14.0), compared to an average age of 66 years for non-AA participants (standard deviation 15.7) with a p value <0.001.

Medical vs. Nonmedical-Related Screen Failures

Upon review of screen failure reasons within the AA and non-AA race groups, African Americans were *less* frequently excluded due to biological/research strategy reasons (see Table 3).

For the medical screen failure category, AA had a *lower* percentage of patients excluded at the Upper Age Limit (AA: 5.6% vs. non-AA: 16.0%), Aneurysm (AA: 9.2% vs. non-AA: 13.4%), and Etiology Tumor (AA: 0.2% vs. non-AA: 0.8%). However, AAs had a *higher* percentage of exclusions for GCS/Herniation/Brain Dead/Deceased (AA: 1.4% vs. non-AA: 0.8%), Historic Rankin not 0 or 1 (AA: 2.7% vs. non-AA: 1.7%), ICH > 30 cc (AA: 14.6% vs. non-AA: 12.6%), and no obstruction of 3rd and/or 4th (AA: 14.9% vs. non-AA: 11.5%). Other remaining screen failure reasons were statistically insignificant.

For the nonmedical reasons screen failure category, AAs had a lower percentage of patients who were DNR (AA: 3.4% vs. non-AA: 4.5%) and a higher percentage of patients who were eligible but refused consent (AA: 3.1% vs. non-AA: 1.2%). Remaining screen failure reasons for this category were statistically insignificant.

One category, "MD/Surgeon chose not to enroll," had too broad a response, combining both medical and nonmedical reasons. For screen failure category, AA had a *higher* percentage of screen failures for MD/Surgeon chose not to enroll (AA: 3.2% vs. non-AA: 1.2%) and Other (AA: 10.9% vs. non-AA: 6.8%). Other reasons were statistically insignificant (see Table 3).

Discussion

AAs *enrolled* in CLEAR III at a rate greater than expected by available census data, regardless of city or geographic region. Although AAs refused consent at a greater rate, they enrolled 2.5 times more often than non-AAs.

When we compared CLEAR III performance to other brain hemorrhage randomized clinical trials during the same period, CLEAR III enrolled AAs at 45.1% compared to 9% to 30% in the other trials, though AA screening and enrollment data are not available for some trials, limiting the comparison (see Table 4). Further limiting comparison is that these trials were international and did not break out racial data by countries.

When comparing reported enrollment windows and follow-up intervals, there is one notable difference—time from onset to randomization. CLEAR III participants had a much longer enrollment window, allowing more time to communicate with families. Moreover, the communication period occurred in the ICU rather than the Emergency Department. Prospective research on the relationship between enrollment windows, follow-up intervals, social support, recruitment monitoring, and minority enrollment/retention may provider stronger correlations.

Gorelick et al. published the recruitment triangle in 1998,{32} illustrating the social support triangle that reduces barriers and lessens disparities. The design of the 72-hour enrollment time window could be essential to enrollment and retention, particularly among AA participants, allowing communication time with the social support stakeholders and within the insulated ICU

where trust reduces barriers, regardless of race or ethnicity. Initial and ongoing training of site teams emphasized that temporary I/E factors could resolve over a three-day period and the use of the entire time window.

CLEAR III utilized intensive site management oversight with strong emphasis on best screening, consenting, and enrollment practices. We evaluated recruitment monthly and retrained annually on best consent practices, and we gave a presentation on common reasons for refusals both from families and investigators and on how to solve fixable refusal reasons. Furthermore, our training included the recruitment triangle social support principles{30} of taking time and connecting with families; earning trust, not only of families but also of the ICU teams involved in the treatment and care of the patient; using best consent practices; providing family access to an interested and caring investigator; and respecting the cognitive and physical concerns of families in distress and sensory overload throughout the trial participation continuum.

Limitations

While biological/research strategy exclusions, city census, and being younger may have contributed to CLEAR III's high enrollment of AAs, any causal mechanisms behind these associations remain unclear. Several limitations impact the interpretation of our analysis.

Race categories were presented as checkboxes in the EDC and no specific definition for each category was provided, nor were directions for choosing race included in training. Thus, different interpretations of race categories may have occurred at the time of data entry. Furthermore, we recognize that there may have been inconsistencies across sites whether the race reported was determined by the patient, patient relative(s), medical record, site coordinator, or physician.

While race was more closely monitored for enrollment data, the same standards were not applied to screen failures. Of the 8,587 screens, 924 were missing race data (of which five were enrolled), introducing potential sampling error. Screen failure reasons such as "MD/Surgeon chose not to enroll," "Patient eligible but refused consent," and "Other" did not allow details, possibly obscuring causal factors related to race and recruitment. Another possible limitation is that the traditional categories "comorbidity," "likely not able to complete the protocol," and "…otherwise, in the investigator opinion, not eligible…" were grouped together and labeled as

"Investigator Decision," thus not identifying whether these screen failures were for medical or nonmedical reasons or providing further details as to who made the decision.

Screening logs were not monitored prospectively. Tracking diversity in clinical trials is essential, and monitoring screening logs monthly for content (and not just submission) can determine how teams are doing (beyond overall screening and conversion rates) as they recruit the underrepresented and underserved. Additionally, recognizing minority screen failures early allows the opportunity to redesign poorly constructed forms and retrain poorly performing teams. Further, including recruitment diversity and disparities metrics when publishing clinical trial results is imperative for comparative research where sub-populations are under active investigation.

Last, the analysis covered only city-level data; data are limited on the demographic characteristics of eligible patients at non-trial hospitals and patients coming to trial hospitals from other cities.

Conclusions

AAs were willing to enroll in a novel, acute stroke trial, such as CLEAR III. Enrollment was systematically consistent in proportion to the subjects' demographics, taken from census data, suggesting higher enrollment was a function of the overall trial characteristics and national population characteristics. The enrollment of AAs was proportional to disease prevalence and allows for a robust estimate of minority population characteristics and responses.

That CLEAR III AA enrollment exceeded census percentages is an important finding that requires further exploration. Cities densely populated by AAs should be considered when selecting recruitment sites. Census rates may be useful when setting recruitment goals, particularly for ICH trials.

Consent training in disparity recruitment methods appears to have been rewarded. Better screening instruments, screening standardization, and recruitment metrics will be important to the design of any trial. Prospective recruitment monitoring, along with surveys and interviews

following refusals, could improve understanding of screening-to-enrollment conversion rates among research participants.

Efforts are under way to understand and improve recruitment of AAs and other underrepresented minorities into clinical trials. If we are to improve proportions of minorities enrolled, then we should apply the recruitment triangle to minority recruitment, interviewing, and data-entry training at investigator meetings and as part of best consent coaching.

This trial may provide some structure to those "trial-in-progress" practices. When designing clinical trials, determining underlying reasons for participation probably helps find solutions for eliminating disparities. Interestingly for CLEAR III, such an approach during the trial might have provided information about lower participation rates of non-AAs. When the incidence of stroke or other diseases is higher in minorities, we must develop minority-specific training programs to teach investigative teams about the importance of diversity.

Future trials should consider such factors as incorporating minority recruitment goals in data collection design and consent training; incorporating targeted enrollment data into screening logs to manage enrollments *during* the trial to avoid falling short of minority representation; and bringing diversity awareness to the design of I/E criteria, data collection materials, and consent practices.

Acknowledgments

The authors thank the CLEAR III patients and their families for participating in the trial and contributing to this very important research to find a treatment for a devastating and otherwise untreatable form of stroke. We especially acknowledge and thank our AA patients, who historically share the greater burden of severity, mortality, and disability, for improving the generalizability of the CLEAR III trial results and raising the standard of patient-centered stroke care. We also thank Megan Clark for her editorial assistance.

CLEAR III is supported by the grant 5U01 NS062851-05, awarded to Daniel Hanley from the National Institutes of Health (NIH)/National Institute of Neurological Disorders and Stroke (NINDS). This work is also supported through a NINDS for Conference Funding Support of the

Health Equity Symposium (Grant R13NS101924, *6th World Intracranial Hemorrhage Conference Grant*), awarded to Karen Lane. We also thank Genentech, Inc. for its donation of alteplase for use in the CLEAR III trial.

References

1. Colby SL, Ortman JM. 2015. Projections of the size and composition of the US population: 2014 to 2060. *Current Population Reports* 25-1143:9. census.gov/content/dam/Census/library/publications/2015/demo/p25-1143.pdf
2. Paskett ED, Reeves KW, McLaughlin JM, et al. 2008. Recruitment of minority and underserved populations in the United States: the Centers for Population Health and Health Disparities experience. *Contemporary Clinical Trials* 29(6):847-61.
3. Bonner GJ, Miles TP. 1997. Participation of African Americans in clinical research. *Neuroepidemiology* 16(6):281-4.
4. Levkoff S, Sanchez H. 2003. Lessons learned about minority recruitment and retention from the Centers on Minority Aging and Health Promotion. *The Gerontologist* 43(1):18-26.
5. Harris Y, Gorelick PB, Samuels P, Bempong I. 1996. Why African Americans may not be participating in clinical trials. *J Nat Med Assoc* 88(10):630.
6. Dancy BL, Wilbur J, Talashek M, Bonner G, Barnes-Boyd C. 2004. Community-based research: barriers to recruitment of African Americans. *Nursing Outlook* 52(5):234-40.
7. Ross S, Grant A, Counsell C, Gillespie W, Russell I, Prescott R. 1999. Barriers to participation in randomised controlled trials: a systematic review. *J Clin Epidem* 52(12):1143-56.
8. Corbie-Smith G, Thomas SB, Williams MV, Moody-Ayers S. 1999. Attitudes and beliefs of African Americans toward participation in medical research. *J Gen Int Med* 14(9):537-46.
9. Branson RD, Davis K, Butler KL. 2007. African Americans' participation in clinical research: importance, barriers, and solutions. *Am J Surgery* 193(1):32-9.
10. Chandra A, Paul III DP. 2003. African American participation in clinical trials: recruitment difficulties and potential remedies. *Hospital Topics* 81(2):33-8.

11. Huang H-h, Coker AD. 2010. Examining issues affecting African American participation in research studies. *J Black Studies* 40(4):619-36.
12. Shavers VL, Lynch CF, Burmeister LF. 2002. Racial differences in factors that influence the willingness to participate in medical research studies. *Ann Epidem* 12(4):248-56.
13. Krishnamurthi RV, Moran AE, Forouzanfar MH, et al. 2014. The global burden of hemorrhagic stroke: a summary of findings from the GBD 2010 study. *Global Heart* 9(1):101-6.
14. Howard G, Cushman M, Howard VJ, et al. 2013. Risk factors for intracerebral hemorrhage. *Stroke* 44(5):1282-7.
15. Qureshi AI, Giles WH, Croft JB. 1999. Racial differences in the incidence of intracerebral hemorrhage: effects of blood pressure and education. *Neurology* 52(8):1617-21.
16. Rincon F, Mayer SA. 2013. The epidemiology of intracerebral hemorrhage in the United States from 1979 to 2008. *Neurocritical Care* 19(1):95-102.
17. Ovbiagele B, Nguyen-Huynh MN. 2011. Stroke epidemiology: advancing our understanding of disease mechanism and therapy. *Neurotherapeutics* 8(3):319.
18. Flaherty ML, Woo D, Haverbusch M, et al. 2005. Racial variations in location and risk of intracerebral hemorrhage. *Stroke* 36(5):934-7.
19. Broderick JP, Brott T, Tomsick T, Huster G, Miller R. 1992. The risk of subarachnoid and intracerebral hemorrhages in blacks as compared with whites. *NEJM* 326(11):733-6.
20. Broderick J, Brott T, Kothari R, et al. 1998. The greater Cincinnati/northern Kentucky stroke study. *Stroke* 29(2):415-21.
21. Collaborators NMSS, Sacco RL, Boden-Albala B, et al. 1998. Stroke incidence among white, black, and Hispanic residents of an urban community: the Northern Manhattan Stroke Study. *Am J Epidem* 147(3):259-68.
22. Sturgeon JD, Folsom AR, Longstreth W, Shahar E, Rosamond WD, Cushman M. 2007. Risk factors for intracerebral hemorrhage in a pooled prospective study. *Stroke* 38(10):2718-25.
23. Grysiewicz RA, Thomas K, Pandey DK. 2008. Epidemiology of ischemic and hemorrhagic stroke: incidence, prevalence, mortality, and risk factors. *Neurologic Clinics* 26(4):871-95.

24. Labovitz DL, Halim A, Boden-Albala B, Hauser W, Sacco R. 2005. The incidence of deep and lobar intracerebral hemorrhage in whites, blacks, and Hispanics. *Neurology* 65(4):518-22.
25. Johnston SC, Selvin S, Gress DR. 1998. The burden, trends, and demographics of mortality from subarachnoid hemorrhage. *Neurology* 50(5):1413-8.
26. Howard G, Anderson R, Sorlie P, Andrews V, Backlund E, Burke GL. 1994. Ethnic differences in stroke mortality between non-Hispanic whites, Hispanic whites, and blacks. The National Longitudinal Mortality Study. *Stroke* 25(11):2120-5.
27. Boan AD, Feng WW, Ovbiagele B, et al. 2014. Persistent racial disparity in stroke hospitalization and economic impact in young adults in the buckle of stroke belt. *Stroke* 45(7):1932-8.
28. Hanley DF, Lane K, McBee N, et al. 2017. Thrombolytic removal of intraventricular haemorrhage in treatment of severe stroke: results of the randomised, multicentre, multiregion, placebo-controlled CLEAR III trial. *Lancet* 389(10069):603-11.
29. Freeman W, Macek M, Lane K, et al. 2014. Simulation of best-consent and failed-consent elements from CLEAR III: a randomized, placebo controlled trial. Poster 170. Paper presented at the 12th Annual Neurocritical Care Society Meeting, Seattle, Wash.
30. Burke J, Brown D, Lisabeth L, Sanchez B, Morgenstern L. 2011. Enrollment of women and minorities in NINDS trials. *Neurology* 76(4):354-60.
31. U.S. Census Bureau. *American FactFinder*. factfinder.census.gov/
32. Gorelick PB, Harris Y, Burnett B, Bonecutter FJ. 1998. The recruitment triangle: reasons why African Americans enroll, refuse to enroll, or voluntarily withdraw from a clinical trial. An interim report from the African-American Antiplatelet Stroke Prevention Study (AAASPS). *J Nat Med Assoc* 90(3):141.

Karen Lane, CCRP, (klane@jhmi.edu) is an assistant professor of neurology and the administrative director of research in the Johns Hopkins University Division of Brain Injury Outcomes.

Maningbe Keita, BA, (mberete1@jhu.edu) is a research assistant in the Johns Hopkins University Division of Brain Injury Outcomes and a doctoral student in health policy and management at the Johns Hopkins Bloomberg School of Public Health.

Radhika Avadhani, MS, (ravadha1@jhmi.edu) is a senior research data manager in the Johns Hopkins University Division of Brain Injury Outcomes.

Rachel Dlugash, MSPH, (rdlugas1@jhmi.edu) is a senior research data manager in the Johns Hopkins University Division of Brain Injury Outcomes.

Steven Mayo, PD, CCRA, PMP, (smayo@emissary.com) is the founder and president of the contract research organization Emissary International and director of quality assurance in the Johns Hopkins University Division of Brain Injury Outcomes.

Richard E. Thompson, PhD, (rthompso@jhsph.edu) is a senior scientist in the Department of Biostatistics at the Johns Hopkins Bloomberg School of Public Health.

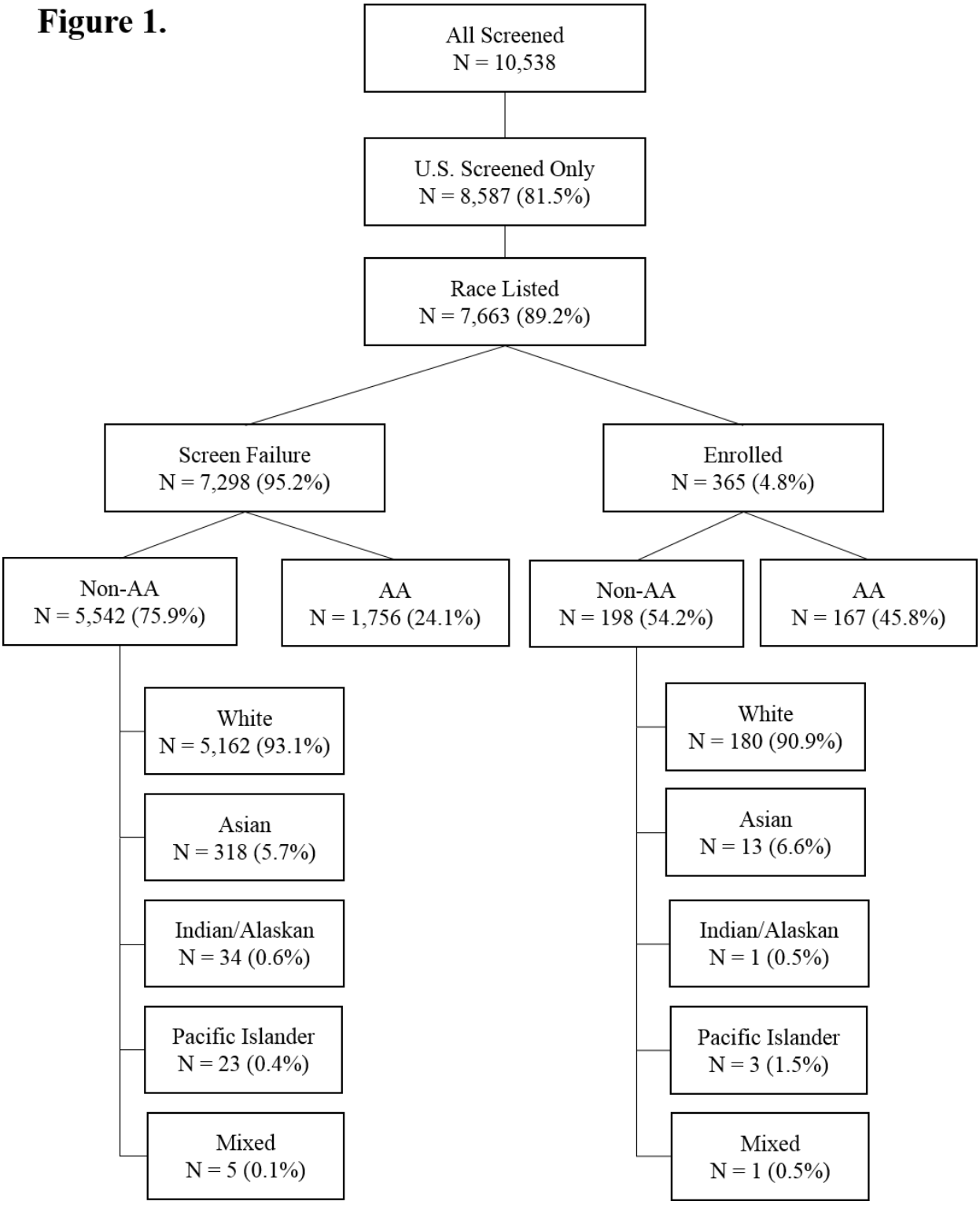
Issam A. Awad, MD, MSc, FACS, FAHA, (iawad@uchicago.edu), the John Harper Seeley Professor in Neurological Sciences and director of Neurovascular Surgery at the University of Chicago Medicine and Biological Sciences, was the co-principal investigator and surgical chairman of the CLEAR III trial.

Nichol McBee, MPH, CCRP, (nmcbee@jhmi.edu) is the division manager of the Johns Hopkins University Division of Brain Injury Outcomes.

Wendy Ziai, MD, (weziai@jhmi.edu) is an associate professor of neurology, neurosurgery, and anesthesiology and critical care medicine at the Johns Hopkins University School of Medicine.

Daniel F. Hanley (dhanley@jhmi.edu) is the Jeffrey and Harriet Legum Chair of Acute Care Neurology and director of the Johns Hopkins University Division of Brain Injury Outcomes.

Figure 1: CLEAR III trial screens from 2009 to 2014. AAs comprised 25.1% of the U.S. screens for which race was listed.



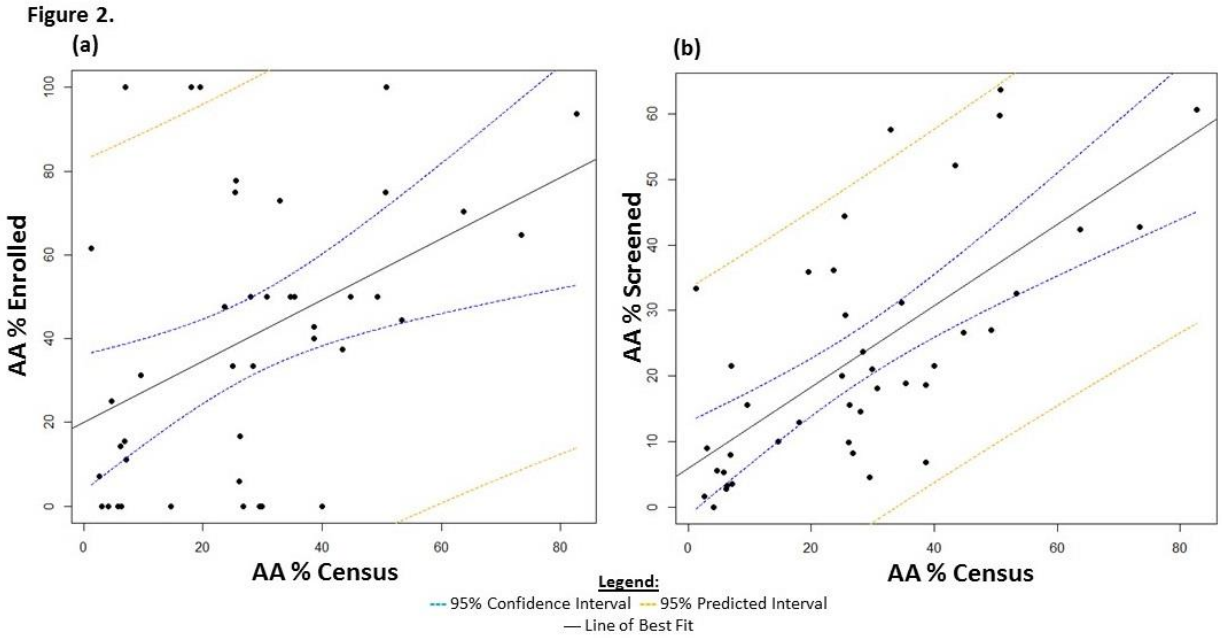


Figure 2: a. AA enrollment by city (%) compared to AA census data (%) for each city. Cities with a higher percentage of AAs enrolled more AAs into the trial (p-value: 0.004, R^2: 0.17). **b.** AA screening by city (%) compared to AA census data (%) for each city. Cities with a higher percentage of AAs screened more AAs into the trial (p-value: <0.001, R^2: 0.46). 95% confidence interval indicates the likely location of the true population parameter, and 95% predicted interval forecasts where to expect the next data point sampled.

Table 1: CLEAR III Enrollment Rates Compared to NINDS Rates and the U.S. Census Population During the Same Periods

	Period	AA Trial Representation (%)	U.S. Population (%, Year)
Pre-NIH Revitalization Act	1985-1995	11.6%	12.1% (1990)
56 NINDS trials			12.9% (2000)*
	1996-2008	19.8%	
			13.0% (2010)**
CLEAR III U.S. trial subjects (AAs)	2009-2014	45.1%	14.1% (2014)***

*** Includes persons identifying as African American and one or more additional races**

**** An additional 1% of the U.S. population identified as African American in addition to one or more other races**

***** Projected U.S. population**

Table 2: Conversion (Randomization) Rates: U.S. Overall and by Geographic Regions

Regions (n=sites)	AA (%)	Non-AA (all other) (%)	P-value
U.S. overall (n=61)	8.7	3.4	<0.001
Northeast (n=20)	7.7	2.9	<0.001
South (n=16)	8.2	4.0	<0.001
Midwest (n=16)	10.3	3.6	<0.01
West (n=9)	8.9	3.8	0.02

Table 3. Screen Failure Categories (N = 7,298)					
	AA		Non-AA		P-value
	N	%	N	%	
Medical	**1,292**	**73.6%**	**4,581**	**82.7%**	**<0.001**
Abnormal PTT, PLT < 100K, INR > 1.3	34	1.9%	122	2.2%	0.503
Age < 18 or > 80 years	98	5.6%	884	16.0%	<0.001
Aneurysm, mycotic aneurysm, moyamoya, etc.	161	9.2%	743	13.4%	<0.001
Craniectomy/other surgical procedures	21	1.2%	51	0.9%	0.308
Etiology - tumor	3	0.2%	47	0.8%	0.003
GCS < 3/herniation/brain dead/deceased	25	1.4%	43	0.8%	0.014
Historic (pre-bleed) Rankin not 0 or 1	47	2.7%	96	1.7%	0.013
ICH > 30 cc on diagnostic CTC	256	14.6%	700	12.6%	0.035
Infratentorial bleed	150	8.5%	451	8.1%	0.591
No EVD placed	220	12.5%	733	13.2%	0.449
No obstruction of 3rd and/or 4th	261	14.9%	636	11.5%	<0.001
Unstable bleeding	16	0.9%	75	1.4%	0.146
Non-medical	**199**	**11.3%**	**471**	**8.5%**	**<0.001**
Improper screening	9	0.5%	21	0.4%	0.446
Participation in another trial	6	0.3%	10	0.2%	0.208
Patient eligible but refused consent	54	3.1%	66	1.2%	<0.001
Patient is DNR	59	3.4%	250	4.5%	0.037

Study staff not notified within window	11	0.6%	21	0.4%	0.171
Study staff unavailable	2	0.1%	8	0.1%	0.764
Unable to dose within time window	58	3.3%	95	1.7%	<0.001
Combination medical and non-medical reasons	**265**	**15.1%**	**490**	**8.8%**	**<0.001**
MD/Surgeon chose not to enroll	56	3.2%	65	1.2%	<0.001
Not an IVH patient	18	1.0%	49	0.9%	0.59
Other	191	10.9%	376	6.8%	<0.001
Total	**1,756**	**100.0%**	**5,542**	**100.0%**	

Table 4: Enrollment Window and Race Reporting in Major ICH Clinical Trials

Trial	Inter-national	Medical or Surgical Trial	Enrollment Window (Hours)	F/U (Days)	Total Enrolled	% White Reported	% AA or Black Reported
CHANT	N	Medical	6	90	607	*	*
ICES	N	Surgical	48	365	24	45.8	33.3
FAST	Y	Medical	4	90	841		9.0
ATACH-2	Y	Medical	4.5	90	1,000		13.1
PREDICT	Y	Medical	6	90	268	86.0	
Deferoxamine	N	Medical	18	90	20	85.0	
NovoSeven	Y	Medical	3	90	399	81.0	
MISTIE II	Y	Surgical	**48**	365	96	56.0	30.0
CLEAR III	Y	Medical	**72**	365	500	61.0	34.0
CLEAR III	U.S. only	Medical	**72**	365	370	48.6	45.1

*** Race not reported**

Clinical Researcher—August 2018 (Volume 32, Issue 7)

SPECIAL FEATURE

The Anatomy of a Great Clinical Research Coordinator

Cyenthia Willis, RN, BSN, CCRP; Karen Bratcher, MSN, RN, CNL, CCRC; Tawni Kenworthy-Heinige, BS, EMT-I, CPT, CCRP; Conor McBurney, MPH; Aliya Asghar, MPH, CCRC; Danielle Beck, MPH, CCRC; Debra L. Condon, MSN, RN, CCRP; Grant D. Huang, MPH, PhD

Clinical trials are critical for developing and delivering evidence-based care. The successes of these research studies often rely on clinical research coordinators (CRCs), who carry out many of the key clinical, administrative, and regulatory compliance responsibilities.

The demand for *good* CRCs is high, especially given recent emphasis on quality in clinical trials.{1} While several professional research groups offer training and/or certification for CRCs, there are other approaches that can assist them in reaching a higher performance level. The following provides practical considerations based on experiences conducting such studies within the Veterans Health Administration, the nation's largest integrated healthcare system.{2}

Part I: Setting the Stage

Though principal investigators (PIs) are responsible for all clinical trial activities from a regulatory standpoint,{3} it is essential that CRCs and PIs collaborate together to ensure that studies are conducted in accordance with both the protocol and the tenets of Good Clinical Practice.

The success of clinical trials relies heavily upon CRCs' abilities to effectively manage day-to-day study tasks. This journey begins by successfully selecting an ideal CRC. While this may be challenging, there are specific methods that can help to simplify the process and increase the likelihood of selecting the best candidates. These include developing an applicable position

description, identifying and screening the appropriate pool of applicants with the desired qualifications, and implementing a well-planned, structured interview process.

Employers or supervisors should collaborate with their Human Resource departments to create well-design position descriptions, keeping in mind the needs of specific types of studies and therapeutic areas, including required skills, education, certifications, and experience. It is optimal to have a panel of at least three interviewers with diverse experience in human subjects' research and managing clinical trials. The interview panel should review resumes and highlight requisite characteristics desired, thereby increasing the likelihood of identifying the most qualified CRC applicants to interview.

Figure 1: The "Five C's" of a Good CRC

During the interview, the panelists should ask the applicant a variety of structured open-ended, hypothetical (or situational), and behavioral questions to ascertain research-related experience. A great CRC candidate will provide responses that demonstrate effective communication skills and give examples of problem-solving, initiative, efficient time management, collaboration, and prioritization of tasks.

It may be difficult to identify all the qualities of a good CRC; however, there are traits that distinguish a good CRC from a great CRC, which we describe as the "Five C's" (see Figure 1).

Coordination

Over the lifetime of a clinical trial, an experienced CRC is responsible for coordinating and implementing many study-related activities. A key attribute of a successful study is the organizational capabilities of its CRC. Serious complications can result when records (e.g., regulatory binders) and data management are disorganized. These complications can result in institutional review board (IRB) sanctions, funding withdrawal, probation, administrative suspension or termination, and unusable data.

Anticipating problems can help prevent potential punitive actions. It is therefore imperative that a CRC efficiently coordinates the crucial activities of a study, such as initiating timely start-up, navigating strict eligibility criteria, minimizing participant travel and/or financial burden, ensuring data monitoring accuracy, and having continued awareness of competing clinical trials.

Study Start-Up: There are a variety reasons why a study may fail to launch in a timely manner. The CRC is typically responsible for facilitating study start-up activities to ensure that a study begins within the projected timeframe. A great CRC will develop and implement organizational techniques, such as a checklist to prioritize and complete tasks. These tasks include engaging stakeholders, creating budget projections, identifying study staff, determining space needs, and ensuring timely submission of documents.

Appropriate time management during start-up activities can decrease delays in recruitment, help the site meet its study goals, and increase overall study efficiency. Timely start-up also avoids fiscal pitfalls that may have a negative impact on sponsors.

Navigate Strict Eligibility Criteria: Every study is unique in terms of its inclusion/exclusion criteria. The stricter the eligibility of a research study, the more difficult it can be to find appropriate participants. A great CRC will be well organized and will establish a quick mental checklist using a methodical approach.

To enhance navigating eligibility, a great CRC might create a laminated quick-reference pocket guide for easy elimination of ineligible participants during the screening process. For example, if two exclusions are AIC < 5.7 % and participants < 40 years old, then the quickest method to determine if the participant is ineligible would be to simply look at the age first. If a prospective participant is more than 40 years old, then the CRC can quickly move to the next potential participant to screen. Once the CRC has determined a participant meets all criteria, then he/she can proceed per protocol.

Minimize Participation Burden: Historically, participant travel, financial hardships, and other logistical concerns have been barriers to recruitment into clinical trials.{4} Demographic disparities exist among prospective research subjects, limiting participation to those who meet the eligibility criteria. A well-versed CRC understands the importance for participants to be adherent to their study appointments. A great CRC will seek alternative means of transportation, visit locations, and investigate reimbursement options for the participants to help offset potential travel and financial burden and to better facilitate logistical issues that might otherwise disrupt study participation.

Ensure Data Monitoring Accuracy: The CRC collects and inputs data from many sources; therefore, data must be accurate, reliable, and verifiable. One of the crucial data points of a clinical trial is reporting adverse events (AEs), serious adverse events (SAEs), and safety issues in a timely manner. A great CRC will have methods in place to help alert and determine if a participant has experienced AEs/SAEs. A well-organized CRC may create electronic medical record alerts (e.g., alerting that a participant is hospitalized or has abnormal lab values) or may develop a source checklist to ensure all study activities and AEs/SAEs have been captured during study visits with the participant.

Clinical Trials Awareness: Having a clear understanding of other competitive trials allows the CRC to better navigate or facilitate recruitment strategies. A great CRC will be aware of competing clinical trials within the same geographical and therapeutic areas involving the same target population.

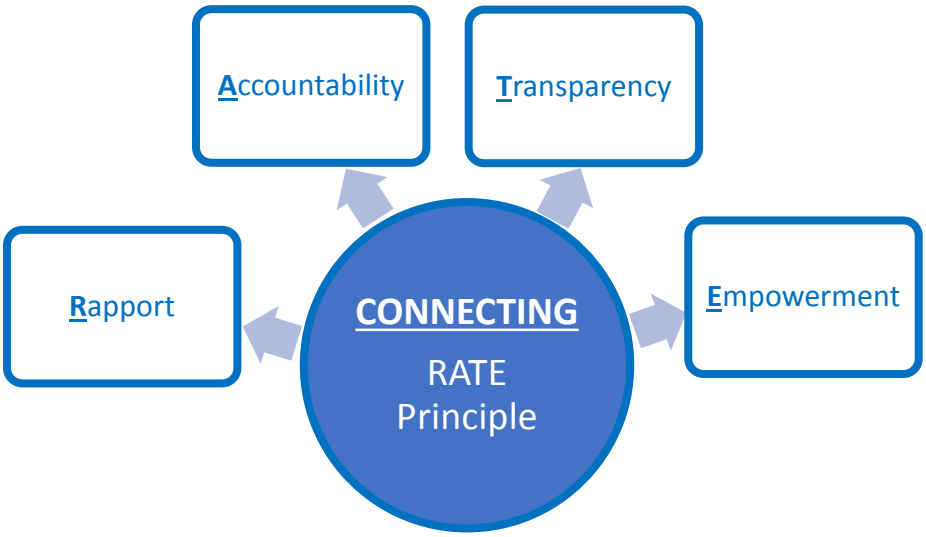
In addition to being knowledgeable of other projects (current or upcoming), a great CRC should be a resource for individuals interested in opportunities for participating in clinical trials. Former research participants often inquire about other projects for which they may qualify—especially studies that fall within a health condition of interest

Connection

A CRC is often the "face" of the study for participants. First impressions matter, and can develop into relationships lasting the duration of each trial; this fact alone can increase patient retention rates.

In addition to recruiting subjects, one of the primary responsibilities of a CRC is to help them navigate the various research entities involved in studies (e.g., labs, pharmacy, imaging, etc.). Therefore, the CRC must create a relationship of trust and dependability as a research case manager for the participant. A great CRC adheres to the RATE Principle, which explores the ideas of Rapport, Accountability, Transparency, and Empowerment (see Figure 2).

Figure 2: The RATE Principle



The RATE Principle is a creation of the Network of Dedicated Enrollment Sites (NODES), a core component of the Veterans Administration (VA) Cooperative Studies Program (CSP).

Rapport: It is advantageous for CRCs to build rapport with potential participants who express interest in studies. Addressing participant questions, translating study jargon, and achieving a mutual understanding about the purpose of the study before proceeding with the informed consent can establish a solid relationship foundation. The development of this initial relationship strengthens participants' likelihood for adherence and retention throughout a study's lifecycle.

A great CRC personalizes each participant's encounter with a positive interaction—providing additional education and creating a "safe zone", while maintaining professional boundaries. This safe zone creates an atmosphere in which participants can share their personal or health information relative to studies, communicate concerns about being research subjects, and discuss any other barriers that may prohibit their participation. As CRCs develop a better understanding of participants' needs, they able to anticipate patient engagement and proactively assist them with navigating the study process. By establishing a strong rapport with participants, CRCs become a trusted point-of-contact for studies.

Accountability: The PI is ultimately accountable for the overall conduct of a study, while the CRC is generally responsible for day-to-day operations. A good CRC supports the PI in ensuring the safety and well-being of the study participant, and is often the link among the PI, study participants, other study team members (e.g., sub-investigators, research assistants, etc.), the IRB, study sponsor, and other governing bodies.

The CRC customarily oversees the proper execution of, and adherence to, an approved protocol by ensuring accurate and timely study data collection, and by maintaining the highest standards of regulatory compliance. The CRC understands the significance of the consenting process and emphasizes the importance of participants' comprehension of the study objectives and their commitment to study procedures. A great CRC is knowledgeable about the research infrastructure, has an acute awareness of team communication and cohesiveness, and strives to keep stakeholders informed of new study developments.

Transparency: Being transparent about a study's intent with participants is crucial. When considering infamous instances of unethical research (e.g., Tuskegee Syphilis Study), participants may be resistant and fearful of joining a clinical trial.{5} An ethical CRC is honest

and without bias, and answers participants' questions openly, sincerely, and directly. The CRC must provide full disclosure of study-related resources, safety issues, costs/benefits (e.g., emotional, physical, financial), and research design and group randomization details, as well as potential outcomes of the study. A great CRC will emphasize participants' rights, how privacy and confidentiality are maintained, and the fact that research is voluntary, and ensure that participants know that they may withdrawal at any time without loss of healthcare benefits. Ensuring full understanding of the study will enhance participants' trust regarding their safety and well-being.

Empowerment: Once rapport, accountability, and transparency have been established, facilitating participant empowerment is a fundamental task for a CRC. Empowerment occurs with shared decision-making, self-management, and enhanced health literacy and knowledge. Empowering participants can strengthen their sense of control and commitment, as well as increase their levels of satisfaction while participating in studies.

Widely discussed in healthcare is placing participants at the center of care—ensuring they are major contributors in the decision-making process. A great CRC ensures participants are empowered with the information necessary to make informed decisions about study participation. The CRC should discuss in depth the side effects of study medications and/or procedures to enhance the participants' health literacy and knowledge. Empowerment and autonomy help participants to develop and practice self-managing skills (e.g., observing medication schedules, maintaining diaries, attending study visits), thereby improving study adherence and outcomes.

Commitment

When CRCs find value in their organizations and are committed to research projects, the projects will have better chances of accomplishing their end goals. Studies have shown that organizational performance is highly related to work commitment.{6} Additionally, a committed employee is adaptable to accommodate the needs of the job.{7} A great CRC demonstrates the attributes of commitment in terms of being willing to be challenged, seeking ways to overcome obstacles, and exceeding minimal expectations.

Willingness to be Challenged: Great CRCs are not intimidated by study challenges beyond their expertise or comfort levels; they are eager to expand their skill sets through training, observation, mentorship, and performance.

Seeking Ways to Overcome Obstacles: Even the best-planned research project will encounter unexpected obstacles. A great CRC seeks ways to contribute innovative ideas, and learns from these barriers to create and share best practices for the study.

Exceeds Minimal Expectations: A great CRC strives to apply flexibility and adaptability to the needs of the study, which may include undertaking additional tasks, adjusting competing priorities, extending work schedules, or attending educational opportunities outside the work setting.

Communication

The CRC must communicate with participants, PIs, sponsors, key stakeholders, ancillaries, regulatory agents, and coworkers on an ongoing basis. A great CRC possesses excellent verbal and written communication skills.

Ensure Participant Understanding: When communicating with participants, the CRC should be able to explain a complex research protocol at the patient's level of understanding. A great CRC will ensure this understanding, as demonstrated by the participant's ability to verbalize the purpose of the study and the procedures involved.

Develop Synergistic Relationships: Communication is an essential foundation of team building. A CRC must also be able to concisely communicate and respond quickly with a variety of regulatory boards and oversight bodies. Consistent communication with these entities will enhance transparency and develop synergistic relationships. A great CRC will use a variety of communication methods with peers and ancillaries to facilitate the daily operations of a clinical trial.

Collaboration

While serving as an integral part of a network of researchers, the CRC often works independently or as part of a small team. A great CRC is self-motivated, autonomous, and assumes more of a leadership role in building collaborative relationships.

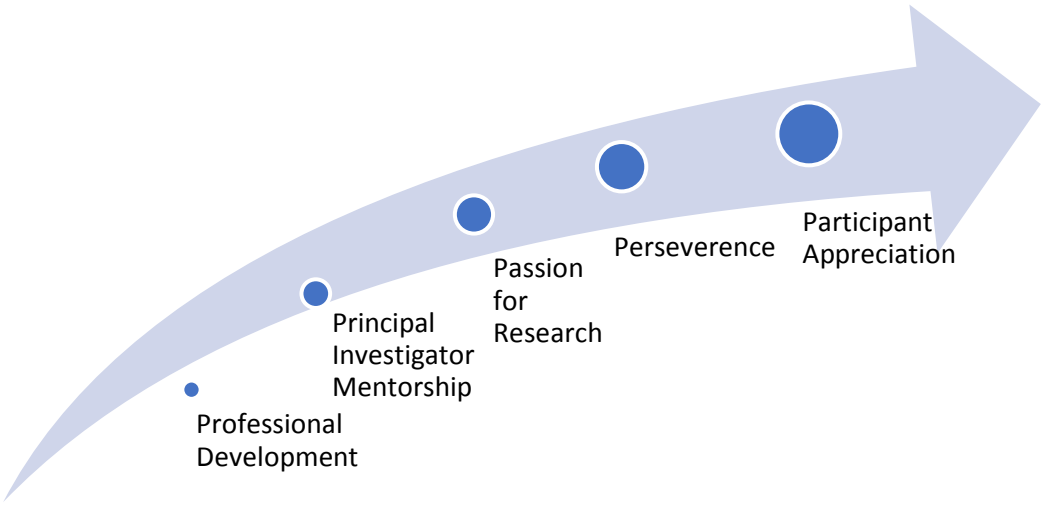
Develop Partnerships: The study team often relies upon ancillary entities to provide services that fulfill the study protocol. A great CRC will recognize and explore necessary resources to facilitate an efficient trial. Enhancing these resources are often done by partnering with clinical departments (e.g., diagnostic labs, pharmacy, outpatient/community clinics, etc.), medical disciplines (e.g., primary care, occupational health, mental health, etc.), and supportive services (e.g., public affairs, information technology, etc.) by establishing contacts to foster successful collaboration and communication.

Become a Clinical Research Resource: Through the dynamics of collaboration, a great CRC will seek ways to close communication gaps, empower team members, provide mentorship, and assume a preceptor role, thereby becoming an invaluable resource in clinical research.

Part II: Behind the Scenes

While the "Five C's" delineate the differences between a good and a great CRC, the question that presents is how one may transition from "good" to "great"? We believe that there are five key elements that prepare a good CRC to becoming a great one. We describe these as the "Five P's" to Propagate a Great Clinical Research Coordinator (see Figure 3).

Figure 3: The "Five P's" to Propagating a Great Clinical Research Coordinator



The "Five P's" Principle is a creation of the Network of Dedicated Enrollment Sites (NODES), a core component of the Veterans Administration (VA) Cooperative Studies Program (CSP).

Professional Development

A CRC will progress from novice to expert when exposed to a dedicated support system (e.g., a mentor, a network of coordinators, educational resources, etc.). The opportunity to discuss confusing issues, experiences in problem solving, and sharing best practices can be powerful both professionally and personally.

A great CRC will consistently seek ways to enhance his/her education and knowledge. There are several internal and external resources available to enhance one's research career; these include clinical research professional organizations and universities that offer continuing education and certifications. Attending applicable, topic-related conferences and webinars is also recommended.

PI Mentorship

The PI can be crucial in propelling a good CRC toward being a great CRC. While it is important that the PI be highly involved in study oversight, micro-managing CRCs could alter their interdependent relationship. Conversely, when a PI allows a CRC to become isolated or siloed without support, he or she may become detached, leading to a lack of accountability or commitment.

Engaged PIs will meet regularly with CRCs at their sites to discuss study status, and will mentor them to enhance their skill levels. This mentorship may include guidance on conducting more clinically based identification of potential study participants, providing clinical support during the patient consent process, explaining the differences between AEs and SAEs, facilitating connections with fellow colleagues, affording training and educational opportunities, and fostering authorship contributions for publications.

Passion for Research

A good CRC has full knowledge of studies at his or her site and the ability to connect with prospective participants; however, a great CRC not only understands the intent of the study, but also promotes the study with passion and enthusiasm. When CRCs are passionate about studies, they portray confidence to proficiently conduct research. The passion of a CRC can lead to increased participant recruitment and retention, improved data compliance and quality, and successful achievement of study goals.

Perseverance

A clinical trial can be a long journey that is filled with frequent challenges. While good CRCs will hold themselves accountable to study expectations, great CRCs will view those milestones as minimal expectations. A great CRC will pursue opportunities for improvement by reaching out to other study teams, sponsors, and/or other entities for ways to enhance study performance. A great CRC also will develop novel methods to maneuver study barriers and navigate resource accessibility throughout the lifecycle of a clinical trial.

Participant Appreciation

A good CRC appreciates research participants, but a great CRC understands their value as volunteers. By developing a deeper respect for participants' personal sacrifices (e.g., time, expense, commitment), the dynamic between CRCs and participants may become more synergetic, with research visits being viewed as opportunities for connection, rather than as cumbersome or stressful activities.

Within the Department of Veterans Affairs Health Care System, we honor our American Heroes and recognize the sacrifices our Veterans have made for our country. Participating in research is often viewed as another way for them to serve and contribute to the enhancement of healthcare.

Conclusion

Clinical trials are critical for developing and delivering evidence-based care. The success of these research studies often relies on the CRC's work as a vital member of the clinical research team.

It may be difficult to identify all the qualities of a good CRC; however, there are traits that distinguish a good CRC from a great CRC. A great CRC will demonstrate effective competencies of coordination, connection, commitment, communication, and collaboration—or the "Five C's." These attributes, combined with an engaged PI, perseverance, gratitude for research participants, and desire for professional development—or the "Five P's"—will transform a good CRC into a great one.

A great CRC requires a network of support and encouragement from multiple stakeholders. As one of these stakeholders, the VA Cooperative Studies Program (CSP) Network of Dedicated Enrollment Sites (NODES) has been instrumental in enriching the characteristics of the "Five C's" as well as promoting the qualities of the "Five P's." This ultimately ensures the success of every CRC managing a clinical trial through education, mentoring, and sharing best practices in clinical research. For more information regarding NODES, please visit https://www.research.va.gov/programs/csp/nodes.cfm.

Disclaimer

The views expressed in this article are those of the authors, and do not necessarily represent the views of the Department of Veterans Affairs or any U.S. government agency.

References

1. Tenaerts P, Madre L, Archdeacon P, Califf RM. 2014. The Clinical Trials Transformation Initiative: innovation through collaboration. *Nat Rev Drug Discov* (13)797-8.
2. Veterans' Health Administration. https://www.va.gov/health/aboutvha.asp
3. U.S. Department of Health and Human Services, Food and Drug Administration. 2009. Guidance for Industry: Investigator Responsibilities – Protecting the Rights, Safety and Welfare of Study Subjects. www.fda.gov/downloads/Drugs/.../Guidances/UCM187772.pdf
4. Institute of Medicine Forum on Drug Discovery, Development, and Translation. 2010. Transforming Clinical Research in the United States: Challenges and Opportunities: Workshop Summary. Washington (D.C.): National Academies Press (U.S.). Challenges in Clinical Research. https://www.ncbi.nlm.nih.gov/books/NBK50888/sited 3/8/2018
5. Davis A, et al. 2002. The invisible hand in clinical research: the study coordinator's critical role in human subjects' protection. *J Law Med Ethics* 30(3):411-9.
6. Redmond BF. The Pennsylvania State University. Confluence. Psych 484: Work Attitude and Job Motivation. Part 12: Work and Organizational Commitment. https://wikispaces.psu.edu/display/PSYCH484/12.+Work+and+Organizational+Commitment
7. Heibutzki R. 2018. What It Means to Be Committed to a Job. http://work.chron.com/means-committed-job-12508.html

Cyenthia Willis, RN, BSN, CCRP, (Cyenthia.Willis@va.gov or cwillis747@yahoo.com) is with the VA North Texas Health Care System in Dallas, Texas.

Karen Bratcher, MSN, RN, CNL, CCRC, is with the VA Palo Alto Healthcare System in Palo Alto, Calif.

Tawni Kenworthy-Heinige, BS, EMT-I, CPT, CCRP, is with the VA Portland Healthcare System in Portland, Ore.

Conor McBurney, MPH, is with the Edward Hines, Jr. VA Hospital in Hines, Ill.

Aliya Asghar, MPH, CCRC, is with the Tibor Rubin VA Medical Center in Long Beach, Calif.

Danielle Beck, MPH, CCRC, is with the VA San Diego Healthcare System in San Diego, Calif.

Debra L. Condon, MSN, RN, CCRP, is with the Minneapolis VA Health Care System in Minneapolis, Minn.

Grant D. Huang, MPH, PhD, is with the Cooperative Studies Program Central Office, VA Office of Research and Development, in Washington, D.C.

Clinical Researcher—August 2018 (Volume 32, Issue 7)

DEVICES TODAY

Removing the Negative Connotation: It *Can* Make Sense to Transition Your Device Study to a CRO

Adam Steadman

There can be a negative perception around a device clinical trial being transitioned to a contract research organization (CRO). It is time, however, that we took a more pragmatic view of why this should happen, and contemplate whether we should be considering and enabling it more often.

Let's start with "Why?" Why would you transition an ongoing study that is being managing reasonably well, and for which you have obtained your primary objective of gaining regulatory approval?

This evokes a multifaceted response. Let me break down the question into bite-sized chunks—how I like to look at every problem, because the solutions are far less daunting when you take this approach.

Don't Let Perfect be the Enemy of Good

First up, let's look at "managed reasonably well." Whatever your background, whichever company you have worked with, can you really claim perfect delivery? I hope you can, but face it, we all encourage an environment of continual improvement—one which would be redundant in a perfect world.

Professionals in medical device companies are dissimilar to those in drug companies in that their products change and evolve. A drug that changes or evolves is a different drug, plain and simple.

Unlike the drug study experts, this means we device folks are often faced with multiple iterations of a product undergoing simultaneous clinical trials. Post-market commitments are maintained for legacy products in parallel with the latest innovations, and it is realistic to assume that the enthusiasm for the latest product garners the greatest attention.

So we have our first challenge. How do you keep true attention on a legacy product that we no longer market or generate revenue from, but for which we have ongoing moral and regulatory obligations to patients and regulators? This is a "soft" challenge—and when I say soft, I don't mean that it is easy; I mean that it is intangible. It's not tied to patient outcomes (we usually can't change those post-hoc) and it's not tied to revenue.

Approaches to Approval

Let's now look at our "primary objective of gaining regulatory approval." The most obvious comment here is that there is so much more that hinges on your pivotal trial than gaining regulatory approval.

Being approved goes only so far, getting buy-in from the medical community is of huge value, and still more importantly, getting the payers to understand your economic proposition is the only way to be truly successful. It's not about profitability, it's about viability; even not-for-profit organizations have to remain economically viable.

Bottom line, there aren't just regulatory commitments that must be delivered upon, but there is also a community of patients, prescribers, and payers to keep happy, for both patient-centric and economic reasons.

Think of it This Way…

Time for some deep soul searching—are the factors described here keeping the leading scientific innovators in your organization working to midnight, and returning to the office before sunrise? I'm sure they aren't, because these innovators are always seeking a better result than they got today—they are looking forward all the time, and revisit the past only for how it informs the future.

So why would you transition an ongoing project away from our immediate care and into the arms of a CRO? To make sure that it is getting the attention it needs with the scientific and quality rigor that we expect from robust clinical trials and, most importantly, that patients who have been subject to experimental therapies have appropriate follow up and ongoing care.

Taking on the Transition

Now the question is "How?" How exactly do you go from getting an approval after a one-year interim data cut of a five-year (often 10-year) clinical study, to transitioning the post-marketing/post-approval follow-up phase of the same study, without stopping, to a CRO? (This situation also applies to changing from a current CRO to a new CRO—a classic "rescue study.")

The answer is one that is not always appreciated at first; as with any successful complex delivery, it is down to planning, process, and discipline. Transition or rescue of a study from a sponsor to a CRO, or from a CRO to another CRO, requires highly detailed processes that have been developed over time with insights borne from experience. This is not a place for learning for the first time on the fly—it demands careful application of all the wisdom you have gained from years of conducting research.

It starts with detailed planning; not just amending existing plans (e.g., your data monitoring plan, your clinical monitoring plan, or your communications plan), but overlaying a highly detailed transition plan. This takes into account a wide array of considerations, and takes a deep dive into risks and mitigations, strengths and weaknesses, and opportunities for improvement.

In my experience, I've found it helpful to use a detailed agenda and checklist that includes a face-to-face forum where legacy and future teams work together for a smooth transition and reach a common agreement on the management of handing over tasks and responsibilities. This can help disparate teams engage to ensure a smooth and efficient transition of tasks, responsibilities, and, above all, accountability.

Putting Theory into Action

Finally, what are the interpersonal and intercorporate clashes that arise? Can this really be done? I have no doubt there is some variability based on the specifics of each situation, but let me illustrate my answer through a case study.

I was approached in late 2016 by a large transcatheter device manufacturer and asked if we could help with the safety phase of one of its ongoing trials. The development team had surpassed its one-year data cut, had provided the interim results to the U.S. Food and Drug Administration, and had just been granted Premarket Approval.

This study incorporated three iterations of the product in development and multiple registries. The manufacturer's fear was that handing this over to a CRO would result in a decrease in data quality, reduced performance overall, and negative impacts to a highly valuable brand and image in terms of key opinion leaders, including physicians at leading interventional sites. This was of particular concern, as the company had clinical research associates and field clinical engineers calling these clinicians on an ongoing basis.

Using a detailed transition planning process, we went through a critical process of alignment and a highly detailed planning process with this client. The end result was a very smooth transition, but the real victory was a comparison of leading metrics after a year. Data quality had improved, queries were at an all-time low, and the average time between a visit and final report had dropped sharply. Not only did this deliver exceptional results, but the manufacturer has since redesigned its study approach to include the transition of the safety phase of future studies to a CRO as a standard.

Conclusion

Let me leave you with some parting thoughts. First, if you are a sponsor, should you be focusing the efforts of your brightest minds on your legacy products? Upon contemplating a service provider switch, or even switching from your own teams to a new service provider, do you have robust processes and procedures available to you that will guarantee success?

Second, you must be aware that transition is never any easy proposition. Due consideration of the circumstances, the economic benefits, the risk and mitigations, and the overall strategic objective will allow you to decide whether transitioning to a CRO is an appropriate strategy for closing out your existing clinical trial commitments, and to continue to drive innovation and market dominance.

Finally, if you are in the unenviable position of having a failing provider today, know that there is a way to rescue your study without further jeopardy.

Adam Steadman is Vice President—Clinical Development; Business Unit Head, Medical Device & Diagnostics at Syneos Health.

Clinical Researcher—August 2018 (Volume 32, Issue 7)

GOOD MANAGEMENT PRACTICE

Virtual Team Enables Successful Approval of Moxidectin for River Blindness

Mark Sullivan; Craig Rayner

[Editor's Note: This is a follow-up to a February 2018 column about this project.]

Medicines Development for Global Health (MDGH), a small, not-for-profit biopharmaceutical company from Australia, is celebrating several remarkable regulatory firsts, but it is the potential of the organization to impact global health that is exciting the field. On June 13, 2018, it received U.S. Food and Drug Administration (FDA) approval for moxidectin, an oral treatment for river blindness (onchocerciasis) in patients aged 12 years and older. Onchocerciasis is the second leading cause of infectious blindness and the fourth leading cause of preventable blindness worldwide.

MDGH became the first not-for-profit company to achieve FDA approval of a drug as a sole sponsor, and the first not-for-profit to be awarded a priority review voucher by the FDA. In the process, MDGH created a new model for developing medicines for neglected tropical diseases.

Developing a New Model

As a not-for-profit drug developer working in global health, MDGH faces the challenge of needing to achieve the same regulatory quality and data requirements as a large commercial biopharmaceutical company, but with fewer staff, and at a much lower cost.

MDGH overcame these hurdles by structuring itself around the project leader/project manager hub with a small core team in house to drive the development. This team identified, engaged, and coordinated an experienced, virtual drug development team of consultants and companies selected for their talent regardless of geography—an approach that allowed MDGH to hire the

best drug development team members. It also enabled the company to have minimal internal costs and adjust its access to the right skills to match the drug lifecycle requirements.

Mark Sullivan* identified the need to integrate model-informed clinical pharmacology into the program and engaged several Certara Strategic Consulting® staff members, including Craig Rayner**, to become a key part of MDGH's virtual drug development team. Craig and members of the wider Certara team brought their broad drug development expertise in clinical pharmacology, translational medicine, and regulatory science into the mix on the project.

One of the critical success factors for any drug development team is ensuring genuinely cross-functional input into decisions. At MDGH, Mark's leadership style was intended to create a culture of creativity and innovation. Mark assembled a competency-based drug development team, so there was a great deal of mutual respect among team members for their domain expertise. Mark's recruitment trick, apparently, was to hire people to whom you would like to report.

In addition, Mark articulated the data that needed to be collected and the fiscal constraints they faced. By always listening and accepting dissenting views, Mark created a respectful, challenging culture and empowered his team to be innovative. Craig said they were highly motivated to garner the best information possible from the leanest design. For example, they opted for a population pharmacokinetics analysis of existing data instead of running a series of dedicated drug-drug interaction studies.

Post-approval, MDGH plans to take a similar outsourcing approach with its communications requirements, such as the development of disease- and drug-specific training materials, which will be needed to help implement moxidectin in the field. Also, while MDGH will oversee the ongoing safety monitoring and recordkeeping for moxidectin, it will establish external pharmacovigilance hubs to help manage those processes.

MDGH also intends to leverage existing systems as it prepares to distribute moxidectin for onchocerciasis. MDGH manufactures moxidectin under contract, and is working with existing drug distribution networks, including those created and managed by the World Health

Organization (WHO) during the past 30 years, and other non-governmental organizations that are also involved in distribution.

Planning New Research

Even though moxidectin has received FDA approval for onchocerciasis, there are still studies that need to be conducted to facilitate its use in the field. For example, MDGH is planning a pediatric age de-escalation study to enable moxidectin's age of use to be brought down to four years. Certara has already modeled the starting doses for two pediatric age groups, and recruitment for that study will occur in June and July 2019 in Ghana.

MDGH also wants to investigate *Loa loa*, another filarial disease that can occur as a coinfection in parts of sub-Saharan Africa with onchocerciasis. While *Loa loa* does not cause disease itself, when people are treated with ivermectin, the current standard of care for onchocerciasis, a serious adverse reaction can occur if they also have a high *Loa loa* burden. MDGH is conducting a small study to provide guidance for how to use moxidectin in those with a *Loa loa* coinfection.

The company also plans to study the public health impact of multiple administrations of moxidectin over several years. MDGH anticipates that moxidectin's improved efficacy over ivermectin will reduce transmission of onchocerciasis and significantly improve people's health.

Exploring Other Indications

Moxidectin has the potential to be one of the world's most significant global health medicines. MDGH is investigating moxidectin as therapy for several other diseases. First it will study scabies, a highly contagious mite infection. Scabies causes severe itching, which provokes vigorous scratching that can break the skin and lead to a wide range of local and systemic infections. As moxidectin stays in the body for longer than ivermectin, it may be possible to treat people with moxidectin just once and clear the infection completely.

There are three other worm-based, neglected tropical diseases for which MDGH believes moxidectin may prove to be an effective treatment—lymphatic filariasis, soil-transmitted

helminths, and strongyloides. Soil-transmitted helminths alone affect between 1 and 2 billion people around the world.

Leveraging Modeling and Simulation

Consistent with contemporary drug development programs, MDGH views modeling and simulation of available preclinical and clinical data to be an essential tool for making better decisions in drug development: providing data to inform a particular approach and helping to predict what might occur in the clinic is logical. The data subsequently generated will either confirm or refute the hypothesis, and then the team can adjust its approach accordingly.

Mark says it is easy to see why modeling and simulation has become an indispensable part of contemporary drug development programs because it reduces costs and waste, while improving key decision making and accelerating development. MDGH has integrated modeling and simulation in both its pediatric onchocerciasis and scabies studies.

Building a Health Economic Argument

MDGH is breaking ground in developing a new health economic model for the global health community. It is exploring how to fund a treatment when the disease and/or drug are of no interest to the pharmaceutical industry because the patients who will benefit cannot pay for it.

Sale of MDGH's priority review voucher, which it received from the FDA for its moxidectin for onchocerciasis approval, will be used to fund the drug's ongoing development. Its earlier work was financed by a $13 million investment from the Global Health Investment Fund. Going forward, MDGH intends to donate moxidectin based on affordability, and at worst, plans to charge only what it costs to manufacture and supply moxidectin. It is already considering ways to be as transparent as possible with its costs, including publishing them online.

Conclusion

Mark and Craig agreed that the most valuable lesson they learned during the development of moxidectin for onchocerciasis was "Never give up!" Even when the odds seem insurmountable,

the right small, virtual team with the right leader and project management can indeed get a new drug to treat a neglected tropical disease approved by the FDA.

***Mark Sullivan** is Managing Director of Medicines Development for Global Health (MDGH).

****Craig Rayner** is Senior Vice President, Integrated Drug Development, with Certara Strategic Consulting.

How to Recruit Specialty Volunteer Populations for Early-Phase Clinical Research

SPECIAL ADVERTISING SUPPLEMENT

Celina Alvarez, Quotient Sciences

Participant recruitment is one of the biggest bottlenecks in clinical research today. In early drug development, effective volunteer recruitment is critical for building a robust package of clinic trial data, ensuring scientific validity, containing study costs and maintaining timelines. In studies that require specific types of volunteer populations, it's important to develop a focused plan for recruitment.

Because of physiological and lifestyle disparities, different populations may demonstrate widely varying responses to drug therapies. To safeguard those for whom standard requirements may not offer sufficient protection, special populations provide evaluation of factors such as dosage or dose interval modifications to address these differences. For example: One estimate says that 15–20 percent of people over the age of 65 take multiple drugs concurrently, which makes drug interactions of particular concern.[1] Because geriatric populations respond differently than younger patients to drug therapy, it is imperative to procure clinical efficacy and safety data for these populations in early drug development.[2]

Furthermore, expanding sales growth in global pharmaceutical markets is driving drug development to Europe and Asia. Therefore, multi-ethnic approaches to clinical trial programs, such as ethnobridging for native Asian populations living in other countries, must account for cultural differences to satisfy international regulatory authorities.[3]

Recruitment of special populations can be especially challenging, but following a few basic practices will improve your results. In addition to identifying the appropriate study participants, the right partner can help minimize screen failures due to multiple exclusion/inclusion criteria.

Work with an experienced partner

An experienced partner can effectively target hard-to-recruit populations such as the elderly, post-menopausal, hypertensive, Type II diabetics, healthy smokers, obese and Japanese subjects.

Such a partner will demonstrate a successful track record and can provide metrics regarding:

- Number of studies completed
- Database size and number of active healthy volunteers
- Recruitment timelines and strategies for special subject populations

Communicate effectively
If you're a sponsor, it will be of utmost importance to work with a CRO that is transparent about timelines and can guide your expectations. An organization that has completed multiple studies with similar types of populations will have a baseline understanding of recruitment challenges. Such a partner can thus provide an honest assessment of the time expected to recruit the full cohort. When studies have stricter criteria or more screening procedures for qualification, recruitment will require more time. Therefore, it's important to find a partner that provides a realistic, trust-based approach to recruitment rather than one that promises to quickly recruit every participant.

Inquire about the database
When rapid study startup is critical, a robust database provides an immediate starting point for recruitment. A large database demonstrates that the CRO has access to an adequate population of volunteers who understand clinical research and are amenable to participating. Furthermore, consistently recruiting and performing multiple trials keeps the volunteer database active.

Consider the location
Whether your trial must be conducted at a single site or multiple sites, you may want to consider the location of the sites available and their advantages and disadvantages. For example, facilities in larger cities tend to recruit from ethnically diverse, large populations that have better access to public transportation options. The longer the facility has been in existence, the more established relationships it will have with the local community and population.

Know what questions to ask
To determine how the CRO will prioritize your study, ask whether it is recruiting for multiple studies of the same kind concurrently. If so, your study would compete with others for the same volunteers and consequently have access to a smaller pool of potential participants, which could delay your recruitment completion. Ask about recruitment and screening timelines, because extended timelines could indicate difficulty recruiting that population. Determine if full trial cohorts can be enrolled at one time or if there is a need to divide them into sub-cohorts for admission, which could be another indicator that the site has difficulty enrolling a specific population.

Employ best practices regarding patient safety
If you have concerns about volunteers participating in overlapping studies, work with a partner who uses a registry that tracks volunteers and their participation in trials, including the date of the last dose of a study drug. This information will help establish a sufficient wash-out period, during which the participant receives no active medication. Such registries are confidential and established through fingerprinting, and they enhance patient safety as well as facilitate data integrity.

Find an integrated solution
When you need volunteers for your study, look beyond the CRO's ability to recruit large cohorts of volunteers; examine its track record of complete study delivery, including the expertise of its medical directors and project management capabilities. The right partner can also provide

guidance on protocol development and study design to maximize your clinical data output, and rapidly deliver data and insights quickly to move you to the next milestone.

Quotient Sciences
When you are looking for a partner who is dedicated to Phase I trials and early development, rely on Quotient Sciences. With a proven track record that spans more than 30 years, Quotient Sciences offers numerous resources to drive the success of your program:

- Over 1,300 Phase I studies completed
- 245 beds globally
- Industry-leading Phase I medical directors
- Ability to rapidly recruit large cohorts of volunteers
- 99 percent of studies start on time
- 98 percent enroll with full cohorts

About Quotient Sciences
Quotient Sciences, a global pharmaceutical development, clinical pharmacology, and clinical and commercial manufacturing organization, delivers innovative, customized solutions for pharmaceutical and biotech customers through both individual and integrated services. Its Translational Pharmaceutics® platform integrates formulation development, real-time adaptive GMP manufacturing and clinical research for the continuous improvement of drug development programs, and is proven to accelerate timelines and reduce cost. For more information, visit quotientsciences.com.

Author
Celina Alvarez, Executive Director of Project Management and Client Services, Quotient Sciences (CAlvarez@quotientsciences.com)

References

1. Howes M. Why We Need More Older Patients in Clinical Trials. *CenterWatch*, March 30, 2015.
2. Shenoy P, Harugeri A. Elderly Patients' Participation in Clinical Trials. *Perspectives in Clinical Research*, October-December 2015, 6(4):184–9.
3. *Applied Clinical Trials* Editors, Ethnobridging to Accelerate Global Drug Development, *Applied Clinical Trials*, October 16, 2013.

Innovations in Patient-Centric Care Address Common Patient Recruitment Challenges

SPECIAL ADVERTISING SUPPLEMENT

Chad Moore, MBA, President, Elligo Health Research

Overcoming patient recruitment challenges is one of the most complex and competitive investments for today's drug developers. Despite using various recruitment tools and technologies and spending heavily on patient outreach, there continues to be a shortage of study-participating patients. In fact, as many as 86 percent of trials do not reach their enrollment goals within their targeted timeline (Huang, et al. 2018) (Christel 2015). Missed last-patient-in deadlines are not only costly — resulting in up to $8 million in lost revenues each day (ePatientFinder 2016) — they are generally unsuccessful and often result in lengthened, suspended or terminated studies.

When more patients are needed to fill a trial, the industry typically uses traditional recruitment methods. Generally, these approaches target patients and caregivers through geofenced advertising online, or locally on billboards, radio and television and in the newspaper. Although these tactics can reach a wide audience, recruiting in this manner is limited, expensive and largely inefficient. Study sponsors often experience delays because large numbers of responding patients do not qualify for study participation after they are evaluated against trial inclusion and exclusion criteria.

Alternatively, study sponsors have seen some success with direct-to-patient outreach. Several methods to access patient pools exist, including social media, newsletters, blogs and advocacy through physician investigators at known central research sites. But even this more-targeted style of patient recruitment has its drawbacks: Patients, in most cases, must participate in a study at a research facility and under the care of a medical professional who is unfamiliar to them. This often requires lengthy travel, and the patient may endure additional costs to attend appointments and receive treatment that causes them to reconsider joining or perhaps to drop out of a study.

Today, numerous companies are working on new approaches that address the most common downfalls to these outdated recruitment methods. Through these efforts, we are learning that the closer we can work with protocol-eligible patients, the better recruitment becomes. The most successful approaches are evolving traditional service offerings and patient outreach tactics to make them more patient-centric. The outcome of this approach is accelerated study timelines and improved trial quality due to quality patient recruitment and retention.

Innovation plus service to reach patients

According to Tufts Center for the Study of Drug Development, patient-centric initiatives improve trial feasibility, enhance patient convenience, improve treatment relevance and create higher ownership and participation among physicians and their patients (Getz 2015). To be successful, it won't be enough to use technology to identify patients: Interaction with physicians and patients is also essential to make participation more convenient and comfortable.

To understand how the industry can better reach eligible patients, we look at some of the technologies and services that companies are implementing and how innovations — combined with the service necessary to reach patients and physicians — can make a difference.

Maintaining the physician-patient relationship

Research shows that patients prefer to receive clinical research information from their primary or specialty care physician (The Center for Information & Study on Clincal Research Participation 2013). Study sponsors and CROs are recognizing this and have begun improving patient enrollment and retention by taking research directly to patients and their health care provider. By using electronic health record information, providers can identify patients under their care that meet a specific trial protocol. In some cases, these health care providers are partnering with integrated research organizations to deliver a comprehensive suite of services and technologies that allow physicians and their patients to participate in a more convenient manner.

Improving trial feasibility

One of the core reasons sponsors miss recruitment deadlines is because they rely on estimates for the number of patients that will be enrolled at a research site. In most cases, these estimates are simply guesses and not supported by data. Some companies are enabling sponsors to better gauge enrollment timelines, estimate budgets and pinpoint the best geographies for their studies using datasets to run protocol simulations and assess feasibility. Other companies are deploying real-time analytics and predictive technologies with good results, allowing sponsors to avoid unproductive sites.

Enhancing patient convenience

Keeping enrolled patients engaged for the full length of a trial can be just as challenging as recruiting them. To combat this, trial sponsors are beginning to incorporate new technologies — like Bluetooth devices and digitally based studies — to gather data. These tactics often make participation easier for patients and keep them informed and engaged; some studies using electronic devices even make it possible for patients to get real-time information about their participation and health.

Patients need a voice

Patient recruitment begins with identifying qualified patients, but success lies in our ability to educate them on the benefits of clinical trials, remove barriers to participation and engage them

throughout the duration of the trial. The key is finding opportunities to give patients a voice. The most successful companies will not only increase awareness of research opportunities among patients, but will allow them to participate closer to home and under the care of their own physician. With this approach, we will find success in filling clinical trials and see improvement in patient compliance and retention as well.

Chad Moore is president and co-founder of Elligo Health Research which offers the only platform that brings clinical research direct to clinical health care. Since Elligo's inception, Moore has helped concept and build the approach that is innovating and diversifying clinical trial participation.

References

Applied Clinical Trials. 2015. New Approaches to Speeding Up Clinical Trials – What Works and What Doesn't. May 27.

ePatientFinder. 2016. "epatientfinder.com." *ePatientFinder*. Accessed July 18, 2018.

Getz K. 2015. *Clinical Trials Transformation Initiative*. January. Accessed July 17, 2018.

Huang GD, Bull J, McKee KJ, Mahon E, Harper B, Jamie RN. 2018. "Clinical trials recruitment planning: A proposed framework from the Clinical Trials Transformation Initiative." *Contemporary Clinical Trials* 66: 74-79.

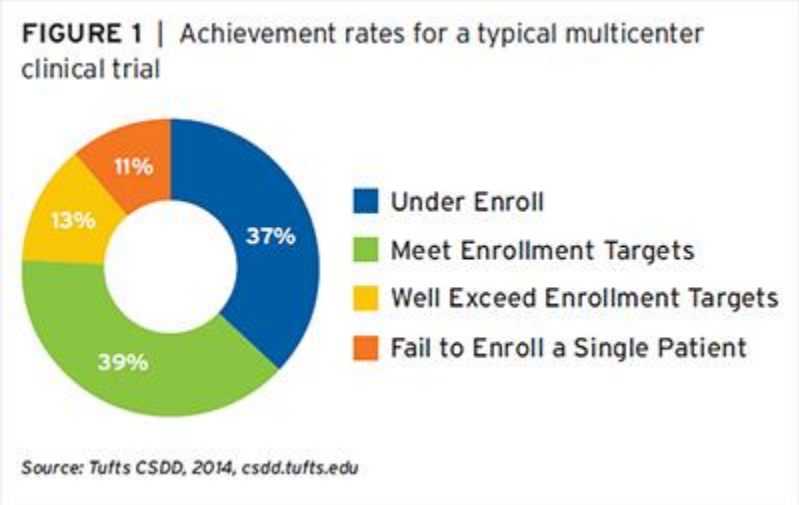
Research as Care

SPECIAL ADVERTISING SUPPLEMENT

Kurt Mussina, MBA, vice president and general manager at Frenova Renal Research

Three Ways to Blast Through the Patient Recruitment Bottleneck

Speed is key in bringing new drugs to patients. Speed in clearing regulatory hurdles, gearing up to product launch, gaining market share—a setback at any point in a drug's journey deprives patients of novel treatment, inflates costs and truncates patent protection. In short, delays diminish revenue: A 2017 report by Nature Reviews Drug Discovery indicated that each additional month in a typical Phase III trial added a median expense of $671,000 to developmental costs. (1) Eliminating traditional clinical trial bottlenecks can dramatically accelerate the pace of innovation and preclude undesirable inefficiencies.



Patient recruitment is notorious for causing study delays and failures. A 2014 study by the Tufts Center for the Study of Drug Development (Tufts CSDD) concluded that 48 percent of clinical research sites fail to achieve patient enrollment targets, including 11 percent that fail to enroll a single patient (Figure 1). (2)

Fortunately, changing the approach to finding, enrolling and keeping study patients can shorten timelines, improve data quality and heighten a study's odds for success. Identifying patients by searching comprehensive databases is more efficient than searching databases with limited reach. Designing the study protocol with patients and investigators in mind will ease recruitment,

improve protocol adherence and diminish dropout. And finally, enlisting trusted clinical caregivers to ask patients to participate is far more likely to elicit a "yes".

Access bigger data to find patients more efficiently

The search for study patients is always time-consuming — and hit or miss. The typical procedure is to search through electronic health records — or, slower yet, review individual records — to find patients with relevant diagnoses, select for inclusions and screen out exclusions. These low-yield, shotgun approaches are usually performed one site at a time. When the disease in question is uncommon or combinations of diseases are sought, this tactic is even less productive.

Greater results with less effort can be achieved using a larger, specialized database. Finding an organization focused on the specific patients you need and tapping into that group's system offers numerous advantages, including higher productivity. Finding a subgroup of patients with concomitant conditions is also much easier.

Moreover, these specialized data sets may provide valuable information unavailable elsewhere. For example, Frenova specializes in renal studies and leverages the data assets of our parent company, Fresenius Medical Care North America, to help inform protocol design and facilitate recruitment for renal-related studies.

Design patient-centric protocols for easier acceptance and adherence

Different kinds of patients — and their caregivers — have different needs. A family member caring for a spouse or parent on in-center hemodialysis is dealing with a challenging schedule. An elderly patient with severe cardiovascular disease and little support may have transportation limitations. These considerations are obvious, but many others are not.

In designing a study protocol, keeping the patient in mind is crucial. Researchers need to ask themselves, "What complexity will my protocol bring to this patient's life? How will it affect caregivers' lives? Will this be practical in the typical investigational setting?" Front-line practitioners who are part of the ecosystem of care and who understand the patients' and clinicians' day-to-day reality will be able to pinpoint significant, but less-than-obvious, protocol weaknesses and suggest corrections.

Sometimes a seemingly minor protocol condition can make or break a study. For example, dialysis patients have a lot to contend with, especially when they start undergoing in-center hemodialysis. They often must reorganize their lives to receive dialysis treatments that are typically four hours, three times per week, making recruiting and retaining these patients difficult — at first. Once they adjust to the routine, these patients typically become easier to recruit and retain. Even so, details matter. One of our clients required patients to initial every page of the informed consent form. Of all the potential issues, this unnecessary requirement turned out to be the deal breaker: Initialing anything while on dialysis is no easy feat. In this instance, leafing through and initialing pages was the detail that turned patients away.

Consulting with people who know the patient population well enough to catch idiosyncratic problems before study startup saves time and prevents costly protocol amendments. According to the Tufts CSDD, the average cost of implementing a single protocol amendment is approximately $500,000 and adds 61 days to the timeline. (3)

Recruit trusted caregivers to help recruit patients

Patients tend to trust the health care practitioners they know well. Someone approached by a familiar face is more likely to join a study. In cases where the study coordinator is unknown to the patient the ideal way to recruit a participant is to enlist help from a caregiver who already has rapport with that patient. The research coordinator should explain the study and its benefits ahead of time to the caregiver. A patient who is approached by a known caregiver and the coordinator together is far more likely to say "yes" than if approached by a stranger.

Speed enrollment by seeking more extensive information about your patient population

Eliminating bottlenecks in clinical research can save much time and expense. Patient enrollment, which accounts for 35 to 50 percent of a trial's timeline (4), is the perfect place to start. Qualify patients faster by accessing a larger, specialized and/or more comprehensive database. Avoid costly and time-consuming changes and amendments by finding people intimately familiar with the needs and idiosyncrasies of your patient population. These specialists can help you design protocols that are patient-centric, site-centric and care environment-centric. Consulting experienced partners who can help you focus in on the patient's position within the research continuum will make your recruitment efforts much more fruitful.

About Frenova Renal Research

Frenova is the only Phase I-IV drug and device clinical development services provider dedicated exclusively to renal research. Backed by Fresenius Medical Care North America (FMCNA), the world's largest provider of dialysis services with a network of 2,400 dialysis clinics, 250 research sites and more than 450 principal investigators, Frenova is an unparalleled resource for biotech, pharmaceutical and medical device companies worldwide.

Visit www.FrenovaRenalResearch.com for more information.

References

1. Bolten BM. Fastest drug developers and their practices. *The CenterWatch Monthly* 2017 August 1;24(8).
2. Fenichel M. Site selection a continuing conundrum. *The CenterWatch Monthly* 2017 Sep;24(9).
3. Ibid.
4. Bolten. Fastest drug developers.