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In This Issue

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Decentralization, Site-Enabling Technology and AI in Industry's Sights in 2023

By James Miessler

Clinical research has seen marked upheaval in just a few short years as traditional methods were rethought and innovative changes enacted. In 2023, the industry can expect significant progress in the use of artificial intelligence (AI), decentralized and hybrid trials, and site-enabling solutions, as well as further efforts to combat ongoing recruitment and workforce challenges. *The CenterWatch Monthly* polled a variety of experts on these and other topics. Here's what they had to say.

Decentralized/Hybrid Trials

It should come as no shock that experts anticipate the decentralized trial (DCT) trend will continue. Yet the conversation has now evolved into one in which hybrid trials may play a bigger role as time goes on.

Mohammed Ali, senior vice president and GM of decentralized clinical care for Medable, believes that with nearly all major industry sponsors having DCT strategies in place and/or making moves to scale up DCTs in their portfolios, the decentralized model is poised to be successful and will in many ways create a consensus for hybrid trials. But industry isn't quite there yet and will need to keep powering ahead to maximize potential.

"To ensure momentum, we would need to keep our foot on the accelerator to realize the full promise of DCTs," Ali said. "Advances in drug development made as a result of research conducted in support of the pandemic response are not yet firmly established, and some believe there is risk that the industry is reverting to prepandemic ways of conducting trials."

Catherine Gregor, chief clinical trials officer for Florence Healthcare, anticipates industry will pump the figurative brakes on fully DCTs this year, citing frustrations for both sites and sponsors that stem from an influx of trial technology. This has led some to veer away from DCTs as the only future direction for clinical research — and Gregor feels the term itself was one of the most polarizing in 2022. Rather than fully DCT experiences, she expects well-thought-out flexibility for sites and participants to become the focus for many sponsors and sites this year.

"Sites want to be able to strategically blend telehealth with in-person visits to meet the needs of their patients and providers. At the end of the day, research sites want to ensure that all of their trials are compliant and provide excellent care to patients," she said. "Fortunately, DCTs can make this a reality by moving away from fully virtual trials and instead combining technology and home

see **2023 Predictions** on page 6

CRA Shortage Persists, Innovative Hiring, Training Solutions Needed

By James Miessler

Industry stakeholders are pessimistic about the state of the CRA workforce and don't believe progress has been made in combatting shortages, underscoring the need for innovation in how CRAs are trained and evaluated, according to a recent survey.

Pharma, biotech and CRO executives responding to the recent Tufts' Center for the Study of Drug Development (CSDD) survey were almost evenly split when asked if the staffing shortage was worse or the same as in previous years, according to Mary Jo Lamberti, lead study author and director of sponsored research for CSDD.

"Our survey showed that an overwhelming majority of respondents indicated that there is a shortage of CRAs in the industry. Not one respondent felt it was getting better," Lamberti told *The CenterWatch Monthly*. "In fact, 43 percent noted that the shortage was getting worse."

The good news, according to the study published in *Applied Clinical Trials*, is that many organizations are moving away from the requirement that new CRAs have two years of clinical trial experience and toward more novel methods of training

see **CRA Shortage** on page 8

Regulatory Update

Industry Shares Concerns on Proposed Informed Consent Requirements, Single IRB Reviews

The FDA's two proposed rules on human subject protections drew dozens of comments as 2022 came to a close, with some voicing concerns about additional informed consent requirements and suggesting FDA think deeper about single IRB reviews for cooperative research.

Participant protections and informed consent

The proposed rule on the protection of participants/IRBs would remove the need for continuing reviews of trials only analyzing data, unless IRBs determine otherwise, in addition to revising continuing review recordkeeping requirements and updating informed consent requirements.

A number of stakeholders, including the Pharmaceutical Research and Manufacturers of America (PhRMA), the Association of American Medical Colleges (AAMC), the Association of Clinical Research Organizations (ACRO), and Public Responsibility in Medicine and Research (PRIM&R), have concerns about the first rule's informed consent requirements.

According to their comments, PRIM&R, ACRO and AAMC believe that requiring the disclosure of how participant information/biospecimens may be used in future research during informed consent is unrealistic. In its comments, PRIM&R said that, as is, the rule's language does not offer enough guidance for drafting adequate consent forms — but "more importantly, the provision ignores the basic fact that researchers may not know, in advance, how data generated by their study will be used in the future."

PhRMA and AAMC also commented on the proposal to include key information at the beginning of informed consent that would be most likely to help patients/patient representatives decide whether they want to participate in a trial. While PhRMA strongly supports the requirement, it urged for clarification on what is considered key information, as it could cause "considerable disagreement amongst sponsors, investigators, CROs and IRBs." It also pointed out that it would likely take industry some time to update established informed consent processes to meet the requirement.

The trade group suggests FDA consider using the most important aspects of the five-factor approach outlined in the revised Common Rule's preamble instead, which it believes would satisfy the proposed key information requirement.

AAMC added that while it recognizes the benefits of imparting such information, "the regulations' sole emphasis on the format and structure of a document undermines HHS' important perspective that 'informed consent is a process, not just a form.'"

Waivers in cooperative research

The second proposed rule would require U.S. institutions participating in FDA-regulated cooperative research to use single IRBs for all domestic trials, with exceptions, and enact new recordkeeping requirements for trials using outside IRBs (CenterWatch, Oct. 3, 2022).

PhRMA also recommends that, instead of a list of exceptions to the second proposed rule's single IRB requirement, the agency use waivers in situations where a cooperative research sponsor feels single IRB review is not appropriate. The group believes the proposal's current approach is overbroad and has implementation challenges.

"A narrowly tailored waiver process, which is already authorized under FDA's current regulations, would bring greater internal consistency to IRB review of FDA-regulated cooperative research and greater harmonization with the revised Common Rule and NIH's single IRB review frameworks," PhRMA commented.

On the single IRB requirement, AAMC proposes that FDA take time to fully understand the costs, benefits and burdens surrounding single IRB reviews, suggesting a two-year implementation period to see if more guidance, exceptions or flexibilities are needed.

Read the comments on the proposed rule on human subject protections and IRBs here: https://bit.ly/3Gn1wXg.

Read the comments on the proposed rule on IRB review and cooperative research here: https://bit.ly/3CsywvS.

ICH Drafts New Guideline on Bioequivalence Testing for Solid Oral Drugs

The International Council for Harmonization (ICH) has released a first draft of a new guideline that offers parameters for bioequivalence (BE) studies of immediate-release solid oral drugs, including considerations for selecting study participants.

The 27-page document, M13A, describes the scientific and technical aspects of study design and data analysis that should be used to support BE assessments during both development and postapproval trials of oral immediate-release dosage forms. The draft is the first in a series of three guidelines on the topic that the ICH plans to develop over the next two to three years.

M13A advises that participants in BE studies should be "at least 18 years of age and preferably have a Body Mass Index

see **Regulatory Update** on page 3

Regulatory Update

continued from page 2

between 18.5 and 30.0 kg." It also stipulates that the "risk to women of childbearing potential should be considered, and the investigators should ensure that female participants are not pregnant or lactating during the BE study and the follow-up."

If the active substance under investigation has harmful side effects deemed unacceptable for healthy participants, the study may instead be conducted "in a targeted patient population under suitable precautions and supervision," the draft guideline says.

In addition, the ICH calls for a randomized, single-dose, two-period, two-sequence crossover study design when comparing two formulations, "as single-dose studies provide the most sensitive conditions to detect differences in the rate and extent of absorption."

However, if safety, ethical or tolerability reasons demand, a multiple-dose study may be conducted in healthy patients and alternative study designs are acceptable if scientifically justified, the ICH says.

The number of participants under evaluation in a pivotal BE study should be no fewer than 12 for a crossover study design or 12 per treatment group in a parallel design, the draft guideline says.

ICH member nations now will review and discuss the draft before the organization can vote on a final guideline, most likely in mid-2024.

Read the ICH draft guideline here: https://bit.ly/3VM2amV.

FDA Draft Guidance Adopts ICH M11 Guideline on Standardized Protocols

The FDA has issued a draft version of the International Council for Harmonization's (ICH) M11 guideline, which provides sponsors with a standardized electronic protocol template, for public comment before publishing it as an officially implemented FDA final guidance.

The guideline covers the format, content and sharing of trial protocols, aiming to enable consistent, efficient exchange of protocol information between sponsors, sites, regulators, IRBs, ethics committees and other stakeholders.

It is based on five principles:

- Building common core content;
- Serving stakeholder needs;
- Defining content that will be electronically exchanged;
- Designing for content reuse; and
- Maintaining flexibility.

The template is designed to help sponsors and sponsor-investigators create protocols that are "complete, free from ambiguity, well-organized and aligned with quality-by-design principles" laid out in other ICH guidelines, M11 reads. The guideline also includes a lengthy technical specification document that recommends details to include for protocol components.

Comments on the draft guidance are due by Feb. 21.

Access the M11 draft guideline here: https://bit.ly/3C7QhRa.

Access the M11 template here: https://bit.ly/3Vw2iqu.

Access the M11 technical specifications here: https://bit.ly/3G3brkD.

EU Paper Tasks Sponsors, Investigators with Oversight of Decentralized Trial Data

In trials using decentralized elements, sponsors and investigators have ultimate responsibility for ensuring the integrity of the data generated, says a draft EU guideline, placing additional oversight duties on their plates.

The release of the paper by the European Medicines Agency (EMA), European Commission and Heads of Medicines Agencies comes at a time when researchers have expressed concern about regulatory barriers to decentralized trials (DCT) (CenterWatch, Dec. 12, 2022).

"Introducing decentralized elements should be considered as an extension of the … site with the inclusion of the trial participants' home, resulting in an additional obligation of oversight for investigators and sponsors," the draft says.

"The protocol should reflect that the sponsor and the investigator are in full control of their respective areas of responsibilities at all times, e.g., with respect to the data processing, the communication flow and, ultimately, the rights, safety, dignity and well-being of the trial participants and reliability of the trial data," the paper reads.

For example, sponsors and investigators should ensure the assignment of activities to different parties is well defined whenever a DCT methodology is introduced. Clearly document which tasks are done when, by whom and in which setting, such as at the trial site or the patients' homes, as well as how the required oversight by the sponsor or investigator will be achieved. An overview of the workflow for these tasks should be laid out generally in the protocol and in greater detail in a protocol-related document, the guidance says.

In addition, trial-specific activities shopped out to a service provider should be specified in a written agreement between the responsible party (as directed in ICH E6) and the provider.

When a sponsor chooses a provider and the investigator is not involved in the agreement, the contract between the sponsor and investigator should clearly document that agreement between the sponsor and service provider when it relates to tasks under the investigator's responsibility, the guidance says. By doing this, the investigator can agree or disagree

see **Regulatory Update** on page 4

Regulatory Update

continued from page 3

to the use of service providers for medical care-related trial tasks.

The guidance also offers the EMA's perspective on informed consent in DCTs, the delivery and administration of investigational products at home, the conduct of trial-related procedures at home, data collection and management, and trial monitoring.

Read the full draft guidance here: https://bit.ly/3hDQLau.

FDA Issues Updated Guidance on Developing Pulmonary Tuberculosis Drugs

The FDA says a single, well-controlled trial may be used to support a drug candidate for treatment of pulmonary tuberculosis (TB) if additional confirmatory evidence is available, in a revised draft guidance.

The 23-page document, which replaces a November 2013 draft, includes detailed recommendations for nonclinical models, early phase studies and trial design considerations, including how to demonstrate efficacy using superiority or noninferiority trial designs.

For demonstrating efficacy, the agency suggests that a "single adequate and well-controlled trial in subjects with pulmonary TB," supported by other confirmatory evidence, such as evidence of antimycobacterial activity from nonclinical data or phase 2 trials, "may provide evidence of effectiveness when the single trial demonstrates a clinically meaningful and statistically robust treatment effect."

The revised draft also includes additional information on the inclusion of children in studies, safety considerations and labeling. The draft does not deal with drug development for latent TB infection or for extrapulmonary TB.

The FDA noted that treatment of TB includes more than one drug in a treatment regimen and that sponsors may be developing more than one investigational drug as part of a new combination regimen, adding that they should consult with the FDA early during development of their plans to develop TB drugs as part of a combination regimen.

Sponsors should also assess potential drug-drug interactions that may occur during coadministration with other antimycobacterial drugs, such as antiretrovirals, because many TB patients have comorbidities and receive medications for those conditions.

The deadline for comment on the draft is Feb. 13.

Read the FDA draft guidance here: https://bit.ly/3huXSSD.

FDA Proposes More Detailed Annual Reporting for INDs

The FDA has issued two proposed rules on investigational new drug applications (IND) that would require more detailed IND reports and exemptions for clinical trials for drug uses of a food, dietary supplement or cosmetic product.

Under the proposed rule on annual reporting requirements, sponsors would be required to provide the agency with a yearly FDA development safety update report (DSUR) that follows the International Council for Harmonization's (ICH) E2F DSUR guidelines.

The provision would make the yearly update required of sponsors more detailed and comprehensive than the IND annual report currently mandated by FDA regulations. Among a number of elements, the DSUR includes an overall safety analysis and a summary of cumulative safety information.

The rule is being put forward to address the growing complexity of trials. In the agency's view, requiring a DSUR that assesses risk at a deeper level than the current annual report will help the agency and sponsors identify and manage potential risks, cut down the amount of unnecessary risks trial participants are exposed to and improve the FDA's assessment of trials conducted outside the U.S.

"Because FDA intends that the DSUR be consistent with the format and content of submission of the DSUR supported by ICH, the annual reporting process for sponsors would be more efficient by supporting one format for submission to FDA and multiple regulatory authorities in the European Union (EU) and other countries and regions," the proposed rule reads.

The second proposed rule would exempt certain trials of legally marketed foods for human consumption (including conventional food and dietary supplements) and cosmetics from requiring an IND when the product is being studied for use as a drug. This would apply to trials that aren't meant to support a drug development plan or labeling change and trials that do not present significant risks to participants, among other factors.

The proposed provisions "are intended to reduce the regulatory burden of conducting such studies while retaining protections for human subjects," the agency said.

Should the proposed rule be finalized, sponsors should be aware that the exempted trials must comply with other regulations meant to protect the rights and safety of participants, including informed consent and IRB review requirements, the agency said.

The comment deadline on the proposed rules is March 9.

Read the proposed rule on DSURs here: https://bit.ly/3Fcth4h.

Read the proposed rule on IND exemptions here: https://bit.ly/3W1p6iq.

see **Regulatory Update** on page 5

Regulatory Update

continued from page 4

EMA Plans New Guidance in Response to Increased Use of Platform Trials

The European Medicines Agency (EMA) is planning to draft new guidance on the planning, operational and reporting challenges inherent to platform trials.

The EMA believes that a "consolidated position" is necessary as industry uses the platform design more and more. Specifically, the agency has begun discussing a guidance on multiplicity and adaptive design that will serve to complement its existing platform trial guidances, not replace or revise them.

Through this guidance, the EMA says it will:

- Clarify terminology and introduce key concepts;
- Describe key methodological topics unique to platform trials and important design features to help guide trial planning and protocol development; and
- Outline the Committee for Medicinal Products for Human Use's position on the increased complexity and uncertainty in decision-making related to platform trials.

The agency said it intends to release a draft guidance in March 2024 and publish the final guidance in December 2024.

Read the EMA's concept paper here: https://bit.ly/3i5EAmP.

FDA Recommends Umbrella Trials for Early Study of Multiple Cell/Gene Therapies

Multiple versions of a cell or gene therapy may be studied under a certain type of umbrella trial in which the products being studied are for a single disease, the FDA says in a new final guidance.

Umbrella trials can make the development of these products more flexible and efficient, the guidance says, by evaluating multiple versions at the same time and helping narrow the list of potential candidates.

"Comparisons can be facilitated by randomization between the study arms, if feasible," the FDA advises. "Additionally, this trial design may facilitate sharing of the control group, potentially facilitating investigator participation and subject enrollment, and may simplify study management relative to conducting a separate clinical trial for each product version."

But because the product versions being studied will significantly differ from each other, the agency advises that sponsors submit each candidate in separate investigational new drug applications (IND) that cross-reference each other.

The guidance provides details on how to submit information for these multiple INDs and file updates as the trial progresses, acknowledging that the structure and organization of multiple INDs for a single umbrella trial can be confusing. It explains how to add arms to the trial, submit protocol revisions and chemistry, manufacturing and controls (CMC) and pharmacology/toxicology information, and respond to clinical holds. It also covers IND safety reporting, and completion of the trial and its arms.

The guidance also includes an appendix containing multiple examples of different versions of cell and gene therapies that could be combined in umbrella trials and those that could not.

Read the full final guidance here: https://bit.ly/3EhNSEP.

2023 Predictions

continued from page 1

care with site visits, leading to a more convenient, patient-centric experience."

In the experience of Andy Lee, Merck's senior vice president of global clinical trial operations, DCT methodologies currently differ in their cost effectiveness and full decentralization is confined to certain types of protocols. Hybrid trials are the reality but it will take time for industry to make progress on scaling these "newer ways of working" and thereby lowering their costs, he says. It will be important to address protocol complexity, which has risen significantly over the years.

"Protocol complexity does not lend itself to decentralization, so there's this big drive now to simplify protocols. To enable them to operate more smoothly, we have to reduce complexity," he said.

With DCTs almost certainly here to stay regardless of what path they take this year, Ali believes industry will be active in seeking and obtaining clarification about their conduct in 2023. Topics are likely to include:

- Clarification of DCT regulatory guidance, particularly on inconsistencies across multiple guidance documents;
- Questions about accountability for study teams conducting DCTs, especially for principal investigators and when third-party vendors are involved;
- Change management mapping that will evolve beyond technological access to include people and processes; and
- Updating obsolete budget models to reflect today's trial implementation tasks.

Site-Enabling Solutions

In 2023, Gregor believes the tech spotlight will be focused on site enablement technologies, systems that make sites' lives easier by enabling real-time data creation/exchange with less effort. This will make the arduous task of recruitment an easier endeavor, she contends. At this stage, industry has realized that sites will continue to play a critical part in paving pathways to patients, especially for underrepresented and hard-to-access patients, and as a result, sites will need technology that allows them to focus their time and effort more on patient care, she says.

Solutions like electronic investigator site files (eISF), eSource, eConsent and electronic patient reported outcomes (ePRO) will help do away with repetitive, wearisome activities at the site level, such as inputting data into multiple portals or copying documents, by enabling the seamless transition of documents and data from sites to sponsors, Gregor believes. These technologies are growing rapidly in adoption, she notes, including eISF solutions, which Florence anticipates a large majority of sponsors will plan to implement at sites this year.

"Sites and sponsors are in desperate need of technology that links them to one another and facilitates collaboration rather than fragmented data flow. Data flow … will become more seamless as sites and sponsors begin to look for software with open APIs," she predicts. "Sites are also getting louder in their assertion that sites should have the ability to establish and maintain their own study workflows instead of being forced into predefined ones."

This sort of unifying technology will have a huge impact across clinical, regulatory, quality and safety and allow for greater efficiency across these functions, says Jim Reilly, vice president of development cloud strategy for Veeva Systems.

The end result will be a more streamlined drug development process that delivers higher quality data and fosters greater collaboration amongst stakeholders, he believes.

"Connected data across the development lifecycle will enable different functions to coordinate decisions and a common technology framework will eliminate duplicate data capture and inefficient processes," he says. "Automated workflows, data reuse, common training and a simpler technology experience will help companies to adapt quickly to changing market conditions and deliver products more efficiently to the market."

Artificial Intelligence

AI will also see greater focus and progress in key areas of clinical research in 2023, says Neil Sahota, lead AI advisor to the United Nations. For instance, he believes that AI will lead a great resurgence of investigations into discarded drug candidates and, in fact, there are already major investments being made to utilize AI for these purposes.

In the past half decade, there have been a multitude of reasons for drugs being abandoned without rigorous testing, he says, including inconclusive simulations, lackluster trial-patient matching, hastily discounted protein bindings, and others. After examining this, it's been estimated that 40 to 60 percent of drugs may have been unrightfully tossed aside, according to Sahota. This year, significant advancements will be made in using AI to reexamine discarded drugs, he anticipates.

Sponsors will also look to wield AI solutions that bolster their clinical teams with machine capabilities this year. Sahota believes that doing this can cut current clinical research time by about one third. Similarly, he predicts an "explosion of growth" in real-world evidence and data (RWE/RWD) and the continued use of AI systems to make use of that data effectively.

see **2023 Predictions** on page 7

2023 Predictions

continued from page 6

"When AI has substantial access to RWE/RWD, we've seen high quality results. In addition, we're seeing a rising need for synthetic data because there is not enough real data available, a frequent challenge in healthcare," he said. "With enough RWD, we'll see more clinical organizations turn to AI to help generate this synthetic data for their research purposes."

Overall, 2023 will see "acceleration into breaking" when it comes to AI's application in clinical research, Sahota predicts, with industry nearing an inflection point of real solutions ready for the big leagues that will, at least initially, be tempered by skepticism in the technology.

The greatest hurdle to AI's progress this year? Sahota says it will actually be data, or the lack thereof. For many AI systems, there simply won't be enough access to data to train them adequately, and many of the organizations that do have the data needed are disincentivized from sharing them lest they give their competitors a hand.

"Data is the new oil, and [many healthcare companies] don't want to give their data away, even if they're not using it," he says. "This is the biggest barrier this year and beyond, and it is the biggest barrier to advancing medicine in general."

Patient Recruitment

Although site-centric technology solutions may help make recruitment an easier task, Lee predicts that recruitment "is going to be a beast" this year, citing greater competition, fewer available sites and geopolitical unrest, as well as a greater focus on personalized therapies, including in oncology. For trials evaluating these types of therapies, large populations, such as lung cancer patients, need to be broken down into small subtypes almost like rare diseases, making enrollment that much harder, he notes.

In terms of the U.S. landscape, the largest academic centers run hundreds of trials annually and many trials will be competing for patients, meaning recruitment numbers are likely to be very low at these institutions. "When they identify a suitable patient, they have to allocate it to one of several like protocols from different sponsors, so you only get a few for most of your trials from [them]," he said.

Industry has begun addressing this issue by helping to increase capacity at some of those institutions and, critically, by moving trials into underrepresented areas that have the patients but lack the clinical trial infrastructure and staff force. Sponsors will continue to build research capabilities and trust in these communities in 2023, Lee expects, an effort that he feels is imperative to the success of the clinical research industry.

In light of the recruitment hurdles sites and sponsors are likely to face in 2023, Gregor believes they'll be looking for collaborative technology solutions to support the identification, screening and recruitment of patients for trials.

Staffing Crisis

In 2023, Susan Landis, executive director of the Association of Clinical Research Professionals (ACRP), anticipates an unprecedented collaborative effort between industry stakeholders to fix the clinical research staffing shortage, a serious issue that she says has been compounding for more than 15 years and has finally reached a boiling point.

This year will see the use of new and innovative strategies for recruiting, training and retaining a diverse research workforce, she believes, driven by stakeholders and consortia committed to solving the crisis.

"The current landscape is defined by three core challenges: unprecedented staff turnover, a major shortfall in applicants and a lack of diversity among site staff," she says. "Industry stakeholders who desire transformation of clinical research will recognize and verbalize [that] change in the way trials are conducted will only occur with a recognized and well-rewarded workforce."

Though there are certainly big challenges ahead for this year — especially in recruitment and staffing — industry insiders agree 2023 is likely to see significant innovation and collaboration among stakeholders working to break down barriers and move clinical research forward.

CRA Shortage

continued from page 1

and assessing CRAs as well as implementing solutions to mitigate the impact of turnovers and shortages.

A number of processes are currently exacerbating the issue, says David Vulcano, honorary president of the Society for Clinical Research Sites, including the deployment of CRAs that aren't adequately trained, significant turnover and the impact of CRA turnover on sites. CSDD looked at these areas and more.

Experience Requirements

Of 34 respondents, 44 percent (15 companies) said they require less than two years' experience of CRA candidates. One-third (12 companies) said they require at least two years' experience, while 15 percent (five companies) asked for more than two years of experience. Two respondents had "other" experience requirements.

But the survey also shows that industry doesn't appear chained to these conditions. A large majority (69 percent) said that they have hired CRAs with less than two years' experience.

Using years of experience as the key factor behind promotions and not performance was a topic of discussion for a CSDD-convened roundtable of nearly three dozen executives, with attendees considering replacing years of experience as an overall performance metric. And while the survey found 61 percent of respondents do not currently look at CRA performance by experience or job level — and just two respondents did — 30 percent said they plan to use it in the future.

"A commitment to industry training has been acknowledged as a critical element, as well as making accommodations for those who are new to the industry."

—Mary Jo Lamberti, director of sponsored research for CSDD

Some companies are also considering using key performance indicators (KPI), such as site satisfaction, soft skill evaluations and assessments of roles with similar workloads, to gauge CRA performance, although they're still in the early stages, Lamberti said. In the future, it would be useful to conduct research benchmarking these approaches, she noted.

Other approaches, including outreach to elevate awareness of the profession, gathering measures of experience and transferable skills, expanding competency-based training and innovating on recruitment and retention strategies, are all being considered as well.

The roundtable group also agreed that certain therapeutic areas and trial phases can be more taxing for entry-level CRAs, such as rare disease, gene therapy and oncology trials, and larger phase 3 trials.

Training

CSDD's study also shed valuable light on CRA training strategies, what approaches are currently viewed as the most impactful and which strategies are being considered for the future. Overall, roundtable participants all agreed that focusing on improving the training of CRAs will be critical moving forward.

see **CRA Shortage** on page 9

CRA Shortage

continued from page 8

"A commitment to industry training has been acknowledged as a critical element, as well as making accommodations for those who are new to the industry," Lamberti said. "In addition, providing growth opportunities and offering varied incentives is key for senior CRAs."

Respondents chose peer support/mentoring as the most effective training approach by an overwhelming margin (84 percent), followed by 77 percent naming in-person training.

Web-based training modules and observational training were each selected by 52 percent as the most effective methodologies, followed by scenario-based training (42 percent), experiential training (39 percent) and "other" forms of training (3 percent).

Organizations are also looking ahead and considering additional approaches. One roundtable discussion, for example, speculated about using chatbots to field CRA training questions and conduct training through the use of behavioral data, while another considered greater use of protocol and training documents as supportive and training resources.

In addition, stakeholders are considering "critical mistake analysis" for training CRAs and improving their conduct. This methodology uses a high-stakes approach to training that educates CRAs on challenges they might actually run into in the real world. Another option discussed was the use of spiral design, a training strategy that begins with the simplest version of a task and progressively ramps up in complexity.

Hiring

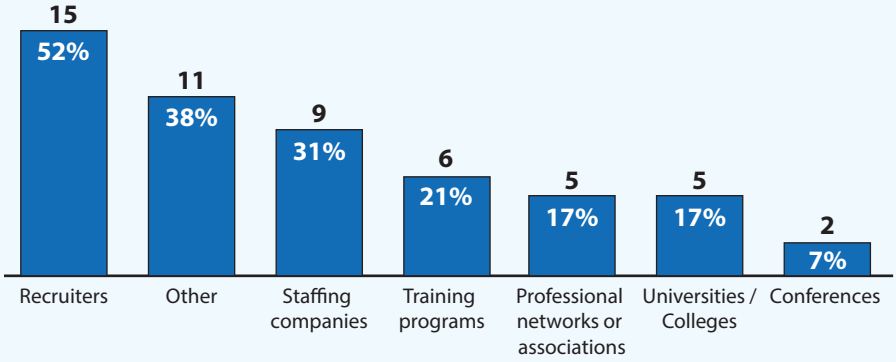
The CSDD survey also asked respondents what recruitment strategies they use, with 86 percent indicating they use recruiters. The second-most popular strategy was using websites and social media for recruitment (69 percent), followed by staffing companies (59 percent), professional networks/associations (45 percent), universities/colleges (41 percent) and "other" (28 percent). Recruiting CRAs through training programs and conferences came in at 24 and 17 percent, respectively, making them the least employed strategies.

Asked what they thought were the most effective strategies, 52 percent chose the use of recruiters. Internal staff referrals, recommendations or applications were named by 38 percent of respondents, followed by staffing companies (31 percent), training programs (21 percent), professional networks/associations and universities/colleges (both 17 percent). Conferences were named by only two participants (7 percent) as the most effective way to recruit CRAs.

One of the most noteworthy findings, Lamberti says, is that sponsors and CROs are addressing the shortage by raising awareness of clinical research as a profession, including at colleges and universities, instead of solely searching for already trained and experienced CRAs. This is being done mainly by recruiting on campuses and offering internship pathways for interested students. Similarly, mentorship and job shadowing have become retention strategies to consider.

"Academic-industry partnerships provide interns with valuable on-the-job experience before they seek a permanent position," Lamberti said. "Some strategies for CRA retention include providing peer support or mentoring and having CRAs work on-site with line managers, so some progress has been made in this area."

Effectiveness of Recruiting Strategies



Source: CSDD

Site Perspective

Roundtable attendees also discussed challenges that sites face when it comes to measuring how CRAs perform. These include challenges gathering metrics from newer CRAs to help the site achieve consistent performance, lack of CRA training/skillsets and site expectations that the CRA serve as the single contact point on inquiries despite the CRA having their hands full.

CRA turnover is also a huge issue for sites because it can bog down recruitment efforts, contribute to delays and even lead to outright termination of trials. CSDD's survey offers insight on yearly CRA turnover rates, with a majority of respondents seeing an average time of more than two years before turnover, making this attrition particularly disruptive.

Despite the problems the current CRA shortage continues to make for sites, trial participants and data quality, "the early success our industry colleagues are having with defining new onramps to the CRA role, especially the recognition of legitimate alternatives to requiring two years of experience in the industry," is very encouraging, says Vulcano.

Study Lead Opportunities

CenterWatch analyzes data in its drug intelligence database to provide advance notice of clinical trials expected to enter the next phase of clinical development soon. Contact information is provided for follow-up. **Sponsors/CROs:** to list an upcoming trial here, contact Leslie Ramsey, 703.538.7661, lramsey@wcgclinical.com.

Company name	Drug name	Indication
phase 1		
ArsenalBio	AB-1015	Platinum-resistant ovarian cancer
Asher Biotherapeutics	AB248	Locally advanced or metastatic solid tumors
BioInvent	BI-1206 subcutaneous formulation	Lymphoma and solid tumors
Biomea Fusion	BMF-219	KRAS-mutated non-small cell lung cancer, colorectal cancer and pancreatic ductal adenocarcinoma
BioNTech	BNT165b1 malaria vaccine	Malaria prevention
BioNTech	BNT163 herpes simplex virus (HSV) vaccine	Prevention of genital lesions caused by HSV-2
Cellf BIO	BioSphincter implant	Severe passive fecal incontinence
Ceruvia Lifesciences	NYPRG-101 (BOL-148)	Neurological and psychiatric disorders
Erasca	ERAS-007 plus ERAS-601	RAS/MAPK pathway-altered solid tumors
Frontera Therapeutics	FT-001	Leber congenital amaurosis-2
JS InnoPharm	JSI-1187	Solid tumors with confirmed BRAF V600E/K mutations
Nuvation Bio	NUV-868 plus olaparib and NUV-868 plus enzalutamide	Advanced solid tumors
Orano Med	212Pb-GRPR	Advanced solid tumors that express gastrin-releasing peptide receptor
ProfoundBio	PRO1184	Ovarian, endometrial, breast, non-small cell lung cancers and mesothelioma
Theriva Biologics	VCN-01	Brain tumors
Trefoil Therapeutics	TTHX1114	Corneal epithelial defects
Trevena	TRV045	Epilepsy and other CNS disorders
VYNE Therapeutics	VYN201	Vitiligo
phase 1/2		
Aprea Therapeutics	ATRN-119	Advanced solid tumors with DDR mutations
Avenge Bio	AVB-001	Relapsed refractory ovarian cancer
Bexion Pharmaceuticals	BXQ-350	Newly diagnosed metastatic colorectal carcinoma
Biomea Fusion	BMF-219	Type 2 diabetes

see **Study Lead Opportunities** on page 11

Study Lead Opportunities continued from page 10

Company name	Drug name	Indication
phase 1/2 continued		
Hemab Therapeutics	HMB-001	Glanzmann thrombasthenia
Immunis	IMM01-STEM	Muscle atrophy related to knee osteoarthritis
Immunitas Therapeutics	IMT-009	Solid tumors and hematologic malignancies
Surface Oncology	SRF114	Advanced solid tumors
phase 2a		
Sensorion	SENS-401 (arazasetron)	Cisplatin-induced ototoxicity
Soligenix	SGX302 (synthetic hypericin)	Mild-to-moderate psoriasis
Tarsus Pharmaceuticals	TP-05	Lyme disease
phase 2		
Acer Therapeutics	ACER-801 (osanetant)	To reduce hot flashes in men with prostate cancer
Acer Therapeutics	ACER-801 (osanetant)	To suppress testosterone production in men with prostate cancer
Alterity Therapeutics	ATH434	Multiple system atrophy
Biocon	Itolizumab	Ulcerative colitis
Cardiol Therapeutics	CardiolRx	Recurrent pericarditis
Compass Therapeutics	CTX-009	Metastatic colorectal cancer
Cyclo Therapeutics	Trappsol Cyclo	Alzheimer's disease
Glycomine	GLM101	Phosphomannomutase 2-congenital disorder of glycosylation
Horizon Therapeutics	Daxdilimab	Moderate-to-severe primary discoid lupus erythematosus
Imago Bioscience	Bomedemstat plus ruxolitinib	Myelofibrosis
InFlectis BioScience	IFB-088 plus riluzole	Bulbar-onset amyotrophic lateral sclerosis
KemPharm	KP1077	Idiopathic hypersomnia
Novavax	COVID-19-influenza combination and influenza stand-alone vaccines	COVID-19 and influenza
OncoC4	ONC-392 plus Keytruda	Platinum-resistant ovarian cancer
ORYZON Therapeutics	Iadademstat	Neuroendocrine carcinomas
Panbela Therapeutics	CPP-1X-T (Eflornithine tablets)	Recent onset type 1 diabetes
Shanton Pharma	SAP-001	Refractory/tophaceous gout

see **Study Lead Opportunities** on page 12

Study Lead Opportunities continued from page 11

Company name	Drug name	Indication
phase 2b		
Apex Labs	APEX-52 (psilocybin)	Depression and anxiety in adults with post-traumatic stress disorder
atai Life Sciences	RL-007	Cognitive impairment associated with schizophrenia
Palatin Technologies	Bremelanotide	Diabetic kidney disease
Plus Therapeutics	Rhenium (186Re) obisbemeda	Recurrent glioblastoma
Theriva Biologics	VCN-01 with chemotherapy	Newly diagnosed metastatic pancreatic ductal adenocarcinoma
Versanis Bio	Bimagrumab	Obesity
Wex Pharmaceuticals	Tetrodotoxin	Chemotherapy-induced neuropathic pain
phase 2/3		
Stemedica Cell Technologies	Allogeneic mesenchymal stem cells	Ischemic stroke
phase 3		
Anthos Therapeutics	Abelacimab	High-risk patients with atrial fibrillation deemed unsuitable for current anticoagulants
AriBio USA	AR1001	Early Alzheimer's disease
Biofrontera Bioscience	Ameluz and BF-RhodoLED XL	Actinic keratosis on the extremities, neck and trunk
BioXcel Therapeutics	BXCL501 (dexmedetomidine) sublingual film	Acute treatment of agitation in patients with Alzheimer's disease
BridgeBio Pharma	Encaleret	Autosomal dominant hypocalcemia type 1
Cingulate Therapeutics	CTx-1301	Attention deficit/hyperactivity disorder in adults
Exelixis	Zanzalintinib plus nivolumab	Advanced non-clear cell renal cell carcinoma
Maggie's Pearl	Epalrestat	PMM2-CDG (phosphomannomutase-2-congenital disorder of glycosylation)
NRx Pharmaceuticals	NRX-101	Severe bipolar depression with acute suicidal ideation and behavior
Ocuphire Pharma	Nyxol	Presbyopia
Viridian Therapeutics	VRDN-001	Active thyroid eye disease
Zenas BioPharma	Obexelimab	Immunoglobulin G4-related disease

FDA Actions

The following is a sampling of FDA regulatory actions taken during the previous month, compiled from CenterWatch and third-party sources, including the FDA and company press releases. For more information on FDA approvals, visit centerwatch.com/fda-approved-drugs.

Company name	Drug name	Indication	FDA action
AB Science	Masitinib	Progressive multiple sclerosis	IND approved
American CryoStem	ATCell	Long COVID/PASC	IND approved
Arugula Sciences	Signature Cord Prime (SIG001)	Knee osteoarthritis	IND approved
Azafaros	AZ-3102	GM2 gangliosidosis and Niemann-Pick disease type C	IND approved
Biocytogen Pharmaceuticals	YH008	PD-(L)1-resistant advanced solid tumors or hematological malignancies	IND approved
Cyrano Therapeutics	CYR-064	Post-viral smell loss	IND approved
Evaxion Biotech	EVX-01 plus Keytruda	Metastatic melanoma	IND approved
Exegenesis Bio	EXG102-031	Neovascular age-related macular degeneration	IND approved
Hoth Therapeutics	HT-001	Rash and skin disorders associated with epidermal growth factor receptor inhibitor therapy	IND approved
HotSpot Therapeutics	HST-1011	Advanced solid tumors relapsed or refractory to anti-PD(L)1 therapy	IND approved
IASO Biotherapeutics	CT103A (equecabtagene autoleucel)	Relapsed/refractory multiple myeloma	IND approved
Immorna	JCXH-105 RNA-based shingles vaccine	Shingles	IND approved
Immuron	Travelan	Prevention of infectious diarrhea caused by enterotoxigenic Escherichia coli	IND approved
Invectys	IVS-3001	Solid tumors	IND approved
Kala Pharmaceuticals	KPI-012	Persistent corneal epithelial defect	IND approved
Minerva Biotechnologies	huMNC2-CAR22 (MUC1*-CAR-1XX)	Metastatic breast cancer in patients with MUC1* positive tumors	IND approved
OKYO Pharma	OK-101	Dry eye disease	IND approved
Orchard Therapeutics	OTL-203	Hurler subtype of mucopolysaccharidosis type I	IND approved
ProfoundBio	PRO1160	Metastatic renal cell carcinoma, metastatic or relapsed nasopharyngeal carcinoma or advanced non-Hodgkin lymphoma	IND approved
Skye Bioscience	SBI-100 ophthalmic emulsion	Primary open-angle glaucoma or ocular hypertension	IND approved
SURGE Therapeutics	STM-416	Bladder cancer	IND approved
Tempero Bio	TMP-301	Alcohol and substance use disorders	IND approved

see **FDA Actions** on page 14

FDA Actions continued from page 13

Company name	Drug name	Indication	FDA action
TransCode Therapeutics	TTX-MC138	Advanced solid tumors	IND approved
Gradalis	Vigil (gemogenovatucel-T)	Advanced ovarian cancer	Study May Proceed letter issued
Orthogen	Orthogen Device	Knee osteoarthritis stages II-IV	IDE approved
Biogen Eisai	Leqembi (lecanemab-irmb)	Alzheimer's disease	Accelerated approval
AbbVie	Vraylar (cariprazine)	Adjunctive treatment for major depressive disorder	Approved for new indication
Radius Health	Tymlos (abaloparatide)	To increase bone density in men with osteoporosis at high risk of fracture	Approved new indication
Genentech	Actemra (tocilizumab) intravenous	COVID-19 in hospitalized adults	Approved for expanded indication
Novo Nordisk	Rybelsus (semaglutide)	First-line treatment for type 2 diabetes	Approved for expanded indication
Luye Pharma	Rykindo (risperidone) for extended-release injectable suspension	Schizophrenia and bipolar 1 disorder	Approved for new formulation
Ferring Pharmaceuticals	Adstiladrin (nadofaragene firadenovec-vncg)	High-risk Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle-invasive bladder cancer	Approved
Genentech	Lunsumio (mosunetuzumab-axgb)	Relapsed/refractory follicular lymphoma in adults	Approved
Gilead	Sunlenca (lenacapavir)	Multi-drug resistant HIV-1 infection	Approved
TG Therapeutics	Briumvi (ublituximab-xiiy)	Relapsing forms of multiple sclerosis	Approved
Abbott	Navitor, transcatheter aortic valve implantation (TAVI) system	Aortic stenosis	Approved
Vericel	NexoBrid (anacaulase-bcdb)	Eschar removal in adults with deep partial- and/or full- thickness thermal burns	Approved
Polarean Imaging	Xenoview contrast agent	Evaluation of lung ventilation in patients 12 and up	Approved

wcg CenterWatch
www.centerwatch.com

300 N. Washington St., Suite 200, Falls Church, VA 22046-3431
Phone: 866.219.3440 or 617.948.5100
Customer Service: customerservice@centerwatch.com

Editorial Director: Leslie Ramsey, 703.538.7661, lramsey@wcgclinical.com
Reporter: James Miessler, 703.538.7650, jmiessler@wcgclinical.com
Sales: Russ Titsch, 617.948.5114, russ.titsch@centerwatch.com