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March 20, 2023

Consider the Five 'W's to Understand Potential Participants

By James Miessler

Recruitment and retention plans will always be molded by the specific trial and population involved; putting careful thought into who your trial's target participant is can help bolster enrollment/retention numbers, an expert advises.

Kicking off WCG Clinical's new patient centricity webinar series, *The Participant Playbook*, Tyler Bye, director of program strategy and product development at WCG Study Acceleration, offered key insights for successfully incorporating patient-centric approaches into enrollment, recruitment and retention efforts.

Building a Participant Profile

One of the first steps to take when developing and considering new recruitment strategies and initiatives is to craft a profile of the participant the trial seeks to enroll, says Bye.

Doing this may take some deep thinking, but the concept itself is relatively simple: use the five Ws (who, what, when, where and why) to lay out the key characteristics of your trial's intended population.

Start with the "who." It isn't always just the patient; consider that some indications will have caregivers, spouses and/or family members lending a hand with someone's participation. This will be the case in pediatric trials or trials for a disabling disease, for instance, and would likely apply to trials enrolling teenagers as well.

In addition, think about how participating will impact a patient's life outside of

see **Consider the Five 'W's** on page 4 »

Perspectives from Smaller-Sized CROs: Q&A with Cheryle Evans

The clinical research industry faces a number of hurdles right now, including workforce struggles, new technologies, growing protocol complexity and enrollment challenges. But things are also on the upswing for small- and mid-sized CROS, says Cheryle Evans, senior vice president of global clinical and biometric operations for Advanced Clinical, a full-service CRO.

Evans shared her insights with *CenterWatch Weekly* ahead of her appearance this May in an Executive Fireside Chat with WCG CEO Sam Srivastava and thought leaders from other organizations at the WCG MAGI Clinical Research Conference – 2023 East in Philadelphia.

CenterWatch Weekly: *From where you stand in the CRO space, what do you think are the biggest changes taking place right now?*

Answer: There is so much positive change happening for all sizes of CROs, but particularly for small and mid-size organizations, where clients — both small and large — are seeking niche and boutique CROs that have demonstrated the ability to be agile and responsive to the new demands of conducting clinical studies post-COVID, including the pre-award process to portfolio and preferred provider alignments and models. We are working at a high intensity in all aspects of our services — from regulatory affairs to operations to biometrics — and leveraging our people and technology to deliver high quality results.

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Upcoming Events

25 APR — CONFERENCE
Effective Root Cause Analysis and CAPA Investigations for Drugs, Devices and Clinical Trials

27 APR — WEBINAR
Califf's FDA, 2023 and Beyond: *Key Developments, Insights and Analysis*

17 MAY — CONFERENCE
2023 WCG Avoca Quality Consortium Summit

21 MAY — CONFERENCE
WCG MAGI Clinical Research Conference – 2023 East

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Industry Briefs

FDA Shares Latest Thinking on Electronic Systems, Signatures and Records

Acknowledging the ever-evolving technological and clinical research landscape, the FDA has published a new draft question-and-answer guidance on using electronic systems, records and signatures in clinical trials, providing greater direction on validation, digital health technologies (DHT) and the applicability of regulatory requirements.

The guidance is a revision of 2017 draft guidance that takes industry feedback into account and provides sponsors, investigators, CROs and other stakeholders with the agency's current thinking on electronic systems in clinical research, which have grown in capacity and use. This latest direction from the FDA also expands upon previous 2003 guidance on the scope and application of electronic records and signatures.

"The capabilities of electronic systems have improved, and features such as automated date and time stamps, audit trails, and the ability to generate complete and accurate copies and to archive records are standard components of many electronic systems [now]," the guidance reads. "Understanding the evolving uses of electronic records, electronic systems, and electronic signatures in clinical investigations is important for FDA in its assessment of the authenticity, integrity, and reliability of data."

Risk-based approach to validation

The agency's latest position on risk-based approaches to validating electronic systems recommends that stakeholders consider:

- The purpose and significance of the record and criticality of the data (how the record and data will be used to support a regulatory decision and/or ensure participant safety);
- The intended use of the electronic system in the trial; and
- The nature of the system, such as whether it's a commercial off-the shelf (COTS) system or a customized system.

The guidance notes that validation is highly important for electronic systems used for data integration, data analysis, adverse event recording/processing, endpoint assessment and medical product dispensation, administration and accountability, and agency staff may ask for system validation documents during inspections.

Validation of COTS office utility software, such as word processing, PDF and spreadsheet products, should follow the organization's internal business practices and the intended use of the product(s) in the trial. These products generally don't need validation when they're used as intended, according to the guidance.

But for new electronic systems tailor-made for a trial, or existing systems that have been customized, such as an interactive response technology (IRT) or electronic case report form (eCRF) solution, the FDA stresses the importance of sponsors reviewing the vendor's standard operating procedures (SOP), the system and software development life cycle model, validation documentation, change control procedures, and change control tracking logs. Additionally, sponsors should perform user acceptance testing (UAT) and document this testing, including test criteria and results, to ensure the system meets its purpose. Alternatively, the agency believes it is acceptable to review the vendor's UAT and document this occurred/met expectations, the guidance says.

Records should be kept for all changes to a system, and changes, such as software upgrades, security and performance patches, equipment/component replacements, and new instrumentation, should be assessed and validated depending on their risk, including changes that impact operational limits or design specifications, FDA said.

DHTs and collecting data

The guidance also offers specific advice on using DHTs to collect data while remaining compliant. For example, DHTs, defined in the latest guidance as systems "that use computing platforms, connectivity, software, and/or sensors for healthcare and related uses," can be used to gather data from participants, but it's important that sponsors define where the data originated from as part of their audit trails. The guidance explains how sponsors should go about doing this.

"Each electronic data element should be associated with an authorized data originator. The data originator may be a person, a computer system, a DHT, or an electronic health record that is authorized to enter, change, or transmit data elements via a secure protocol into a durable electronic data repository, such as an electronic data capture system, a clinical investigation site database, and/or a vendor database (e.g., database of the CRO, IT service provider, DHT manufacturer)," says the guidance.

For instance, when participants manually input data into a DHT and upload the data into an electronic repository, such as when using an electronic patient-reported outcome (ePRO) application or performing a cognitive test, the trial participant should be identified as the data originator, the guidance says. In situations where another person, such as a parent, caregiver, healthcare provider or trial staff member, enters the data on behalf of the participant, the individual inputting the data should be identified as the data originator and the reason for this documented.

Read the full draft guidance here: https://bit.ly/408icdd.

SCRS Launches Collaboration to Alleviate Site Financial Burdens

The Society for Clinical Research Sites (SCRS) has kicked off the Site Payment Initiative, an endeavor that will bring sites, sponsors and CROs together to tackle financial struggles sites frequently name as pain points.

Initially, the program intends to address multiple financial challenges encountered by sites during trials, including holdback payments, delayed payment frequencies

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Industry Briefs

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and taxes on patient stipends, among others. The initiative looks to ensure that sites receive 100 percent of earned revenue, see monthly payments instead of quarterly payments, and enable participants to receive allowances untaxed.

"Many of these payment and financial challenges have unfortunately burdened sites for decades," Allyson Small, SCRS' chief operating officer, said. "A unified voice to advocate for the financial needs of sites and patients is still very much needed, and we are confident that now is the time to enact change. By working with this group of motivated sites and industry partners, we hope to enhance sustainable practices that benefit clinical research as a whole."

Stakeholders interested in taking part in the program should contact SCRS at info@myscrs.org.

Anesthesiologist Warned for IND, Informed Consent Issues in Anesthesia Trial

The FDA has issued a warning letter to a Houston, Texas-based anesthesiologist for failing to submit an investigational new drug application (IND) and obtain informed consent as required in an anesthesia trial.

The warning letter cites Maggie Jeffries, owner of Avanti Anesthesiology and a specialist in ophthalmic anesthesia, for a lack of regulatory compliance during a trial involving oral drug combinations for anesthesia that she led as sponsor-investigator. Specifically, the FDA determined that the protocol had no IND in effect despite requiring one. An IND was necessary, the agency said, because the protocol involved administering diazepam, tramadol, ondansetron and MKO Melt (midazolam, ketamine and ondansetron) to assess and compare their efficacy for anesthesia in patients having cataract surgery.

Jeffries' August 2021 response to the prior Form 483 issued contended that an IND wasn't needed for several reasons: first, that MKO Melt has been in use for years, is not an investigational drug and is often used for sedation during cataract surgery; second, that the drugs in MKO Melt are well-known and frequently used in anesthesia practice; and lastly, that the study met the criteria for IND exemption.

The FDA, however, disagreed on these points, explaining its reasoning in the warning letter.

"[The protocol] required administration of specific drugs, depending on a randomization schedule; assessment and documentation of subjects' answers to questions before discharge and the following day; and comparison of treatment arms to see how many subjects did not need extra medications during surgery," the agency said. "The fact that the drugs individually can be part of a standard of care does not render these drugs non-interventions in a study setting, as was the case here, where the protocols prespecified the drug intervention to be administered."

The protocol also failed to meet all criteria needed to be exempt from an IND, the agency determined, specifically that the investigation meets all informed consent/institutional review requirements and doesn't involve a route of administration, dosage level, use in a population or other factor that significantly increases the risks, or decreases acceptability of risks, associated with use of the trial drugs.

The trial's population — patients undergoing cataract surgery — significantly increased the risks associated with using tramadol alone and with diazepam. Despite this, safety measures, such as safety monitoring before, during and after surgery, adverse event monitoring, study stopping criteria and exclusion criteria, were not established, the FDA found.

In addition, the tramadol dosage level significantly increased the risks of its use, and the use of diazepam and tramadol together created the risk of profound sedation, respiratory depression, coma and death, as tramadol is an opioid agonist and diazepam is a benzodiazepine, the agency said.

With all this in mind, the FDA found that Jeffries also neglected to properly obtain informed consent by failing to identify experimental procedures and describe reasonably foreseeable risks to patients. According to the agency, the informed consent form read: "There are no additional risks or side effects associated with participation in the study. The risks of anesthesia are in the anesthesia consent and do not differ from what you would experience should you not participate in the study."

In addition, a laminated copy of the consent form was given to patients while they waited for surgery, with personal copies only provided upon request.

Avanti Anesthesiology did not respond to a request for comment by deadline.

Read the full warning letter here: https://bit.ly/3Ft8GcJ.

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Consider the Five 'W's

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the trial. Does the trial require long visits, multiple visits or overnight stays, for example? What obligations will the patients likely have outside of the trial, such as taking care of children or pets? Think hard about how participating in the trial could interfere with or affect participants' lives, Bye advises.

Next, think about the "where." Where does the patient need to go to participate in the trial? A number of things are worth considering here. Is the study site convenient for them (assuming they will have to travel there for on-site visits)? Remember that for some institutions, such as larger academic medical centers, patients often take hours-long trips to get to them due to their level of care and ability.

"Is a [travel time] of two hours practical for a long-term, once or twice a week visit?" he asked.

Another factor in the "where" category is a patient's place in the healthcare system. It's important to consider whether they're likely to be part of the site's healthcare system already and whether they're in or out of network, Bye says, noting that there will frequently be standard of care procedures beyond clinical research procedures billed back to insurance. Consider how this might affect individuals and make sure this is made clear to them when they're being presented with a trial opportunity.

"These conversations will be different based on every single subject and study out there."

— Tyler Bye, director of program strategy and product development at WCG ThreeWire

Moving on to the "when," Bye advises considering the trial duration/timeline and when, seasonally, it will be conducted. Seasonality could play a big part in recruitment efforts, he says. For example, certain times of year will be more effective for recruiting patients with asthma and allergies than others.

"There are definitely certain times of the year where recruiting for a study like that makes a lot more sense, where someone is going to be much more in tune with their condition, understanding that their symptoms are there, where they are going to be looking for some other type of option," he said.

Perhaps most importantly, he says, consider the "why" and "what" when crafting enrollment strategies. Why should patients take part? What are the risks and benefits of participation and the impact on their lives?

For example, it's important to consider if participation will ultimately be altruistic, where it is unlikely to benefit the patient personally but will help other generations, or if it could result in treatment the patient wouldn't get anywhere else.

Conversely, it's also important to go into what it will mean to the patient who decides against enrolling. The trial could be a one-time deal that won't be available to them again, for instance, or they might not be able to receive healthcare at that site if they decline. It's critical to bring up these discussions with potential participants.

"These types of things are definitely conversations that will be had at the site … and these conversations will be different based on every single subject and study out there," he said. "I know a lot of this goes into the undertones of what's being done on a day-to-day basis, but I don't think we oftentimes think about it in these more granular levels."

Access *The Participant Playbook* webinar series here: https://bit.ly/3FjiwxK.

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Q&A

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Further, as championed by both regulators and industry, we continue to collaborate on many initiatives and technological innovations aimed at improving the diversity of trial participants. While this has gained momentum in the industry, there's still more to be done for making all studies accessible to a broader and more diverse mix of patients from different ethnic, racial and demographic backgrounds.

CenterWatch Weekly: *What are the biggest challenges that you are seeing?*

Answer: From my perspective, it is navigating the "hybrid clinical trial" where we are implementing decentralized trial (DCT) methodologies with traditional study infrastructure and supporting the sites in these scenarios. In addition, the recent collapse of Silicon Valley Bank (SVB) may be foreshadowing for DCT companies more likely tied to SVB and could negatively impact many smaller companies who rely on funding to run innovative decentralized/hybrid trials and solutions.

Additional challenges include finding and retaining high-quality talent and providing them a work environment that is holistic, meaning work that is meaningful but not overwhelming.

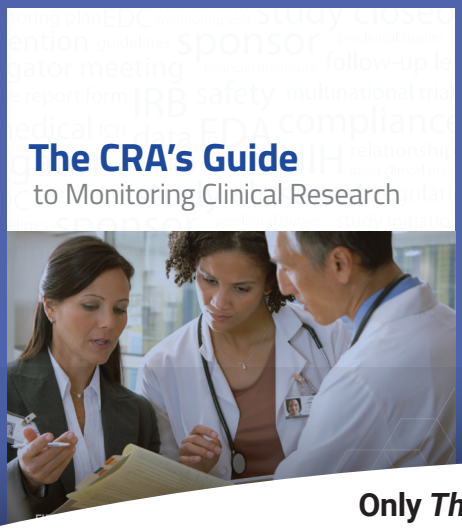
CenterWatch Weekly: *What do you think it will take for smaller and mid-sized CROs to overcome the challenges you've named?*

Answer: It is important for these organizations to have a seat at the table so that we can all understand that smaller and mid-size CROs are a viable choice for the kind of work and product that we want to produce and be a part of.

CenterWatch Weekly: *What does the future look like for smaller and mid-sized CROs?*

Answer: Sunglasses on! The future is bright! That is not to say it is easy, but the work is there and even in this tentative financial market, the global demand for clinical research continues to rise year over year. In short, the industry is at a crossroads for fundamentally changing the way we conduct studies. Small and mid-size CROs are in the game and continue to prove nimble enough to make it happen.

WCG CEO Sam Srivastava, Evans and leaders from other small research companies will be in conversation May 24 at the MAGI 2023 East session, *"Executive Fireside Chat – A Perspective from Small Organizations"* where they will share their insights and experiences on important changes occurring within industry. Register here: https://bit.ly/3YSwvS9.



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Drug & Device Pipeline News

Company	Drug/Device	Medical Condition	Status
Trials Authorized			
Glenmark Specialty	GRC 54276	Advanced solid tumors and lymphomas	IND for a phase 1/2 trial approved by the FDA
Sapience Therapeutics	ST316	Solid tumors	IND for a phase 1/2 trial approved by the FDA
Cognition Therapeutics	CT1812	Geographic atrophy secondary to dry age-related macular degeneration	IND for a phase 2 trial approved by the FDA
Vivasure Medical	Vivasure PerQseal closure system	Percutaneous vessel closure following percutaneous cardiovascular procedures	IDE approved by the FDA
Trials Initiated			
Bio-Thera Solutions	BAT8007	Advanced solid tumors	Initiation of a phase 1 trial
ITM Isotope Technologies	ITM-31	Malignant glioblastoma	Initiation of a phase 1 trial
Anaveon	ANV419	Relapsed/refractory multiple myeloma	Initiation of a phase 1/2 trial
Alterity Therapeutics	ATH434	Multiple system atrophy	Initiation of a phase 2 trial
First Wave BioPharma	Enhanced adrulipase formulation	Exocrine pancreatic insufficiency in patients with cystic fibrosis	Initiation of a phase 2 trial
Microbion	Topical pravibismane	Moderate chronic diabetic foot ulcer infections	Initiation of a phase 2 trial
Tonix Pharmaceuticals	TNX-601 ER	Major depressive disorder	Initiation of a phase 2 trial
Immutep	Eftilagimod alpha plus paclitaxel	Metastatic HER2-/low breast cancer	Initiation of a phase 2/3 trial
Sermonix Pharmaceuticals	Lasofoxifene plus abemaciclib	Locally advanced or metastatic ER+/HER2- breast cancer with an ESR1 mutation	Initiation of a phase 3 trial
Approvals			
Acadia Pharmaceuticals	Daybue (trofinetide)	Rett syndrome in adults and pediatric patients two and older	Approved by the FDA
Pfizer	Zavzpret (zavegepant)	Acute treatment of migraines with or without aura	Approved by the FDA

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