CenterWatch Weekly

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April 17, 2023

CRCs Share Perspectives, Advice on Trial Processes, DCT Strains

By James Miessler

Screening, initial appointment logistics and first visits are the most frustrating trial processes for site staff, according to a new study on the burdens of critical processes and decentralized trial (DCT) methodologies that interviewed a select group of CRCs about their perspectives.

Trial technology platform provider ClinOne set out to measure the levels of frustration fundamental trial processes and DCT methodologies place on trial participants and sites, gathering insight from eight CRCs that together encompassed a broad range of therapeutic areas, including oncology, cardiology and rheumatology, at rural and urban sites of varying sizes.

The CRCs ranked trial processes and DCT approaches on a scale of one (least frustrating) to five (most frustrating) for site staff and participants and provided valuable insights on potential solutions.

For site staff, the patient screening process, rated a 3.00 on average, was the most frustrating of the five fundamental processes examined, followed by initial logistics (2.75), first patient visits (2.75), compensation (2.00) and labs (1.88), according to the study.

Elaborating on screening, the CRCs explained that many of their trials have numerous tests that must be completed within two to four weeks and require expedient scheduling. One CRC described

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Ask the Experts: Caregivers and Employees as Trial Participants

This monthly feature presents questions from clinical trial professionals with answers from experts. This month features insights from WCG IRB Chair Currien MacDonald and WCG IRB Quality Assurance Advisor Yvonne Higgins.

Question: *Can employees be enrolled as trial participants?*

Answer: For supervisors including their employees in their research, involvement brings in the main issues of coercion or undue influence during the consent process. For all coworkers, including supervisors, there is the added issue of awareness of research data of which they would not otherwise have knowledge.

Bioethicist David Resnik offers several possible solutions in a 2016 paper, *Employees as Research Participants: Ethical and Policy Issues*.

To support voluntary participation by minimizing the possibility of coercion or undue influence, Resnik recommends:

- Not allowing the direct supervisor to be involved in recruitment, consenting or the conduct of the study; and
- Being explicit in the consent process that the employee's decision does not affect performance evaluations, employment status or benefits.

To help protect the privacy of the participant, consider conducting private aspects of the research offsite or at off hours.

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Upcoming Events

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

26 APR — CONFERENCE
FDA's New Laws and Regulations: *What Drug and Biologics Manufacturers Need to Know*

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

17 MAY — CONFERENCE
2023 WCG Avoca Quality Consortium Summit

[VIEW ALL EVENTS]

Industry Briefs

Q&A Guidance Gives Additional Risk-Based Monitoring Advice for Sponsors

Following up on 2013 guidance, the FDA has issued a new question-and-answer guidance with additional recommendations for trial monitoring approaches, monitoring plan content and follow-up/communication of issues caught through risk-based monitoring.

The 13-page final guidance rehashes FDA's expectations that sponsors use a risk-based approach to developing and revising trial monitoring plans to ensure data integrity and participant protections, then delves into a number of Q&As on implementing risk-based monitoring and communicating and pursuing identified issues.

For example, the guidance directs sponsors on how to address and share serious issues their monitoring systems catch. The guidance advises sponsors to evaluate issues in depth, in a timely fashion, at the appropriate level (such as the sponsor or site level) and according to the trial's monitoring plan, with a prompt root cause analysis followed by appropriate corrective and preventive actions (CAPA).

In addition, the guidance advises that the risk assessment and monitoring plan should be reevaluated and revised as needed to reduce or eliminate the chance of an issue recurring. Sponsors should document and share any significant issues uncovered through monitoring — as well as their respective CAPAs — with the appropriate parties, the guidance says.

The guidance also expands on the content for monitoring plans beyond the 2013 guidance, advising that sponsors include:

- A description of the trial design, including blinding and randomization procedures if applicable;
- Processes for confirming randomization is done per the protocol and investigational plans;
- Sampling plans used to identify specific records and data that will be monitored, including rationale and implementation strategy;
- A description of the types of issues identified through monitoring that would be immediately escalated; and
- An approach for determining whether a significant issue identified at one site may be present at other sites and whether the finding suggests a systemic-level problem with the protocol or associated trial plans that needs to be addressed.

Read the guidance here: https://bit.ly/30VaGE8.

Researchers Identify Breakthrough Biomarker for Parkinson's Disease

In a monumental moment for Parkinson's disease trials, researchers from the Michael J. Fox Foundation's Parkinson's Progression Markers Initiative (PPMI) have validated a biomarker that can define the disease biologically and detect it before movement symptoms show.

Rather than employing clinical assessments and patient-reported outcomes, researchers will now be able to use the new biomarker, a spinal fluid test known as the alpha-synuclein seed amplification assay (αSyn-SAA), to identify, define and track Parkinson's disease in patients.

According to PPMI's large-scale study of the test, published in *The Lancet Neurology*, the assay is able to distinguish Parkinson's disease from control groups with 88 percent sensitivity and 96 percent specificity.

"Our results show that the assay classifies people with Parkinson's disease with high sensitivity and specificity, provides information about molecular heterogeneity and detects prodromal individuals before diagnosis," the researchers wrote. "These findings suggest a crucial role for [αSyn-SAA] in therapeutic development, both to identify pathologically defined subgroups of people with Parkinson's disease and to establish biomarker-defined at-risk cohorts."

The new biomarker is likely to serve a significant role in future clinical trial designs, the evaluation of investigational treatment effects and the early detection of disease pathology, the Michael J. Fox Foundation said.

"Using αSyn-SAA, we are already unlocking new understanding of Parkinson's, which will transform every aspect of drug development and ultimately clinical care," said Kenneth Marek, PPMI principal investigator and president and senior scientist at the Institute for Neurodegenerative Disorders. "We will rapidly be in a position to test new therapies in the right populations, target the right therapy to the right patient at the right time and launch studies of agents with potential to prevent Parkinson's disease altogether."

Read the paper here: http://bit.ly/3ocGMvQ.

CRCs Share Perspectives

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the process as inflexible and challenging logistically for both sites and patients. For participants, screening ranked 2.63 on the frustration scale for the simple fact that they were raring to start the trial treatment; CRCs reported that patients felt frustrated by any process impediment during a trial.

On first visits, which were considered less frustrating for patients (2.38) than for site staff, the interviews revealed that lengthy, dense consent and prescreening documents were particularly aggravating for patients, as were first visits at which there were struggles to operate electronic patient-reported outcome (ePRO) devices or infusion nurses were unavailable.

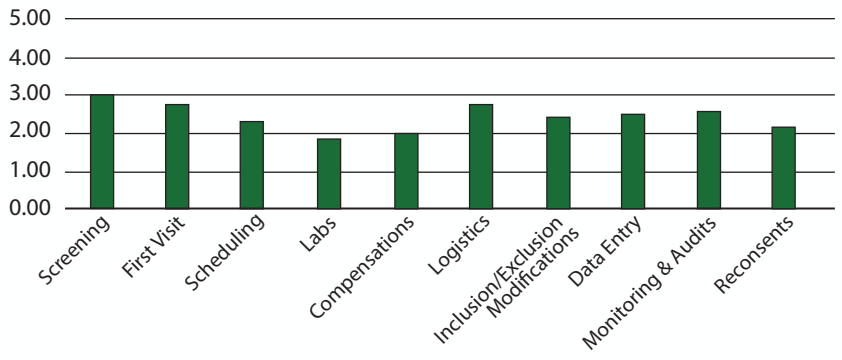
To overcome this frustration, the CRCs suggested technologies could be used to provide participants with the ability to understand the protocol, investigational drug and study logistics in greater detail.

"Augmenting manual screening and scheduling technologies with visual aids, such as a study portal displaying relevant information, may help participants consume study activity information more easily," ClinOne's report reads.

In addition, the CRCs noted that information provided through very long consent documents is especially challenging for patients to digest and suggested employing supplementary learning resources "that give participants summarized, smaller amounts of information ahead of consenting so they [are] better prepared to absorb information once the formal consenting process begins."

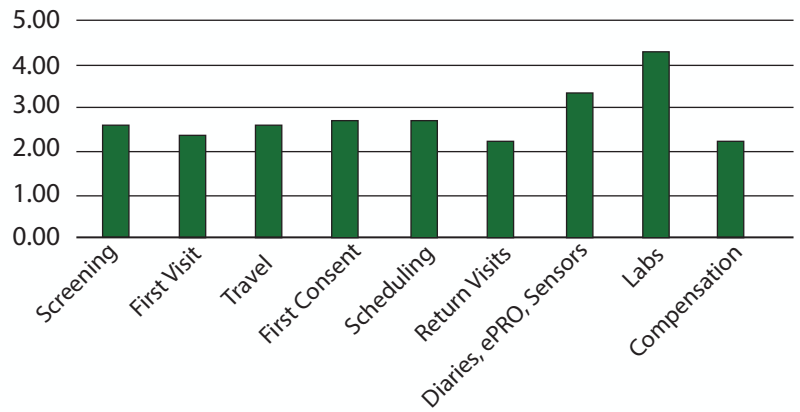
ClinOne found greater adoption of departments and schedulers specifically delegated with handling first visit activities and labs have been successful in addressing many historical site staff issues. Additionally, easy access to medical monitors, clinical research assistants and physicians on call are helpful, logistics-wise, for modern trials, the report reads.

CRC Frustration Levels by Trial Process



Source: ClinOne

CRC-Perceived Participant Frustration Levels by Trial Process



Source: ClinOne

The CRCs interviewed indicated the most frustrating components for patients are labs, diaries/ePROs/sensors, scheduling and first informed consent, with labs far and away the most aggravating, with a rating of 4.33.

In particular, the interviewees felt it especially important for coordinators to be on the ball when it comes to reminding patients of their lab appointments; frustration mounts when patients aren't reminded of a lab and end up missing it, the paper notes. In addition, the CRCs cited difficulties in establishing efficiencies for labs due to their manual nature.

Diaries, ePROs and sensors were also a source of serious frustration for patients, rating 3.38 on the scale. The CRCs raised a number of considerations:

- Malfunctioning devices are a common occurrence;
- Patients sometimes forget to bring the device to their site visit;
- Some patients find it challenging to remain compliant with electronic devices;
- Some forget how to use the device; and
- Some participants do not have the dexterity to hold thin devices.

For first informed consent, which rated 2.75 on the patient stress scale, the CRCs suggested the process would be smoother with electronic consent (eConsent) applications but acknowledged this may not be the best approach for all patients, as many older participants were uncomfortable consenting

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CRCs Share Perspectives

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electronically. Recent data from Memorial Sloan Kettering Cancer Center support the greater use of eConsent (*CenterWatch Weekly*, April 10).

Scheduling, which also scored 2.75 on the rating scale, was a notable pain point as well. For example, it can be difficult to book time slots with doctors for patients who require labs 90 minutes before their appointments. Combining therapies added to patient frustration in this area.

The CRCs recommended developing organizational templates capable of managing study expectations and logistics, citing difficulty in managing participant-specific activities, lab requirements and timing across multiple trials, especially when sites were forced to interpret the protocols themselves. Sponsors could provide resources that make the protocol clearer and more manageable for site staff and even patients, they suggested.

"Materials that explicitly and sufficiently detail activities at given time points, anchored to pertinent dates, would help reduce errors caused when interpreting unclear protocol descriptions," the report said.

The CRCs also recommended sharing patient-friendly versions of organizational and informational materials to help communicate timelines, expectations and what would occur during lab visits. "CRCs saw the potential for educational material to minimize fatigue-driven disengagement they observed in participants overloaded with information."

All in all, what should research professionals and sponsors take away from the findings of the study? Lead study author Allison Barnard, ClinOne's product owner of site and patient adaptive experiences, tells *CenterWatch Weekly* that the results shed light on the most urgent site strains present in today's clinical research landscape. While the rapid adoption of technology has introduced a number of new problems, technology can also help remedy them, she says.

"Based on our findings, the most pressing unmet needs for easing site burden are creating formal feedback mechanisms capturing site experience and feasibility observations and bootstrapping them into future study designs, and creating platforms that unify disparate technologies, ultimately decreasing the amount of technologies sites and patients are juggling," Barnard said.

Access the report https://bit.ly/416BAZ4.

Ask the Experts

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To further protect the confidentiality of employee participant data collected as part of the research, Resnik suggests:

- Describing in both the research plan and informed consent document who will have access to stored data and specimens, for example, using coded data or restricting the supervisor's access to the employee's identified data; and
- Including in the consent form a description of how privacy and confidentiality will be protected and any limitations on those protections for the employee.

The strategies to mitigate these risks are dependent on the design of the study and the specific application of risks of participation. There is no one-size-fits all answer to the question; so, it would be important to work in close collaboration with the IRB to ensure that study-specific employee risks are addressed.

Question: *Are caregivers considered trial participants in a trial where their role is limited to helping the study participant complete a symptom diary?*

Answer: Caregivers may offer support throughout a clinical trial by providing transportation to the research site, administering study medications, assisting the participant with diary entries or the completion of quality-of-life questionnaires, or observing and reporting clinical outcomes, such as adverse events.

When the caregiver's role is limited to facilitator, observer or reporter, the caregiver is not considered a human subject as defined by the regulations and informed consent is not required.

Federal regulations (45 CFR 46.102e) define a human subject as "a living individual about whom an investigator (whether professional or student) conducting research:

- Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
- Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimen."

However, the caregiver would be considered a research subject when a clinical trial is designed to collect data about the caregiver, such as caregiver quality of life or the physical or emotional burden of caregiving tasks. For example, some Alzheimer's disease clinical trials have adopted caregiver outcomes as secondary endpoints.

Even when the caregiver is not a research subject and informed consent is not a regulatory requirement, you may want to consider providing the caregiver with educational materials, such as an information sheet that clearly outlines their role and responsibilities.

Drug & Device Pipeline News

Company	Drug/Device	Medical Condition	Status
Trials Authorized			
Aviceda Therapeutics	AVD-104	Geographic atrophy secondary to age-related macular degeneration	IND for a phase 2 trial approved by the FDA
Trials Initiated			
QurAlis	QRL-201	Amyotrophic lateral sclerosis	Initiation of a phase 1 trial
Sirnaomics	STP122G	Anticoagulation disorders	Initiation of a phase 1 trial
Vega Therapeutics	VGA039	Von Willebrand disease	Initiation of a phase 1 trial
SciNeuro Pharmaceuticals	SNP318	Neurodegenerative and inflammatory diseases	Initiation of a phase 1 trial in Australia
Nuvectis Pharma	NXP800	Platinum-resistant, ARID1a-mutated ovarian carcinoma	Initiation of a phase 1b trial
HotSpot Therapeutics	HST-1011	Treatment of patients with advanced solid tumors who are relapsed/ refractory to anti-PD-L1 therapy	Initiation of a phase 1/2 trial
Kineta	KVA12123	Advanced solid tumors	Initiation of a phase 1/2 trial
ONL Therapeutics	ONL1204	Macula-off rhegmatogenous retinal detachment	Initiation of a phase 2 trial
Panbela Therapeutics	CPP-1X-T (eflornithine tablets)	Recent onset type 1 diabetes	Initiation of a phase 2 trial
Quadriga BioSciences	QBS72S	Brain metastases of breast cancers	Initiation of a phase 2 trial
Bridge Biotherapeutics	BBT-877	Idiopathic pulmonary fibrosis	Initiation of a phase 2a trial
Nuance Pharma	Ensifentrine	Maintenance treatment of chronic obstructive pulmonary disease	Initiation of a phase 3 trial in China
Approvals			
Takeda	Hyqvia (immune globulin infusion 10% (human) with recombinant human hyaluronidase)	Primary immunodeficiency in children age two to 16 years	Approved by the FDA for expanded age indication

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