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Nov. 22, 2021

Onsite Inspections Back to Normal, But Some Things Remain Changed

By James Miessler

After nearly two years of postponed or remote site inspections due to the pandemic, the FDA appears to have returned to normal on its good clinical practice (GCP) inspections and routine surveillance.

"If they're not [back to a normal schedule], they're close to it," Dave Borasky, vice president of IRB compliance for WCG, said during the WCG FDAnews FDA Inspections vSummit. "IRBs were one of those things that I think they, I wouldn't say totally backburnered, but if it wasn't for-cause, that wasn't the first thing they were jumping out of the gate to look at in terms of surveillance audits. The fact that they're doing those again now, I would say is getting quite back to normal."

But even though Bioresearch Monitoring Program (BIMO) inspectors are back on the road, teams that respond to FDA inspections may not be able to travel as freely as they could prior to the pandemic to be there, in-person, for an agency visit.

"The tide has changed, and general expectations for who needs to get up out of their seat and go travel somewhere have really changed," said Denise Lacey, founder and principal of Ready Room, an inspection management platform. "And I think that even the government has to catch up with that at some point."

Tellingly, the FDA is now routinely asking about ClinicalTrials.gov compliance, another sign, beyond issuing its first enforcement

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eConsent: Sites and Sponsors Tout Benefits, Confront Obstacles

By James Miessler

As more sponsors and sites use the flexibility offered by eConsent and remote consent, they're also dealing with some concerns attached to those approaches, especially the documentation that the FDA will ask for during inspections.

"When sites or sponsors contacted the IRB and they asked about remote consent, one of the biggest recommendations I gave was that they create forms on their remote consent process, either checklists or forms, so that their documentation was consistent, especially for audit purposes in the future," Heather Kim, WCG IRB's Quality Assurance Manager told the WCG FDAnews FDA Inspections vSummit.

"That way you wouldn't have some remote consents with a witness and some without, or some that had the investigator sign the remote consent process and some that just noted their names."

Kim added, for example, that a patient may be unable to send back the informed consent form (ICF) if they don't have access to a printer, camera phone and/or email.

When patients don't have access to a printer, Kim recommended that their verbal consent be obtained and documented with a witness present. Also, a subject could, after doing the consent discussion, be allowed to email that they consent and agree to sign the ICF when they next visit the site, if they have email access. Recordings of phone or video calls done to consent a patient can also be used as documentation, Kim said, and

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CenterWatch Holiday Notification

In observance of Thanksgiving in the U.S., *CWWeekly* will not be published Monday, Nov. 29. The next issue will be published Monday, Dec. 6.

Upcoming Events

7 DEC
VIRTUAL CONFERENCE
Modern SOP and Quality Systems: Streamlined, Effective and Flexible Compliance for the 21st Century

8 DEC
WEBINAR
Simplifying Oncology Trials: Make the Most of Remote Monitoring and Decentralization

[VIEW ALL EVENTS]

Industry Briefs

Advocacy Group Pushes FDA to Disqualify Minneapolis IRB, Investigators from Running Trials

Public Citizen has called on the FDA to take strong action against two Minneapolis, Minn., investigators and the IRB at Hennepin County Medical Center (HCMC) over IND and informed consent issues on some of their trials.

The two clinical investigators — Jon Cole and Lauren Klein — received warning letters earlier this year for initiating and conducting trials without submitting and obtaining INDs. Though the investigators contended that they didn't need to seek INDs for their trials because the drugs administered weren't research interventions, the agency didn't agree.

In the case of the IRB, it received a Form 483 from an Aug. 7-23, 2018, inspection that identified multiple observations. Among those, the agency observed that the IRB should not have approved waivers of consent for the investigators' studies. The agency also observed that the IRB had approved research "in a situation where some or all of the subjects were likely to be vulnerable to coercion or undue influence" but didn't check to see if safeguards had been established to protect these vulnerable patients (who had an impaired ability to give informed consent).

Public Citizen wants the FDA to make an example out of the investigators, their co-investigators and the medical center, arguing that the violations are serious enough that a "slap-on-the-wrist approach for such noncompliance … will not suffice."

Although *CenterWatch Weekly* asked the FDA to elaborate on the situation, the agency declined, stating that it would "review the petition and respond directly to the petitioner."

Hennepin Healthcare issued a statement on Nov. 16, explaining that the FDA had deemed its corrective actions sufficient. The statement also includes a summary of the changes the institute made to bolster its research program.

"Hennepin Healthcare, the Hennepin Healthcare Research Institute and the researchers involved in studies approved in 2014 and 2016 have taken many actions to strengthen and improve the clinical research program across the institution since the studies were closed in 2018," HCMC said. "These changes have been shared with the FDA in detail and in October the FDA informed the researchers that the measures taken result in compliance with FDA regulations."

Read the Public Citizen letter here: https://bit.ly/3qK7OKm.

FDA Should Get Far More Aggressive About Clinical Trial Reporting, Study Says

When the FDA gets tough on clinical trial transparency, the industry listens. The problem is the FDA doesn't get tough with enough regularity.

That's the upshot of research published in the *Journal of the American Medical Association* (*JAMA*), which showed that 90 percent of those conducting clinical trials who got preliminary warnings from the FDA about overdue clinical trial results promptly provided the requested information.

The researchers argue that the FDA should be more aggressive at pushing drugmakers, universities and National Institutes of Health grantees for transparency in their trial results. "The FDA can and should harness its enforcement tools to ensure timely submission of trial results information to ClinicalTrials.gov," they wrote.

The researchers used Freedom of Information Act requests to obtain 58 preliminary warnings — called pre-notices — that the FDA sent to sponsors from 2013 through April 2021. Fifty-seven of the 58 pre-notices obtained described potential missing trial results and one referred to missing information about registering a clinical trial. The median time trial sponsors took to post results after getting these notices from the FDA was three weeks, the researchers found.

The FDA Amendments Act (FDAAA) — which requires trial sponsors to register trials on ClinicalTrials.gov within 21 days after the first human subject is enrolled and submit summary results information to the database within 12 months after the trial's completion date — took effect in 2007. And in 2017, a rule strengthening its reporting requirements was added.

Recent estimates cited by the researchers suggest that approximately 60 percent of trials fail to report results on time and more than 30 percent (almost 3,000 clinical trials with primary completion dates between Jan. 18, 2017, and Jan. 18, 2021) have not yet reported results.

Among 3,951 trials sponsored by industry, just 43.2 percent complied fully with the FDAAA results reporting requirements. Among the top 40 U.S. research universities (by number of trials subject to the FDAAA), only 17 complied fully with reporting of trial results, said the researchers.

In April of this year — 14 years after the law was passed — the FDA issued its first-ever notice of noncompliance with the FDAAA to Acceleron Pharma for failing to submit required summary results information on candidate drug dalantercept in combination with an FDA-approved drug, axitinib. These results were based on a phase 2 trial that reached its primary completion date in June 2017.

Acceleron not only missed its 2018 deadline for submitting results to ClinicalTrials.gov, but also ignored an initial warning that the FDA sent the company in July 2020, the researchers said.

Since then the FDA has issued two more notices of noncompliance — one to Accuitis for a phase 2 trial of a topical treatment for acne rosacea and another to an academic investigator for a phase 4 trial

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Industry Briefs

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of a postoperative combination ice and analgesic treatment.

In addition to not communicating nearly enough with trial sponsors about missing trial information, the researchers found that the FDA also did not communicate with other agencies such as the National Institutes of Health (NIH), even though the NIH and FDA share responsibility for enforcing FDAAA.

Rather than wait for the FDA to send pre-notices and notices, the NIH could use its own list of FDAAA 801 problems to identify noncompliant trials and send reminders to the responsible parties, the researchers said.

Additionally, if a responsible party is an NIH grantee, the NIH could also warn them that future grant funds may be withheld until the trial comes into compliance.

The researchers suggested that the FDA send more pre-notices, adding, "The FDA has yet to send Pre-Notices (or Notices) to thousands of responsible parties that have not reported results, including government sponsors such as the NIH."

In lieu of relying on inconsistent on-site inspection investigations and third-party complaints to identify noncompliant trials, the researchers suggest that the FDA instead use a continually updated list of FDAAA 801 problems maintained by the NIH to quickly identify potential noncompliant trials and issue pre-notices as appropriate.

The FDA could also get more compliance by publicizing all pre-notices it issues, as opposed to sharing them only with the responsible parties. "Such transparency would improve public accountability and encourage prompt submission of missing information," the researchers wrote.

Also, the pre-notices could show more teeth. The researchers suggest that the FDA include clear timelines for further enforcement actions if results remain unreported. Currently, pre-notices don't say anything about when any enforcement actions will take place.

The researchers anticipate that the FDA's response to these suggestions will be that they don't have the necessary staff — to which the researchers suggest taking a risk-based approach to identifying where the enforcement efforts should be rather than not enforcing anything at all.

The FDA did not respond to a request for comment by press time.

Access the *JAMA* report here: https://bit.ly/3cgF3ws.

IACT Health, LMC Manna Team Up to Form Massive U.S.-Canada Site Network

Site networks IACT Health and LMC Manna Research have combined their operations in a strategic alliance, joining forces to create one of the largest research networks in North America.

The pair, based in the U.S. and Canada, respectively, said that their new extensive site network brings more than 40 sites, 1.5 million potential participants and 150 active investigators together.

IACT Health said that it is the largest network of research sites in the southeastern U.S., conducting clinical trials in more than 30 therapeutic areas as well as routine, urgent and emergency healthcare. A Tufts University assessment found that the company's enrollment rates were more than 212 percent higher than the average research site.

LMC Manna claims to be Canada's largest clinical research network and uses a networkwide decentralized technology system in its trials. The company has conducted more than 2,000 clinical trials to date and more than 4,000 patient randomizations since 2013.

Onsite Inspections

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letters this year, that it's taking the timely reporting of trial information seriously. While the FDA investigators didn't actually check to see if the data was up to date on the website, at least during the visit, they did inquire if people were aware of the updating and reporting requirements.

Lacey said she believes the rise in vendors being hired by sponsors to support sites during the pandemic, such as remote clinics, telehealth vendors and contract study coordinators, should be carefully considered, as their increased use could potentially come up during inspections.

"I think… that's going to be kind of a flashpoint for future inspections, looking at those relationships, who is transferring obligations to whom, who's on the [1572 — Statement of Investigator], who is supervising these vendors — is it the site's responsibility, is it the sponsor's? Are there any inherent conflicts of interest in having the sponsor hire somebody that is then being supervised by the site and is really supporting the site?" she said.

"I think it could get interesting when you're looking at site inspections, sponsor inspections and then those vendor inspections, what kind of documentation is getting requested in each one and who is providing it. I expect that we'll see [further] guidance from FDA on that. I expect as people are encountering these situations more and more during inspections that FDA will eventually come out with some guidance on best practices for approaching these relationships and for documenting these situations."

For Patty Mendoza, manager of regulatory affairs, compliance and clinical trial management at Houston Methodist Research Institute, the pandemic has not dramatically altered her inspection experiences. Having gone through 18 inspections since the 1990s, Mendoza's latest experience just a few months ago was largely the same, she said, although the first thing the agency asked about was the site's SOP for COVID-19 and people and participants coming into the site.

The agency looked at everything on the site's BIMO review checklist as normal, but she noted that they asked for specifics about the site's principal investigator (PI), making it clear that they expected him to be available for the inspection and able to talk in-depth about the study. Mendoza, who nearly always preps for inspections, didn't have that opportunity this visit due to the timing, and the difference was definitely noticeable: the PI wasn't as clear as he could have been if there had been time for preparation. Mendoza swears by making a "cheat sheet" to ensure sites and investigators are ready when the agency comes knocking.

"Sometimes studies are reviewed so [much] later that the research team, the PI have moved on, so I make, basically, a high summary for the PI. I recommend and always stay with the same plan: go through a high-level summary of the study once it was approved all the way through the amendments, any SAEs, high-level issues that came up, deviations. Focus on the monitoring visits, follow reports, look for trends and be able to speak to that. It's hard to go back and do that, but one of the things the FDA [investigator] said — she pulled one of the studies at random that had no opportunity for a check — was that she's used to people coming in and preparing for reviews."

Mendoza urges research staff to act, on every trial, like they're going to be reviewed and to have a proactive quality assurance (QA) program in place. Mendoza's own system includes decision-making skills she's learned, such as Six Thinking Hats and Lean Six Sigma.

"You work with teams on improving areas that they want, and you do it in real-time. From [the point of] IRB approval, you have checks all the way through, you do mock runs, you review the source, you review processes and how they're following up on issues," she said. "That proactive QA has made such a difference in our inspection readiness. I can tell you that it's night and day, and it has a better staying power compared to traditional compliance."

Suellen Bigaj, vice president/principal consultant for Pharma Compliance Partners, also found that the FDA's inspection process and site selection methods aren't changing as a result of the pandemic — but the logistics (how they're conducted) are.

"Moving forward, are those things going to continue to stay in existence? I think … the things that have worked well and the things that we know and that came about as of COVID, they're going to stay, but there's also gaps that we've learned. There's things we can accept and things we do still need to be conscious of from the old ways. I don't see it moving forward in any other way at this point in time," she said.

The biggest issues Bigaj has seen right now have been related to trial master file and investigator site file maintenance. These files should both be ready for an FDA inspection at all times, and not ensuring that they're ready for agency eyes can lead the issue to "trickle down" to sites that are already busy with other activities. The problem is one that should be viewed with concern, Bigaj said.

Mendoza, who belongs to a U.S.-based IND task force with other academic centers, recently participated in a session with the group about their recent audits. Seven sites at that meeting underwent inspections, and all had the same things selected for their investigator-initiated trials.

The agency was straight up: they wanted to know what the sponsors' responsibilities were, how those were determined, how the PI either covered those responsibilities or made sure they were covered and how the monitoring process worked, she said.

Still, because so many people are working remote all or part of the time, it has become a challenge for sites to make sure that all staff are onsite when the FDA comes knocking.

Lacey predicts — though she noted she's seen no signals from the FDA on this yet — that future GCP inspections may incorporate some of the remote approaches brought on during the pandemic, though it's a "wait and see" situation right now.

eConsent

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stamped return envelopes can be provided to patients alongside mailed ICFs so they can return the signed form easily. Importantly, these need to be documented and stored in a way that makes them easily accessible if they're requested by an investigator.

For eConsent, the FDA has laid out specific expectations for sponsors and sites. For one, the identity of the patient must be verified prior to establishing or certifying their electronic signature. This includes, for each subject, official ID documentation (such as a driver's license or passport), security questions to confirm identity and a username/password. eConsent also still requires one of the most pivotal elements of informed consent — giving subjects a suitable opportunity to ask questions. Additionally, a record of the eConsent must be given to the subject and all electronic records must be accessible when and if the FDA turns up for an inspection.

A number of eSignature tools have been used successfully for eConsent, including Adobe Sign, DocuSign, REDCap (Research Electronic Data Capture) and the FDA's MyStudies App. When picking a tool, it's integral for sites and sponsors to ensure that the system and signature process is fully compliant with the agency's Part 11 regulations, which cover electronic records and signatures. This was especially important for Adobe Sign and DocuSign, which have both noncompliant and compliant versions.

"Even when a site receives or decides to implement an eSignature tool, they have responsibilities that the tools themselves might be Part 11 compliant, but there are elements of Part 11 that are on the sponsor and site," she said. "For example, defining how the sponsor, monitors or inspectors will have access to eConsent documents — that should be outlined either in training or SOPs, and Part 11 does require documented training for staff on Part 11 systems before implementation. While the system itself may be Part 11 compliant, sites also need to remember that they have responsibilities under Part 11 as well."

"When a site receives or decides to implement an eSignature tool, they have responsibilities that the tools themselves might be Part 11 compliant, but there are elements of Part 11 that are on the sponsor and site."

—Heather Kim, WCG IRB's Quality Assurance Manager.

Suellen Bigaj, vice president/principal consultant for Pharma Compliance Partners, foresees that sponsors and sites will evaluate their approaches to signing informed consent in the next year and act accordingly to adjust them — but she believes remote methods are here to stay.

"Every site, every sponsor, everyone involved will make their assessments and then be able to look back and then make a better assessment of 'OK, this can stay, this can go, this we can make better,'" she said. "I don't see it moving forward any other way but as a hybrid."

And Patty Mendoza, manager of regulatory affairs, compliance and clinical trial management at Houston Methodist Research Institute, predicts that eSignatures will "keep being a big deal" as we move into the future. For Mendoza, they've been highly effective.

"I told people, I'm a monster now. I use my electronic signatures, DocuSign, for training, reviewing newsletters. There were [principal investigators] I would literally have to stalk outside the bathroom to get a signature, and now they sign right away because the peer pressure, all the other investigators are listed on that same document," she said. "I use them to adjudicate adverse events, serious adverse events, etc., so I think that's going to be something."

Thankfully, trials that move to implement remote consent or eConsent do not, by regulation, need to have their ICFs revised accordingly or approved by the FDA, which could take a significant amount of time. Instead, subjects can be sent ICF Addendums or "Dear Participant" letters to reflect new information, Kim said. But regulations do require IRBs to review and approve moves to remote consent or eConsent, and failure to document these reviews and approvals could result in an inspection finding.

The pandemic, still not yet over, has made these approaches indispensable options for patients hesitant to come onsite, and they've even shown to foster greater interaction during the consent process than the traditional way.

"Since some sites had implemented video and telephone conferencing to obtain consent, it was more face time than some subjects had experienced previously where they were just given the consent form, told to read it and [to] come back if they had questions," Kim said. "That was an interesting observation."

These remote tools also showed benefit in that they, in some cases, helped to ensure patients were seeing the most current version of the ICF and pointed out missing fields, including checkboxes, dates and signatures that weren't filled out. These missing fields have been among the most frequent site monitoring findings, according to Kim.

But, as expected, challenges have been encountered, too. Remote and eConsent are not exempt from the potential cost and implementation burdens that are placed on sites when onboarding new approaches, Kim said, including the extra work of training staff and implementing SOPs.

The use of remote and eConsent has highlighted the issue of lengthy and complex ICFs and, with that, the importance of communicating key trial information to patients. When consenting patients, Kim said it's critical that patients are presented with "information that would be most relevant in helping a subject decide whether or not to participate," rather than inundating them with the entire consent form, which could span 30 pages of information to scroll through.

Drug & Device Pipeline News

Company	Drug/Device	Medical Condition	Status
Trials Authorized			
InnoCare Pharma	ICP-189	Advanced solid tumors	IND approved by the FDA
MyMD Pharmaceuticals	MYMD-1	Aging	IND approved by the FDA for a phase 2 trial
Paradigm Biopharmaceuticals	Zilosul (pentosan polysulphate sodium)	Knee osteoarthritis pain	IND approved by the FDA for a phase 3 trial
Vitro Biopharma	AlloRx stem cells	Pitt Hopkins syndrome	IND approved by the FDA
Cardialen	MultiPulse therapy	Paroxysmal and persistent atrial fibrillation	IDE approved by the FDA
Paracrine	Celution system to deliver adipose derived regenerative cells	Diabetic foot ulcers	IDE approved by the FDA
MimiVax	SurVaxM	Newly diagnosed glioblastoma	Approval for a phase 2b trial granted by the FDA
Emergex Vaccines	COVID-19 vaccine	COVID-19	Approval for a phase 1 trial granted by Switzerland's regulatory authority
Gannex Pharma	ASC42	Primary biliary cholangitis	Approval for phase 2 and 3 trials granted by China's regulatory authority
HebaBiz Biotech	Clevudine (L-FMAU)	Chronic hepatitis B virus	Approval for phase 3 trial granted by China's regulatory authority

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Drug & Device Pipeline News (continued from page 7)

Company	Drug/Device	Medical Condition	Status
Trials Initiated			
Revelation Biosciences	REVTx-99	Allergic rhinitis and chronic nasal congestion without polyps	Initiation of phase 1b trial in Australia
Eureka Therapeutics	ET140203 ARTEMIS T-cell therapy	Pediatric cases of relapsed or refractory hepatoblastoma, hepatocellular neoplasm not otherwise specified or hepatocellular carcinoma	Initiation of phase 1/2 trial
Graphite Bio	GPH101	Sickle cell disease	Initiation of phase 1/2 trial
Inozyme Pharma	INZ-701	ENPP1 deficiency in adults	Initiation of phase 1/2 trial
NiKang Therapeutics	NKT2152	Clear-cell renal-cell carcinoma	Initiation of phase 1/2 trial
Rafael Pharmaceuticals	CPI-613 (devimistat)	Clear-cell sarcoma	Initiation of phase 1/2 trial
Biosight	Aspacytarabine (BST-236)	Relapsed or refractory myelodysplastic syndrome or acute myeloid leukemia	Initiation of phase 2 trial
Dermata Therapeutics	DMT310	Moderate-to-severe rosacea	Initiation of phase 2 trial
Oryzon	Vafidemstat	Schizophrenia	Initiation of phase 2b trial in Spain
Saniona	Tesomet	Hypothalamic obesity	Initiation of phase 2b trial
Merck	Verquvo (vericiguat)	Chronic heart failure and reduced ejection fraction in patients who have not had a recent worsening heart-failure event	Initiation of phase 3 trial
Approvals			
Merck	Keytruda	Adjuvant treatment of patients with renal-cell carcinoma at intermediate-high or high risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions	Approved by the FDA for expanded indication
PharmaEssentia	Besremi (ropeginterferon alfa-2b-njft)	Polycythemia vera	Approved by the FDA
AbbVie	Skyrizi (risankizumab)	Active psoriatic arthritis in adults	Approved by the European Commission

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