CenterWatch Weekly

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Post-BIMO Update, FDA Trial Inspections Heavy on Outsourcing Scrutiny

By James Miessler

FDA inspections have been heavily focused on sponsor, CRO and site outsourcing activities since the Bioresearch Monitoring (BIMO) Program revised its manual for inspection processes in September 2021.

Outsourcing was given its own section in the BIMO manual for the first time, signaling the concerns the agency has about how the trial industry is working with third parties to provide clinical trial services and products, according to Karen Harvey, senior director of WCG Avoca Quality Consortium (AQC). AQC is a collaboration of sites, sponsors, CROs, service providers and other groups that work together to engage on trial quality improvement.

The updated BIMO manual tasks investigators with looking closely at critical outsourced services, Harvey told attendees at last week's WCG FDAnews 17th Annual FDA Inspections Summit held in Washington, D.C. Services considered critical include those related to primary endpoints; safety data and/or significant deviations; selection of outsourced services and the criteria used; and preferred vendor lists.

The agency is taking this seriously, she said, sharing the experiences and insights of AQC members. FDA has scrutinized sponsors and CROs so heavily in this area, virtually all AQC members were asked for the written agreements for their critical outsourced

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Ask the Experts: Dealing with Duplicate Documentation

The FDA's Office of Good Clinical Practice responds to inquiries on a variety of trial-related subjects, providing answers on the agency's official regulations as well as best practices. The following is a selection of questions and answers excerpted from the CenterWatch publication *GCP Questions, FDA Answers*.

This issue's questions involve a site where administrative errors in documents, such as an incorrect date on the header of a monitoring visit confirmation letter, were previously dealt with by the monitor issuing a revised version of the document. The inquirer wonders if leaving the original, erroneous versions of documents in the trial master file (TMF) could result in confusion later on, especially for longer trials, and asks if the issuance of a corrected replacement letter, along with an email notifying the site of the correction for audit trail and justification purposes, would suffice in situations where the monitoring visit has not yet occurred.

Question: *Are there any specific regulations surrounding the best practices for documents that have been already issued/provided to the site? Should the monitor not issue a revised (corrected) letter if an error is identified? What should be done with duplicates?*

Answer: The FDA regulations do not specifically address your question about best practices for document management but do address which documents must be maintained for FDA-regulated clinical

see **Ask the Experts** on page 4 »

CenterWatch Holiday Notification

In observance of Thanksgiving in the U.S., *CenterWatch Weekly* will not be published Monday, Nov. 28. The next issue will be published Monday, Dec. 5.

Upcoming Events

1 DEC — WEBINAR
Engaging with the FDA: Best Practices for Dealing with Warning Letters, Seizures, Injunctions — and More

8 DEC — WEBINAR
2022 Year in Review: The Future of Clinical Research Sites Series Finale & Look to 2023

[VIEW ALL EVENTS]

Industry Briefs

Clarivate Unveils Annual List of Highly Cited Researchers

Analytics firm Clarivate has published its 2022 Highly Cited Researchers list, a global listing of influential individuals at research institutes, commercial sponsors and universities across a range of research fields.

This year, the list comprises nearly 7,000 researchers from 69 countries and regions who have in the past decade published multiple papers that have ranked in the top 1 percent of citations in Clarivate's Web of Science, a publisher-independent international citation database, the company said.

The U.S. accounts for 2,764 of this year's highly cited researchers, or 38.3 percent of the total. China comprises 16.2 percent of the list, doubling its amount of highly cited researchers in the past five years, while the UK accounts for 8 percent, an impressive statistic considering its population size.

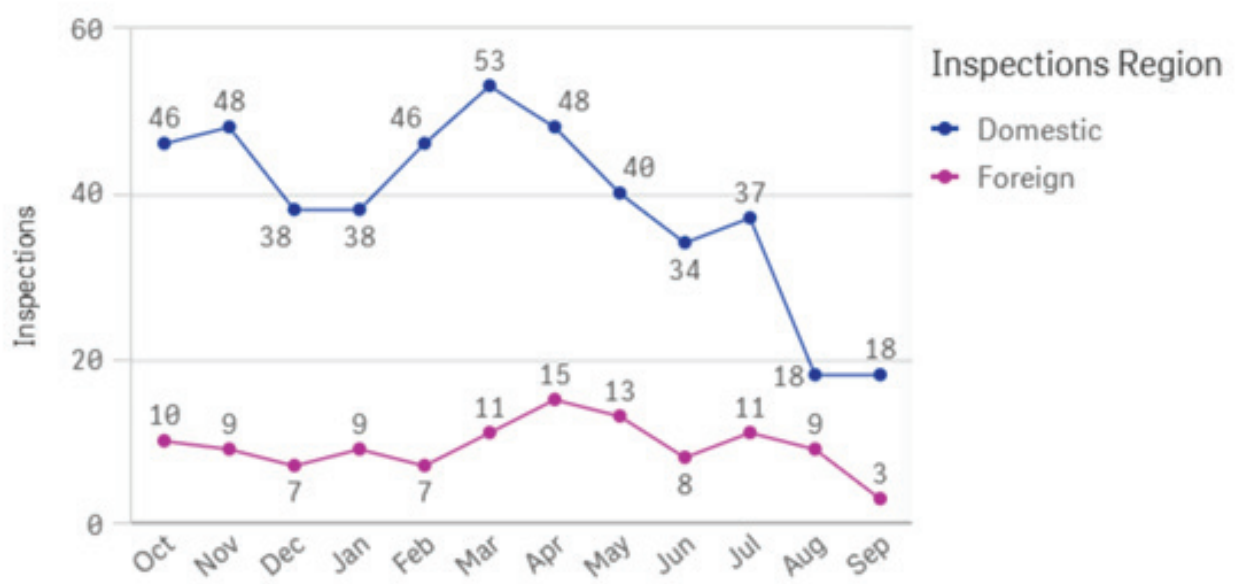
According to Clarivate, all the publications on this year's list have undergone deep analysis to address concerns of possible misconduct, including plagiarism, image manipulation and fake peer review.

"Research misconduct is an ever-increasing concern in our world. Activities such as unusual citation activity and fake peer review may represent efforts to game the system and create self-generated status," said David Pendlebury, head of research analysis at Clarivate's Institute for Scientific Information. "This is why we've expanded our qualitative analysis this year to ensure the Highly Cited Researchers list reflects genuine, communitywide research influence. Our efforts are part of a wider responsibility across the whole research community to better police itself and uphold research integrity."

Access the list here: https://bit.ly/3EDNzVk.

Data Point

Number of Bioresearch Monitoring Program Domestic and Foreign Inspections, Fiscal 2022



Source: FDA

Post-BIMO Update

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services during inspections conducted after the FDA issued its BIMO update last year. If AQC members' experiences are any indication, sponsors should be prepared to field agency requests for documentation related to vendors — but the extent of this request will vary.

"Some reported that FDA requested all versions of all written agreements for all vendors from beginning of [the] study to current, along with scopes of working contracts to assess if there were any gaps and confirm alignment between documents. Some reported they only had to provide the most current versions," she said. "In our current clinical trial landscape, I think this [BIMO manual update] acknowledges the importance of sponsor oversight while acknowledging the complexity of managing lots of vendors."

In line with this, FDA is also asking for documentation related to CROs during inspections, Harvey says. This includes:

- Qualifications of CRO staff;
- Lists of audit, communication plan, escalation plan and contingency plan standard operating procedures (SOPs), including ownership of SOPs and which impact assessments and corrective and preventive actions (CAPA) were performed;
- Vendor oversight plans and any audits that occurred, including their scope;
- Protocol-specific training provided to CROs; and
- Sponsor communications with CROs.

The latter item, for example, was an area of focus during many AQC members' inspections and included requests for meeting minutes. It can be easy to lose track of minutes when there are so many meetings, said Harvey, but those involved should be prepared to produce documentation. Nearly all AQC members were told to provide meeting minutes, and some were surprised at the depth of discussion FDA investigators went into on these.

"In our current clinical trial landscape, this acknowledges the importance of sponsor oversight while acknowledging the complexity of managing lots of vendors."

—Karen Harvey, senior director of WCG Avoca Quality Consortium

Harvey urged sponsors to avoid the impulse to combine meeting minutes across trials, and instead document them separately. Keeping them separate can mean not having to take the time to redact a lengthy all-in-one meeting record down to one specifically requested by an investigator.

For protocol deviations, AQC members report that investigators want to know how they were communicated, to whom and in what timeframe. They are also looking to see if sponsors have escalation plans and accompanying documentation.

In addition to outsourcing-related information, Harvey said to expect the agency to now request point-of-contact information for all vendors, including their names, phone numbers and e-mail addresses.

The BIMO manual update has also kindled a greater focus on sponsors' selection and monitoring of clinical investigators. According to Harvey, AQC members report that FDA has sought clinical investigator lists as well as information on sites placed on hold, criteria for site selection, previous experience with sites, and the workload and resources of clinical investigators and study staff.

FDA investigators are also seeking lists of sites that underwent clinical investigator changes and accompanying documentation, consortium members say. Upon providing documents that supported their rationale for freezing sites or taking sites off hold, the agency was generally satisfied and moved on to other inquiries.

Data collection and handling, which saw the most extensive revision to an already existing section in the BIMO manual, is a focal point as well, according to AQC members' experiences. For example, FDA investigators looked at their data management plans, SOPs and procedures with a focus on critical data, as well as procedures for data modification/correction and the creation of audit trails.

Vendor oversight comes into play in this section as well, Harvey said, with nearly all members reporting that they were asked for a data flow diagram during their inspections — a presentation showing how data flows and what it looks like when it comes in from a vendor. Members said that FDA investigators held onto these charts during the inspection and repeatedly referred to them throughout.

Similarly, many members point to requests for organizational charts, reflecting the BIMO manual update's addition of a new section on staff responsibilities. The section tasks FDA investigators with confirming that staff have not been given responsibilities they're unqualified for or shouldn't be handling, such as blinded staff doing unblinded tasks.

"It's clear FDA is following the new BIMO. For those inspections that happened close to the update, FDA explicitly stated they were following the new BIMO expectations. More than one AQC member reported that FDA investigators walked into the inspection with the manual in their hands," Harvey said.

Overall, the update to the BIMO manual and the FDA's adherence to it haven't turned inspections upside down, and members note that the key focus areas are basically the same as they were before the update. Instead, the update serves to provide industry with greater clarity on the primary documentation requests to expect during agency inspections.

Ask the Experts

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investigations. When the regulations are silent, sponsors, CROs, investigators, IRBs and institutions are free to develop their own procedures and practices as long as applicable regulatory requirements are met. Some FDA guidance documents, such as *Electronic Source Data in Clinical Investigations*, suggest that data should be attributable, legible, contemporaneous, original and accurate (ALCOA) and must meet the regulatory requirements for recordkeeping. This recommendation applies to all records (e.g., hard copy or electronic).

How and when your company decides to make corrections to study documents is something you should discuss with the appropriate company officials. Study records must be accessible to the FDA on an inspection so there is an expectation that the records will be adequately maintained. Your organization, or any sponsor you are working with, may have a standard operating procedure (SOP) that addresses document management (including document corrections) that you need to follow. As you noted, when an error is discovered, there should be an appropriate audit trail to explain what transpired. If not, there could be confusion surrounding what appear to be duplicate documents.

There is flexibility in the methods you can implement to manage study documents. You may find publicly available information regarding what some call "best practices" or "good documentation practices" that may be helpful to you in developing an SOP to address document management for your organization that best suits your business needs.

Question: *Are investigational sites (and CROs) allowed to destroy/remove the incorrect letter (or any documents with errors) from their files if a revised, corrected version is issued? And if not, what is the best practice if they find a document that serves the same purpose but is "slightly" different from another? (i.e., one is the correct version, the other contains incorrect information).*

Answer: Again, the FDA regulations do not specifically address your question. In general, removing/destroying study documents from study files is typically not recommended. As noted in the previous question/response, there is flexibility in the methods you can implement to manage study documents and create adequate audit trails to address errors in study documents and/or to identify duplicate documents. Developing an SOP that best suits your business needs is also recommended to provide a consistent method for all in your organization to follow.

For more information on the publication *GCP Questions, FDA Answers*, click here: https://bit.ly/3EhS2vg.

Drug & Device Pipeline News

Company	Drug/Device	Medical Condition	Status
Trials Authorized			
YS Biopharma	PIKA COVID-19 vaccine	COVID-19	IND approved by the FDA
Gmax Biopharm	GMA131	Diabetic kidney disease	IND approved by the FDA
Ascletis Pharma	ASC10	Monkeypox	IND approved by the FDA for phase 1b trial
Asieris Pharmaceuticals	APL-1401	Moderately-to-severely active ulcerative colitis	IND approved by the FDA for phase 1b trial
J INTS BIO	JIN-A02	Advanced non-small cell lung cancer	IND approved by the FDA for phase 1/2 trial
NeuroSense Therapeutics	PrimeC	Amyotrophic lateral sclerosis	IND approved by the FDA for phase 2b trial
AUM Biosciences	AUM001	Metastatic colorectal cancer	Approval for a phase 2 trial granted by Australia's regulatory authority
Trials Initiated			
Virogin Biotech	VG201	Advanced solid tumors	Initiation of phase 1 trial
Beam Therapeutics	BEAM-101	Severe sickle cell disease in adults	Initiation of phase 1/2 trial
Equillium	EQ101	Alopecia areata	Initiation of phase 2 trial
EpiEndo Pharmaceuticals	EP395	Chronic obstructive pulmonary disease	Initiation of phase 2a trial in Germany and the UK
Ayala Pharmaceuticals	AL102	Desmoid tumors	Initiation of phase 3 trial
Innovent Biologics	Mazdutide (IBI362)	Obesity	Initiation of phase 3 trial in China
Approvals			
Sobi North America	Kineret (anakinra)	COVID-19-related pneumonia in hospitalized adults requiring supplemental oxygen	Emergency Use Authorization granted by the FDA
AstraZeneca	Imfinzi (durvalumab) plus Imjudo (tremelimumab) plus platinum-based chemotherapy	Non-small cell lung cancer	Approved by the FDA
ImmunoGen	Elahere (mirvetuximab soravtansine-gynx)	Treatment of previously treated adults with folate receptor alpha-positive, platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer	Accelerated approval granted by the FDA
Medicines360	Liletta (levonorgestrel-releasing intrauterine system)	Pregnancy prevention for up to eight years	Approved by the FDA for extended treatment duration
Seagen	Adcetris (brentuximab vedotin)	Previously untreated high-risk classical Hodgkin lymphoma in children age two years and older	Approved by the FDA for expanded age indication
Agios Pharmaceuticals	Pyrukynd (mitapivat)	Pyruvate kinase deficiency in adults	Approved in the EU

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