**FDA to Require GCP Compliance for Device Trials Conducted Outside the U.S.**

*By Conor Hale*

In February 2019, the FDA will require that data from medical device studies conducted outside the U.S. be gathered in accordance with good clinical practices, including review and approval from an independent ethics committee and well-documented informed consent.

While many sponsors may already conduct international clinical investigations in accordance with GCPs, the agency said these practices will now be mandatory. However, the FDA will allow for flexibility when the requirements cannot be met, and grant waivers on a case-by-case basis.

The agency’s final rule applies to data intended to support IDE applications, 510(k) submissions, and de novo classification requests, as well as applications for premarket approval, product development protocols and humanitarian device exemptions. It also applies to bench and in vitro diagnostic studies of de-identified specimens.

The new mandates would replace the current pre-market approval regulations that require clinical studies to conform to the Declaration of Helsinki or the law of the country where the research is conducted, whichever carries greater protection for human subjects, the FDA said. The rule does not apply to all clinical investigations performed overseas, but only sets criteria for FDA acceptance of data used to support device marketing applications or submissions.

see [GCP Compliance](#) on page 3

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**Early Chart Reviews Can Provide Steady Flow of Potential Study Subjects, Experts Say**

*By Conor Hale*

Beginning chart reviews before initiating a site can generate a list of prequalified candidates for outreach — and give sponsors the chance to examine the study’s inclusion and exclusion criteria, and their potential to cause enrollment issues, according to experts during two WCG webinars on acceptable methods for sites and sponsors, and best recruitment practices.

Reviewing patient charts and both paper and electronic medical records through an end-to-end, systematic process can help identify patients within each site that may be eligible for the protocol, said Amanda Plucinak, program manager at ThreeWire.

“We have access to these patients’ charts, we know their medical history and these patients are already familiar with each site,” Plucinak said. “The nice thing about an electronic medical record review is that you could run a report that has the top criteria for where patients are going to be disqualified — for example, by a diagnosis or an age range.”

“That’s easily going to get rid of a number of charts that you don’t have to review,” she said. “You can really hone in on these chart review efforts by specifically looking at patients who are the most eligible.”

Institutional review boards get a lot of questions about the use of electronic health

see [Chart Reviews](#) on page 4
**Industry Briefs**

**NHGRI Launches Strategic Planning Process for Genomic Research and Funding**

The National Human Genome Research Institute has began to re-focus its research and funding strategies with new emphasis on the development of precision medicines, exploring the basis for certain diseases and supporting the industry’s education in data science. The main federal institution behind the Human Genome Project, NHGRI plans to prioritize its efforts in emerging areas, such as the use of genomic information in patient care and drug development, and plans to gather input from the industry and the public over the next two years. The NHGRI’s strategic plan is expected to be finalized in October 2020, which commemorates the Human Genome Project’s 30th anniversary. The institute expects to prioritize emerging areas that are not well-defined, that will benefit from significant investments and are not specific to particular diseases. Well-established areas, such as cancer and microbials, genomics, are expected to be deemphasized during the upcoming process, the institute said.

**ClinEdge and BTC Network Acquire GuideStar Research**

Clin-X, the parent company of ClinEdge and BTC Network, has acquired GuideStar Research, to build a new research site services category dedicated to streamlining operations at the institutional level. ClinX plans to support GuideStar by broadening product lines, according to Al Peters, president of BTC Network and ClinEdge VP. Best practices from ClinEdge, BTC Network and now GuideStar Research will be incorporated across the organization’s global network of sites and through all of its service offerings, the company said.

**Charles River Enters Agreement to Acquire MPI for $800 Million**

Charles River Laboratories entered into an agreement to acquire MPI Research for approximately $800 million. MPI, a non-clinical contract research organization, provides testing services to biopharmaceutical and medical device companies worldwide. The acquisition aligns with Charles River’s strategy to expand its biotechnology client base, the company said, adding MPI’s work in ototoxicity and abuse liability, and expand Charles River’s existing capabilities in general toxicology and specialty toxicology, including ophthalmology, juvenile toxicity, molecular biology and surgery, as well as medical device testing. The transaction is expected to close in the second quarter of 2018.

**ACRP Partners with Singapore Clinical Research Institute to Train CRCs**

The Association of Clinical Research Professionals is partnering with the Singapore Clinical Research Institute to train clinical research coordinators employed in the Singapore healthcare system. Under the agreement, ACRP’s CRC Boot Camp will form part of the SCRI Academy Clinical Research Coordinator Level 1 training program.

**Pharmatech and TransMed to Combine Enrollment and Precision Medicine Screening Programs**

Pharmatech and TransMed Systems announced a partnership to combine Pharmatech’s site startup enrollment system with TransMed’s precision medicine platform and automated screening solutions to improve trial feasibility and research patient pre-identification using real-world data. The strategic alliance looks to employ a repository of longitudinal patient data housed within healthcare technology systems encompassing electronic medical records, laboratory information, practice management, molecular diagnostics, pathology reports and other data sources, the companies said. The data will be aggregated for hundreds of oncology practices across the combined networks of care sites.

**Sponsors Voice Concern over Draft Guidance Closing Orphan Drug Study Loophole**

An FDA draft guidance that proposes to close what the agency sees as a “loophole” allowing drugmakers to bypass pediatric clinical trial requirements would impact product development if it becomes final, according to some drug developers and patient advocacy groups. Issued in December, the draft guidance said the agency no longer intends to grant orphan drug designations in pediatric subpopulations of common diseases, due to the way subpopulation designations and the Pediatric Research Equity Act’s orphan drug exemption work together. The agency said their interplay creates an “unintended loophole” where a sponsor can exempt itself from conducting the pediatric studies required by PREA. Aevi Genomic Medicine commented that “the proposed remedy is likely to impede and delay development of important new medicines for children” because without the orphan drug designation, developing novel drugs and biologics for children is more difficult and “in many cases, practically impossible.” The National Organization for Rare Disorders said the guidance did not provide sufficient evidence of the perceived loophole, and asked the agency for “further evidence of the exploitation of this loophole, including how many therapies that received a pediatric designation in pediatric subpopulations of common diseases, due to the way subpopulation designations and the Pediatric Research Equity Act’s orphan drug exemption work together. The agency said their interplay creates an “unintended loophole” where a sponsor can exempt itself from conducting the pediatric studies required by PREA.”
GCP Compliance  (continued from page 1)

Included in 21 CFR 812.28, the updated regulations do not specify a particular GCP standard for sponsors to follow, but instead include a more flexible definition of principles that it describes as well-recognized and generally accepted. The rule defines GCP as standards for the “design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical investigations” that assure results are accurate and the rights and safety of subjects were protected. This includes initial and continuing ethics committee approval, and obtaining freely given informed consent.

This definition allows sponsors of clinical trials conducted outside the U.S. to determine their own appropriate standard, the FDA said.

As an example of an applicable standard, the agency pointed to the ISO’s GCPs for medical device clinical investigations, ISO 14155:2011, which was recognized by the FDA in 2012 and was developed with the participation of several countries and device companies. The ISO standard is also recognized by most of the members of the International Medical Device Regulators Forum, the agency said.

“Such standards help provide assurance not only that the research results are credible and accurate, but that the rights, safety and well-being of patients participating in these studies are protected,” Scott Gottlieb, commissioner of the FDA, said, describing how the new regulations can also make product development more efficient, by helping device companies determine earlier in the process whether their global clinical trials can support an FDA marketing authorization.

The final rule requires sponsors to provide statements of compliance, the names of the investigators and their qualifications; a description of the research facilities and their addresses; the location of sites used for maintaining study records; and a detailed summary of the protocol and results of the investigation. Descriptions of the informed consent process, participation incentives, monitoring procedures, and GCP training should be provided as well.

Sponsors must also summarize the ethics committee’s decision to modify or approve the investigation, and records describing the qualifications of committee members must be available for agency review upon request.

The final rule includes several changes to the version first proposed by the FDA in February 2013 — including different requirements for supporting information based on whether the device carries significant risk. Sponsors of non-significant risk devices need to submit their rationale for the categorization, and do not need to submit demonstrations that their data constitutes valid scientific evidence.

The FDA also published a frequently asked questions guidance on how to meet the agency’s requirements, request waivers and provide the required information to support clinical data submissions.

Outside of official waiver requests, sponsors can include statements in premarket submissions and applications explaining why the investigation was not conducted under GCPs, while describing the steps taken to ensure accurate results and patient well-being.

The agency does not expect many waivers to be requested, but allows that certain circumstances may require it. For example, the FDA requests investigator case records, hospital records or additional background data that cannot be provided as required because disclosure is prohibited by local laws. For the FDA to rely on the affected data, the guidance said, the sponsor and the agency would have to agree on an alternate validation procedure.

Waiver requests should include the sponsor’s rationale and an alternative course of action, and should be submitted as part of a pre-submission, submission or application amendment. Waivers may also be requested before initiating a clinical study.


records as a vehicle for identifying potential subjects, and what is acceptable and not acceptable when it comes to recruitment, said David Borasky, WCG’s VP of quality management.

In theory, IRBs shouldn’t have any issue using EHRs for recruiting and finding patients, Borasky said.

“It happens all the time,” he added. “Obviously things like HIPAA may come into play, depending on whether or not the entity involved is a covered entity,” and sponsors should examine any permission or privacy standards that may already be in place at an institution or site.

Many of the questions stem from the lack of updated federal guidance on patient recruitment, Borasky said. FDA information sheets on recruiting study subjects and screening tests prior to enrollment have not been updated since 1998.

While sponsors and investigators may use several patient recruitment tactics, they still need to optimize their efforts to get the best returns. And with most clinical trials chronically lagging behind schedule — dovetailing with expensive delays in patient enrollment and the costs of increasing the number of sites — sponsors need to understand the importance of implementing robust recruitment plans from the beginning of a study, Plucinak said.

“Oftentimes, sponsors will opt to add more sites in response to underenrollment,” Plucinak said. “However, the more sites required to meet the enrollment goals, the more sponsors will pay for startup, monitoring and study management.”

Instead, effective, one-on-one interactions with potential patients — and even early confirmation of informed consent — can be pursued in the community, through booths at health fairs, advocacy group events or even farmers’ markets, she said. The goal of a study’s outreach programs should be to build and maintain relationships with candidate patients, and to educate them about clinical research in general.

But effective community engagement can be time consuming and require dedicated attention from staff, said Fabian Sandoval, CEO of Emerson Clinical Research Institute. One of the reasons that all sponsors and sites don’t reach out to community events or health fairs is simply because they don’t know where to go.

“You have to have a lot of planning. You can’t just show up and put down your table and start setting up,” Sandoval said. In addition to finding the proper event, you have to have the right materials to attract potential patients.

“The worst thing to do at these community events is to be that boring table, right?” he said. “We actually do screenings at health fairs — we do our own kind of glucose test or blood pressure screenings.”

Hiring staff dedicated to patient recruitment, even a single person, can make a dramatic impact in the workflow of a study by eliminating bottlenecks, said Kari Lotsberg, manager of site services at ThreeWire.

The time needed to conduct prescreening phone interviews, for example, can add up quickly, Lotsberg said. Even at an average of 10 minutes per conversation with a potential patient, the total process to equal one enrollment can equal 8 hours.

And with patient recruitment delays reaching several months on average, having dedicated staff can alleviate burdens on study coordinators, Sandoval said, allowing them to focus more on handling site visits and keeping patients flowing through the study.

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– Julie Bouma, Clinical Research Manager, Borgess Research Institute
## Drug & Device Pipeline News

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Celgene announced OTEZLA study Showed Improvements in Patients with Oral Ulcers

Celgene announced that data from the Phase III RELIEF clinical trial of OTEZLA (apremilast) in patients with active Behçet’s Disease with oral ulcers showed statistically significant reductions in oral ulcers with apremilast 30mg twice daily (BID) versus placebo through week 12. OTEZLA (apremilast) is Celgene’s oral selective inhibitor of phosphodiesterase 4 (PDE4). The RELIEF study is a Phase III randomized, placebo-controlled, double-blind study evaluating apremilast 30mg BID in 207 patients with active Behçet’s Disease who were previously treated with at least one topical or systemic medication. This 52-week study was conducted at 63 sites across ten countries. In the study, a total of 207 patients were randomized to apremilast 30mg BID or placebo. At week 12, the area under the curve (AUC) for the number of oral ulcers was statistically significantly reduced with apremilast 30mg BID versus placebo (129.5 vs. 222.1; P<0.0001), the trial’s primary endpoint. The most common adverse events observed in the trial were diarrhea (41.3 percent with apremilast, 19.4 percent for placebo), nausea (19.2 percent with apremilast, 10.7 percent for placebo), headache (14.4 percent for apremilast, 9.7 percent for placebo) and upper respiratory tract infection (11.5 percent for apremilast, 4.9 percent for placebo). This study primarily evaluated the effect of apremilast on recurring oral ulcers in patients with active Behçet’s Disease who were previously treated with at least one topical or systemic medication.

AbbVie Presents New Data on Upadacitinib in Atopic Dermatitis

AbbVie presented new positive results from a Phase II dose-ranging study evaluating upadacitinib, an investigational, once-daily oral JAK1-selective inhibitor, in adult patients with moderate to severe atopic dermatitis. This dose-ranging study is an ongoing 88-week Phase II, randomized, double-blind, parallel-group, placebo-controlled multicenter study designed to evaluate the safety and efficacy of upadacitinib in adult patients with moderate to severe atopic dermatitis. In Period 1, subjects were randomized in a 1:1:1:1 ratio to one of four treatment for 16 weeks. At week two of treatment with upadacinib showed all dose groups (30/15/7.5mg once-daily) achieved significant improvement in extent and severity of atopic dermatitis. Secondary endpoints included a proportion of patients achieving EASI 90, EASI 75, an Investigator Global Assessment (IGA) of 0 or 1 and percent change in pruritus/itch numerical rating scale from day one to week 16 in comparison with placebo.

Aimmune Therapeutics announced AR101 met Primary Endpoint for Peanut Allergies

Aimmune Therapeutics announced that its pivotal Phase III PALISADE efficacy trial of AR101 met the primary endpoint. In the United States, AR101 has U.S. Food and Drug Administration (FDA) Breakthrough Therapy Designation for peanut-allergic patients ages 4–17. PALISADE was an international, randomized 3:1, double-blind, placebo-controlled, Phase III trial of the efficacy and safety of AR101 in a Characterized Oral Desensitization ImmunoTherapy (CODIT) approach in patients with peanut allergy. PALISADE enrolled 499 patients ages 4–17, 496 of whom received treatment. After approximately one year of treatment, patients completed an exit double-blind, placebo-controlled food challenge (DBPCFC). In the primary analysis of 496 patients ages 4–17, 67.2 percent of AR101 patients tolerated a single highest dose of at least 600mg of peanut protein (1043mg cumulative) with no more than mild symptoms in the exit DBPCFC, compared to 4.0 percent of placebo patients. The corresponding difference in response rates was 63.2 percent (p<0.00001, 95 percent CI=53.0–73.3 percent), and, at 53 percent, the lower bound of the 95 percent confidence interval greatly exceeded the pre-specified success criterion, which was 15 percent. Of patients ages 4–17, 296 patients (79.6 percent) from the AR101 arm completed the trial, compared to 116 patients (93.5 percent) from the placebo arm. Of these AR101 completers, 96.3 percent tolerated a single highest dose of at least 300mg (443mg cumulative) of peanut protein in the exit DBPCFC, 84.5 percent tolerated at least 600mg (1043mg cumulative), and 63.2 percent tolerated 1000mg (2043mg cumulative). Additionally, AR101 significantly reduced symptom severity at each exit DBPCFC dose level, compared to placebo.

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