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INSIDE THIS ISSUE

FDA Updates Guide on Clinical Study Data eSubmissions

An updated FDA guide on electronically submitting clinical study data, released last month, clarifies a number of requirements for preparing data sets and reviewers' guides.

The agency is now asking sponsors to prepare an analysis data reviewer's guide to help orient agency reviewers to the sponsor's analysis data sets. This section should include a summary of analysis data model conformance findings such as the study protocol, the statistical analysis plan and the clinical study report, the guide says.

Individual data sets should be included in a single transport file and should be no larger than one gigabyte. Each column should match the maximum length of the variable used across all data sets in the study.

(See **Study Data**, *Page 4)*

Year in Review: Transparency Leads The Clinical Trial Conversation Again

Regulators, sponsors and clinical investigators wrestled with trial data transparency and reporting requirements for the second year in a row, with the European Medicines Agency trying to pin down the most effective ways to require sponsors to share the results of their studies. U.S. officials were primarily concerned with stimulating development of new antibiotics, encouraging sponsors and investigators to more deeply analyze subgroup outcomes and promoting the use of biomarkers in drug trials. In India, regulators provided more detail regarding their expectations for informed consent and compensation for patients who are injured or die during the course of a trial. And Ebola was on everyone's mind.

Trial Transparency. The European Medicines Agency's trial transparency policy officially took effect on Jan. 1, 2015, following adoption by the agency's board of directors in October. The final policy was amended to let members of the public search, download, print and save data.

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Year in Review, *from Page 1*

The European Federation of Pharmaceutical Industries and Associations expressed concern last spring that the clinical trials regulation, which includes the transparency mandate, would allow for release of commercially confidential information, which could get into the hands of competitors. An amendment allowing for the redaction of some data eased those concerns.

Critics such as University of Maryland School of Pharmacy Professor and *British Medical Journal* Associate Editor Peter Doshi remained concerned that the vague wording over what was commercially confidential and eligible for redaction would allow sponsors to black out data that researchers should be able to see. While sponsors must justify their redactions, those concerns still stand. EU Ombudsman Emily O'Reilly asked the EMA in December to clarify why it allowed AbbVie to black out data in a clinical study report.

The agency told *CTA* that it hopes eventually to release individual patient data, but only after consulting with patients, physicians, academics and industry.

New Antibiotics & Study Demographics

Antibiotic Resistance. Efforts to bolster development of new antimicrobial drugs continued last year, with U.S. lawmakers floating a bill in January that would not require sponsors to submit as much information supporting new antibiotics or antifungals.

The Antibiotic Development to Advance Patient Treatment (ADAPT) Act of 2013, introduced in December of that year, would create a Limited Population Antibacterial Drug approval pathway. Sponsors could get LPAD products approved based on more limited datasets from Phase II clinical trials, instead of broader data from larger Phase III trials.

Subgroup Data. The FDA released an action plan in September detailing how it would like sponsors to look at trial outcomes from subgroups based on race, age, ethnicity and other factors. The plan followed an August 2013 report to Congress on encouraging more diversity in clinical trials.

The agency eventually plans to release draft guidance outlining sponsors' responsibilities for improving the collection and reporting of demographic data in the integrated summaries of the safety and effectiveness sections of their product labels.

This matters because patients' genetic differences can cause them to respond differently to drugs or medical devices. Sponsors won't have to do this part on their own, however. The FDA plans not only to beef up training for agency staff but also to work on identifying barriers to enrolling more diverse patients in clinical trials.

Indian Regulations & U.S. Development Tools

Biomarkers and Development Tools. In January, the FDA released a blueprint for qualifying biomarkers and other drug development tools. The qualification process will occur in three stages: initiation, consultation and advice, and review for the qualification determination. A review team will start the process by reviewing the sponsor's initial briefing package following receipt of an initiation request and letter of interest.

Throughout the year, the FDA released guidance on the use of various biomarkers in clinical trials. For example, one guidance focused on the use of galactomannan as an indication of aspergillosis infection.

Trial Compensation. India's Central Drugs Standard Control Organization spent much of 2014 developing policy on informed consent and compensation for patients injured or killed as the result of a clinical trial. Guidance on informed consent stressed that patients with differing levels of literacy must be able to give informed consent to participate in trials, whether in writing or via videotaped oral discussion. The guidance also recommends that patients be informed of

(See **Year in Review***, Page 10)*

Final Guidance Clarifies Study Data Submission Expectations

In two years' time, manufacturers must submit applications for NDAs, ANDAs, INDs and BLAs using a set of approved electronic formatting standards, which the FDA finalized last month.

The final guidance, covering general submissions and study data, outlines the acceptable file standards that were called for under the 2012 FDA Safety and Innovation Act. The final versions carry over suggestions from the drafts.

According to the two documents, the FDA will support:

- File format standards such as Adobe Acrobat Portable Document (.pdf), SAS Institute 111 Transport File format (.xpt), text files (.txt) and Extensible Markup Language (.xml);
- Study data exchange standards such as CDISC's Study Data Tabulation Model (SDTM);
- Analysis standards such as CDISC's Analysis Data Model (ADaM); and
- Terminology standards, including the National Drug File reference terminology for drug classifications, CDISC controlled terminology and the Medical Dictionary for Regulatory Activities (MedDRA).

The documents also clarify that the standards should be used for all NDAs and ANDAs, as well as some BLAs and INDs. Neither guidance applies to medical devices regulated as biologics or to noncommercial INDs.

In addition, the guidance confirms that drugmakers may apply for waivers to use different versions of previously approved submission formats. The FDA will inform a drugmaker within 30 days of receiving a waiver of its status, allaying concerns that the draft version didn't hold the agency to a timeline.

Companies will have 18 months to implement any updates to new versions of the standards, up from the original 12 months proposed in the draft.

View *Providing Regulatory Submissions in Electronic Format – Standardized Study Data* at www.fdanews.com/12-17-18-Studydataguidance.pdf and *Providing Regulatory Submissions in Electronic Format – Submissions Under Section 745A (a) of the Federal Food, Drug and Cosmetic Act* at www.fdanews.com/12-17-14-745Aguidance.pdf. — Lena Freund

India Issues Ream of Clinical Trial Regulations at Year End

Indian authorities issued a number of clinical trial regulations last month, covering compensation for trial injuries, exemptions for local Phase III trials and penalties for conducting trials without permission.

Patients who have become 100 percent disabled as a result of an experimental intervention will now be entitled to 90 percent of the compensation that drugmakers would provide for a death — 10 percent more than proposed last May (*CTA*, May 2014).

For patients with less severe disabilities, sponsors should use the following formula: compensation = (C x D x 90)/(100 x 100). "C" represents the amount that a drugmaker would have to pay in a trial-related death, while "D" represents the percentage of disability suffered.

However, the Central Drugs Standard Control Organization's final compensation formula still lacks any burden of proof on the sponsor's part that the injury was in fact caused by trial participation, says Mark Barnes, a partner at law firm Ropes & Gray. And it is still left up to investigators to determine what qualifies as a 100 percent disability.

For patients whose injuries are life-threatening, sponsors will have to pay out twice the minimum wage of unskilled workers in Delhi for as many days as the patient is hospitalized. Patients will be entitled to roughly $6,301, which will incur monthly interest, CDSCO says.

(See **India***, Page 6)*

NIH Wants Trial Sites To Use a Single IRB

Sponsors of multisite clinical trials should take greater advantage of their ability to use a single institutional review board, according to a draft policy that requires the practice for all NIH-supported domestic trial sites.

Multiple IRBs are unnecessary and may actually cost time and money, the NIH says. One central IRB can address a study's risks and benefits and ensure adequate informed consent procedures, and individual sites or experienced consultants can take care of ensuring the competence of investigators and suitability of sites.

A number of pharmaceutical companies started using single IRBs years ago to avoid dealing with multiple boards, says Mark Barnes, a partner at Ropes & Gray and member of the HHS Secretary's Advisory Committee on Human Research Protections. Advantages include eliminating delays in patient enrollment, improving research protections and shortening trial initiation times and overall approval times.

But the approach has some drawbacks, Barnes says. If the central IRB makes a mistake about anything, that mistake is replicated over all of the sites, rather than being contained to one site.

Centralized oversight also may trigger a debate over the relative value of local versus national ethics, Barnes tells *CTA*. Local opinions differ on issues such as HIV prevention and abortion services, and central oversight may end up diluting those voices, he warns.

The Society for Clinical Research Sites says conflicts could arise, too, between local IRBs, which would continue to function at a site, and the central IRB for a specific trial taking place at that site.

Comments on the draft are due Jan. 29 to SingleIRBpolicy@mail.nih.gov. View the draft policy at www.fdanews.com/12-04-14-IRBpolicy.pdf. — Lena Freund

Study Data, *from Page 1*

The agency also asks that names and labels not exceed a certain number of characters. Variable names, for example, should be capped at eight characters, with variable descriptive labels and dataset labels not exceeding 40 characters.

Those data sets, and any supportive files, should be organized into a specific file structure when using the electronic common technical document, the guide says. This allows automated systems to detect and prepare data sets, minimizing the need for manual processing.

Version 2.0 of the Study Data Technical Conformance Guide is meant to complement the final guidance, *Providing Regulatory Submissions in Electronic Format — Standardized Study Data* guidance which was released last month (*see story, page 3*).

View the guide at www.fdanews.com/01-09-15-version2.pdf. The *Federal Register* notice is at www.fdanews.com/01-09-14-studydata.pdf. — Lena Freund

Most GCP Infractions Tied To Sponsors, CROs: EMA

Clinical trial sponsors and contract research organizations incur the majority of good clinical practice violations, a European Medicines Agency panel reports.

The GCP Working Group reviewed 398 GCP inspections conducted between 2000 and 2012 — 21.1 percent sponsor sites and 71 percent investigator sites. While sponsors and CROs were almost fully responsible for GCP violations at their own sites, they also accounted for 32.1 percent of the citations at investigator sites.

Violations were classified as critical, major or minor. According to the working group, most of the critical lapses attributed to sponsors and CROs were due to underreporting of serious adverse event and inconsistencies in efficacy results in clinical study reports, inadequate monitoring activities and corrective and preventive actions, and data management problems, such as insufficient quality control.

These three areas accounted for a quarter of critical findings overall, the report says. Investigators were mainly cited for errors in reporting, source and essential documentation — concerns that were also raised for sponsors at investigator sites.

Overall, there were 5,685 GCP violations during the study period. Of those, 532 were critical, 2,583 major and 2,570 minor. Most of the inspections were carried out in the EU, European Economic Area and U.S., with other jurisdictions falling far behind.

While there was a wide geographical distribution in numbers of inspections, the average number citations per inspection was fairly constant, ranging between 12.1 and 16.2, the report says. Critical violations accounted for a minority of violations across all regions. Only the U.S. and EU had more major violations than minor ones.

View the working group's report at www.fdanews.com/01-13-15-EU-GCP.pdf. — Lena Freund

FDA Outlines Clinical Pharmacology Considerations in Pediatric Trials

Sponsors submitting pediatric study plans should consider whether a product affects adults and children similarly when choosing an approach, the FDA says.

According to draft guidance released Dec. 8, a pharmacokinetic approach measuring drug concentrations in blood, urine, tissue or cerebrospinal fluid samples is useful when evidence suggests that disease progression and treatment response is similar in both populations.

If evidence doesn't exist or if there's no standard pediatric dose or information about pediatric dosing, sponsors should conduct a study to determine the optimal dose before beginning pediatric tests, the FDA says. The guidance covers considerations for clinical pharmacology in pediatric studies.

In cases where disease course and treatment are similar in adults and children, but there is no accepted pediatric dose-response data, sponsors may extrapolate from well-known adult data to children using biomarkers characteristic of adult drug responses, the agency adds.

If the disease course is unique in children or comparative responses to drug therapy are different or unknown, the FDA recommends evaluating multiple doses across multiple pediatric studies using population data from efficacy studies to determine the best doses for specific age groups.

Choice of age group should be based on knowledge of drug-metabolizing enzymes, excretory mechanisms and safety considerations specific to certain developmental stages, the FDA says. For drugs intended for newborns, the sponsor should specify whether the indication

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India, *from Page 3*

Sanctions for conducting trials without proper permits would vary based on the offense, with sentences of up to three years for investigators, according to draft legislation released by India's Department of Health and Family Welfare. Repeat offenders could face five years and thousands of dollars in fines.

Investigators also could face up to a year in prison for not compensating a clinical trial participant or family member for an injury or death. The addition of jail time represents a drastic shift from current punishments, which include prohibiting an investigator from performing trials in the country, Barnes says.

India's clinical trial regulations are complex and ambiguous, and it is unclear what violation may constitute jail time, Barnes adds. For example, if a patient shows up late for a scheduled review, that could be a violation of protocol and subject to potential penalty.

The draft bill, which has yet to be introduced in Parliament, has a good chance of passage since it is supported by India's majority governing party, Barnes tells *CTA*.

Local Trial Waivers

Meanwhile, local clinical trials would be waived for drugs that may be used during a national emergency or epidemic, and drugs for rare diseases for which no alternative therapy exists, according to India's Apex Committee, a year-old body that monitors clinical trials. Such drugs must have been approved outside of India.

Examples include Gilead Sciences' hepatitis C therapy Sovaldi (sofosbuvir), which has proven to be more effective than other therapies used in India, the committee says. Gilead must conduct a postmarket safety study of the drug in India.

The committee has also called on sponsors of cancer drugs approved without local trials to submit postmarket safety and efficacy data on the first 500 patients who use their products.

The policy is an ad hoc way of skirting the fact that no clinical trials are currently being approved in India while recently proposed reforms such as credentialing of investigators and ethics committees and trial compensation make their way through the courts, a source knowledgeable about India's clinical trial industry tells *CTA*.

View the final compensation formula at www.fdanews.com/12-29-14-trialinjuries.pdf, the penalty bill at www.fdanews.com/01-05-15-IndiaBill.pdf and the waiver exemption proposal at www.fdanews.com/01-07-15-Indiatrials.pdf. — Lena Freund

Pediatric Trials, *from Page 5*

includes premature infants or babies who are small for their gestational age.

Sampling Frequency

In terms of sampling frequency, sponsors can administer single or multiple doses of a product to a small number of patients with frequent collection of blood and urine samples, which are then tested for drug concentrations, or collect samples less frequently from a greater number of patients. The latter approach is preferable for children, since they'd be subjected to fewer needle pricks, the FDA says. This also allows the sponsor to estimate a drug's effects in a broader population and in more individual patient groups.

Sponsors should discuss the proposed number of patients in each age range with the FDA, the guidance says.

In recent years, the FDA has offered incentives such as added marketing exclusivity to companies developing drugs for children in an attempt to increase pediatric testing and improve pediatric use information in drug and biological product labeling.

Comments on the draft guidance are due Feb. 7 to regulations.gov, docket no. FDA-2013-D-1275. View it at www.fdanews.com/12-08-14-pediatricguidance.pdf. — Lena Freund

Debate Rages Over Placebo Controls in Ebola Trials

Clinicians, bioethicists and regulators disagree over whether or not some patients in Ebola drug trials should be given placebos, and the debate is pitting the FDA against some international organizations.

During an October meeting on Ebola drugs, Office of Antimicrobial Products Director Edward Cox delivered a resounding "yes," calling placebo controls the "gold standard" of clinical trial design.

Proponents of placebo controls, such as Seton Hall University law professor Carl Coleman, argue that supportive care would pose a problem in a nonplacebo-controlled trial. In studies being run by Oxford University and Doctors Without Borders, patients will be receiving both an experimental drug and traditional supportive care.

In a recent blog post for Harvard Law School, Coleman writes that using a placebo would give investigators better confidence that the outcomes are the result of the experimental drug instead of supportive care.

Alternate Viewpoints

But a group of researchers and bioethicists, including London School of Hygiene and Tropical Medicine Director Peter Piot, points out in *The Lancet* that not all trials supporting U.S. regulatory approval use placebo controls. They note, for example, that therapies for aggressive cancers with poor prognoses are tested without placebos and accepted by regulators. In such cases, postmarket monitoring is relied upon to give a fuller picture of the drugs' safety and efficacy.

Piero Olliaro, head of intervention and implementation research at WHO's Special Programme for Research and Training in Tropical Diseases, and a coauthor of *The Lancet* piece, says the FDA recently approved two drugs for multidrug-resistant tuberculosis without comparative trials.

Besides, the group contends, placebo-controlled trial designs don't account for current on-the-ground facts in West Africa. Placebo controls are appropriate for situations where there is reasonable cause to believe that an intervention's risks might exceed those of conventional care, the article says.

In this case, "conventional care," which mostly involves rehydration and treatment of other infections such as malaria, still has a mortality rate of about 55 percent, Olliaro tells *CTA*.

At that rate, no one would consent to be potentially randomized to placebo, the paper says.

The Value of Supportive Care

In a paper published in the *New England Journal of Medicine*, the FDA's Cox argues that differences in the quality of supportive care in a placebo-controlled trial might make all the difference. Patients involved in these trials will likely be given more aggressive supportive care than patients treated before the trials began, and it will be very difficult to determine whether any difference in outcomes is due to the experimental drug or to quality of supportive care, he writes.

"In a randomized trial, by contrast, all patients would receive similar supportive care, so that the effect (or lack of effect) of the added treatment could be assessed," Cox adds.

The FDA leaves some wiggle room. Cox says sponsors and investigators should use adaptive elements in their trials, incorporating therapies that show clear benefit into current standards of care and using them as controls in future trials of other Ebola drugs.

The three-drug trial being conducted at Oxford University does have some adaptive elements built into its design, Olliaro says. The drugs will be classed into three groups: those showing up to a 50 percent survival rate will be discarded as ineffective, drugs with survival rates around 80 percent will be deemed effective and drugs in the middle will be pegged for further study. — Lena Freund

BRIEFS

HHS Updates Global Standards List

Ghana, Guinea, Liberia, Malaysia, Saudi Arabia, and Sierra Leone have been added to HHS' 2015 compilation of international research standards. The list includes links to more than 1,000 laws, regulations and guidelines in 113 countries, classified as general research, drugs and devices, research injury, privacy/data protection, human biological materials, genetic research, and embryos, stem cells and cloning. View it at www.fdanews.com/12-09-14-researchstandards.pdf.

OHRP Extends Comment Deadline

Stakeholders have until Jan. 22 to comment on draft guidance on dealing with reasonably foreseeable risks in standards of care research. The Office of Human Research Protections extended the original Dec. 23 deadline due to stakeholder concerns it didn't provide sufficient time for a full review. The guidance directs sponsors of trial comparing two or more standards of care to ensure that enrollees understand the pros and cons of each treatment option (*CTA*, December 2014).

MHRA Names Clinical Director

Janet Valentine has been named director of the Medicines and Healthcare products Regulatory Agency's Clinical Practice Research Datalink. She previously was head of population health and informatics at the Medical Research Council. CRPD kicked off three years ago and is jointly funded by the MHRA and the UK's National Health Service.

OHRP Seeks New SACHRP Members

HHS' Office of Human Research Protections is looking for candidates to fill two seats on its Secretary's Advisory Committee. Nominations are open until Feb. 12. Previous nominees will be considered.

Texting as a Recruitment Tool

Patients are five times as likely to answer a text message as an email, researchers studying the best methods to enroll clinical trial participants conclude. Over an eight-week period, the researchers sent 1,541 text messages, resulting in the screening of 795 patients and enrollment of 265. While people read about 98 percent of the texts they received — 90 percent in the first three minutes, the researchers found only about 22 percent of emails were read. Noel Chandler, cofounder and CEO of Mosio, which made the texting tool, said the study demonstrates that "text messaging through a strategic and powerful patient engagement platform is an effective tool to engage patients for clinical trial recruitment and enrollment by connecting with participants on the devices they use every day."

J&J Kicks Off Ebola Vaccine Trial

Johnson & Johnson has initiated a Phase I trial of its experimental Ebola vaccine, sponsored by the Oxford Vaccine Group in the UK. The company also ramped up production of the vaccine, which joins at least one other candidate from GlaxoSmithKline and the National Institutes of Health. As of this month, J&J had produced some 400,000 regimens of the dual-shot vaccine. GSK's vaccine is set to enter a Phase II trial.

Medidata: mHealth Can Help In Tracking Patient Outcomes

Mobile health programs can unburden clinical trial sponsors and investigators by streamlining procedures, eliminating unnecessary activities and reducing site visits, according to GlaxoSmithKline and Medidata. The companies studied the effects of two mobile health devices on trial efficiency.

During the course of the joint study, conducted over four days in October by GSK's Human Performance Lab, patients were given a wrist device and a skin patch and asked to go about their lives normally while their smartphones captured data from the devices and sent it to a clinical cloud app.

Capturing endpoint data in this way, rather than during an in-office visit, has the potential to reduce both the number of visits and procedures carried out during those visits, says Kara Dennis, vice president of Medidata.

According to Dennis, mobile health devices can record as many as 18 million data points per day, including a person's activity levels, skin temperature or respiratory or heart rate, and sleep patterns. Some can even determine whether a patient is upright or reclining, she says.

Giving patients the ability to see and track their own data may also encourage trial participation and reduce drop-out rates, she adds.

Mobile health devices could also be used to simplify the extensive data checking and monitoring that sites and sponsors perform throughout clinical trials. "As it's being streamed, data can be checked for outliers or potential issues," Dennis tells *CTA*. "That can reduce a lot of the work effort associated with quality checking of data."

Medidata plans to support a number of Phase I-IV clinical trials with mobile devices, once data from the joint study are in. — Lena Freund

Tufts Pegs CROs, Cancer, Trial Design Hottest Trends of 2015

Drug sponsors are expected to expand their investments in developing new cancer therapies this year, spurred by a growing understanding of tumors' molecular bases and immunotherapy techniques, according to a new report that projects pharma and biotech trends for 2015.

Roughly 40 percent of all orphan drug approvals over the next five years will target cancer indications, says Kenneth Kaitin, director of the Tufts Center for the Study of Drug Development and the author of the 2015 Outlook Report.

Continued development of biosimilars also will be a key focus this year in both the U.S. and Europe, Kaitin says. In the fourth quarter of 2014, several hundred companies were testing biosimilars, with 30 to 40 molecules in late-stage trials in the U.S. and the European Union, he notes.

This trend will be aided by anticipated FDA guidance in 2015 on topics such as biosimilars labeling, demonstrating interchangeability and using statistical approaches to show biosimilarity.

In addition, sponsors this year will focus on improving clinical trial efficiency by working more closely with CROs. Drug companies and CROs together will make greater use of adaptive trial designs and mining big data, Kaitin says. Access to large, comprehensive data sets will help sponsors perform better predictive analyses, refine research and protocol designs, engage volunteers, track metrics in real time and improve regulatory submissions.

A shift to more adaptive trial designs, such as sample size reestimation, early futility, dose-response and randomization ratios, will both increase data quality and clinical trial success rates, the report says. Congress and the FDA are expected to support drugmakers' moves in this area through new legislation and regulations that create single pathways for testing multiple drugs at the same time.

Read the 2015 Outlook Report at http://csdd.tufts.edu/reports/outlook_reports. — Lena Freund

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potential payments resulting from adverse events during informed consent sessions.

The guidance includes a formula to calculate the amount of that compensation. That formula was finalized in June, though it still required Supreme Court approval. Payouts range from $7,000 to about $124,000. In extreme cases in which a patient will likely die within 30 days, compensation is set at about $3,500.

In May, draft guidelines were released requiring sponsors to cover the medical costs of patients harmed during the course of the trial "as long as required or till such time it is established the injury is not related to the trial." Drugmakers may now be absolved of responsibility for an injury not resulting from the trial — but the onus is on them to prove a lack of causation.

Ebola drugs: During the second half of 2014, sponsors around the globe scrambled to develop therapies to combat or protect against Ebola. A much-lauded vaccine produced by the National Institutes of Health and GlaxoSmithKline is the farthest along in development, with all 20 healthy volunteers in a Phase I trial reacting well to the vaccine, producing both Ebola antibodies and T cells. Phase II trials are planned in Senegal, Ghana, Mali, Nigeria and Cameroon by the second week of February, GSK spokeswoman Jenni Ligday tells *CTA*.

Many companies are also developing therapies for patients already infected with Ebola. San Diego's Mapp Biopharmaceutical's monoclonal antibody ZMapp was given to a number of doctors and nurses treating patients in Sierra Leone, Guinea and Liberia. Also on the map are Tekmira Pharmaceuticals' TKM-Ebola and Chimerix's brincidofovir, as well as vaccines by NewLink Genetics and Janssen.

Coming Up?

"I think the biggest issue is probably going to end up being risk-based monitoring and centralized monitoring," says Darshan Kulkarni, the principal attorney at the Kulkarni law firm. Sponsors and investigators are still confused about what exactly the FDA means when it says it expects stakeholders to primarily engage in this kind of monitoring, he tells *CTA*. In a multisite trial, does it mean that one site is responsible for monitoring another site? "There's a lot of confusion about what the expectations are," Kulkarni says.

Kulkarni also expects the momentum on trial transparency to rev up in the year ahead. He notes that HHS has been releasing a lot of data over the last 18 months or so, and he expects the FDA will join in and release data sets that include noncommercially confidential information, such as adverse event reports.

U.S. regulators will also likely be dedicating more time and effort to guidance on how to provide aggregate clinical trial results that can be returned to patients without violating antipromotion statutes, says Ropes & Gray partner Mark Barnes. — Lena Freund

FDANEWS

Customer Service
(888) 838-5578 • +1 (703) 538-7600
customerservice@fdanews.com

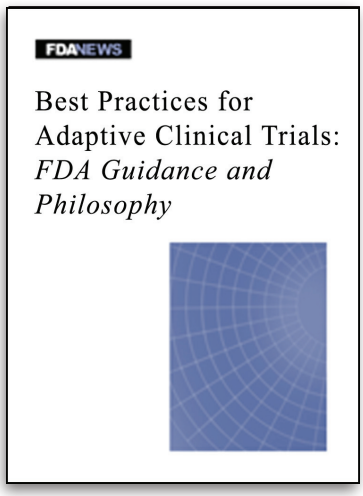
Editor: Lena Freund
(703) 538-7660
lfreund@fdanews.com

Ad Sales: Jim Desborough
(703) 538-7647
jdesborough@fdanews.com

300 N. Washington St., Suite 200 • Falls Church, VA 22046-3431 • Phone: (888) 838-5578 • +1 (703) 538-7600 • Fax: +1 (703) 538-7676
www.fdanews.com

Reporters: Elizabeth Orr, Robert King, Kellen Owings, Bryan Koenig, Jonathon Shacat

President: Cynthia Carter; **Content Director:** Dan Landrigan; **Executive Editor:** Meg Bryant



Best Practices for Adaptive Clinical Trials: *FDA Guidance and Philosophy*

Adaptive clinical trials are one of today's best tools for finding new drugs that improve on existing therapies in targeted populations. Now, take your own planning and preparation to the next level by turning the FDA's preferences into rock-solid best practices for speeding your approval.

By combining a concise overview with a detailed analysis of FDA's preferences, this one report advises you on everything thing from the best trial model to use to the best way to avoid technical problems with final data analysis. Turn the **FDA's own guidance** and **examples** of acceptable modifications into real-world best practices for "rejection-proofing" your adaptive clinical trials, including:

- **Prospective Planning:** How to anticipate the types of modification that will occur in trial design to avoid what the FDA does not want to see in terms of making changes to dosing, exclusion criteria, target subject populations and other criteria.
- **Trial Models:** What the FDA considers valid vs. invalid models for adaptive trial design — what questions adaptive designs raise — and how best to answer them.
- **Controls:** How to factor in bias and error controls early in the design phase to present the FDA with assurance that sponsors won't simply see what they want to see in the interim results.
- **Protocols and Statistical Analysis Plans:** How to pull all elements of the adaptive clinical trial together into protocols and plans that support the trial effectively from startup through reviews and final data analysis.
- **Trouble Shooting:** How to spot and avoid common difficulties that may arise in adaptive trials; the FDA's central concerns — the agency's most frequent complaints about adaptive trials.

Don't let technical problems derail your adaptive clinical trial!

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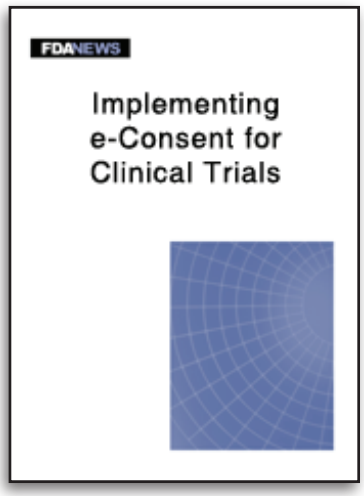

Implementing e-Consent for Clinical Trials: *Pitfalls and Practical Considerations*

Long, dense clinical trial informed consent documents may satisfy the lawyers, but they don't satisfy anyone else. They're difficult for study subjects to understand. Time consuming for investigators to deliver. Arduous to audit and monitor. And, as changes to study documents take place, the forms are a version control nightmare.

All that is why some sponsors and CROs are looking toward electronic consent. The challenges of e-consent fall into two categories: technical and regulatory. If done right, adopting e-consent technology will yield tremendous benefits. In this management report, you'll learn how the technology of e-consent can:

- Overcome language and literacy barriers
- Simplify data gathering and remote monitoring
- Maintain version control and audit trails
- Speed up trial enrollment
- Improve investigator compliance

In addition, the report offers a step-by-step approach to making sure your e-consent processes align with regulatory requirements. It shows you:

- How you must work with the IRB when initiating e-consent
- Essential features that every e-consent system must have for compliance
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