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Industry Leads in Reporting Results To ClinicalTrials.gov, Study Finds

The drug industry outperforms academic researchers in reporting clinical trial results on clinicaltrials.gov., according to a group of Duke University researchers.

At one year after the end of a trial, 17 percent of industry-funded studies had reported results, compared with 8.1 percent of NIH-funded trials. Trials funded by other government or academic sources were even less likely to have reported results — just 5.7 percent.

Earlier-phase trials and trials without FDA oversight were also less likely to be reported. Of the trials that did not report results, 6.1 percent had some kind of legal certification or exemption request.

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FDA Finalizes Guidance On Critical Path Meetings

The FDA has laid out the procedures drugmakers should follow in preparing for critical path innovation meetings designed to bring drugmakers, patient groups and regulators together to decide how to use experimental and untested methodologies that can advance drug development.

The FDA lists five available topics for a CPIM:

- Biomarkers in the early phase of development but not yet ready for the Biomarker Qualification Program. CPIMs can help sponsors to prepare proposed biomarkers for qualification;
- Clinical outcome assessments in the early phase of development but not yet ready for the Clinical Outcomes Assessment Qualification Program. Likewise, the meetings may assist companies in developing COAs and preparing them for qualification;
- Natural history study designs and implementation. Here, the CPIM could aid in designing studies that generate data useful in planning interventional clinical trials, the FDA says;

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The gap closes among older trials. Looking at trials that were five years post-completion, 41.5 percent of industry-funded trials had reported results, while 38.9 percent of NIH-funded trials and 27.7 percent of trials paid for by other sources had reported. For trials that reported results, the median time that it took sponsors to do so was 14 months for industry, 23 months for the NIH and 21 months for others.

Later-stage trials were also more likely to report results on time, the researchers concluded, possibly because earlier-phase trials often focus on demonstrating proof-of-concept and tend to be considered valuable, closely guarded intellectual property.

In attempting to explain the industry/academia discrepancy in reporting times, the authors note that preparing results summaries can take up to 60 hours of staff time, which may not be paid for by government research grants.

Overall, about 80 percent of industry-sponsored studies either reported results or had a legal reason for delay. This number decreases to 50 percent for NIH-sponsored studies and 45 percent for other studies.

The researchers looked at 13,237 trials that they projected should have reported at least one primary outcome to the government website within one and five years after completion.

One way to encourage more parties to report results may be to ramp up enforcement of existing legal penalties, such as publication of "failure to submit" notices and lists of sanctions on clinicaltrials.gov, the authors suggest. They note the government may be reluctant to enforce its reporting requirements because the proposed rule that better defines them is still open for public comment (*CTA*, December 2014).

The research was published in the *New England Journal of Medicine*. Read the article at www.fdanews.com/03-12-15-resultsreporting.pdf. — Lena Freund

EMA Updates Recommendations For Blood Clot Treatment Trials

The European Medicines Agency is revising the way drugmakers conduct studies for drugs to treat blood clots, for the first time separating out the clinical requirements for different types of clots.

The updated guideline adds recommendations for testing drugs for superficial vein thrombosis, or clots that are close to the skin, as opposed to deep in the legs. Trials for sVT should enroll patients with extensive, symptomatic clots that are at least 5 cm long, the guideline says. Primary endpoints should focus on extension or recurrence of these clots — via documented extension or recurrence of superficial clots, or documented symptoms of deep vein clots or nonfatal clots in the lungs.

Noninferiority trials for these near-surface clots should use clot-related deaths as a primary endpoint, while superiority designs should look at all-cause deaths, the EMA recommends.

The agency generally wants study drugs evaluated against active comparators in Phase III trials, but leaves drugmakers the choice of which comparator to use in certain patient groups.

Sponsors treating patients with first-time clots, for example, may use either direct oral blood thinners or some combination of an oral vitamin K antagonist and an anticoagulant, such as low molecular weight heparin. Sponsors should follow these patients for the first time for three months to a year, the EMA says. For patients who are at high risk of recurrence, the treatment period should be at least six months with one month of follow-up.

For special patient populations whose clots resulted from another condition, such as pregnancy or cancer, however, low molecular weight heparin is the best choice, the EMA says.

The EMA also recommends secondary safety outcomes include stroke, heart attack, death

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Study Points to Trial Length as Target for Policy Changes

The FDA needs to work with medical device-makers and Congress to understand why clinical development takes longer here than in other countries and then implement changes to speed up the process, a new study concludes.

Changes could include the FDA's recent expedited access PMA proposal, which would allow approval of some innovative devices after smaller or shorter clinical trials. Under such a program, the agency could have granted earlier approvals for innovative products looked at in the study, say Joshua Rising and Ben Moscovitch of the Pew Charitable Trusts.

In a first-of-its-kind study, Rising and Moscovitch analyzed public data on clinical trials and premarket reviews for devices intended to fill an unmet need. The study in *PLOS One* looked at pivotal trial length, primary endpoint, FDA review, the number of trial patients and country of first approval.

Median Trial Length

Of 27 approved priority review devices from January 2006 through August 2013, most were available in other countries before they got U.S. approval, the authors note. And while FDA reviews can take years, pivotal clinical trials were responsible for more of the development timeline and delays getting to market.

The median length of pivotal trials was three years, with some taking as long as seven years. Trials had a median primary outcome measure evaluation time of one year and a median enrollment of 297 participants. Meanwhile, median FDA review time for the devices in the study was one year and three months.

Many efforts to speed device innovation focus on FDA reviews, but this study shows that reduction of clinical trial time should be another key target for new policies, the authors say. These should address not only the length of clinical trials but also contributing factors like primary outcome measures and enrollment. They urge the FDA to work with manufacturers, researchers and federal agencies to narrow the gap between primary outcome completion and overall trial length.

The study also found that about one-quarter of priority review applications received during the time frame were not approved. "This indicates that devices considered to be innovative advances were not able to meet FDA's standards for safety and/or effectiveness," the authors write.

Had those devices been approved under the EAP process, postmarket data may have shown they did not meet FDA standards. For the process to work, the FDA must have strict postmarket controls, the authors stress. The agency also needs authority to remove products from market soon after finding they fall short of FDA standards.

The article is available at journals.plos.org/plosone/article?id=10.1371/journal.pone.0117235. — April Hollis

Study: Informed Consent Process Needs Rethinking in Big Data Era

Future models for obtaining informed consent from patients in secondary data-based studies need to consider patients' feelings about when they feel further consent should be required, a recent study concludes.

The current consensus — that research participants should consent anew to any new use of their data — may no longer be feasible, considering the volume of information amassed in large-scale international big data studies, researchers from the University of Exeter and Kings College London in the UK say.

In looking at what motivated patients to allow use of their data in a subsequent study, trust emerged as a major factor.

(See **Informed Consent**, *Page 4)*

Electronic Informed Consent Forms Should Be Secure: FDA

Clinical trial sites using software to obtain patients' informed consent remotely should make sure the data is stored securely, the FDA says.

That means any computerized system used for presenting and obtaining informed consent information should be encrypted and restricted to authorized personnel, the agency says in March 6 draft guidance on handling electronic informed consent.

It must also include methods to ensure the confidentiality of the subject's identity, participation and personal information after giving consent. For example, information stored on a remote computer or in the cloud should comply with the site's data privacy rules and with rules such as the Health Insurance Portability and Accountability Act, and data storage or processing agreements should detail both the investigator's and the associate's responsibility to comply.

The FDA leaves the door open for companies and sites to determine how best to design electronic informed consent software and to present it to patients. The agency asks, for example, that informed consent programs ensure that any signatures actually come from the patient or a legally authorized representative, but makes no specific suggestions on how best to assure this.

The guidance does make clear that electronic informed consent forms must contain all the elements the FDA requires of paper versions, including presenting the information at the subject's reading level, along with explanations of scientific or medical terms, and spelling out all abbreviations at first usage.

Informed Consent Design

The documents should also be presented in a way that minimizes the chance of undue influence or coercion, the FDA says. This can be done using diagrams, images, video technology,

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The research team conducted an online survey of patients in the TwinsUK registry and found that people were more willing to allow their genetic or medical information to be used in a subsequent study without giving further consent if they knew the clinical investigator. When the investigator was someone new, willingness to forego additional consent fell.

Consent preferences differed somewhat depending on age and gender. Women and younger subjects, for example, were more likely to request reconsent, the study says.

The survey also found that patients were more willing to be automatically enrolled in a new study if it covered their illness. When it didn't, men were more likely to allow enrollment, as were older patients.

Read the study at www.fdanews.com/03-25-15-informedconsentstudy.pdf. — Lena Freund

EMA Releases Guideline On Lupus Trial Design

The European Medicines Agency has issued final guidance on clinical trial design for drugmakers developing targeted products to treat lupus — in an effort to encourage more companies to target the underserved disease.

The final guideline, which takes effect Sept. 1, lays out how trials should be designed to show either complete remission or major or partial clinical response specific to lupus. Most lupus treatments, such as corticosteroids or antimalarials, are not specific to the disease, according to the Lupus Foundation of America. Only GlaxoSmithKline's Benlysta (belimumab) targets lupus specifically.

To demonstrate complete remission, patients must show no lingering lupus symptoms and require no ongoing drug treatment, the EMA says. Major or partial clinical responses should be measured by disease scales, including the Systemic Lupus Erythematosus Disease Activity Index that assigns points commensurate with onset and severity of symptoms.

To show short-term efficacy, sponsors need four-to-eight week trials, but establishing longer-term or chronic disease outcomes may require trials lasting up to a year.

Include Patient Responses

In addition to establishing clinical efficacy, sponsors should include patient-centric response measures, such as health-related quality of life, in their trials, the guideline says. This could involve use of tools such as the Lupus Quality of Life checklist, or it could mean measuring levels of one specific serious symptom, such as fatigue.

The EMA prefers double-blind, parallel group, randomized superiority trials that evaluate the study drug against an active comparator. If a sponsor chooses to use a placebo as a comparator, patients on placebo must be given the current standard of care, the EMA says.

Studies targeting forms of lupus that primarily affect the kidneys should use outcomes such as improvement in protein or other sediments in patient urine or improvements in creatinine levels in the blood that specifically measure kidney symptoms. Patients should be followed for three to six months to track partial responses, and for at least a year to document a complete response, the EMA says. Preventing kidney flare-ups or long-term organ damage could also be primary endpoints in these cases, the agency adds.

Read the final guideline at www.fdanews.com/03-27-15-EMAlupusguideline.pdf. — Lena Freund

FDA, DOJ Pursuing Cases Of Clinical Trials Fraud

The FDA and Department of Justice are pursuing prosecutions of several international drugmakers, investigators and clinical trials coordinators for conduct and data integrity violations, underscoring the agency's increasing tendency to treat quality violations as fraud.

The information was released March 19 in the HHS inspector general's annual report on activities of the pharmaceutical fraud program, which provides a look at the types of prosecutions the FDA and DOJ are pursuing.

Overall, the FDA opened 24 criminal investigations during the 12-month period ending Sept. 30, 2014, one more than the previous year. Of those, 12 involved fraudulent clinical trial data submissions — the most common agency investigation last year.

Charges include improperly conducting clinical trials, falsifying data, forging investigators' signatures, enrolling ineligible or nonexistent subjects and falsifying FDA approval or clearance applications, according to the report.

The report notes one completed trial-related prosecution in 2014: a clinical trial coordinator pleaded guilty to falsifying patient data and is currently awaiting sentencing.

HHS' healthcare fraud and abuse control programs recovered $3.3 billion through civil penalties during the period, with payments from drugmakers representing the bulk of the settlements.

See the full report at www.fdanews.com/03-19-15-HealthFraudReport.pdf. — Bryan Koenig

Clot Treatment Trials, *from Page 2*

resulting from clots, fatal lung clots or sudden, unexplained deaths for which lung clots can't be ruled out. Sponsors should categorize deaths as "nonvascular," "vascular" or "unknown etiology."

All patients should be followed for bleeding complications over the same time period, regardless of stratification, the EMA says.

The guideline updates definitions for different types of bleeding that sponsors should use as primary safety outcomes.

For example, "major bleeding" is defined as an intracranial, intraocular, intraspinal, pericardial, retroperitoneal, intra-articular or intramuscular event that causes hemoglobin to drop more than 2 g/dL, requires transfusion of two or more units of blood and necessitates surgery or is fatal.

When it comes to diagnosing clots, the EMA recommends commonly used methods such as bilateral compression ultrasonography or pulmonary angiography, as well as newer methods, such as computed tomography venography and magnetic resonance venography.

CTV is similar to ultrasound in diagnosing deep vein thrombosis and allows clinicians to see the pelvic and deep femoral veins, leading to detection of an additional 3 percent of cases, the agency notes.

Comments are due to CVSWPSecretariat@ema.europa.eu by Sept. 30. View the guideline at www.fdanews.com/04-01-15-EMAbloodclotsguidance.pdf. — Lena Freund

eConsent, *from Page 4*

graphics or narration, and should be flexible enough to account for a patient's age and language proficiency, the guidance says.

Patients should be able to navigate the programs easily, with options to move forward or back a page or stop and continue at a later time.

The FDA also suggests that designers and sites incorporate methods of gauging patients' comprehension, possibly through questions at the end of each section.

Patients should have the opportunity to ask questions and get answers before signing, either through in-person discussions or some combination of electronic messaging, phone calls, videoconferences or live chats.

Patients should retain the appropriate contact information for any follow-up questions or reports of adverse events, the FDA says.

The guidance reminds sites that institutional review boards are responsible for overseeing the evolution of informed consent technology and urges investigators to communicate with their IRBs before finalizing any software.

Comments are due to regulations.gov, docket no. FDA-2015-D-0390, by May 8. Read the draft guidance at www.fdanews.com/03-06-15-informedconsent.pdf. — Lena Freund

Ontario Streamlines Trial Ethics Oversight in New System

Ontario, Canada, is jumping on the centralized-IRB bandwagon with a simplified ethics review program that went live recently.

Historically, sponsors have needed a separate research ethics review at each institution participating in the same clinical trial, says Susan Marlin, a spokeswoman for Clinical Trials Ontario.

By contrast, the streamlined research ethics review system allows any qualified ethics board to review multiple research sites in multicenter clinical trials.

CTO's system will lessen everyone's workload by allowing an investigator or sponsor to enter the system and fill out just one form describing the trial and its sites, Marlin tells *CTA*. The form will cover both the initial review and any ongoing review that may be needed as details of the trial change.

Once the documentation is in place, CTO will find an IRB to review the protocols at each site of the trial, based on that single submission.

The system is expected to cut the time it takes to complete initial start-up and other critical trial phases from two to six months to just days, Marlin says.

"If 10 IRBs review a study [at 10 different sites], each is going to come back with different questions, or with the same questions," which can take a lot of time for the sponsor to sort out and respond to, she adds.

CTO's system mirrors a recent National Institutes of Health draft policy released in January that encourages sponsors of multisite clinical trials to make use of a single IRB. — Lena Freund

MHRA Releases Trial Approval Statistics

The UK's Medicines and Healthcare products Regulatory Authority approved approximately one-quarter of Phase I and one-third of Phase II-IV clinical trials on first review between April 2014 and March of 2015.

That means that approximately three-quarters of Phase I trials and two-thirds of other trials were referred for "grounds for nonacceptance," during that time, according to a report released March 10. The report contains statistics on the number of commercial and noncommercial trials approved, the number of applications submitted and the time it took the agency to review those applications.

More specifically, regulators approved 41 trials on first review in 10 to 15 days, the report says. For 101 applications that were denied, the first review times were the same, but sponsors then took about two weeks to issue responses. The MHRA conducted a second review in about 1.5 weeks.

In the Phase II-IV group, 211 applications were approved after first reviews lasting approximately 2.5 weeks.

First reviews of denied applications took much longer — nearly 4 weeks. Sponsors spent more than three weeks preparing responses, but second review times declined to just five or six days.

Between April 2014 and February 2015, the month-to-month volume of Phase II/III trial applications ranged from a low of two to a high of 15, while the number of Phase IV trials applications ranged from six to 17.

Total average review times were between 18.5 and 25.9 days.

Read the report at www.fdanews.com/03-12-15-MHRAtrials.pdf.
— Lena Freund

European Drugmakers Ask to Defer Disclosure of Trial Information

The UK BioIndustry Association and EuropaBio are calling on European regulators to defer plans to report Phase I clinical trial reports, saying the information they contain is commercially sensitive.

Under the European Medicines Agency's transparency policy, sponsors would have to report summary results of Phase I trials 12 months after the trial's end.

In a consultation launched last month, the agency also said it is considering releasing summaries of trial protocols, preliminary assessments of early trial results, the agency's decisions on trial submissions, including reasons for not authorizing a trial, and reasons for withdrawal if the sponsor decides not to proceed (*CTA*, February).

BIA worries that a 12-month time period for disclosing summary results would significantly cut down the window for filing and securing patents, spokeswoman Jessica Gray tells *CTA*.

"A company or researcher may require longer than 12 months to prepare and file appropriate patent applications for innovative approaches or uses discovered during early stages of development, as the results of the Phase I trial may be needed to support these applications," she says.

The EMA has proposed several scenarios under which sponsors would be required to report study-specific and product-specific documents, such as investigator brochures with clinical and nonclinical data on the investigational product and a technical and scientific description of the product.

For trials of not-yet-approved products, for example, the EMA suggested letting sponsors post these documents at the time of decision on the trial, the time of marketing authorization or nine years after the first summary results are posted for Phase I and II trials, or the time when the first summary results are posted for Phase III trials.

Comments on the proposals have closed. — Lena Freund

Critical Path, *from Page 1*

- Emerging technologies — other than manufacturing technology — or new uses of existing technologies. The CPIM may help sponsors weigh the value of using these technologies at different stages of drug development; and
- Novel approaches to clinical trial design and analysis.

CPIM requests should be submitted electronically and include the requester's name, date of request, type of organization, purpose of the meeting and desired outcome. CDER will respond to meeting requests within 14 days.

The meetings, described in final guidance released March 30, are part of ongoing efforts to modernize the agency's drug approval process and encourage the use of new technologies. The guidance is unchanged from an October draft.

View the guidance at www.fdanews.com/03-30-15-CriticalPathGuidance.pdf. — Bryan Koenig

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