Clinical Trial Transparency Is Up for Grabs
The FDA and Congress Are Expanding Public Access to Data
Stephen Barlas

Pressure from patient advocacy groups, Congress, and the National Institutes of Health (NIH) probably had more than a little to do with Johnson & Johnson’s announcement in May that it was establishing an outside advisory board to recommend ways J&J can expand access to experimental therapies in its clinical trials.1 J&J’s effort will focus on patients arguing for “compassionate use.” Its Janssen Pharmaceutical Companies will pilot the program, but the first experimental drug to be subject to the panel’s recommendations has not been named. Janssen typically establishes an expanded-access program (EAP) for investigational medicines when a favorable benefit–risk profile has been reported in a pivotal trial and a viable regulatory path to approval has been confirmed with a health authority.

By definition, every drug in pre-approval clinical trials is an experimental drug, although not all are for “serious or life-threatening” diseases, which is the category where compassionate use comes into play. But a wide range of disease advocacy groups, not all of them contending with life-threatening ailments, has criticized the U.S. clinical trial system. Some of their concern involves inadequate access for potential compassionate-use patients and lack of information about existing company programs in that area. But there is broader unhappiness with the opacity of the ClinicalTrials.gov website, administered by the NIH’s National Library of Medicine (NLM). That registry contains some information about some of the clinical trials being conducted in the U.S.

At hearings of the House Energy and Commerce Committee’s health subcommittee on April 30, 2015, U.S. Rep. Leonard Lance (R-New Jersey) told of receiving a letter from a constituent whose son had recently died from brain cancer. The father voiced “deep concern and frustration” with ClinicalTrials.gov after trying and failing to find a clinical trial his son might have qualified for. “Not only did the site lack a significant amount of information, but it was also confusing and ultimately unusable,” Lance stated. He and another member of the committee, U.S. Rep. Morgan Griffith (R-Virginia), have authored a provision included in the committee’s draft 21st Century Cures proposal2 that would improve ClinicalTrials.gov. Both Democrats and Republicans on the committee have been working on a 21st Century Cures proposal for more than a year. The bill is meant to modernize the U.S. clinical trial system. Some of their concern involves inadequate access for potential compassionate-use patients and lack of information about existing company programs in that area. But there is broader unhappiness with the opacity of the ClinicalTrials.gov website, administered by the NIH’s National Library of Medicine (NLM). That registry contains some information about some of the clinical trials being conducted in the U.S.

Among ClinicalTrials.gov’s perceived shortcomings is a lack of clarity about who should register, underlined by the fuzziness of terms such as “applicable clinical trial” and “responsible party.” According to Ann C. Bonham, PhD, Chief Scientific Officer of the Association of American Medical Colleges (AAMC), “The current ClinicalTrials.gov database lacks a structure that renders the reporting of clinical trials results usable to many clinical investigators who wish to build on the reporting and results of their peers.”

NLM Is Finally Implementing a 2007 Law
The exasperation with ClinicalTrials.gov may be growing because that online registry was supposed to be expanded eight years ago after Congress passed Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA).3 That title included a provision to enhance patient enrollment, provide a mechanism to track subsequent progress of clinical trials, provide more complete results, and enhance patient access to and understanding of the results of clinical trials. Those provisions were a tip of the hat to stated concerns about potentially misleading information on adverse effects and the lack of clinical trial recruitment among certain population groups, such as women, minorities, and older adults. “Numerous studies have found that these populations have long been under-represented in cardiovascular clinical trials,” says Elliott M. Antman, MD, President of the American Heart Association.

Last November, the NLM finally issued a proposed rule implementing the 2007 amendments and suggesting various implementation steps.4 The wide-ranging proposal touches on compassionate-use access—for example, via a requirement for companies to create an expanded-access record within ClinicalTrials.gov—and many other issues, all aimed at broadening the data available about clinical trials, as well as how and when that data will be made publicly available. A key element of the proposed rule was a requirement for “structured data entry,” which the NLM says is necessary “to enable the clinical trials data bank to accommodate the full range of study design and data types common or emerging in the clinical trials community, while simultaneously ensuring that all required data elements are provided; optimize the presentation of submitted data, including adverse event information, for various types of users, including those with less experience in interpreting information about the relative risks and benefits associated with particular interventions; and allow for efficient search capabilities, including searching by the data fields specified by the statute.”

But drug and device manufacturers are attempting to fight off a number of key components of the NLM’s proposed rule—apparently with some success, much to the dismay of patient advocacy organizations and physician groups. Even the AAMC, which has criticized the registry’s unwieldy structure, has raised concerns about the potential new data-reporting requirements. “The pro-

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posed rule may actually go to the other extreme, establishing an overly complicated, "one-size-fits-all" structure," Dr. Bonham states.

At the April 30 hearings of the House health subcommittee, Kathy Hudson, PhD, NIH Deputy Director for Science, Outreach, and Policy, stated, "The structured data elements may be less useful at the end of the day." She added that while she wants to make sure people can get the information they need, she does not want to place "inordinate burdens" on researchers, nor does she want to "box them in in ways that would be less useful for people trying to retrieve the information."

At the same time its NLM unit issued the proposed rule last November, the NIH issued a draft policy that would apply the same registration and reporting requirements in the proposed rule to all clinical trials funded by the NIH, including phase 1 trials that are not otherwise subject to registry reporting and trials of behavioral and other interventions not regulated by the FDA.2

21st Century Cures Bill Prods NLM Further

Reflecting the political potency of the issue of patient access to clinical trials, Congress is seeking to pass new legislation even as provisions of the 2007 FDAAA remain unrealized. The 21st Century Cures initiative sponsored by the Democratic and Republican leaders of the House Energy and Commerce Committee contains numerous provisions related to clinical trials.3 Section 1102 would enhance patient searches for ongoing trials by requiring NIH to standardize certain patient inclusion and exclusion information across all trials housed in ClinicalTrials.gov. Section 1121 would create a third-party system for sharing scientific research for trials funded solely by the federal government in order to allow the use and analysis of data beyond each individual research project. Another provision (Sections 2082–2083) would institute transparency requirements for certain drug companies regarding their expanded-access programs and require the FDA to finalize guidance regarding how it interprets and uses adverse drug-event data resulting from use of such expanded-access programs.

“The Lance/Griffith proposal centers on connecting patients with viable treatment options in what is now a very difficult field to connect in,” explains John Byers, a spokesman for Lance. "By standardizing the data we will clarify the expectations of both the trial and the patient.”

NLM’s Proposed Rule Stirs Industry Opposition

The ClinicalTrial.gov provisions in the draft 21st Century Cures proposal would essentially add a thin layer of new requirements on top of those the NLM is already considering. The 2007 law mandated a number of new requirements and deadlines for their implementation: registration information in 2007, summary results information for clinical trials of approved products starting on September 27, 2008, and adverse-events information by September 27, 2009. Those requirements are in effect, but the NLM’s proposed rule expands the reporting requirements in each instance. The proposed rule does not impose requirements on the design or conduct of clinical trials or on the data that must be collected during clinical trials. Instead, it specifies how data that were collected and analyzed in accordance with a clinical trial’s protocol are to be submitted to ClinicalTrials.gov. No patient-specific data are required to be submitted under this proposed rule or under the law that this proposed rule is intended to implement.

Results would have to be submitted within one year of the completion of the clinical trial. That would apply to drugs that are still not approved by the FDA. Those results would include tables of data summarizing demographics and baseline characteristics of the enrolled participants and primary and secondary outcomes, including results of any scientifically appropriate statistical tests. Submission of results could be delayed for up to two additional years with certification that either 1) an unapproved, unlicensed, or uncleared product studied in the trial is still under development by the manufacturer; or 2) approval will be sought for a new use of an approved, licensed, or cleared product that is being studied in the trial. This proposed rule also permits responsible parties to request extensions to the results-submission deadlines for “good cause.”

Pharmaceutical Research and Manufacturers of America (PhRMA) says the proposed rule “represents an important step towards expanding ClinicalTrials.gov.” But the group believes that the proposed rule “can be improved in key ways that will enhance the utility of the database to patients and the general public and reduce the expected burden on research sponsors while also protecting the innovative process.”

Two of PhRMA’s key objection relate to having to report any data for unapproved drugs prior to discontinuation of that trial and the enumeration of “structured data elements.” The opposition to providing data on clinical trials involving unapproved drugs has to do with sensitivity about the possible inadvertent release of trade secrets. “For drugs that are unapproved but under active development, premature government-required disclosure of research results would benefit commercial competitors who may ‘free-ride’ of the investments made by other companies—and therefore perversely reduce incentives for innovative biomedical research,” says William W. Chin, MD, Executive Vice President of Scientific and Regulatory Affairs for PhRMA.

While the proposed rule allows a company to delay submission of those results for up to two years, Dr. Chin argues that this “limited and uncertain delay would not adequately mitigate the commercial harms of premature disclosure.” However, PhRMA supports information-sharing around discontinued research programs to avoid the loss of research knowledge on molecules that are not being actively developed into new medicines.

PhRMA is not alone among major biomedical trade groups in opposing the release of data on unapproved products. “We believe the disclosure of proprietary, confidential clinical trial data associated with products which are not approved, licensed, or cleared or other such disclosures of proprietary confidential information will chill interest in developing new and innovative devices in the U.S.,” says Tara Federici, Vice President of Technology and Regulatory Affairs for AdvaMed, which represents medical device companies. “Companies and venture capital firms will be reluctant to fund device development in the U.S. if disclosure of clinical trial information enables competitors to shortcut research and development for competing products. Unlike the drug industry where entire molecules are patented and are frequently patented even before the first clinical trial begins, patents provide little protection in the device industry.”

However, physician and patient groups want pre-approval information. “It may create opportunities to verify findings, develop an expanded understanding of how to use products (including for new indications), identify rare but serious side
effects, advance research to develop new treatments, and improve our understanding of the heterogeneity of the disease process,” says Peter P. Yu, MD, President of the American Society of Clinical Oncology. “In addition, the data could help improve the efficiency and reduce the costs of the clinical trial process by minimizing redundant trials.”

Some of the new data-reporting requirements don’t seem terribly onerous. However, the drug and device manufacturers are fighting many of the additions to current reporting. Dr. Chin explains that the NIH proposal would require submission of several data elements that increase the regulatory burden on research sponsors but do not create a corresponding benefit to patients, health care professionals, and the public.

Twenty-five specific data elements grouped into four categories must currently be reported: Descriptive information, recruitment information, location and contact information, and administrative information. Expanded information would be required in some of these categories. For example, the “IND/IDE protocol number,” already required, would have to include the name of the FDA center that issued the IND or IDE number and any serial number that has been assigned by the sponsor to that filing. Another new element would be whether the product under study is manufactured in the U.S. Clinical trials are often conducted overseas. If a clinical trial has not been required by law to seek approval from a human subjects protection review board, that would have to be indicated.

Adverse-Events Reporting

The requirement to submit data on adverse events (AEs) would seem to be more significant in terms of establishing the efficacy and safety of a drug. Here the NLM proposes to require the submission of the total number of human subjects affected and the total number of human subjects at risk for each organ system that has one or more serious AEs or one or more AEs that occur with a frequency that exceeds 5%.

The criticism of this data element is that it exceeds the “default requirements” of the Public Health Service Act. Those default requirements have to do with reporting of “serious AEs” as distinguished from plain “AEs,” and how those two types of AEs are presented in the registry. The current requirements have been in place since 2009 and, for the most, part, the NLM has argued that it is simply keeping them as is. That is true for the existing requirement to submit information about AEs by organ class for each arm of a trial, and for both serious AEs and other AEs. The wrinkle here—one that drug companies are not thrilled about—is that the NLM wants responsible parties to use the organ system classes specified in the Medical Dictionary for Regulatory Affairs (MedDRA) to classify the specific AE terms (e.g., nausea) by organ system.

“We sampled a number of our investigators currently posting results. None classified adverse events by organ system. And none were familiar with the MedDRA system,” states P. Pearl O’Rourke, MD, Director of Human Research Affairs for Partners Healthcare.

Another AE reporting enhancement would require trials to submit the total number of participants affected by an AE at the organ-system level. The objective here is to enable comparisons across arms even when there are variations in the level of specificity or granularity of the data submitted. However, the NLM probably did not go as far as some critics of its AE reporting proposal would have liked. For example, it is not requiring the number of occurrences of each serious AE (in addition to the number of participants affected by a serious AE), the number of occurrences of each serious AE considered causally related to the intervention(s) studied, the time frame for collecting AEs, the collection approach (systematic versus nonsystematic), and all-cause mortality information.

Compassionate Care Information Expanded

New requirements on reporting of expanded-access data are also at issue. The proposed rule doesn’t require drug companies to expand compassionate use, but it does require companies that have expanded-access programs to provide more information on that subject. Although it does not require any company to offer an expanded-access program, companies that do so would have to submit a separate expanded-access record containing details about how to obtain access to the investigational drug. If an expanded-access record has already been submitted in conjunction with a different clinical trial for the same drug, the responsible party for the new clinical trial could link to the existing expanded-access record rather than create a new one.

PhRMA has complained that implementing the NLM’s proposal could transform ClinicalTrials.gov into a pseudo-repository for expanded-access program information, which appears to go beyond the scope of Congressional intent. This might confuse vulnerable patients, who could incorrectly assume to their detriment that the records in ClinicalTrials.gov cover the universe of opportunities available to them. PhRMA believes that rather than having ClinicalTrials.gov serve as a repository for incomplete information on obtaining access to investigational products, biopharmaceutical companies and other research sponsors should establish their own telephone- or Internet-based information resources devoted solely to facilitating communication between health care providers and biopharmaceutical companies.

The NLM may want to wait before publishing a final rule to see whether Congress passes the 21st Century Cures bill, which the House Energy and Commerce Committee approved 51–0 on May 21. But whenever the final rule arrives, it probably won’t require ClinicalTrials.gov reporting to be quite as rich as some would prefer, given drug and device industry opposition to numerous elements of the proposed rule.

REFERENCES


