FDA: New Guidance for Expansion Cohort Trials

By Bill Myers

Expansion cohorts can help bring life-saving drugs to market quickly, but sponsors should be sure to update informed consent for patients and convene expert safety panels that meet regularly, the FDA says in new draft guidance.

In the 17-page draft, the agency says it wants to “establish an infrastructure” to help sponsors use cohorts to expand oncology trials swiftly without compromising safety. But that means sponsors would have to stay on top of rapidly changing developments—and keep their patients in the loop, too.

“It is critical that investigators, IRBs and regulators are updated with new safety information so that they can provide the necessary oversight for the protection of human subjects and so that investigators can ensure that patients can provide adequate informed consent,” the document stresses.

On its face, the recommendations aren’t radical, but they do acknowledge the pace at which these kind of adaptive trials are being adopted, says Lindsay McNair, chief medical officer at WCG Clinical.

“I think [the FDA] recognizes that these studies are unique in both the type of safety data that is accumulating during them and the speed and volume at which the data may be accumulated,” she says.

Perhaps the most well-known drug to come through an expansion cohort trial is

see Cohort Trials on page 4 »

NIH Delays Basic Brain Research Rules

By Bill Myers

NIH has delayed a controversial new policy that would have required basic brain and behavioral researchers to treat their work as clinical trials.

The measure, originally set to take effect next month, called for scientists who study human cognition or behavior — for example using brain scans with healthy volunteers — to follow the same rules as studies testing drugs or diagnostics, including registering their studies and publishing results in the ClinicalTrials.gov federal database.

NIH made the move in response to a 2016 Government Accountability Office (GAO) report that slammed the agency for failing to keep track of nearly $3 billion in taxpayer dollars it had allocated to support scientific research.

Psychologists and neurologists had pushed back against the policy, insisting it would subject them to extraneous government oversight of experiments that, in their view, didn’t involve any real risk to human subjects and made no sense for studies that weren’t testing a treatment.

They also balked about massive unnecessary paperwork and administrative nightmares they predicted the new requirements would create — and complained that some of NIH’s language about “priority” research could be misinterpreted and block funding for exploratory research and training.

see NIH Delays Rules on page 4 »
First Human Zika Vaccine Trial
Researchers are launching the first human trial of an experimental live Zika vaccine. The vaccine, which contains a weakened version of the virus, was developed by scientists at the National Institute of Allergy and Infectious Diseases (NIAID). The trial plans to enroll a total of 28 healthy, non-pregnant adults, ages 18 to 50, at Johns Hopkins School of Public Health Center for Immunization Research and at the Vaccine Testing Center at Larner College of Medicine at the University of Vermont. Trial participants will be randomly assigned to receive a single subcutaneous dose of the experimental vaccine (20 participants) or a placebo (eight participants). Neither they nor investigators will know who is receiving the real thing. Participants will keep track of their temperature on diary cards at home – and return to the clinic for periodic checkups for about six months. Researchers will take blood samples during visits to see if they’re developing antibodies in response to the vaccine. Anna Durbin, a professor of International health at Hopkins School of Public Health, is leading the Phase I clinical trial. Most people infected with the Zika virus — primarily transmitted by certain mosquitoes — have mild to no symptoms. But it can cause serious birth defects and developmental problems in babies born to women infected during pregnancy. That’s why the Centers for Disease Control and Prevention advises women who are pregnant or planning to become pregnant not to travel to areas with a known Zika risk. “Zika virus infection remains a significant threat to pregnant women and their developing fetuses, and we can expect to see periodic outbreaks and cases in areas where Aedes aegypti mosquitoes thrive,” said NIAID Director Anthony Fauci. “NIAID remains committed to developing safe and effective Zika vaccines, and we are pleased to begin clinical testing of a live attenuated candidate.”

“Triple Pill” May Keep a Lid on BP
A low-dose, three-in-one pill may be an easy new way to treat high blood pressure. A trial led by The George Institute for Global Health in Sydney, Australia, found that a whopping 70 percent of patients who took the so-called Triple Pill — containing half doses of three different meds — reached blood pressure targets, compared to just over half of those who received usual care. Typically, patients begin treatment with one drug at a very low dose that’s gradually increased with other drugs added to the mix to reach target blood pressure measures. It takes time and tinkering with meds and doses to come up with the most effective cocktail. That means patients have to frequently visit their doctor to see if the meds are working or if they need to be changed or doses adjusted to meet treatment goals. “This is not only time inefficient, it’s costly. We also know that many doctors and patients find it too complicated and often don’t stick to the process,” said study co-author Ruth Webster. In an attempt to find a simpler approach, researchers enrolled 700 patients with an average age of 56 and blood pressure of 154/90 mm Hg in a six-month trial. Participants were randomly assigned either the combo pill or standard care. The test tablet contained the blood pressure meds telmisartan (20 mg), amlodipine (2.5 mg), and chlorthalidone (12.5 mg). The findings, published in JAMA: a significantly higher proportion of patients receiving the “Triple Pill” hit their target blood pressure of 140/90 or less (with lower targets of 130/80 for patients with diabetes or chronic kidney disease). The three-in-one option was not only more effective, it was also found to be safe, researchers said. The George Institute says it plans to examine the cost-effectiveness of the “Triple Pill” — and test its appeal among doctors and patients. An estimated one in three U.S. adults — around 75 million people — suffer from high blood pressure. But only about 54 percent have it under control, according to the Centers for Disease Control and Prevention (CDC). The condition ups the risk for heart attack and stroke, two of the leading causes of death in the U.S.

FDA OKs Opdivo for Lung Cancer
The FDA last week approved Bristol-Myers Squibb’s Opdivo (nivolumab) for patients with metastatic small cell lung cancer (SCLC) that fails to respond to platinum-based chemotherapy and at least one other therapy. “Small cell lung cancer can be a very challenging disease, particularly for those who have already been through multiple types of treatment, as most patients relapse within a year of diagnosis,” said Andrea Ferris, president and chairman of the LUNGevity Foundation. “This approval marks a major milestone for the patients touched by this unrelenting disease and may motivate them to pursue further treatment where there previously were no other approved options.” The agency OK’d Opdivo after 12 percent of 109 patients (in the SCLC cohort of the ongoing Phase I/II CheckMate -032 clinical trial) responded to it after chemo and another therapy failed. According to researchers, 12 patients had a partial and one (0.9 percent) a complete response. The median duration of response (DOR) was 17.9 months.

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Optivo

The drug was discontinued in 10 percent of patients and one dose was withheld in 25 percent because of side effects. Some 45 percent of trial participants experienced serious side effects. SCLC is a very aggressive cancer that makes up about 10 to 15 percent of all lung cancers. About 27,000 cases are diagnosed in the U.S. each year.

Schizophrenia: If At First You Don’t Succeed, Try Clozapine?

A new study suggests doctors may want to consider prescribing the potent, atypical antipsychotic drug clozapine earlier for schizophrenia if a typical antipsychotic doesn’t work. Physicians generally don’t prescribe clozapine for newly diagnosed patients until they’ve tried at least two other less potent antipsychotics. But a trial found that if the first drug didn’t help, switching to another similar antipsychotic usually didn’t have much of a clinical impact, either. So researchers concluded it might be more effective to skip the second antipsychotic – and move onto clozapine earlier. New York’s Mount Sinai Hospital recruited 486 newly diagnosed schizophrenia patients and gave them up to 800 mg per day of the antipsychotic amisulpride for four weeks. Patients whose symptoms didn’t subside were then either continued on amisulpride or switched to up to 20 mg per day of olanzapine, another typical antipsychotic, for six more weeks. After 10 weeks, patients still suffering from hallucinations and/or other schizophrenia symptoms were given up to 900 mg per day of clozapine for 12 weeks. Ten weeks is generally considered very early to start prescribing clozapine. But lead researcher Rene Kahn says the trial found that trying it then “could potentially save time and reduce suffering.” The findings were published The Lancet Psychiatry.

Cetuximab Can’t Clear Trial for Throat and Mouth Cancer

Cetuximab, a targeted anti-cancer drug believed to be less toxic than its rival cisplatin, has failed to show it can help curb the growth of throat and mouth cancers caused by HPV. There was a lot of hope for cetuximab when researchers began a Phase III trial of 849 patients with HPV-related mouth or throat cancers in June 2011 in which they received a combination of radiation therapy and either cetuximab or the more potent cisplatin. But researchers found that cetuximab was far less effective than cisplatin at controlling tumor growth. “The goal of this trial was to find an alternative to cisplatin that would be as effective at controlling the cancer but with fewer side effects. We were surprised by the loss of tumor control with cetuximab,” said lead investigator Andy Troatti of the Moffit Cancer Center in Tampa, Florida. Cetuximab, most commonly known by its brand name Erbitux, is already approved for treatment of metastatic colorectal cancer, some cancers of the head and neck, non-small cell lung cancer and a form of skin cancer. Its most common side effects are relatively mild — ranging from a rash to nausea. Cisplatin, on the other hand, may cause kidney damage, hearing loss and bone marrow suppression. Researchers plan to release their full findings in October.

FDA Approves EpiPen Generic

The FDA last week approved the first direct generic competitor to the EpiPen, paving the way for cheaper competition that may lower prices. The new generic will be made by Israeli generic manufacturer Teva Pharmaceuticals. It was greenlighted after the FDA issued new guidance for generic copies of products like the EpiPen, the most widely prescribed epinephrine auto-injector in the U.S. Epinephrine reduces swelling in airways and increases blood flow in people suffering anaphylaxis or life-threatening reactions to foods, insect stings or medicines. “This approval means patients living with severe allergies who require constant access to lifesaving epinephrine should have a lower-cost option, as well as another approved product to help protect against potential drug shortages,” FDA Commissioner Scott Gottlieb said in a statement.

Mylan, which bought the rights to the EpiPen from Pfizer, has been under fire for hiking the price of the EpiPen to more than $600 for a twin pack. The approval covers generic copies of EpiPen and EpiPen Jr. for kids. Teva Pharmaceuticals can market its generic epinephrine auto-injector in 0.3-milligram and 0.15-milligram doses, the FDA said. The company didn’t say how much it would charge for the generic version or when it would be available. Anaphylaxis occurs in approximately one in 50 Americans, according to the FDA. “People who have had an anaphylaxis episode always face the risk of another one,” Gottlieb said. “Because of this risk, they must carry an emergency dose of epinephrine at all times. Many must keep more than one dose at hand.”

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Merck’s anti-cancer blockbuster Keytruda, which some analysts predict could reach $10 billion in annual sales. The drug, which hit the market in May 2017, has been approved for treatment of 10 different types of cancer.

Dozens of other, similar drugs are in the pipeline, FDA records show. ClinicalTrials.gov lists nearly 147 expansion cohort trials completed in recent years—and another 416 in some stage of development.

Despite the successes, not everyone is on board. Some researchers worry expansion trials open the door to potential safety gaps—an issue the FDA hopes oversite committees can keep an eye on and avoid. Plus, the jury’s still out on whether adding cohorts enhances the success rate in later trials by catching and fixing possible snags early.

A 2017 study, published in a Journal of the American Association for Cancer Research, analyzed 533 phase I cancer trials between 2006 and 2011. It found the ones that used expansion cohorts went on to have successful phase II trials at nearly twice the rate (48 percent) as those that didn’t (27 percent). But just a year earlier, a team of researchers analyzed 252 cancer trials (conducted between 2004 and 2014) and found expansion cohorts made little or no statistical difference between success or failure in phase II trials.

Still, WCG’s McNair says there’s no question they help researchers “get to decision-making points more quickly.” And the FDA believes that with recommended new protections, they’ll prove to be a safe, quick way to bring new potentially vital meds to people who need them.

“A lot of time and cost of clinical development is spent waiting in between the start and end of the phases of trials,” FDA Commissioner Scott Gottlieb said in a statement. “Expansion cohort trials can bring efficiency to drug development, potentially reducing development costs and time.”


NIH postponed the policy for a year – until Sept. 24, 2019 – after Congress asked it to delay action.

In the interim, behavioral researchers will still have to register their proposed studies “with the expectation that data will eventually be transported to ClinicalTrials.gov,” the NIH says. They’ll also have to take special training on clinical practices, regardless of the focus of their research.

NIH is the nation’s largest funder of clinical trials. After the GAO released its report, the agency acknowledged that it “had difficulty re-reporting how many clinical trials it has funded” and that “results from many NIH-funded clinical trials are never published or reported in a public database.”

The new policy was among steps it took designed to remedy the lapses and increase transparency of NIH-funded clinical trials.

Last year more than 3,500 scientists signed an online petition urging NIH Director Francis Collins to scrap the plan—and opponents had hoped NIH would scuttle it. But they said they’re pleased to have extra time to adjust and provide more input.

“APA supports policies that encourage open science approaches such as preregistration of studies and data sharing,” Howard Kurtzman, executive director of the American Psychological Association, which opposes the policy, told CenterWatch. “Such policies should be developed with the input of the research community and be sensitive to the purposes and nature of the research being conducted.”

The NIH said it plans to work with scientists to iron out wrinkles and ease compliance over the next year.
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Upcoming Event Highlights

Conferences

SEPTEMBER 10-12, 2018  
Mastering EU Medical Device Regulation  
Philadelphia, PA

SEPTEMBER 27, 2018  
Emerging Biopharmaceutical Therapies  
Washington, DC

OCTOBER 9-10, 2018  
Medical Device Complaint Management  
Waltham, MA

OCTOBER 23-25, 2018  
FDA Inspections Summit - 13th Annual  
Bethesda, MD

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Training Programs

SEPTEMBER 1-31, 2018  
Program Phlebotomy Training — Two Day Training  
Various locations

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Webinars

SEPTEMBER 12, 2018  
Top Tips for Establishing Device Supplier Quality Metrics: Develop a World-Class Program to Boost Productivity & Compliance

SEPTEMBER 17, 2018  
Complying with Advertising & Promotion Requirements: Top Tips for Conforming to FDA, FTC, NAD, BBB and State Mandates

SEPTEMBER 19, 2018  
Medical Device Software and Risk Management

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Palo Alto, CA

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Emory University  
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Clinical Project Manager  
Integrium, LLC  
Phoenix, AZ

Clinical Research Coordinator  
Allergy Partners of Western North Carolina  
Asheville, NC

Infectious Diseases - Tenure leading Position  
UNMC College of Pharmacy  
Omaha, NE

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