Experts Ask FDA to Rethink Trial Exclusion Criteria
By Bill Myers

Ethical concerns about testing on vulnerable groups may be unnecessary and may be depriving trials of key critical data, a panel of experts says, urging the FDA to reconsider rigid rules excluding certain groups from clinical trials—or at least make decisions on a case-by-case basis.

Debate has swirled around this issue for years, with critics questioning whether the exclusions have led to trial pools that don’t accurately reflect potential treatment targets. So the FDA in the spring convened a roundtable of experts to address barriers preventing some populations, including children, seniors, pregnant women and those with multiple health conditions, from enrolling in trials.

In a summary report released last week, the panel—which consisted of sponsors, researchers and academics—said it’s time to revisit and update those rules.

“Excluding these patients limits the ability of a trial to generate data that are relevant to the actual users of the drug and limits the ability to describe how investigational therapies affect the pathophysiology of common chronic conditions and interact with other therapies,” the report cautions, calling for regulators to explore erasing or at least considering exclusions on a per case basis.

The report notes that the 21st Century Cures Act requires the NIH to take another look at issues blocking older adults from see Exclusion Criteria on page 5.

FDA: New Flexibility for Blinding Cancer Trials
By Bill Myers

Cancer patients in clinical trials should be told whether they’ve been given placebos or experimental drugs if their tumors reappear or get worse—and patients and researchers should be told if sponsors are worried experimental drugs may be triggering bad reactions, the FDA says in new draft guidance.

Using placebos in double-blind, randomized trials is a traditional way to protect against bias, but it also raises “both practical and ethical concerns,” the agency says. For one thing, giving a mere placebo to someone who is getting sicker could be perceived as tantamount to denying them care. For another, many experimental drugs may have toxic side effects and it can be dangerous to keep patients and/or researchers in the dark about whether a med or disease is to blame for symptoms.

“For example, in a blinded immunotherapy trial, a patient who develops adverse events … may receive unnecessary treatments,” the FDA says. “Maintaining the blind [status] after disease progression could also affect a patient’s subsequent therapy, potentially preventing a patient who had been on a placebo from receiving an approved therapy, or delaying or preventing the patient’s entry into other clinical trials.”

In an effort to assuage concerns, many recent cancer trials take an open-label see Cancer Trial Blinding on page 5.
New Scale for Tumor Treatments

Europe’s largest oncologist association has approved a new scale to measure tumor DNA mutations, a move that backers hope will simplify and standardize choices for targeted cancer treatments and clinical trials.

The European Society for Medical Oncology (ESMO) approved a six-tier scale that groups mutations in tumors’ genetic makeup based on their relevance as markers for targeted treatments. The tool is designed to “help distinguish between alterations in tumor DNA that are important for decisions about targeted medicines or access to clinical trials, and those which aren’t relevant,” said Fabrice Andre, chair of the ESMO committee that created the new guide.

The scale ranges from Tier I to Tier V. Tumors in the first tier are those with mutations that render them candidates for relatively routine targeted treatments—and they take priority in any treatment plan, ESMO officials say. Those in Tier V are tumors whose genetic blips require more than one kind of targeted treatment. The scale also has a sixth level called Tier X, which includes tumors considered untreatable.

ESMO has an estimated 18,000 members in more than 150 countries.

The new scale was published in the journal Annals of Oncology.

Trials May Close Survival Gap

Rural cancer patients’ access to clinical trials may be a matter of life and death, new research finds.

Stats show that people in rural areas are much more likely than denizens of big cities or suburbs to die of cancer. According to the Centers for Disease Control and Prevention, an estimated 180 per 100,000 people in rural areas died of the disease compared to an urban cancer death rate of 158 per 100,000 between 2011 and 2015, the most recent data available.

But SWOG, a nonprofit cancer research group funded by NIH, found that clinical trials could play a major role in erasing the survival gap.

SWOG compared the survival rates of nearly 37,000 patients with 17 different types of cancers in 44 phase II and phase III cancer trials between 1986 and 2012—and reports in JAMA Open Network that there was no meaningful difference between those who lived in urban areas and those who lived in rural areas.

The one exception was in patients with estrogen receptor-negative, progesterone receptor-negative breast cancer. Researchers found that women in rural settings had a higher hazard ratio—were more at risk of dying—compared to those living in cities or suburbs. They blame several factors, including that women in rural areas often lack quick access to follow-up chemotherapy after their first round of treatment.

Lead study author Joseph Unger, a SWOG statistician and health services researcher at Fred Hutchinson Cancer Research Center, says the study’s lesson is clear: “If people diagnosed with cancer, regardless of where they live, receive similar care and have similar outcomes, then a reasonable inference is that the best way to improve outcomes for rural patients is to improve their access to quality care.”

A growing number of experts agree that for many patients—especially those suffering from rare diseases—clinical trials are their first, and sometimes best, chance of getting quality care.

This is the first study to compare survival outcomes in rural and urban cancer patients enrolled in clinical trials.

“These findings were a surprise, since we thought we might find the same disparities others had found,” Unger said. “But clinical trials are a key difference here. In trials, patients are uniformly assessed, treated and followed under a strict, guideline-driven protocol. This suggests that giving people with cancer access to uniform treatment strategies could help resolve the disparities in outcomes that we see between rural and urban patients.”

New Arthritis Drug Guidance

The FDA is asking stakeholders to suggest structural endpoints for use in trials of medical products aimed at treating the root cause of osteoarthritis.

Regulators have already approved drugs to address the symptomatic pain of osteoarthritis. So far, though, no treatments have been found to prevent the underlying structural damage it causes.

The draft guidelines mark the first time the agency has wrestled with structural endpoints for osteoarthritis in nearly two decades. But they offer few concrete suggestions, instead pitting the stakeholders for comment.

“This draft guidance is intended to serve as a focus for continued discussions among the FDA, sponsors of medical products, the academic community, and the public regarding the assessment of structural endpoints,” the FDA says.

The Centers for Disease Control and Prevention estimates that some 30 million Americans suffer from osteoarthritis. It’s the most common joint disorder in the U.S. and the cases of knees affected have more than doubled since the mid-20th century, leading to millions in taxpayer dollars being spent on joint replacement surgeries and rehab.

Yet the pathology of the disease is still largely opaque and the amount of structural damage often doesn’t correlate with patients’ self-reported pain and/or mobility problems.

“The ultimate goal of treatments,” the FDA says, “is to avoid or significantly delay the complications of joint failure and the need for replacement surgery.”

continues on next page »
joint replacement, and, also, to reduce the deteri-oration of function and worsening of pain.”

Given the vagaries of the disease, it’s “unclear what magnitude of change in structural end-
points would translate to a clinically meaningful benefit to patients,” the FDA says.

Read the draft guidance here: www.fdanews.
com/ext/resources/files/2018/08-22-18-Osteoar-
thritis.pdf?1534952766

Brain Melanoma Breakthrough

A combined immunotherapy treatment has shown dramatic results stunting and even shrinking metastatic brain tumors in advanced mel-

anoma patients, offering a potential breakthrough for a disease that kills 95 percent of its sufferers within five years.

Researchers at MD Anderson Cancer Center enrolled 94 melanoma patients, whose cancer had spread to their brains, in a phase II trial to see if combined doses of the T-cell inhibitors nivolumab (Optivo) and ipilumab (Yervoy) could help halt or slow symptoms.

Participants were given the combo therapy every three weeks for up to four doses, followed by a course of just nivolumab every two weeks. Nine months into the trial, brain tumors in nearly 60 percent of the patients had stopped growing—or become smaller—and more than 56 percent of the patients had stopped growing within five years.

The team enrolled five men in a clinical trial during which they underwent 15 minutes a week of stimulation from a magnet placed on their lower backs. The findings, published in the journal Science Reports: participants began to show significant improvement after just four sessions.

“All five of the men regained the ability to urinate on their own during stimulation,” lead researcher Daniel Lu said. “In one case, the patient was able to stop using a catheter and empty his bladder several times a day—up to two weeks after his last treatment.”

During the four-month trial, participants’ bladder capacity, on average, grew from 244 mm to 404 mm. Their self-rated quality of life rating improved by 60 percent, Lu said.

Some 250,000 Americans a year suffer a spinal injury and an estimated 80 percent lose

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Industry Briefs

the ability to control their bladders, researchers said. They noted that many say they’d prefer to regain the ability to go to the bathroom before the ability to walk on their own.

**FDA Slaps CRO with Warning**

The FDA has issued a warning letter to a Minnesota CRO alleging sloppy leadership and failure to track materials carefully and safely.

The move follows an inspection late last year of a Brooklyn Park lab run by North American Science Associates. In the letter, inspectors charge the facility’s lab director “failed to assure that all experimental data . . . were accurately recorded and verified” and ignored protocols for an animal study the lab was running. The FDA warning letter also says lab employees:

- Failed to identify study specimens adequately;
- Didn’t provide “orderly storage and expedient retrieval of all raw data”; and,
- Improperly labeled solutions and reagents in the lab.

The company created a corrective action plan, but it “appears incomplete,” the letter says.

The FDA said the company must come up with fixes within 15 days or risk being shuttered.

Science Associates did not respond to CenterWatch requests for comment.

**Liver Cancer Trial Approved**

Singapore has given the go-ahead for a clinical trial testing whether a precision T-cell receptor immunotherapy may help ward off liver cancer in transplant patients.

Drugmaker Lion TCR is slated to begin phase I/II trials to see if its experimental med LioCyx can help treat patients who suffer a relapse of Hepatitis B-related liver cancer after they’ve received a transplant. (Nearly 80 percent of the world’s 800,000 new liver cancer cases are diagnosed in the Asia-Pacific region. Some 80 percent involve Hepatitis B, and the cancer frequently recurs even after a transplant, the company says).

In June, Lion TCR announced that it had raised $20 million from investors to fund LioCyx trials. These are the first such clinical trials approved in Singapore.

Researchers hope to recruit up to 12 patients for phase I and another 60 for phase II trials over the next four years.

The company says it plans to begin enrolling patients at Singapore’s National University Hospital, and then expand to other sites in Singapore and China.

**FDA Urged to Ease MDD Limits**

Janssen and Takeda have called for more flexibility in the FDA’s draft guidance for sponsors of drugs to treat major depressive disorder (MDD).

Janssen said it disagreed with the agency’s proposal to limit treatment-resistant depression (TRD) studies to monotherapies. The company is currently developing a ketamine-based nasal spray for major depressive disorder that combines esketamine with an oral antidepressant. In May, Janssen unveiled Phase III clinical study results indicating a statistically significant reduction of depressive symptoms.

Takeda also called for more flexibility in trial designs in the final guidance. “In accordance with American Psychiatric Association clinical practice guidelines, TRD patients should be included in adjunctive or combination therapy trials in cases where the studies are properly designed and scientifically sound,” the company said.

Takeda urged the agency to address how an antidepressant would demonstrate an effect on specific symptoms, such as cognitive dysfunction or reduced liability of common adverse events.

It said the guidance should also include specific recommendations for use of digital technologies to collect patient data in clinical trials.


**FDA Finalizes Guidance on Microdose Radiopharmaceutical Diagnostic Drugs**

Sponsors conducting nonclinical radiopharmaceutical diagnostic drug trials can seek waivers for specific nonclinical pharmacology or toxicology studies, according to final guidance from the FDA.

The sponsors should tailor the amount and type of nonclinical supporting data to take account of low adverse event potential, the agency said.

The guidance, which finalizes the agency’s August 2017 draft with no major changes, makes specific recommendations for various study types. For example, pre-phase 1 pharmacology studies should be sufficiently sensitive to ensure pharmacologic effects at the predicted clinical dose are ruled out.

In extended single-dose toxicities in one species, the FDA recommends sponsors use the intended clinical route as the route of exposure in animals, using a formulation as similar as possible to the one that will be used in clinical trials. Genotoxicity, safety pharmacology and repeat dose toxicity studies are not needed or recommended nor are developmental and reproductive toxicity studies in cases in which sponsors obtain a waiver, the guidance says.

Because each drug is unique, the agency encourages sponsors to consult CDER’s Division of Medical Imaging Products before submitting an IND and during drug development, adding that “If, at any stage of development, a sponsor determines that particular nonclinical pharmacology or toxicology studies are not needed and provides adequate justification in a waiver request, the agency may grant a waiver for specific studies.”


**NIH Shuts Down Alcohol Trial**

NIH has pulled the plug on what was supposed to be a 10-year, $100 million clinical trial to study the health effects of moderate drinking but that critics say was suspect because of influence from the beer and booze lobby.

The Moderate Alcohol and Cardiovascular Health (MACH) trial was slated to enroll 7,800 participants. But it collapsed before it even began after an NIH advisory committee said its objectivity had been compromised by officials who actively tried to “persuade the industry to support” the effort. NIH says it’s conducting “a thorough review.”
Exclusion Criteria

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participating in clinical trials—and urges regulators to move quickly to broaden access for what is now the nation’s largest single demographic group.

The panel also advises sponsors, researchers and regulators to be more open with patients about how eligibility criteria are determined and even to solicit patients’ views on how to structure trials.

“More frequent and routine patient involvement in trial design could lead to more trials that explicitly address outcomes important to patients and achieve greater patient enrollment,” the summary stresses. It adds that expanded access not only can inform a drug’s risk-benefit profile but may also offer hope to patients out of other options.

“It is critical to consider the need for humanitarian access to an investigational therapy while not undermining the overall clinical trial process,” the summary states.

The bottom line, concludes the report: “Enhancing inclusion and encouraging greater diversity in clinical trial populations is a priority for regulators, sponsors, investigators, and patient advocates.”

Read the roundtable summary here: www.fdanews.com/08-22-18-FDAsummary.pdf

Cancer Trial Blinding

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approach where patients are given an already-approved treatment instead of placebos to compare against the experimental one. Other trials use an add-on approach—all patients are given standard treatment plus either a placebo or an experimental treatment.

But in some cases there aren’t other treatments available. In those rare instances, the FDA suggests trials “un-blind” patients if their disease recurs or worsens while taking placebos.

“Excluding these patients limits the ability of a trial to generate data that are relevant to the actual users of the drug.”

— FDA Roundtable Report

Using placebos in double-blind, randomized trials is a traditional way to protect against bias, but it also raises “both practical and ethical concerns.”

— FDA in draft guidance

The draft guidance—released late last week—says both patients and investigators should also be “un-blinded” if an experimental treatment causes harmful side effects and the patient may need another med or even surgery. But it recommends patients be allowed to stay in trials even if they’re un-blinded.

The FDA notes that if sponsors insist on keeping trials “blind” throughout, at the least, they need to carefully explain this may happen—and the risks involved—in informed consent documents before patients sign up.


Compliance for Sponsors

The SOP for Good Clinical Practice by Sponsors of Clinical Trials ensures safe, effective and successful clinical trials and is a comprehensive customizable and easy-to-use SOP.

Highlights include:

✓ FDA guidance documents
✓ Risk-based monitoring templates
✓ CAPA plan information and forms
✓ Site selection and feasibility procedures
✓ Site initiation visit and training guidelines
Together, we’re helping our partners deliver on the promise of precision medicine.

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<td>AVB-S6-500</td>
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<td>Biohaven Pharma</td>
<td>BHV-0223</td>
<td>Social anxiety and public speaking anxiety disorders</td>
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<td>Sun Pharmaceutical Industries Ltd.</td>
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<td>beigene.com</td>
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<td>Escalier Biosciences, BV</td>
<td>ESR-114 topical gel</td>
<td>Mild-to-moderate psoriasis</td>
<td>Phase I/II clinical trial initiated</td>
<td>escalierbio.com</td>
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<td>Sangamo Therapeutics, Inc.</td>
<td>SB-525, a cDNA gene therapy candidate</td>
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<td>ADC Therapeutics</td>
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<td>Relapsed or refractory diffuse large B-cell lymphoma (DLBCL)</td>
<td>Phase II clinical trial initiated</td>
<td>adcterapeutics.com</td>
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<td>Alexion Pharmaceuticals, Inc.</td>
<td>ALXN1210, investigational long-acting CS complement inhibitor</td>
<td>Paroxysmal nocturnal hemoglobinuria (PNH)</td>
<td>FDA accepted Biologics License Application (BLA) for approval</td>
<td>alexion.com</td>
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<td>Merck &amp; Co.</td>
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<td>Metastatic non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations</td>
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<td>SPR Therapeutics</td>
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<td>Tolero Pharmaceuticals, Inc.</td>
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<td>toleropharmaceuticals.com</td>
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<th>CONTRACT RESEARCH ORGANIZATION</th>
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| **CROMSOURCE**  
Waltham, MA  
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