NCI Formulary Launched for Clinical Trials

The National Cancer Institute (NCI) on January 11 announced the launch of the NCI Formulary, designed to give investigators at NCI-designated cancer centers quicker access to approved and investigational agents for use in preclinical studies and cancer clinical trials. The overall intent is to accelerate the rate at which more effective treatment options can become available to patients with cancer. The NCI Formulary is a public/private partnership between NCI and pharmaceutical and biotechnology companies. It is also part of the larger Cancer Moonshot initiative, which, at its launch under the Obama administration, called for greater collaboration and faster development of new therapies. In a press release, the NCI noted that the availability of agents through the NCI Formulary will expedite the start of clinical trials by alleviating the lengthy negotiation process (sometimes up to 18 months) that has been required for investigators to access such agents on their own.

"The NCI Formulary will help researchers begin testing promising drug combinations more quickly, potentially helping patients much sooner," said NCI Acting Director Douglas Lowy, MD. "Rather than spending time negotiating agreements, investigators will be able to focus on the important research that can ultimately lead to improved cancer care." The NCI Formulary started its activities with 15 targeted agents from 6 pharmaceutical companies: Bristol–Myers Squibb, Eli Lilly and Company, Genentech, Kyowa Hakko Kirin, Loxo Oncology, and Xcovery Holding Company LLC. "The agreements with these companies demonstrate our shared commitment to expedite cancer clinical trials and improve outcomes for patients," said James Doroshow, MD, NCI Deputy Director for Clinical and Translational Research. "It represents a new drug development paradigm that will enhance the efficiency with which new treatments are discovered."

The establishment of the NCI Formulary will enable NCI to act as an intermediary between investigators at NCI-designated cancer centers and participating pharmaceutical companies. After company approval, investigators will be able to obtain agents from the available formulary list and test them in new preclinical or clinical studies, including combination studies of formulary agents from different companies. The NCI Formulary leverages lessons learned through the NCI Cancer Therapy Evaluation Program and the NCI Molecular Analysis for Patient Choice trial. NCI staffers expect to double the number of available targeted agents by the end of 2017.

The Formulary will complement NIH's plans for another new public/private partnership in oncology, the Partnership to Accelerate Cancer Therapies (PACT). Through PACT, the NIH, U.S. Food and Drug Administration, biopharmaceutical groups in the private sector, foundations, and cancer advocacy organizations plan to collaborate to support new research projects to accelerate progress in cancer research as part of the Cancer Moonshot. PACT research will center on identification and validation of biomarkers of response and resistance to cancer therapies, with special emphasis on immunotherapies. PACT, which is expected to launch in 2017, will also establish a platform for selecting and testing combination therapies.

More information about the NCI Formulary is available at: https://nciformulary.cancer.gov/.

National Cancer Institute

FDA Draft Guidance on Medical Product Communications

On January 18, U.S. Food and Drug Administration (FDA) Commissioner Robert Califf, MD, announced the release of 2 new draft guidance documents on medical product communications. The first, "Drug and Device Manufacturer Communications with Payors, Formulary Committees, and Similar Entities," explains the FDA's current perspective and recommendations on firms' communication of health care economic information about approved drugs under section 502(a) of the federal Food, Drug, and Cosmetic Act, which was recently amended by the 21st Century Cures Act. The draft also answers common questions and provides the FDA's recommendations about firms' communications to payors about investigational drugs and devices that are not yet approved or cleared for any use.

The second draft guidance, "Medical Product Communications that are Consistent with the FDA-Required Labeling," explains the FDA's current perspective on firms' medical product communications that include data and information not already contained in their products' FDA-required labeling but that concern approved or cleared uses of their products. The FDA is seeking public comment before April 10 on these documents.

In a separate effort to secure stakeholder input, the FDA is seeking comment on communications about unapproved uses of approved or cleared medical products. For more information or to submit comments, see http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm537371.htm.

U.S. Food and Drug Administration

HHS Final Rule on Research Participant Protections

The U.S. Department of Health and Human Services (HHS) and 15 other federal agencies issued on January 18 a final rule to update regulations safeguarding individuals who participate in research. Most provisions in the new rule will go into effect in 2018. The new rule strengthens protections for individuals who volunteer to participate in research but also addresses simplifications to

research oversight to avoid "inappropriate administrative burdens, particularly to low-risk research." The current regulations, which have been in place since 1991, are often referred to as the Common Rule. They were developed at a time when most research was conducted at universities and medical institutions and each study generally took place at a single site. Research with human participants has grown in scale and become more complex, at the same time that data acquisition, analysis, and reporting have been computerized.

The final rule will now generally expect consent forms to include a concise explanation at the beginning of each document with key information that would be most important to individuals considering participation in a study, including the purpose of the research, associated risks and benefits, and appropriate alternative treatments that might be beneficial. "Over the years, many have argued that consent forms have become these incredibly lengthy and complex documents that are designed to protect institutions from lawsuits, rather than providing potential research subjects with the information they need in order to make an informed choice about whether to participate in a research study," said Jerry Menikoff, MD, who directs the HHS Office for Human Research Protections, which led the government's efforts to revise the regulations. "We are very hopeful that these changes and all the others that reduce unnecessary administrative burdens will be beneficial to both researchers and research participants."

Important elements in the final rule issued today include: (1) The requirement for better consent form introductory explanations; (2) Requirements, in many cases, to use a single institutional review board (IRB) for multi-institutional research studies (with several notable exceptions); (3) Introduction of an option for broad consent for future research (as an alternative to IRB waivers) for studies on stored identifiable data or identifiable biospecimens; (4) Establishment of new exempt research categories based on level of risk; (5) Removal of the requirement to conduct continuing review of ongoing research studies in certain instances where such review does little to protect subjects; and (6) Requirement that consent forms for certain federally funded clinical trials be posted on a public website.

The final rule covers only clinical trials that are federally funded, but the new standards are likely to be adopted in a broader range of research activities. The final rule is available at: https://www.federalregister.gov/documents/2017/01/19/2017-01058/federal-policy-for-the-protection-of-human-subjects.

U.S. Department of Health and Human Services

Patient Advocacy Groups, Guideline Committees, and COI

Two articles published online in *JAMA Internal Medicine* on January 17 looked at industry ties and other potential conflicts of interest (COI) for members of medical consensus guideline committees and patient advocacy groups. The first article, by Jefferson and Pearson from the National Institutes of Health (Bethesda, MD) and the Institute for Clinical and Economic Review (Boston, MA), focused on the degree to which 2 recent guidelines adhere to COI standards issued by the Institute of Medicine (IOM). The authors looked at the 2013 American College of Cardiology and American Heart Association cholesterol management guideline and the 2014 American Association for the Study of Liver Diseases and Infectious Diseases Society of America hepatitis C virus management guideline. The IOM standards stipulate that guideline committee chairs and cochairs should have no commercial COI and that <50% of committee members should have such industry ties. The authors searched article disclosure statements for committee members on each of the published guidelines and compared these to the standards. In the document statements of the 16 cholesterol guideline committee members, 7 (44%) disclosed commercial COI; each of these 7 reported industry-sponsored research, and 6 (38%) also reported paid work as consultants. Of 3 cholesterol guideline chairs and cochairs, 1 (33%) reported commercial COI. A review of articles published by these individuals in the same time period identified additional commercial COI. Among the 29 hepatitis C virus guideline committee members, 21 (72%) reported commercial COI. Eighteen (62%) disclosed industry-sponsored research, 10 (34%) served on advisory boards, 5 (17%) served on data safety monitoring boards, 3 (10%) were consultants, and 3 (10%) reported other honoraria. Of 6 hepatitis C guideline cochairs, 4 (67%) disclosed commercial COI. Again, review of articles published by these same individuals identified additional commercial COI. The authors concluded by suggesting that "adoption of consistent COI frameworks across specialty societies may help ensure that clinical guidelines are developed in a transparent and trustworthy manner."

In the second article, Rose and colleagues from the Cleveland Clinic (OH), Case Western Reserve University (Cleveland, OH), the University of Chicago (IL), and the University of Pennsylvania Perelman School of Medicine (Philadelphia) reported on COI in patient advocacy organizations, which now act as influential stakeholders in health care decision making at the local, regional, and national levels. The authors conducted a representative random survey of 439 patient advocacy organization leaders (representing 5.6% of those identified) in the United States. Survey items assessed their professional activities within the organizations, financial relationships with industry, and perceptions about current COI policies. A total of 289 (65.8%) of those contacts returned surveys with at least 80% of questions answered. The median total revenue among responding organizations was $299,140, with a very broad range of sizes, funding, and activities. A total of 165 organizations reported receiving industry funding, with 19 receiving more than half of their funding from industry. Among the subset of organizations

that received industry funding, the median amount was $50,000. A total of 220 of 269 respondents (81.8%) answering questions about COI indicated that these issues are very or moderately relevant to patient advocacy organizations, and 94 of 171 (55.0%) responding believed that their organizations' COI policies were very good. A total of 22 of 285 leaders (7.7%) reported pressure to conform their positions to the interests of corporate donors.

JAMA Internal Medicine

Plasma Tau and Sports Concussions

In an article e-published on January 6 in *Neurology*, Gill et al. from the National Institute of Nursing Research (NINR; Bethesda, MD), the University of Rochester School of Medicine and Dentistry (NY), and Quanterix Corporation (Lexington, MA) reported on a study designed to determine whether plasma tau changes after sport-related concussions in collegiate athletes correlate with elapsed time before returning to play. The study included 632 soccer, football, basketball, hockey, and lacrosse athletes from the University of Rochester who underwent preseason blood plasma sampling and cognitive testing. Forty-three athletes experienced a concussion during the season, and, for comparison, a control group of 37 teammate athletes without concussions was also included, as well as a group of 21 healthy nonathletes. The 43 athletes who experienced concussions underwent plasma tau sampling at 6, 24, and 72 hours and at 7 days after injury. Athletes who returned to play after concussions were categorized as having long (>10 d; $n = 23$) or short (≤ 10 d; $n = 18$) recovery periods. Total tau was measured using an ultrasensitive immunoassay. The authors found that both those with concussions and athlete controls had significantly higher mean tau at baseline than nonathletes. Elevated plasma tau concentrations within 6 hours after a sports-related concussion were significantly correlated with prolonged time before returning to the sport, "suggesting that tau levels may help inform" or predict recovery. The correlations between plasma tau concentrations and time required for recovery were consistent across all sports and both sexes. "Keeping athletes safer from long-term consequences of concussions is important to players, coaches, parents, and fans. In the future, this research may help to develop a reliable and fast clinical lab test that can identify athletes at higher risk for chronic postconcussion symptoms," said NINR Director Patricia A. Grady, PhD, RN, in a related press release.

Neurology

FROM THE LITERATURE

Each month the editor of Newsline selects articles on diagnostic, therapeutic, research, and practice issues from a range of international publications. Most selections come from outside the standard canon of nuclear medicine and radiology journals. These briefs are offered as a monthly window on the broad arena of medical and scientific endeavor in which nuclear medicine now plays an essential role. The lines between diagnosis and therapy are sometimes blurred, as radiolabels are increasingly used as adjuncts to therapy and/or as active agents in therapeutic regimens, and these shifting lines are reflected in the briefs presented here. We have also added a small section on noteworthy reviews of the literature.

^{11}C-MET PET/CT and Parathyroid Adenomas

In an article e-published on January 14 in *Langenbeck's Archives of Surgery*, Noltes et al. from the University of Groningen (The Netherlands) reported on the diagnostic utility of ^{11}C-methionine (^{11}C-MET) PET/CT after initial inconclusive or negative localization in preoperative primary hyperparathyroidism. The retrospective study looked at the records of 28 such patients in whom preoperative localization by ^{11}C-MET PET/CT was correlated with later surgical localization, duration of surgery, histopathology, and follow-up data. Differences in duration of surgery with and without correct preoperative localization were also analyzed. PET/CT accurately localized the parathyroid adenoma in 18 (64%) patients after previously negative or inconclusive imaging, with 3 false-positives and 7 false-negatives. The sensitivity of ^{11}C-MET PET/CT was 72%, and the duration of surgery was significantly shorter in patients with accurate imaging localization. The authors concluded that "a preoperatively correct localized adenoma leads to a more focused surgical approach. . .potentially reducing duration of surgery and potentially health care costs."

Langenbeck's Archives of Surgery

^{18}F-Flutemetamol PET and Early-Onset Dementia

Zwan et al. from the VU University Medical Center (Amsterdam, The Netherlands) and Maastricht University (The Netherlands) reported in the January 17 issue of *Alzheimer's Research and Therapy* (2017;9:2) on a study assessing the diagnostic significance and management results of ^{18}F-flutemetamol PET imaging in patients with early-onset dementia. The study included 211 patients with a suspected diagnosis of early-onset dementia on the basis of Mini Mental State Examination scores ≥ 18 and age at assessment ≤ 70 y, with diagnostic confidence at $<90\%$ after routine clinical work-up. All patients underwent ^{18}F-flutemetamol PET imaging, with results visually categorized as