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Outlook 2013

Funding Said Top Medical Research Area In 2013; Common Rule, COI Also Make List

Regardless of what happens with the fiscal cliff negotiations in Congress and the Obama administration, research funding will continue to dominate the regulatory, legal, and policy landscape for medical research in 2013 as institutions and investigators prepare for tighter research budgets.

Members of the *Medical Research Law & Policy Report* editorial advisory board, representatives of research-related organizations, and other experts spoke to BNA about what they thought would be the top issues for medical research in 2013.

In this postelection environment, the combined tax increases and federal funding cuts of the fiscal cliff and research funding came up in most interviews, along with potential regulatory changes that indicate an increasing focus on compliance and transparency.

"The number one issue over the next year is going to be funding," Carrie D. Wolinetz, speaking on behalf of United for Medical Research, an umbrella organization that advocates for steady growth in National Institutes of Health funding, told BNA Dec. 18, 2012. "Clearly, we don't know what's going to happen with the fiscal cliff. But it's hard to imagine anything that's going to come out of these negotiations that won't in some way affect nondefense discretionary funding, and NIH of course is a very large agency in that small pool of funds."

Jack E. Dixon, vice president and chief scientific officer for the Howard Hughes Medical Institute, told BNA Dec. 17, 2012, that the economy and research funding levels also top his list of the most important research-related issues.

"It's imperative that the government fund agencies like the NIH to basically keep this country at the top of the heap. And the budgets have not been increasing as you probably know in substantial ways. Over the last

Top Research Issues in 2013

1. Reduction in federal funding anticipated regardless of fiscal cliff outcome.
2. Tighter budgets mean more grant, contract compliance efforts, audits expected.
3. Mixed opinions on whether or how Common Rule ANPRM will move forward.
4. Financial conflict of interest, Physician Payment Sunshine Act.
5. Genetic research.
6. Personalized medicine.
7. Electronic health information.
8. Privacy.
9. FDA initiatives.
10. Increased regulatory oversight.

several years, things have largely been status quo. And for us to continue to play a leading role in the work of biomedical research, it's just really imperative that the funding levels at the NIH be maintained," he said.

Mary Woolley, president of Research!America, expressed similar thoughts Dec. 19, 2012.

"It's going to be difficult to maintain even the current funding lines, and it means we're going to be at increased risk of losing the United States' global leadership in all science, frankly, and very definitely the life sciences," Woolley said. "We've already seen indications that we're slipping badly in this area in terms of commitment of our money toward research when other countries are spending more proportionately to their economies."

According to the American Association for the Advancement of Science, NIH could lose \$11.3 billion to \$26.1 billion in funding over the next five fiscal years under sequestration cuts (11 MRLR 737, 11/21/12). Even if a deal is reached to avoid sequestration—automatic spending cuts set to take effect in early 2013 because Congress in 2011 could not reach agreement on trim-

ming the federal budget—several commenters said there likely will be cuts in federal spending.

“It’s now pretty clear—and this is of concern—that both the Congress and the administration are prepared to make significant cuts to nondefense, discretionary spending. . . . That means everything from education to the [Transportation Security Administration] infrastructure to medical research and the [Food and Drug Administration], and many more activities,” Woolley said. “We’ve got a lot to worry about with what now looks like unavoidable cuts.”

Discussing all the budget concerns in the abstract is one thing, she said, but it is another issue to decide which programs will be funded and which will be cut. “That really hasn’t been worked out,” she said. “That’s the challenge going forward, but it’s a significant challenge.”

Ann C. Bonham, chief medical officer at the Association of American Medical Colleges, said Dec. 20, 2012, that the budgetary environment will dominate as it has in the past.

“I think now we’re looking at a period of austerity with a seriousness that may even be different than it was last year because regardless of whether the fiscal cliff negotiations are successful or not, we anticipate reduced discretionary spending,” she said.

Greater Enforcement, More Audits Anticipated. Mark Barnes, a MRLR advisory board member and attorney in Ropes & Gray’s Boston office, told BNA Dec. 26, 2012, that these budgetary issues mean that NIH as well as other agencies that fund federal research grants and contracts such as the Department of Defense will pay more attention to how those funds are used.

“The enforcement of the financial terms and the contract terms and conditions is probably going to be much more rigorous in 2013 and the years beyond than it’s been in previous years,” Barnes said. “It means there will probably be an increase in the number of audit notices and audits undertaken [for] research grants and contracts. And that ultimately probably means a number of repayments by institutions of money that the government finds under audits that’s been inappropriately spent.”

Bonham said the budgetary discussions extend beyond just NIH funding because AAMC members use a significant portion of revenue from the clinical side to invest in the research mission of their academic medical centers and teaching hospitals. In addition to NIH funding, potential federal discretionary spending cuts include graduate medical education programs and reimbursement of teaching hospitals that provide uncompensated care to indigent populations.

“That really puts in peril the ability of medical schools and teaching hospitals to make the same kinds of investments in research,” Bonham said. “We have reduced discretionary spending for research for NIH plus reductions in clinical revenue and that puts in peril the ability to sustain a research mission.”

Training and Workforce. Those cuts will have an adverse long-term effect on the future of the biomedical workforce, Bonham said.

“If we lose our best and brightest from going into biomedical research, we’re going to face a lack of discoveries for Alzheimer’s and childhood obesity that’s going to go beyond this year and next year,” she said. “It’s going to haunt us in the next decade. I always think we

have to look beyond the next year and the domino effect of that.”

Dixon of HHMI said because most research projects extend over a multiyear period, fluctuating funding levels can create challenges for investigators and their ability to keep staff they have trained on their payroll.

“One has to try to find support for people, and if people drop out it takes a very long time to retrain and redo things,” he explained.

Clinton D. Hermes, a MRLR board member and senior vice president and chief legal officer at St. Jude’s Research Hospital, expressed similar thoughts.

“This isn’t just a revenue issue; it affects a whole generation of upcoming scientists,” Hermes wrote in a Dec. 18, 2012, email.

Woolley said the impact can be seen among current graduate students. “It’s starting to become more common that young people completing their education at a graduate level here in the U.S. are considering—and some of them taking—jobs in other nations where they are more assured of a productive, sustained career,” she said.

Wolinetz noted that an NIH advisory panel issued two reports in June 2012 recommending modernization of training programs to tailor the biomedical workforce to the current environment as well as to create a diversity office at NIH (11 MRLR 805, 12/19/12).

“NIH is looking a lot at how it operates and how it spends its money, and certainly training and workforce seems to be a big recent focus of the agency,” Wolinetz, associate vice president for federal relations at the Association of American Universities, said. “There are a lot of potentially big changes that they’re proposing, and I think they’re being very smart and cautious in their implementation. They’re looking to receive a lot of feedback from the community, but certainly in terms of the way NIH funds training and the scientific workforce could be an area of great movement for the next year.”

Regulatory Focus, Burden. Bonham of AAMC cited a number of recently enacted or highly anticipated rules expected to come out next year that she said are making a significant impact on the regulatory environment for research.

“We have this environment where we have these regulatory realities now with the implementation of the financial conflicts of interest [rule] from NIH. Certainly the [Physician Payment] Sunshine Act is on the horizon. There’s a continued push for registration of clinical trials at ClinicalTrials.gov, there are privacy initiatives with sweeping changes to HIPAA, [and] other privacy measures such as cybersecurity could sweep in health and research-related activities inadvertently,” Bonham said. “You take those regulatory realities and you mesh them in this climate of economic uncertainty, we’re clearly looking at austerity in the future regardless of what happens in the next few days with the Congress.”

Wolinetz also mentioned a trend over the past decade to increase the regulatory requirements that investigators and institutions must meet, citing as examples regulations governing select agents, increased requirements for animal research and stem cells, and conflict-of-interest final regulations from NIH.

“There is very much a feeling that we’re beginning to reach the breaking point of regulatory burden related to research.”

—CARRIE D. WOLINETZ, UNITED FOR MEDICAL RESEARCH

“We are hearing a lot from the researchers themselves and research institutions that they’re really struggling to meet these compliance demands [and] that they’re very expensive. And these are unfunded mandates, so universities are having to put more and more money into [trying] to comply with these regulations,” she said. “There is very much a feeling that we’re beginning to reach the breaking point of regulatory burden related to research.”

Physician Payment Sunshine Act. The final rule for the Sunshine Act, *Transparency Reports and Reporting of Physician Ownership of Investment Interests* (CMS-5060-F) from the Centers for Medicare & Medicaid Services, has been sent the White House Office of Management and Budget for review, a key indication that a final rule will be released soon (11 MRLR 777, 12/5/12).

Scott J. Lipkin, a MRLR advisory board member and chief of the office of research and innovation at Lehigh Valley Health Network in Allentown, Pa., told BNA in a Dec. 24, 2012, email that there is still “widespread concern amongst organizations and research administrators regarding how they will implement the new rule and how they will deal with the financial burden of implementation.” He added that there is still uncertainty about how the final rule will differ from the draft version.

Carol Pratt, a MRLR advisory board member and partner in K&L Gates’ Portland, Ore., office who focuses on regulatory issues associated with research, said Dec. 20, 2012, that she does not anticipate the final sunshine rule to be very different from the proposed version.

“The impact on the research community is going to be really having to be in compliance, and operationally to figure out how to stitch together in a matrix the [requirements under the] varying laws for financial disclosure and conflicts of interest,” she said, citing the anti-kickback law, the Stark law, which prohibits physician referrals if the physician has a financial relationship, and NIH and FDA requirements. “So you’ve got multiple reporting and record keeping requirements.”

NIH Conflict-of-Interest Rule. Several commenters said the NIH financial conflict-of-interest rule will continue to be an important issue in 2013. The rule, *Responsibility of Applicants for Promoting Objectivity in Research for Which Public Health Service Funding Is Sought and Responsible Prospective Contractors* (42 C.F.R. Part 50; 45 C.F.R. Part 94; 10 MRLR 858, 12/21/11), went into effect in August 2012.

“The research community is responding with all seriousness and commitment to maintaining the ethical goals yet minimizing the burden,” Bonham said.

Kate Gallin Heffernan, a MRLR advisory board member and principal with the research consulting firm KGH Advisors LLC, told BNA Dec. 13, 2012, that ques-

tions relating to the conflict-of-interest rule continue to linger, such as on what the tough implementation issues are, where clarity is still needed, and how to measure how well the new requirements address the concern that conflicts introduce bias into research.

Bonham said AAMC is partnering with 70 institutions to look at the effectiveness of the financial conflict-of-interest regulations over the next three years.

“It’s something we really wanted to do because it’s an opportunity. We have a new financial conflict-of-interest rule and all institutions have to implement it,” she said. “So let’s just look at the implementation and see if we can develop a way to think about the evidence base for the future policies.”

Several commenters said that together, the new sunshine law and the financial conflict-of-interest rules indicate a trend in the federal government toward requiring greater transparency in the research enterprise.

“There are increasing expectations for transparency of research, not only by the Congress but also by the patients and the public,” Bonham said.

Research Integrity, Fraud. Dixon of HHMI said the research community has to be aware of these transparency issues for conflicts of interest as well as for research fraud and fabrication and anything that “gives science a black eye.”

“We have to be concerned that we’re spending the public’s money in the best possible way,” he said.

These scientific integrity issues become particularly important as the economy and budgets continue to be dominating policy discussions, Dixon said.

“It’s important all the time, fundamentally, but I think in times where there are constraints on resources, being sure you spend every dime wisely is a very important thing,” he said.

Barnes told BNA an increasing number of research misconduct cases are being reported in the mainstream media.

“We have seen at the institutional level around the country really an uptick in the numbers of investigations that have been opened and the seriousness of the investigations,” he said.

However, Barnes noted, because it can take years for an institution to complete a formal research misconduct investigation, which then is submitted to the Department of Health and Human Services Office of Research Integrity so it can conduct its own investigation, there is a lag time between when the research occurs and when the intentional fabrication or falsification of data becomes public. Further, he said, two unknown variables are how much research misconduct is taking place and how often it is detected.

Nevertheless, in addition to increased media attention, Barnes said, there “certainly is more chatter about it” among lawyers and research vice presidents across the country.

“That’s an emerging issue not only for 2013, but beyond,” he said.

Common Rule ANPRM. The federal government’s effort to modernize the human subject protection regulations also will continue to be an important regulatory issue in 2013, several commenters said.

HHS issued an advance notice of proposed rulemaking (ANPRM) in July 2011 that would make sweeping changes to subject protection requirements under the

so-called Common Rule (76 Fed. Reg. 44,512; 10 MRLR 513, 8/3/11).

“One of the critical issues is going to be whether the [HHS] Office for Human Research Protections issues a notice of proposed rulemaking following the ANPRM,” MRLR advisory board member Michele Russell-Einhorn told BNA Dec. 12. “If that comes out, that will be an important event,” according to Russell-Einhorn, senior director of the Office for Human Research Studies and director of the Office for Protection of Research Subjects at the Dana-Farber Cancer Institute.

Lipkin said there is a widespread view that the ANPRM is “dead in its tracks.”

“Nonetheless, [there is a], strong ‘buzz’ that central [institutional review board] review of multi-site trials is the wave of the future,” he wrote.

Pratt of K&L Gates also said she does not expect to see a proposed rule that encompasses all the components of the ANPRM into a single, consolidated document. Rather, she said she anticipates a more piecemeal approach by the HHS Office for Human Research Protections involving actions on the less controversial, individual parts of the ANPRM.

“The easiest thing if you’re on the government side is to do the things where there’s more consensus. What we don’t know—and I don’t have any insider information on this—is whether they will stick to some of the consensus things like improving the readability of informed consent forms and maybe preparing guidance on some more updated boiler plate or suggested template language for some of the elements of the informed consent form,” Pratt said. “That would be welcome by everybody and is not terribly controversial.”

At the same time, Pratt said she is more interested in other aspects of the ANPRM, such as the proposal to require a single IRB of record for multisite studies, broadening the applicability of the Common Rule to any research conducted by an institution that receives federal funding, and requiring informed consent for future research using biospecimens, even for specimens that have been stripped of identifiers.

“I would really like to see some movement on those issues, and I’m not terribly optimistic that I’m going to see that in 2013,” she said.

Industry already is moving somewhat in the direction of the ANPRM, Pratt said, adding that she has noticed increased use of consent forms that are more “ambitious” on the front end by including language seeking consent for future research.

“But then you’ve got the disconnect between the Common Rule and [the Health Insurance Portability and Accountability Act], where you can’t ask that under HIPAA but you can under the Common Rule,” she said.

The omnibus final HIPAA rule is expected to be issued by mid-2013 (11 MRLR 821, 12/19/12).

Wolinetz of United for Medical Research said amid the trend of increasing regulatory burden, the ANPRM is a rare example of the government seeking to make regulations more efficient.

“I actually saw that as a very positive step, in the absence of crisis, the agencies were looking at a regulation,” she said. “But of course that hasn’t actually gone anywhere. Yet I think we would love to see more of that, in which we take some of the regulations that are really created in siloed processes and are often reactions to something bad happening.”

Genetic Research, Biobanks. Genetic research issues will continue to be important in 2013 as well, commentators said.

Hermes said this field creates challenges for both IRBs and scientists regarding the identifiability of banked specimens as well as challenges for scientists relating to the ethics of obtaining re-consent from individual donors for future research involving banked specimens.

Heffernan said genetic research will become even a more significant issue if OHRP publishes a proposed rule addressing the inherent identifiability of tissue specimens.

“Regardless, I think that people are still trying to establish best practices around setting up banks, obtaining ‘front door consent’ for large scale institutional data and tissue repositories, and managing downstream uses, particularly when those uses involve genetics research,” Heffernan said.

Russell-Einhorn said targeted genetic research, or research involving genetic mutations, also will be an important issue in 2013.

“That raises this whole specter of genome sequencing research and genomic and genetic research and what kind of parameters and guidelines we want to have on this research,” she said. “It’s also referred to in a lot of places as the kind of research that’s going to lead to more personalized medicine, where people will have research done or clinical work done looking to target some specific mutation that they have and then the treatment will be focused on what’s the appropriate treatment given that mutation.”

Personalized Medicine. Pratt said personalized medicine will remain an important issue in 2013 as there is a move to partner in vitro diagnostic assays with a drug or biologic therapeutic product.

“Historically, we’ve had a lot of in vitro diagnostic assays that are laboratory developed tests,” she explained. “The assay is not sold, the result of using the assay is what’s marketed.”

FDA for the most part has exercised its enforcement discretion by not requiring these LDT applications to have pre-market approval. However, Pratt said, FDA issued draft guidance in July 2011 on how to get these companion diagnostics approved, which has implications for research (10 MRLR 505, 7/20/11).

“FDA said if you have a drug or you’re developing a diagnostic that’s intended to only target a subset of people that have a particular genetic mutation,” she said, the assay has to be screened and it is necessary to identify the people being screened and to make the new therapeutic safe and effective.

Under the draft guidance, FDA would want to see a single proposed clinical investigation submission for an assay and companion therapeutic.

An LDT, when coupled with a therapeutic, now becomes a companion diagnostic for which FDA would require clinical data and prefer to see the assay and the therapeutic developed at the same time, Pratt said.

Big Data, Internet Research. Woolley said big data—large, complex collections of data sets that are difficult to process with traditional applications—will be addressed in relation to personalized medicine in 2013.

“We have now the capability to collect just more than anybody knows what to do with, and that’s the point.

We're not clear what we're going to do with it," she said.

The Research!America president said the question of how to store the data is the easiest part to solve; the challenges lay in how to coordinate the information, use it appropriately, and evaluate it.

"Now there are obvious openings here for standardization and for cooperation. But it's just not clear how that's all going to happen," she said.

"FDA has shown some real clear signals in the last half of 2012 that it is ramping up its oversight of clinical investigations."

—CAROL PRATT, K&L GATES

Woolley added that there are some myths about patients' lack of willingness to share their own health data out of privacy concerns, especially when patients and their families are faced with a severe illness or diagnosis.

"People want to share data if they are aware . . . there might be a chance that this could help them and other people," she said. "So there's increasing recognition that personalized medicine means all of us are individuals with unique personal data and it isn't a one-size-fits all world anymore."

Heffernan said a separate issue related to employing technologic advances in human subjects research—internet research—also will continue to be of growing importance over the next year.

"The use of technology as a research tool has been exploding in recent years and developing appropriate institutional policies around how to apply existing human subject protection regulations has proven quite challenging," she said. "I think the next few years will help to cement what are best practices in this area (i.e., what is 'private' information in the Facebook era, etc.)."

FDA Initiatives, Oversight. Commenters identified several FDA initiatives as important for research in 2013, from risk-based monitoring, to efforts to prevent potential therapeutics from falling into the so-called "valley of death" in terms of financial investment, to proposed changes in medical device application requirements.

"FDA has shown some real clear signals in the last half of 2012 that it is ramping up its oversight of clinical investigations," Pratt said.

For risk-based monitoring, FDA released draft guidance in August 2011, *Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring*. The draft guidance described an approach to monitoring clinical investigations that focuses on critical study parameters and relies on a combination of monitoring activities to effectively oversee a study (10 MRLR 595, 9/7/11).

"This is a big initiative that the FDA has undertaken in recent years, and I think we are going to see their approach start to spill over to the site side," Heffernan said. "In other words, the FDA has been tying its enforcement and auditing to level of risk."

This model also can be seen in the ANPRM for the Common Rule, Heffernan said, which focuses on violations that may have significance for safety and data va-

lidity. She said it makes sense to tie the degree of review, monitoring, and enforcement to the risk level.

"I question how much time it will take (if it hasn't already occurred) before one sees a correlated impact on the way in which institutional and sponsor monitoring and compliance programs are run," she said.

Woolley said efforts at both FDA and NIH have helped to curb the valley of death, defined as the gap in funding between early-stage discovery and the later stages of commercialization that prevents development of many potential drugs or devices from moving forward. The Research!America president credited the regulatory science efforts at FDA, establishment of the NIH National Center for Advancing Translational Sciences, and efforts in the private sector to address research gaps that slow discovery. FDA defines regulatory science as "the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products."

"We've reached kind of a turning point, and it's exciting that regulatory science and related efforts to overcome the so-called valley of death of disinterest in funding from the private sector" could ease the transition from discovery to delivery of new drug devices and prevention, she said. "We're going to see more of this after years of trying to get there. I think that's a positive."

With respect to medical devices, Pratt said, FDA has proposed changes that could increase the need for 510(k) applicants to collect and submit clinical trial data to gain marketing approval. A 510(k) is a type of premarket submission made to FDA to demonstrate that the device to be marketed is substantially equivalent to a legally marketed device (21 C.F.R. § 807.92(a)(3)), according to FDA's website. Generally, a 510(k) submission requires fewer clinical data to demonstrate safety and efficacy compared to a standard premarket application for a new type of device.

In August 2011, FDA issued a draft guidance that describes different study design principles relevant to the development of medical device clinical studies that can be used to fulfill 510(k) premarket clinical data requirements (10 MRLR 558, 8/17/11).

"That's going to have an impact on research because there will be a need for more clinical data on devices that historically have been going through the 510(k) doorway" and have been able to rely on animal and bench data, Pratt said. "That will mean more issues for the IRB."

Pratt said she expected FDA to issue the final guidance in the first half of 2013.

FDA Draft Guidance on Investigator Responsibility. Pratt and Russell-Einhorn also mentioned as important in 2013 the draft guidance on IRB responsibilities, *IRB Responsibilities for Reviewing the Qualifications of Investigators, Adequacy of Research Sites, and the Determination of Whether an IND/IDE Is Needed*, issued by FDA in November 2012 (11 MRLR 741, 11/21/12).

"The proposal is that IRBs would have more responsibility for in-the-weeds review of investigators," Russell-Einhorn said, by tasking them with looking at investigators' curricula vitae and qualifications for the study.

Joanne Less, director of FDA's Good Clinical Practice Program, said at the Public Responsibility in Medicine

& Research annual research ethics conference in December that the draft guidance was issued in response to the controversy in 2009 surrounding Coast IRB. The now-shuttered independent IRB was involved in a federal investigation for approving a fake clinical trial protocol that had the potential to expose study volunteers to significant risk (8 MRLR 227, 4/1/09).

Pratt said a lot of IRBs are “scratching their heads” on how to assess investigators’ qualifications, particu-

larly for new faculty who submit studies supported by industry funding.

“That draft guidance is a message to IRBs to say, ‘You can’t punt on this. You have some responsibility to investigate and if you don’t have that information you need to figure out ways of getting that,’ ” Pratt said.

BY JEANNIE BAUMANN