tions have emerged, and the regulatory framework under which such therapies are evaluated should evolve accordingly. The FDA remains committed to innovative approaches to the evaluation of drugs that are in clinical development. Effective treatments for the devastating disorder that is Alzheimer's disease are urgently needed, as the world's population continues to age.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Division of Neurology Products, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD.

This article was published on March 13, 2013, at NEJM.org.

1. Jack CR Jr, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 2010;9:119-28.
2. Guidance for industry: Alzheimer's disease: developing drugs for the treatment of early stage disease. Washington, DC: Center for Drug Evaluation and Research, February 2013 (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM338287.pdf).
3. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging–Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:270-9.
4. Dubois B, Feldman HH, Jacova C, et al. Revising the definition of Alzheimer's disease: a new lexicon. Lancet Neurol 2010;9:1118-27.
5. Albert MS, Blacker D, Moss MB, Tanzi R, McArdle JJ. Longitudinal change in cognitive performance among individuals with mild cognitive impairment. Neuropsychology 2007;21:158-69.

DOI: 10.1056/NEJMp1302513

Safeguarding Children — Pediatric Research on Medical Countermeasures

Amy Gutmann, Ph.D.

In 2011, a bioterrorism-preparedness exercise conducted by the U.S. government examined the likely result of a large-scale release of weaponized anthrax spores in a city such as San Francisco. Code-named Dark Zephyr, the simulation was sobering: nearly 8 million people would be affected, nearly a quarter of them children.[1] If such an event occurred, current response plans call for distribution of appropriate antibiotics and vaccination of affected civilian populations using anthrax vaccine adsorbed (AVA). Although the vaccine has been produced for more than four decades and has been safely administered to more than a million adults in the military, there is no history of use in children and no definitive understanding of how the vaccine would affect them.

Last year, Secretary of Health and Human Services Kathleen Sebelius asked the Presidential Commission for the Study of Bioethical Issues, which I chair, to review the ethical considerations regarding conducting research on AVA in children. More generally, the Bioethics Commission was asked to consider pediatric research on medical countermeasures encompassing any products and interventions regulated by the Food and Drug Administration and designed for use in response to chemical, biologic, radiologic, or nuclear attacks. The request followed a recommendation from the National Biodefense Science Board that the government study AVA's safety and immunogenicity in children before an anthrax attack occurs, contingent on a thorough ethics review.

The Bioethics Commission concluded in a report released on March 19 that before pre-event pediatric AVA trials can be considered, further steps must be taken, including additional research in adults, to help ensure that the research risks to children — who do not stand to benefit directly from participation in the study — can be reduced to a level posing no more than minimal risk to their health or well-being. The Commission recognized both the government's duty to protect individual children from undue risk during research and the obligation to protect all children during an emergency by being prepared.

Pediatric research is ethically distinct from research in adults. Whereas competent adults can consent to accept risks for the benefit of others, children are legally prohibited and ethically unable to do so. Pediatric research on medical countermeasures therefore presents additional ethical challenges both in the abstract (absent a terrorist event, or "pre-event," when the likelihood of an attack is unknown and perhaps unknowable) and after an event, when individual lives are at stake.

The Bioethics Commission concluded that pre-event pediatric research on medical countermeasures is ethical, in general, only if it presents no more than minimal risk to study participants. Minimal risk is comparable to that which healthy children living in a safe environment routinely face in everyday life or during a routine medical examination.[2]

This conclusion, which seeks to limit research risk to individual child participants, emanates from consideration of three characteristics of such research that challenge traditional research ethics: the research involves the potential treatment or prevention of a highly disabling or lethal condition that no one has yet contracted; it aims to determine how best to treat a condition resulting from an event whose likelihood of occurring is unknown; and though the knowledge gained could be useful for future treatment, we hope never to have occasion to use it.

To be ethical, research involving children must generally pose no greater than minimal risk to participants unless the research presents the prospect of direct benefit. A minor increase over minimal risk — which is still very limited and poses no substantial risk to health or well-being — is permissible only when research is likely to yield generalizable knowledge about participants' specific condition. It may also be permissible, with extensive national-level review, under exceptional circumstances outlined in Title 45 of the Code of Federal Regulations (45 CFR §46.407 [2012], referred to as Section 407).[3]

Pre-event studies of a medical countermeasure cannot directly benefit participants, who are not affected by the condition it is designed to treat. Furthermore, only when unusual circumstances prohibit completing such testing in consenting adults and developing a minimal-risk research design can pre-event research in children involving "a minor increase over minimal risk" proceed to national-level review. That risk level is defined by only a "narrow" expansion of minimal risk, which still "poses no significant threat to the child's health or well-being."[2,3]

Minimal-risk pre-event pediatric testing of medical countermeasures may be made possible through age-deescalation studies, which generally entail gradually lowering the age criterion for participants in a series of studies. To determine whether such testing is feasible, prior testing such as modeling, testing in animals, and testing in adults must first identify, delineate, and characterize research risks. Then, if an intervention is shown to pose minimal risk in 18-year-olds, it might be possible to infer that a study involving 16- and 17-year-olds would present only minimal risk. There might be key points along the developmental trajectory at which age is only one of several factors to consider, depending on the countermeasure being tested; for example, groups might have to be defined by stages of puberty as well as by age.

In response to the Secretary's broader request, the Bioethics Commission developed a framework for Section 407 review. We first clarified the circumstances in which proposed research presents a "reasonable opportunity" to address a "serious problem."[3] One threshold condition, for example, is that the research must be of "vital importance" to addressing that problem.[4] Second, we specified a rigorous set of conditions that would all need to be satisfied to justify a determination that the research adhered to "sound ethical principles." These conditions fall into five categories: an ethical threshold of acceptable risk and adequate protection from harm, ethical study and trial design, post-trial requirements to ensure ethical treatment of children and their families, community engagement, and transparency and accountability. Finally, the Commission reiterated the importance of informed parental permission and meaningful and developmentally appropriate assent by children.[5]

The Commission recommends that reviewers use this framework when assessing protocols for pre-event pediatric research on a medical countermeasure involving a minor increase over minimal risk without direct benefit, to ensure thoroughness and ethical rigor. But it should be applied only in rare circumstances in which minimal-risk research cannot be designed.

Post-event research on medical countermeasures should also be limited to minimal risk whenever possible, but since it could directly benefit participants who are exposed to a pathogen during the event, different ethical and regulatory standards apply. Children exposed to a pathogen could enroll in research likely to yield information of vital importance to elucidating or ameliorating both their own condition and that condition generally in other children.

The Commission recommends that post-event research be planned in advance and be conducted when a relatively untested medical countermeasure is administered to children in an emergency, with health officials collecting data during the event so we may learn as much as possible about use of the countermeasure. Adequate processes must be in place for informed parental permission and meaningful assent by children; the research design must be scientifically sound; enrolled children must have access to the best available care; there must be adequate plans for compensating

anyone injured by research; and provisions must be made to engage communities throughout the course of research.

Routine preexposure prophylaxis in military personnel has resulted in observational studies of AVA in young adults, but additional data from adult populations — from dose-sparing studies, for example — are needed before pediatric testing can be ethically considered. With additional safety data, the level of risk to young adults could be inferred with increased statistical confidence. Such an inference, in turn, would influence a possible minimal-risk design of a series of age-deescalating safety and immunogenicity studies.

Sound science must always respect our ethical obligations to protect children from unnecessary risks. Medical countermeasure research warrants an ongoing national conversation to ensure an unwavering commitment to safeguard all children both from unacceptable risks in research and through research promoting their health and well-being.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the Presidential Commission for the Study of Bioethical Issues, Washington, DC, and the Office of the President and Department of Political Science, University of Pennsylvania, Philadelphia.

This article was published on March 19, 2013, at NEJM.org.

1. White R. Anthrax vaccine trials for children: precautionary or premature? Bioethics Forum. May 22, 2012 (http://www.thehastingscenter.org/Bioethicsforum/Post.aspx?id=5852).
2. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Research involving children. Washington, DC: Department of Health, Education, and Welfare, 1977 (http://bioethics.georgetown.edu/pcbe/reports/past_commissions/Research_involving_children.pdf).
3. Code of Federal Regulations, Title 45, Public Welfare. Department of Health and Human Services. Part 46, Protection of human subjects, Section 407.
4. Code of Federal Regulations, Title 45, Public Welfare. Department of Health and Human Services. Part 46, Protection of human subjects, Section 406.
5. Presidential Commission for the Study of Bioethical Issues (PCSBI). Safeguarding children: pediatric medical countermeasure research. Washington, DC: PCSBI, 2013.

DOI: 10.1056/NEJMp1302093

Generalist plus Specialist Palliative Care — Creating a More Sustainable Model

Timothy E. Quill, M.D., and Amy P. Abernethy, M.D.

Palliative care, a medical field that has been practiced informally for centuries, was recently granted formal specialty status by the American Board of Medical Specialties. The demand for palliative care specialists is growing rapidly, since timely palliative care consultations have been shown to improve the quality of care, reduce overall costs, and sometimes even increase longevity.[1,2] The field grew out of a hospice tradition in which palliative treatment was delivered only at the end of life, but its role has expanded so that palliative care specialists now also provide palliative treatment in the earlier stages of disease alongside disease-directed medical care, improving quality of care and medical decision making regardless of the stage of illness. In an era when health care organizations may soon receive capitated payments for all services that patients receive, many are investing in palliative care to improve overall value.

Although this trend has fostered rapid growth of the palliative care specialty, the current model adds another layer of specialized care for seriously ill patients on top of an already complex, expensive health care environment. As in any medical discipline, some core elements of palliative care, such as aligning treatment with a patient's goals and basic symptom management, should be routine aspects of care delivered by any practitioner. Other skills are more complex and take years of training to learn and apply, such as negotiating a difficult family meeting, addressing veiled existential distress, and managing refractory symptoms. Now that the value of palliative care has been recognized, specialists are sometimes called on for all palliative needs, regardless of complexity.

Although it may theoretically seem optimal for palliative medicine specialists to take on all palliative aspects of care, this model has negative consequences. First, the increasing demand for palliative care will soon outstrip the supply of providers. Second, many elements of palliative care can be provided by existing specialist or generalist clinicians regardless of discipline; adding another specialty team to address all suffering may unintentionally undermine existing therapeutic relationships. Third, if palliative care specialists take on all palliative care tasks, primary care clinicians and other specialists may begin to be-