

## ETHICAL AND LEGAL OVERSIGHT OF HUMAN SUBJECTS RESEARCH IN EMERGING INFECTIONS AND BIODEFENSE RESEARCH: A REVIEW OF RECENT CHANGES AND CALL FOR POLICY REFORM

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The anthrax attacks in the United States in late 2001 served as a wake-up call for national security experts that quickly translated into research dollars for those working in infectious disease. The event ushered in dramatic changes in the federal research agenda, beginning with a projected federal budget of 1.6 billion dollars to develop countermeasures for a possible bioterrorist attack.<sup>1</sup> In May 2005, the National Institute of Allergy and Infectious Diseases awarded \$27 million in grants and contracts to develop therapeutics and vaccines against potential bioterrorism agents including anthrax, botulinum toxin, Ebola virus, pneumonic plague, smallpox, and tularemia.<sup>2</sup> Meanwhile, the SARS and Avian Flu outbreaks, along with perennial seasonal threats such as West Nile Virus in the United States, have brought the public and political spotlight to the global threat of emerging infections and bioterrorism. Along with increased funding and public debate, we are also witnessing significant changes in the laws governing the ethical conduct of research in the life sciences. It is important to reflect on these changes and evaluate alternatives, especially during times of heightened alarm.

These most recent developments coincide with the current debates in human subjects research ethics and policy. There is growing sentiment in the scientific community that the increasingly collaborative and global nature of clinical research has evolved beyond the current federal design.<sup>3</sup> Specific concerns have been raised about the

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<sup>1</sup> Press Release, The Century Foundation, Are Bioterrorism Preparedness Dollars Making Us Safer? Improving Public Health? (Jan. 29, 2004), available at [http://www.tcf.org/pressreleases/gursky\\_turnock.pdf](http://www.tcf.org/pressreleases/gursky_turnock.pdf).

<sup>2</sup> Press Release, U.S. Dep't of Health & Human Services, NIH News: NIAID Awards First \$27 Million Using New Bioshield Authorities (May 9, 2005) available at [http://www3.niaid.nih.gov/news/newsreleases/2005/27million\\_bioshield.htm](http://www3.niaid.nih.gov/news/newsreleases/2005/27million_bioshield.htm).

<sup>3</sup> See generally Eve E. Slater, *IRB Reform*, 346 NEW ENG. J. MED. 1402 (2002); OFFICE OF INSPECTOR GEN., DEP'T OF HEALTH & HUMAN SERVICES, PUB. NO. OEI-97-00193,

efficiency of the current system of research oversight and review in vaccine research involving human subjects.<sup>4</sup> Several studies have pointed to a variation among Institutional Review Boards (IRBs) as contributing to significant delays in developing potentially beneficial vaccines in time for seasonal outbreaks such as the West Nile Virus outbreaks.<sup>5</sup> Similar questions can be raised about the system's ability to efficiently review research on potential countermeasures for potential bioterrorism threats.

The nature of a widespread and potentially deadly infectious disease outbreak, whether a naturally emerging infection or an outbreak caused by terrorists, seems to justify an emergency response framework. That is, a framework designed with the overall public health in mind and one that prevents as many deaths as possible by containing the outbreak through vaccination and physical interventions, such as quarantine. Because preparation of vaccines or countermeasures for a specific biologic agent can only occur in a fairly narrow response window, efficiency of the ethical review process of new vaccines or countermeasures is a necessary means to the goal of containing an outbreak in a population. Since 2001, the significant

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INSTITUTIONAL REVIEW BOARDS: A TIME FOR REFORM (1998); William J. Burman et al., *Breaking the Camel's Back: Multicenter Clinical Trials and Local Institutional Review Boards*, 134 ANN. INTERN. MED. 152 (2001); Robert J. Levine, *Institutional Review Boards: A Crisis in Confidence*, 134 ANN. INTERN. MED. 161 (2001); David Cyranoski, *Critics Slam Treatment for SARS as Ineffective and Perhaps Dangerous*, 423 NATURE 4 (2003); Kendall Powell, *Call for Clinical-Trial Reform Leaves Critics Unmoved*, 419 NATURE 546 (2002); Michael T. Osterholm, *Preparing for the Next Pandemic*, 84 FOREIGN AFFAIRS 24 (2005); INST. OF MED., RESPONSIBLE RESEARCH: A SYSTEMS APPROACH TO PROTECTING RESEARCH PARTICIPANTS (2002); Research Revitalization Act of 2002, S. 3060, 107th Cong. (2002).

<sup>4</sup> Ezekiel J. Emanuel et al., *Oversight of Human Participants Research: Identifying Problems to Evaluate Reform Proposals*, 141 ANN. INTERN. MED. 282 (2004).

<sup>5</sup> See generally OFFICE OF INSPECTOR GEN., DEP'T OF HEALTH & HUMAN SERVICES, PUB. NO. OEI-01-97-00195, RECRUITING HUMAN SUBJECTS: PRESSURE IN INDUSTRY-SPONSORED CLINICAL RESEARCH (2002); Penelope M. Jester et al., *Regulatory Challenges: Lessons from Recent West Nile Virus Trials in the United States*, 27 CONTEMPORARY CLINICAL TRIALS 254 (2006); Kathleen Dziak et al., *IRBs and Multisite Studies: Variations Among Institutional Review Board Reviews in a Multisite Health Services Research Study*, 40 H.S.R. 279 (2005); Rita McWilliams et al., *Problematic Variation in Local Institutional Review of a Multicenter Genetic Epidemiology Study*, 290 JAMA 360 (2003); Thomas O. Stair, *Variation in Institutional Review Board Responses to a Standard Protocol for a Multicenter Clinical Trial*, 8 ACAD. EMERG. MED. 636 (2001); William J. Burman et al., *The Effects of Local Review on Informed Consent Documents from a Multicenter Clinical Trials Consortium*, 24 CONTROL CLINICAL TRIALS 245 (2003); Kurt D. Reed et al., *The Detection of Monkeypox in Humans in the Western Hemisphere*, 350 N. ENGL. J. MED. 342 (2004).

changes that have been made in federal research oversight pertain to the emergency use of potential vaccines or countermeasures in the event of an emergency outbreak like the Avian Flu or a bioterrorism event. However, appeals to emergency conditions are often seen as justifying a temporary suspension of more rigorous (and so more time-consuming) ethical requirements, such as robust informed consent from individual patients. There is also a natural tendency in the media and political debates to conflate the conditions of an actual emergency with the conditions of emergency preparedness. It is worthwhile to keep these separate when thinking through the ethical justifications of human subjects review because what is ethically justifiable in an actual emergency may not be ethically justifiable while ramping up for a possible emergency. With the best or worst of intentions, false appeals to emergency conditions can also obscure overtly unethical practices.

In this article, we pose two important but distinct questions that arise in the context of emerging infections and biodefense human subjects research: (1) which research oversight policy will offer the best mechanism for enforcing law in the public interest, and (2) how can individual human subjects be protected in a system that is designed to promote the public interest in a public health emergency? The standards for success will differ depending on whether one poses the question as predominantly a question of policy or predominantly a question of ethical concern. In the first sense, standards for success will emphasize efficiency of review and reduction of redundancies in oversight mechanisms, with the aim of responding as quickly and efficiently as possible to halt or control the outbreak of an infectious disease. In the second sense, simple appeals to efficiency are constrained by ethical concerns and requirements. Our approach is to recommend an institutional division of labor that attempts to optimize norms of efficiency on the one hand and ethical norms of subject protection on the other.

We begin with an introduction to the FDA and "Common Rule" human research protections regulations prior to amendment by bioterrorism legislation focusing on emergencies. We follow with a review of recent legislation and regulation related to emergency biodefense and public health threats with particular attention to the impact on the ethical review process. Next, we will outline the special ethical and legal concerns that are related to biodefense and public health

research in the non-emergency context but are not well addressed under the current system. Finally, we will propose options for revising the review process to address the inefficiencies of the current system while upholding rigorous standards of human subject protection and addressing the special ethical concerns raised by emerging infection and bioterrorism research with human subjects.

### FDA HUMAN SUBJECTS REGULATIONS, THE COMMON RULE AND EMERGENCIES

Without consideration of the impact of recent bioterrorism legislation, which is discussed *infra*, research activities and human subjects protections are central to the introduction of new drugs and devices. New biomedical drugs and devices are unavailable for general use by the public without undergoing FDA approval through a pre-market application process.<sup>6</sup> To gain FDA approval, an application must contain full reports of investigations which have shown whether the drug or device is safe and effective.<sup>7</sup> Exceptions to the rule against use of unapproved drugs and devices are available to conduct investigations in support of pre-market applications.<sup>8</sup> These investigations are usually performed under a separate investigational new drug application or application for investigational device exemption.<sup>9</sup> Human subjects protections (i.e., informed consent) and IRB approval are necessary conditions for performance of investigations unless use of the drug or device meets certain narrow regulatory exceptions or exemptions.<sup>10</sup>

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<sup>6</sup> "No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of our application filed pursuant to Subsections (b) or (j) of this section is effective with respect to this drug." 21 U.S.C. § 355(a). "A device which because - (i) it (I) cannot be classified as a class I device because insufficient information exists and (II) cannot be classified as a class II device because of insufficient information exists," and (ii) (I) is purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, or (II) presents a potential unreasonable risk of illness or injury, is to be subject to 'pre-market approval . . . .' 21 U.S.C. § 360c(a)(1)(C).

<sup>7</sup> 21 U.S.C. § 355(b)(1)(A); 21 U.S.C. § 360c(a)(3)(A); 21 U.S.C. § 360e(c)(1)(A).

<sup>8</sup> 21 U.S.C. § 355(i); 21 U.S.C. § 360j(g); 21 C.F.R. pt. 312; 21 C.F.R. pt. 812.

<sup>9</sup> 21 U.S.C. § 355(i); 21 U.S.C. § 360j(g); 21 C.F.R. pt. 312; 21 C.F.R. pt. 812.

<sup>10</sup> 21 C.F.R. § 50.20 et. seq.; 21 C.F.R. § 56.101 et. seq.; The exceptions to informed consent are

Two exceptions to the FDA informed consent and IRB approval requirements related to emergencies are relevant here.<sup>11</sup> The first, termed the 'emergency use exception,' applies to situations meeting the following criteria: (1) a patient has a life-threatening condition necessitating the use of the drug or device; (2) the patient is unable to communicate or otherwise give effective informed consent; (3) time is insufficient to get consent from a proper surrogate; and (4) there is no other recognized treatment available with as good or better likelihood of saving the patient.<sup>12</sup> The investigator and another independent licensed physician must certify in writing that the above criteria are satisfied before administering investigational therapy, or if time is too short, the investigator may have the independent physician certify later.<sup>13</sup> Under this exception an investigator must report the emergency use to the IRB within five working days.<sup>14</sup> Also, emergency use of an investigational product qualifies for an exemption from prior IRB review when there is insufficient time to obtain IRB approval; however, any subsequent use requires prior IRB approval.<sup>15</sup> Emergency use of an investigational drug still requires prior FDA approval that may be authorized under an already-effective investigational new drug application or by emergency approval issued specifically for the emergency use.<sup>16</sup> The FDA maintains contact

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codified at 21 C.F.R. §§ 50.23, 50.24, and the exemptions to IRB approval are codified at 21 C.F.R. § 56.104.

<sup>11</sup> There are two other exceptions to informed consent under FDA regulations: one requires a presidential waiver for personnel in particular military operations based on a finding that informed consent is not feasible, contrary to the best interest of the military member, or not in the interests of national security. 21 C.F.R. § 50.23(d). The other pertains to use of investigational *in vitro* diagnostic devices used to identify chemical, biological, radiological, and nuclear agents. This exception was added recently by the FDA after passage of bioterrorism legislation discussed in this article. In light of subsequent discussion below, for emergency use authorization, it somewhat ironically requires investigators to report uses under this exception to the IRB. 21 C.F.R. § 50.23(e).

<sup>12</sup> 21 C.F.R. § 50.23(a) (2006).

<sup>13</sup> 21 C.F.R. § 50.23(a)-(b) (2006).

<sup>14</sup> 21 C.F.R. § 50.23(c) (2006).

<sup>15</sup> 21 C.F.R. § 56.104(c) (2001); 21 C.F.R. § 56.102(d).

<sup>16</sup> FDA, GUIDANCE FOR INSTITUTIONAL REVIEW BOARDS AND CLINICAL INVESTIGATORS, <http://www.fda.gov/oc/ohrt/irbs/drugsbiologics.html#emergency> (last visited Mar. 11, 2008).

numbers for emergency use authorization on its website.<sup>17</sup> Emergency use of devices must be reported to FDA by the investigational sponsor or physician using the device within five working days.<sup>18</sup>

The second exception applies to investigations designed to take place in emergency settings with subjects having life-threatening conditions.<sup>19</sup> An example is the study of emergency use of electrical defibrillators placed in public areas and establishments.<sup>20</sup> Subjects with ventricular fibrillation become suddenly unconscious, yet immediate identification of the need for and use of electrical defibrillation by a trained employee or bystander can be life-saving.<sup>21</sup> This type of research cannot be undertaken if informed consent by the victim were required.<sup>22</sup> FDA adopted this exception so that prospective research of this type could be conducted.<sup>23</sup> Under this exception, prior IRB review and approval of the research is required, and the IRB is authorized to waive the requirement for informed consent if it determines that a stringent set of criteria are satisfied.<sup>24</sup> Regulations require informed consent to be obtained by investigators from the subject or the subject's legally authorized representative, if feasible, and if not feasible, provide for objection by a family member before an investigator may enroll a subject into the research study.<sup>25</sup> Investigators are committed to maintain attempts to obtain effective consent or objection to consent during the potential time in which provision of the investigational intervention may have therapeutic effect.<sup>26</sup> Of course, in studies like the one above involving patients with defibrillation, the therapeutic window would be quite short. Furthermore, once a subject is enrolled, investigators are obligated to inform the

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<sup>17</sup> *Id.*

<sup>18</sup> 21 C.F.R. § 812.150 (1999).

<sup>19</sup> 21 C.F.R. § 50.24 (2001).

<sup>20</sup> 42 U.S.C. § 244 (2003).

<sup>21</sup> See Pub. L. No. 107-188 § 159, 116 Stat. 594, 634 (2002) (finding that "eighty percent of cardiac arrests are caused by ventricular fibrillation, for which defibrillation is the only effective treatment").

<sup>22</sup> 21 C.F.R. § 50.24 (2001).

<sup>23</sup> *Id.*

<sup>24</sup> 21 C.F.R. § 50.24(a) (2001).

<sup>25</sup> 21 C.F.R. § 50.24(a)(6) (2001).

<sup>26</sup> 21 C.F.R. § 50.24(a)(5); 21 C.F.R. § 50.24(a)(7)(v) (2001).

subject, the subject's legally authorized representative if the subject is incapacitated, and if neither of the aforementioned is feasible, the subject's family members about the subject's enrollment in the investigation and allow them to either withdraw the subject or object to the subject's participation, if so desired.<sup>27</sup> All of these activities are regulated under IRB oversight.<sup>28</sup> Investigations conducted under this exception require a separate, effective FDA investigational product application before research activities begin.<sup>29</sup>

Besides the FDA, other federal agencies that conduct, support (i.e., sponsor), or regulate research involving humans have important interests in the protection of human research subjects. In response to the abuses discovered in the Tuskegee syphilis studies, Congress enacted the National Research Act, which mandates that the predecessor Department of Health and Human Services (DHHS) promulgate regulations for human subject protections.<sup>30</sup> On May 30, 1974, the DHHS's Basic Policy for the Protection of Research Subjects (Basic Policy) was published and codified.<sup>31</sup> On January 26, 1981, the DHHS published an amended Basic Policy, and at the same time, the FDA published its regulations for IRBs.<sup>32</sup> The content of these regulations is essentially the same today. Subsequently, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research recommended that all federal departments and agencies adopt as a common core the DHHS regulations governing research with human subjects.<sup>33</sup> In response, the Office of Science Technology and Policy proposed a common Federal Policy for the

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<sup>27</sup> 21 C.F.R. § 50.24(b) (2001).

<sup>28</sup> 21 C.F.R. §§ 50.24(a)(1)–(7) (2001).

<sup>29</sup> 21 C.F.R. § 50.24(d) (2001).

<sup>30</sup> National Research Service Award Act of 1974, Pub. L. No. 93-348, § 201, 88 Stat. 342 (1974); Appendix 1: Historical, Ethical, and Legal Foundations for the NIH's Policies and Procedures, *in* Guidelines for the Conduct of Research Involving Human Subjects at the National Institutes of Health, <http://ohsr.od.nih.gov/guidelines/graybook.html> (last visited Mar. 11, 2008).

<sup>31</sup> See 39 Fed. Reg. 18,914 (May 30, 1974).

<sup>32</sup> Final Regulations Amending Basic HHS Policy for the Protection of Human Research Subjects, 46 Fed. Reg. 8,366 (Jan. 26, 1981); Protection of Human Subjects; Standards for Institutional Review Boards for Clinical Investigations, 46 Fed. Reg. 8,958 (Jan. 27, 1981).

<sup>33</sup> 56 Fed. Reg. 28,003 (June 18, 1991).



Protection of Human Subjects based on the DHHS rule.<sup>34</sup> This policy was later adopted and promulgated by fifteen federal agencies and is referred to as the "Common Rule."<sup>35</sup>

Although both the FDA regulations and the Common Rule are congruent with respect to membership, functions, and responsibilities of IRBs, there exist several important differences between them.<sup>36</sup> Two relevant differences for this discussion relate to emergencies and waivers to informed consent and IRB approval.<sup>37</sup> The Common Rule, unlike the FDA regulations, contains no exception or exemption for emergency medical use; rather, the rule simply asserts that it is not intended to limit the authority of a physician to provide emergency care to the extent permitted by law.<sup>38</sup> However, a federal agency operating under the Common Rule may conduct or fund research only if the research has been reviewed and approved by an IRB.<sup>39</sup> Thus, the Common Rule does not permit research activities to be initiated without prior IRB approval even in an emergency and even if the activities satisfy the FDA exception for emergency use.<sup>40</sup>

The FDA regulations and the Common Rule also differ in the use of waivers to both informed consent and IRB approval.<sup>41</sup> Under FDA regulations, informed consent of a subject may be waived only if the investigation meets a specified regulatory exception.<sup>42</sup> But the Common Rule gives the IRB authority to waive or alter the elements of in-

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<sup>34</sup> *Id.*

<sup>35</sup> Departments and agencies adopting the Common Rule include the Dept. of Agriculture, Dept. of Energy, NASA, Dept. of Commerce, Consumer Product Safety Commission, Agency for International Development, Dept. of Justice, Dept. of Defense, Dept. of Education, Dept. of Housing and Urban Development, Dept. of Veterans Affairs, Environmental Protection Agency, DHHS, National Science Foundation, Dept. of Transportation, and the Central Intelligence Agency by Executive Order 12333.

<sup>36</sup> BONNIE M. LEE, FDA, FDA INFORMATION SHEET: COMPARISON OF FDA AND HHS HUMAN SUBJECT PROTECTION REGULATIONS (2000), <http://www.fda.gov/oc/gcp/comparison.html> (last visited Mar. 11, 2008) [hereinafter FDA INFORMATION SHEET].

<sup>37</sup> *See Id.*

<sup>38</sup> 45 C.F.R. § 46.116(f) (2005).

<sup>39</sup> 45 C.F.R. § 46.103(b) (2005).

<sup>40</sup> OHRP Guidance: Emergency Medical Care, <http://www.hhs.gov/ohrp/humansubjects/guidance/hcdc91-01.htm> (last visited Mar. 11, 2008).

<sup>41</sup> FDA INFORMATION SHEET, *supra* note 36.

<sup>42</sup> *See Id.*

formed consent in certain types of minimal risk research where breach of confidentiality represents the main risk to the subjects.<sup>43</sup> FDA allows sponsors to request a waiver of IRB review requirements; however, the Common Rule contains categories of research exemptions and permits waiver by the agency head.<sup>44</sup> The difference in waiver requirements between these regulations required the Secretary of DHHS to exercise such authority to waive the general requirements for informed consent in the Common Rule and allow compatible IRB review for research conducted under the FDA emergency research exception described above.<sup>45</sup> Having compatibility between FDA regulations and the Common Rule is important because federally sponsored research involving novel drugs and devices must independently satisfy both sets of regulations.<sup>46</sup>

#### RECENT STATUTES AND REGULATIONS GOVERNING COUNTERMEASURES IN BIOTERRORISM OR PUBLIC HEALTH EMERGENCIES

Following the events of September 11th and the anthrax attacks in 2001, Congress responded to future threats of bioterrorism with passage of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (BPRA) and the Project BioShield Act of 2004 (BioShield).<sup>47</sup> Both of these acts amended the Public Health Service Act and the Food, Drug, and Cosmetic Act (FDCA) for the purpose of improving the ability of the United States to deal with bioterrorism or public health emergencies and to develop protections and countermeasures against potential harmful agents in circumstances affecting national security.<sup>48</sup> One express purpose of both pieces of legislation was to streamline the FDA approval process for novel biologics and drugs developed as countermeasures from the research ac-

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<sup>43</sup> *Id.*

<sup>44</sup> *Id.*

<sup>45</sup> Waiver of Informed Consent Requirements in Certain Emergency Research, 61 Fed. Reg. 51,531 (Oct. 2, 1996).

<sup>46</sup> See 21 C.F.R. § 56.101 (2001); 45 C.F.R. § 46.101 (2005).

<sup>47</sup> Pub. L. No. 107-188 § 125, 116 Stat. 594 (2002); 42 U.S.C. § 247d-6 (2004).

<sup>48</sup> *Id.*

tivities funded by these acts.<sup>49</sup>

One reason to alter the traditional FDA approval process was that clinical testing of countermeasures cannot be ethically performed by exposing human subjects to dangerous infectious or toxic agents.<sup>50</sup>

Ordinarily, potential therapeutic agents against infections and toxic agents are tested in target populations with the relevant pathologic conditions.<sup>51</sup> Because the incidence of pathologic conditions caused by bioterrorism agents is so low, it would be impossible to accrue sufficient numbers of subjects in clinical trials to assess the effectiveness of countermeasures without intentionally exposing subjects to the harmful agent first.<sup>52</sup> Producing such a condition in otherwise unaffected subjects would be unjustifiable on ethical principles because of the additional harms involved by producing the pathologic condition in otherwise unaffected individuals.<sup>53</sup> These additional harms are not present in other categories of clinical trials, such as Phase-I oncology trials, where subjects already have the pathologic condition.

Lack of substantial evidence of clinical efficacy for new therapies constitutes mandatory grounds for refusing to approve a new drug application,<sup>54</sup> and thus would prevent introduction and delivery of potentially useful therapies through interstate commerce.<sup>55</sup> Unapproved drugs may be administered to individuals through an exemption of effective approval for drugs and biologics for investigational use.<sup>56</sup> Investigational use of drugs and biologics, however, requires

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<sup>49</sup> *Id.*

<sup>50</sup> Ezekiel J. Emanuel et al., *What Makes Clinical Research Ethical*, 283 JAMA 2701, 2710 n.20 (2000).

<sup>51</sup> See generally U.S. DEP'T OF HEALTH & HUMAN SERVICES, INSTITUTIONAL REVIEW BOARD GUIDEBOOK: CHAPTER V, BIOMEDICAL AND BEHAVIORAL RESEARCH – AN OVERVIEW, available at [http://www.hhs.gov/ohrp/irb/irb\\_chapter5.htm](http://www.hhs.gov/ohrp/irb/irb_chapter5.htm) (last visited Mar. 11, 2008) (discussing the broad outlines of clinical research using human subjects).

<sup>52</sup> See New Drug and Biological Drug Products; Evidence Needed to Demonstrate Efficacy of New Drugs for use Against Lethal or Permanently Disabling Toxic Substances When Efficacy Studies in Humans Ethically Cannot Be Conducted, 64 Fed. Reg. 53,961, 53,962 (Oct. 5, 1999).

<sup>53</sup> *Id.*

<sup>54</sup> 21 U.S.C. § 355(d) (2003).

<sup>55</sup> 21 U.S.C. § 355(a) (2003).

<sup>56</sup> 21 U.S.C. § 355(i) (2003).

an effective investigational new drug application and local institutional review board approval.<sup>57</sup> These approvals are lengthy and unpredictable.

The bioterrorism legislation, reviewed below, creates an emergency use authorization for an unapproved countermeasure, or unapproved use of an otherwise approved countermeasure, in public health emergencies under legal standards that are less stringent than provided by the investigational new drug regulations.<sup>58</sup> Issuance of an emergency use authorization allows rapid access to such countermeasures by the public in a time of need.<sup>59</sup> Recently, the FDA used these powers for the first time to grant emergency authorization for distribution of anthrax vaccine to military personnel in an effort to circumvent an injunction from a federal court prohibiting the vaccine's use. The changes illustrate the tension between the protection of public health and the need to protect human subjects, even in times of emergency or emergency preparedness.

### **Bioterrorism Preparedness and Response Act of 2002**

The BPR Act was introduced to help streamline the process of developing new countermeasures to bioterrorist threats. Subtitle B of this Act contains several provisions aimed at making newly-developed priority countermeasures rapidly available for clinical use. A priority countermeasure is a drug, biological product, device, vaccine, vaccine adjuvant, antiviral, or diagnostic test determined by DHHS to be a priority to treat, identify, or prevent infection by a listed biological agent or toxin, harm by any other agent that may cause a public health emergency, or complication resulting from administering a priority countermeasure.<sup>60</sup> The Act mandates the Secretary (a) to accelerate development on priority countermeasures

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<sup>57</sup> 21 U.S.C. § 360bbb(c) (2007); 21 U.S.C. §§ 355(i)(2), 355(4); 21 C.F.R. pts. 312, 50, and 56 (2001).

<sup>58</sup> See Public Health Security and Bioterrorism Preparedness and Response Act, Pub. L. No. 107-188, 166 Stat. 594 (2002).

<sup>59</sup> Authorization of Emergency Use of Anthrax Vaccine Adsorbed for Prevention of Inhalation Anthrax by Individuals at Heightened Risk of Exposure Due to Attack With Anthrax; Availability, 70 Fed. Reg. 54,52 (Feb. 2, 2005).

<sup>60</sup> Pub. L. No. 107-188 § 125, 116 Stat. 615 (2002); 42 U.S.C. § 247d-6(e).

through the awarding of research grants;<sup>61</sup> (b) to finalize and promulgate, within ninety days of the Act's passage, DHHS's proposed rule for determination of clinical effectiveness of new drugs and biologics when human efficacy studies are not ethical or feasible, i.e. the "two animal" rule;<sup>62</sup> and (c) to maintain a national stockpile of drugs, biologics, medical devices, and supplies that the Secretary determines are appropriate and practicable to provide emergency health security for the United States in the event of a bioterrorist attack or public health emergency and ensure sufficient amounts of smallpox vaccine are developed and available for the nation's needs.<sup>63</sup> The Act also allows a priority countermeasure to be designated and approved as a fast-track product under the FDCA<sup>64</sup> even if evidence of clinical effectiveness is only available via the two animal rule.<sup>65</sup> Thus, as they pertain to countermeasures, these provisions promote increased research and development activity, relax requirements for clinical effectiveness, speed up the approval process, and create a federal marketplace for their sale.

### **FDA's Two Animal Rule**

On May 31, 2002, in response to the mandate of BPRa, the FDA promulgated its final rule entitled "New Drug and Biological Drug Products; Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible" to take effect July 1, 2002. This rule amended the FDA regulations with regard to new drug and biological products studied for efficacy and safety in ameliorating or preventing serious life-threatening conditions caused by exposure to lethal or permanently disabling toxic, biological, chemical, radiological, or nuclear substances.<sup>66</sup>

The scope of the rule applies only for new drugs and biological products that cannot undergo human efficacy studies because it would be unethical to expose healthy human volunteers to such inju-

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<sup>61</sup> Pub. L. No. 107-188 § 125, 116 Stat. 615 (2002); 42 U.S.C. § 247d-6(h)(4).

<sup>62</sup> Pub. L. No. 107-188 § 123, 116 Stat. 594, 613.

<sup>63</sup> Pub. L. No. 107-188 § 121, 116 Stat. 594, 611-13; 42 U.S.C. § 247d-6(b).

<sup>64</sup> 21 U.S.C. § 360e(d)(5) (2004).

<sup>65</sup> 21 U.S.C. § 356-1 (2002).

<sup>66</sup> 67 Fed. Reg. 37,995; 21 C.F.R. § 314.600 (2002).

rious substances, and field trials to study the product's effectiveness after accidental or hostile exposure have not been feasible.<sup>67</sup> The rule does not apply to products that may qualify for accelerated approval based on surrogate markers or clinical endpoints other than survival or irreversible morbidity, nor does it relax safety testing for the drugs to which it applies.<sup>68</sup> The remaining sections of the rule address the types of evidence of effectiveness the agency will require for approval, procedures for the agency to withdraw approval, post-marketing safety reporting, promotional materials, and termination of any requirements placed on approval under the rule.<sup>69</sup>

The rule's key provisions state that the FDA may grant marketing approval for a new drug or biological product within the scope of the rule and for which safety has been established when the results of adequate and well-controlled animal studies establish that the product is reasonably likely to provide clinical benefit for humans. The FDA may rely on other data in addition to those data from the controlled studies, including human data, to determine the sufficiency of the data. The FDA must apply the following four criteria to determine whether animal studies provide substantial evidence of effectiveness in humans:

- 1) There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product;
- 2) The effect is demonstrated in more than one animal species expected to react with a response predictive of humans, unless the effect is demonstrated in a single animal species which represents a sufficiently well-characterized animal model for predicting the response in humans;
- 3) The animal study endpoint must be clearly related to the desired endpoint in humans, generally improved survival or morbidity; and
- 4) Sufficient data is available, whether from animals or humans,

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<sup>67</sup> 21 C.F.R. § 314.600 (2002).

<sup>68</sup> 21 C.F.R. § 314.600; 21 C.F.R. § 601.90 (2002).

<sup>69</sup> 21 C.F.R. §§ 314.610-.650; 21 C.F.R. §§ 601.91-.95.

to select an effective dose in humans.<sup>70</sup>

Based upon the second criterion, the rule has been dubbed the “two animal” rule. All approvals under the two animal rule are subject to three requirements:

- 1) the applicant must perform post-marketing studies to verify and describe the drug’s clinical benefit and safety,
- 2) if the FDA concludes that the product can only be used safely by restricting distribution, then the FDA will impose such restrictions, and
- 3) as part of the labeling, the product information provided to patient recipients must explain that, for ethical and feasibility reasons, the product’s approval was based on efficacy studies conducted in animals alone, as well as any other relevant information required by the FDA.<sup>71</sup>

Recipients must be given this information before administration or distribution of the product to the recipient, if possible.<sup>72</sup>

FDA reviewing officials will make the determination of whether or not it is unethical to conduct a study in humans for purposes of applying the rule; however, the FDA or the sponsor may decide to seek the advice of IRBs, ethicists, clinicians, and advisory committees in difficult cases, though this is not required.<sup>73</sup> Furthermore, in response to another comment suggesting that products approved under the two animal rule should be treated as investigational new drugs (INDs), the agency noted that reliance on the IND regulations was suboptimal for several reasons.<sup>74</sup> First, in truly emergent situations where the population cannot be identified in advance and likely would be large, obtaining informed consent may be impossible.<sup>75</sup> Furthermore, introducing a waiver of informed consent requirements

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<sup>70</sup> 67 Fed. Reg. 37,995; 21 C.F.R. §§ 314.610(a)(1)–(4); 67 Fed. Reg. 37,996; 21 C.F.R. §§ 601.91(a)(1)–(4).

<sup>71</sup> 21 C.F.R. § 314.610(b)(1)–(3) (2002).

<sup>72</sup> 67 Fed. Reg. 37,995; 21 C.F.R. §§ 314.610(b)(1)–(3); 67 Fed. Reg. 37,996; 21 C.F.R. §§ 601.91(b)(1)–(3).

<sup>73</sup> 67 Fed. Reg. 37,988, 37,992.

<sup>74</sup> 64 Fed. Reg. 53,960, 53,963 (Oct. 5, 1999) (to be codified at 21 C.F.R. pt. 314.601).

<sup>75</sup> *Id.*

in situations where a product is to be given to competent individuals has proved extremely controversial, presumably making the IND regulations unworkable.<sup>76</sup> Thus, it was thought to be more reasonable to adopt an alternative basis for granting marketing approval of products potentially having widespread use for treatment or prevention of lethal or disabling toxic effects of injurious agents.<sup>77</sup>

### **Project BioShield Act of 2004**

With the passage of BioShield, Congress intended to hasten development and clinical availability of qualified countermeasures for agents of bioterrorism.<sup>78</sup> A qualified countermeasure is defined as a drug, biological product, or device that the Secretary of DHHS determines to be a priority to treat, identify, or prevent harm from any biological, chemical, radiological, or nuclear agent that may cause a public health emergency affecting national security, or to manage the complications, including mortality, resulting from the use of such drugs, biological products, or devices.<sup>79</sup> This definition uses similar wording found in the FDA's two animal rule. In its first sections, BioShield grants DHHS authority to expedite peer review of research activity, enhance flexibility in contracting for research and development, and purchase security countermeasures for the strategic national stockpile from a specially designated reserve fund.<sup>80</sup>

Of more interest for this discussion is Section Four of BioShield, which authorizes emergency use of medical products by amending the FDCA. Under Section Four, the Secretary may authorize the introduction into interstate commerce of drugs, biological products, or devices intended for use in an actual or potential emergency.<sup>81</sup> An au-

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<sup>76</sup> *Id.*

<sup>77</sup> 67 Fed. Reg. 37,988, 37,992; 64 Fed. Reg. 53,960, 53,963.

<sup>78</sup> Project BioShield Act of 2004, Pub. L. No. 108-276, 118 Stat. 835 (codified at 42 U.S.C. § 247d-6a).

<sup>79</sup> Pub. L. No. 108-276 § 2, 118 Stat. 835 (codified at 42 U.S.C. § 247d-6a(a)(2)).

<sup>80</sup> A security countermeasure is a qualified countermeasure for agents that materially threaten national security as identified by the Secretary of Homeland Security, is necessary to protect the public health, and is approved or licensed for use by the FDA, reasonably likely to receive such approvals within eight years as determined by the secretary, or is authorized for emergency use. Project BioShield Act of 2004, Pub. L. No. 108-276, 118 Stat. 835, 843.

<sup>81</sup> Pub. L. No. 108-276 § 4(a), 118 Stat. 835, 853.



thorization for medical use extends to previously unapproved medical products or unapproved uses of approved medical products.<sup>82</sup> To justify an emergency authorization, the DHHS Secretary must also declare an emergency based on one of the following criteria concerning a specified biological, chemical, radiological, or nuclear agent or agents:

- 1) a determination by the Secretary of Homeland Security that there is, or is a significant potential for, a domestic emergency with a heightened risk of attack;
- 2) a determination by the Secretary of Defense that there is, or is a significant potential for, a military emergency involving a heightened risk to United States military forces of attack; or
- 3) a determination by the DHHS Secretary of a public health emergency that affects, or has a significant potential to affect, national security.<sup>83</sup>

A declaration of emergency is valid until it is terminated by the DHHS Secretary or for one year, unless renewed by the Secretary.<sup>84</sup> Each declaration, determination, and renewal must be published in the Federal Register.<sup>85</sup>

Once an emergency is declared, the DHHS Secretary may issue an authorization for emergency use, following appropriate consultation, when feasible, with the Directors of the National Institutes of Health and Centers for Disease Control, by concluding the following:

- 1) the agents specified in the declaration of emergency can cause a serious or life-threatening disease or condition;
- 2) there is reasonable belief based on the totality of scientific evidence, including any available data from adequate and well-controlled clinical trials, that (i) the product may be effective in diagnosing, treating or preventing such disease or condition or serious or life-threatening complications from use of a qualified countermeasure; and (ii) the known and po-

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<sup>82</sup> Pub. L. No. 108-276 § 4(a), 118 Stat. 835, 854; 21 U.S.C. § 360bbb-3(a)(2).

<sup>83</sup> Pub. L. No. 108-276 § 4(a), 118 Stat. 835, 854; 21 U.S.C. § 360bbb-3(b)(1).

<sup>84</sup> Pub. L. No. 108-276 § 4(a), 118 Stat. 835, 854; 21 U.S.C. § 360bbb-3(b)(2).

<sup>85</sup> Pub. L. No. 108-276 § 4(a), 118 Stat. 835, 855; 21 U.S.C. § 360bbb-3(b)(4).

tential benefits of the product's use outweigh the known and potential risks of the product;

- 3) there is no adequate, approved and available alternative to the product for diagnosing, treating, or preventing such disease or condition; and
- 4) any other criteria the Secretary shall prescribe by regulation.<sup>86</sup>

Each authorization of a product for emergency use must state 1) each disease or condition that the product may be used to diagnose, treat, or prevent within the scope of the authorization, 2) the Secretary's conclusions that the known and potential benefits of the product outweigh the unknown and 3) potential risks of the product, and the Secretary's conclusions concerning the safety and potential effectiveness of the product in diagnosing, treating, or preventing such diseases or conditions, including an assessment of the available scientific evidence.<sup>87</sup>

The Secretary must prescribe conditions for persons acting under the authorization that he finds necessary or appropriate to protect the public's health.<sup>88</sup> For unapproved products, the required appropriate conditions include those designed to ensure both health care professionals and potential individual recipients of the product are informed that the Secretary has authorized the product's emergency use, the significant known and potential benefits and risks of the emergency use of the product, the extent to which such benefits and risks are unknown, and the available alternatives to the product and their risks and benefits. Also, potential recipients must be informed of the option to accept or refuse administration of the product and the consequences of refusing administration of the product. Furthermore, appropriate conditions are required for monitoring and reporting adverse events and manufacturer record keeping, and reporting requirements during emergency use of the product.<sup>89</sup> Additional conditions may apply to distribution of the product, limitations on

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<sup>86</sup> Pub. L. No. 108-276 § 4(a), 118 Stat. 835, 856; 21 U.S.C. § 360bbb-3(c).

<sup>87</sup> Pub. L. No. 108-276 § 4(a), 118 Stat. 835, 856; 21 U.S.C. § 360bbb-3(d).

<sup>88</sup> Pub. L. No. 108-276 § 4(a), 118 Stat. 835, 856; 21 U.S.C. § 360bbb-3(e).

<sup>89</sup> Pub. L. No. 108-276 § 4(a), 118 Stat. 835, 856; 21 U.S.C. § 360bbb-3(e)(1)(A).

individuals who may administer the product, collection of data on safety and efficacy of the product, and record-keeping and reporting requirements for persons other than manufacturers.<sup>90</sup> Slightly modified conditions apply to unapproved uses of an approved product.<sup>91</sup>

An emergency use authorization (EUA) is effective until the earlier of the termination of the declaration of medical emergency or a revocation of authorization.<sup>92</sup> An authorization must undergo periodic review and may be revoked when the criteria under which it was issued are no longer met or other circumstances make revocation appropriate to protect public health or safety.<sup>93</sup> A notice of each authorization and each termination or revocation must be published promptly by the Secretary.<sup>94</sup>

In reviewing the above provisions of Section Four, one can surmise that unapproved products and unapproved uses of approved products, which clearly are experimental in nature, have effectively been removed from traditional review by institutional review boards. Any doubt is removed by the following express language found in subsection 4(k): "the use of such product within the scope of the authorization shall not be considered to constitute a clinical investigation . . . ."<sup>95</sup> Generally, a new drug must have FDA approval before marketing, distribution, and sale.<sup>96</sup> Approvals are based on clinical investigations of the drug demonstrating its safety and effectiveness for the intended use.<sup>97</sup> Clinical investigations of new drugs and biological products proceed under the investigational new drug provisions of the FDCA and its implementing regulations.<sup>98</sup> IRB review and approval of informed consent procedures (including appropriate forms and methods of documentation) is required for such investiga-

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<sup>90</sup> Pub. L. No. 108-276 § 4(a), 118 Stat. 835, 857; 21 U.S.C. § 360bbb-3(e)(1)(B).

<sup>91</sup> Pub. L. No. 108-276 § 4(a), 118 Stat. 835, 857; 21 U.S.C. § 360bbb-3(e)(2).

<sup>92</sup> Pub. L. No. 108-276 § 4(a), 118 Stat. 835, 358; 21 U.S.C. § 360bbb-3(f).

<sup>93</sup> Pub. L. No. 108-276 § 4(a), 118 Stat. 835, 358; 21 U.S.C. § 360bbb-3(g).

<sup>94</sup> Pub. L. No. 108-276 § 4(a), 118 Stat. 835, 358; 21 U.S.C. § 360bbb-3(h).

<sup>95</sup> Pub. L. No. 108-276 § 4(a), 118 Stat. 835, 359; 21 U.S.C. § 360bbb-3(k).

<sup>96</sup> 21 U.S.C. § 355(a) (2007).

<sup>97</sup> 21 U.S.C. § 355(a)-(b) (2007).

<sup>98</sup> 21 U.S.C. § 355(i) (2007); 42 U.S.C. § 201 (1993).

tions.<sup>99</sup> This requirement applies even when recognized exceptions to informed consent are applicable for individual life-threatening situations, presidential waiver for members of the military, and emergency research.<sup>100</sup> Under BioShield, however, the FDA, acting under delegated authority from the Secretary and using a declaration of emergency and authorization of emergency use, is granted the responsibility to weigh the scientific validity and ethical appropriateness of introducing otherwise experimental countermeasures without any IRB review. Even though no IRB review is mandated, the FDA retains discretion to seek such review should the agency perceive a need for it. Again, this is discretionary and not mandatory.

As one can see, BioShield creates efficiencies for approving and distributing qualified countermeasures in the event of an imminent threat or attack through a centralized process within the federal system. However, efficiency is achieved by bypassing the "usual human subjects protection" function of the IRBs. Also, because administration of a countermeasure under an EUA does not constitute research, human research protections under the Common Rule do not apply. As the regulations stand, the FDA will function as a de facto national review board in the event of a public health emergency. It is important to not only ask whether the agency is up to the task, but also whether the current system of federal research oversight is well-suited for handling the specific ethical challenges raised in research on bioterrorism countermeasures and treatment and vaccines for emerging infections.

Although BioShield is designed to rapidly transmit countermeasures to the public, it does not relieve healthcare providers from liability for harm related to dispensing or administering countermeasures. For healthcare providers to gain protection from liability, states would have to enact legislation limiting the liability of private acts for negligence.<sup>101</sup> Having recipients give consent prior to administration of any countermeasure given under an EUA may provide significant protection from claims of battery, and supply evidence that a countermeasure recipient assumed the risk of harm. This raises the ethical

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<sup>99</sup> 21 C.F.R. § 312.40 (2005).

<sup>100</sup> 21 C.F.R. §§ 50.23–50.24 (2006).

<sup>101</sup> Ctr. For Law and the Pub.'s Health, Model Health Powers Act § 804 (2001).

burden for a substantive and meaningful informed consent process.

### **Authorization of Emergency Use for Anthrax Vaccine**

On October 27, 2004, the United States District Court for the District of Columbia permanently enjoined the military's Anthrax Vaccination Immunization Program (AVIP) from involuntary administration of anthrax vaccine adsorbed (AVA) to military personnel and contractors absent informed consent or presidential waiver.<sup>102</sup> The court's ruling was grounded on the determination that AVA was an investigational product because it lacked FDA approval.<sup>103</sup> Without the benefit of an injunction, military personnel who refused AVA administration were subject to disciplinary action up to and including court martial.<sup>104</sup>

Issuance of this injunction was the culmination of months of litigation. The litigation began in March 2003, when six unknown plaintiffs filed suit challenging the lawfulness of the AVIP and sought to avoid undergoing vaccination without penalty.<sup>105</sup> The suit claimed that AVA was not properly approved by the FDA for inhalational anthrax and was thus investigational, and as such should only be administered under the investigational drug regulations, which require either informed consent or a presidential waiver of consent.<sup>106</sup> The plaintiffs asserted, and the court agreed, that AVA had failed to gain proper regulatory approval after the licensing responsibility for biological products was transferred from NIH to FDA.<sup>107</sup>

Finding the AVIP defeated, the Department of Defense (DOD) and the FDA invoked the authority granted by BioShield to rescue the program.<sup>108</sup> On December 10, 2004, pursuant to section 564(b)(1)(B) of the FDCA, as amended by BioShield, the Deputy Sec-

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<sup>102</sup> *Doe v. Rumsfeld*, No. 03-707, 2007 U.S. Dist. LEXIS 60943 at \*5 (D.D.C. Aug. 21, 2007).

<sup>103</sup> *Id.* at \*3-5.

<sup>104</sup> *Doe v. Rumsfeld*, 341 F. Supp. 2d 1, 3 (D.D.C. 2004).

<sup>105</sup> *Id.* at 1-3.

<sup>106</sup> 21 CFR § 50.23.

<sup>107</sup> *Doe*, 341 F. Supp. 2d at 15.

<sup>108</sup> Authorization of Emergency Use of Anthrax Vaccine Adsorbed for Prevention of Inhalation Anthrax by Individuals at Heightened Risk of Exposure Due to Attack With Anthrax; Availability, 70 Fed. Reg. 5452 (Feb. 2, 2005).

retary of Defense determined that there was a "significant potential for a military emergency involving a heightened risk to U.S. military forces of attack with anthrax."<sup>109</sup> On December 22, 2004, DOD sent a letter to the FDA requesting the issuance of an EUA for the use of AVA for protection against inhalational anthrax.<sup>110</sup> In response to this request, the Secretary of Health and Human Services declared an emergency justifying the authorization of the emergency use of AVA effective January 14, 2005.<sup>111</sup> Next, the FDA issued an EUA for AVA effective January 27, 2005.<sup>112</sup> Thus, it took the agencies about six weeks to implement the administrative approval provisions of Bio-Shield in this case. On April 6, 2005, the court modified its injunction to permit voluntary administration of AVA under an EUA.<sup>113</sup> The EUA for AVA remained in effect until February 1, 2006, when the declaration of emergency expired;<sup>114</sup> some six weeks earlier on December 19, 2005, following a proposed rulemaking and comment period, the FDA issued a final order categorizing AVA as "safe and effective and not misbranded" for treatment of all forms of clinical disease caused by anthrax.<sup>115</sup> This example foreshadows the serious ethical and legal issues that would arise in the event of a public health emergency due to a naturally occurring outbreak or bioterrorist attack.<sup>116</sup>

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<sup>109</sup> *Id.*

<sup>110</sup> The Secretary of Health and Human Services has delegated his authority to issue an EUA under § 564 to the FDA Commissioner. See Authorization of Emergency Use of Anthrax Vaccine Adsorbed for the Prevention of Inhalational Anthrax by Individuals at Heightened Risk of Exposure Due to Attack with Anthrax; Availability 70 Fed. Reg. 5452, at 5453 n. 2 (Feb. 2, 2005). Authority is derived from 21 U.S.C. § 360bbb-3 as amended by Project Bio-Shield Act of 2004.

<sup>111</sup> Authorization of Emergency Use of Anthrax Vaccine Adsorbed for Prevention of Inhalation Anthrax by Individuals at Heightened Risk of Exposure Due to Attack With Anthrax; Availability, 70 Fed. Reg. 5452 (Feb. 2, 2005).

<sup>112</sup> *Id.*

<sup>113</sup> *Doe v. Rumsfeld*, No. 03-707, 2005 U.S. Dist. LEXIS 5573 at \*3-5 (D.D.C. Apr. 6, 2005).

<sup>114</sup> Termination, By Expiration of Declaration of Emergency Justifying Emergency Use Authorization of Anthrax Vaccine Adsorbed, 71 Fed. Reg. 5341 (Feb. 1, 2006).

<sup>115</sup> Biological Products; Bacterial Vaccines and Toxoids; Implementation of Efficacy Review; Anthrax Vaccine Adsorbed; Final Order, 70 Fed. Reg. 75180, 75182 (Dec. 19, 2005).

<sup>116</sup> Authorization of Emergency Use of Anthrax Vaccine Adsorbed for Prevention of Inhalation Anthrax by Individuals at Heightened Risk of Exposure Due to Attack With Anthrax; Availability, 70 Fed. Reg. 5452 (Feb. 2, 2005); Medical Devices; Exception From General Re-

### KEY PROBLEMS WITH RESEARCH OVERSIGHT IN BIODEFENSE AND EMERGING INFECTIONS OUTSIDE OF A DECLARED EMERGENCY

The federal statutes and regulations discussed above address the issue of efficient introduction of novel countermeasures by centralizing and streamlining the federal administrative functions. However, the scope remains limited to the context of a declared public health emergency with national security implications. When a declaration of emergency is not in force, existing human subjects research regulations apply to the development and testing of vaccines and treatments for infectious disease-related outbreaks, whether initiated through terrorism or nature. Since the anthrax attacks in 2001, public discussion and federal regulatory changes on biodefense and emerging infection research have concentrated on preparing the scientific and clinical communities for emergency responses to possible outbreaks. It is important to take a longer view of the global public health threats in infectious disease and bioterrorism and to think also about how to better conduct day-to-day research with an eye to predictable events and outbreaks. The regulatory challenges associated with the failure of the West Nile Virus trials in the U.S. during 2003 highlight these problems.<sup>117</sup> Substantial amounts of time were consumed in gaining FDA approval, investigator preparation of IRB submissions, and IRB review and approval.<sup>118</sup> The lengthening and sequential nature of the review process resulted in loss of the opportunity to assess the effectiveness of a potential therapy during the seasonal outbreak.<sup>119</sup> From a public health perspective, the inefficiencies delayed a potentially effective therapy for a serious virus that may have reduced morbidity and mortality. It is important to emphasize the connection here between delays in review and lost benefit to subjects. A central unanswered question to date is whether the additional time for review contributed to greater protection of research subjects, protection from potentially harmful adverse reactions, or inadequate informed consent. This question needs to be put forward

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quirements for Informed Consent, 71 Fed. Reg. 32827 (June 7, 2006) (to be codified at 21 C.F.R. pt. 50).

<sup>117</sup> Penelope M. Jester et al., *Regulatory Challenges: Lessons Learned from Recent West Nile Virus Trials in the United States*, 27 CONTEMPORARY CLINICAL TRIALS 254 (2006).

<sup>118</sup> *Id.* at 256.

<sup>119</sup> *Id.* at 254.

more forcefully, and we need more than anecdotal accounts to establish which particular aspects of the review process are adding unnecessary drag to the review of public health research. In addition, we must know which aspects are essential to human subjects protection, even if they add to significant delays in the review process. In principle, there should be a way to protect time spent on genuine ethical debate over protocols and yet reduce redundant and more bureaucratic aspects of the process.

Such problems with the current regulatory structure governing human subjects research have been widely discussed and substantiated. Emanuel, et al., have significantly advanced the debate by summarizing key problems with the human research protections system in an effort to better evaluate proposed reforms to the system.<sup>120</sup> Relying on this comprehensive summary we will highlight the key structural, procedural, and substantive problems that are particularly pressing or raise distinctive ethical issues in biodefense and emerging infections research. As the debate continues about the optimal IRB function and structure, and as revisions of the FDA review process remain under consideration, it will be important to consider the unique challenges raised by the specialized and rapidly growing area of biodefense and emerging infections research. Beyond concerns about the efficiency of the review process, the special nature of research on biodefense and emerging infections raises difficult problems for ethical oversight. The important aim of protecting individual research participants remains. However, in this context the additional aims of maintaining the public health and minimizing regional, national, and global risks associated with a disease outbreak demand consideration as well. To compound matters, when faced with an imminent outbreak, decisions about risk and benefit must occur within a significantly constrained time frame and with often lower levels of certainty. The locus of decision-making to approve research activities often resides at multiple levels—namely, at local, national, and possibly global scientific and political levels. These important considerations signal a need to examine and evaluate both the structure and substance of the ethical review process for biodefense and emerging infections research.

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<sup>120</sup> Ezekiel J. Emanuel et al., *Oversight of Human Participants Research: Identifying Problems to Evaluate Reform Proposals*, 141 ANN. INTERN. MED. 282 (2004).



*Scope and inconsistencies in various federal regulations.* There are two key structural problems cited in most reform proposals.<sup>121</sup> First is the problem of regulatory scope, and second is the problem of inconsistencies within those regulations. The first problem leads to worries about gaps in human subjects protection as well as concerns about consistent protection across private sector and public sector research. Federal regulations apply to federally funded research. Federally funded research is research funded by one of the fifteen agencies that have adopted the “Common Rule.”<sup>122</sup> Adherence to the Common Rule on human subjects protection in non-federally funded research remains voluntary unless the research falls under the jurisdiction of the FDA (i.e., if a sponsor seeks to gain marketing approval for a regulated product).<sup>123</sup>

Since the vast majority of funding for biodefense and emerging infection research is sponsored by the federal government, it is likely that clinical research investigating qualified countermeasures will require IRB review under both DHHS and FDA regulations. These regulations will apply to safety studies required for drug approvals employing the “two animal” rule as well.<sup>124</sup> So, federal regulations governing research generally apply to biodefense and emerging infections research funded by federal agencies or research activities of test articles regulated by FDA. However, lack of harmonization between FDA and other DHHS agencies’ regulations regarding conflicts of interest, data safety and monitoring boards (DSMBs), and adverse event reporting create ambiguities impairing monitoring of commercial conflicts of interest and consistent human subjects protection.<sup>125</sup> Inconsistencies between the United States regulations and regulations in other countries may pose similar problems for multinational studies on biodefense and emerging infections.<sup>126</sup>

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<sup>121</sup> *Id.* at 284.

<sup>122</sup> Federal Policy for the Protection of Human Subjects, 56 Fed. Reg. 28,003 (June 18, 1991).

<sup>123</sup> *Id.*

<sup>124</sup> Pub. L. No. 107-188 § 123, 116 Stat. 594, 613.

<sup>125</sup> 21 C.F.R. § 54.1 (1998); 42 C.F.R. § 50.601 (1995); U.S. Dep’t of Health & Human Services, Secretary’s Advisory Comm. on Human Research Protections Meeting Minutes (2004), available at <http://www.hhs.gov/ohrp/sachrp/mtgings/mtg03-04/min0329.pdf> (last visited Mar. 11, 2008).

<sup>126</sup> 45 C.F.R. § 46 (2005).

*Variation and redundancy in the review process.* Variation and redundancy among local IRBs has been established as a significant barrier to efficient review of research studies.<sup>127</sup> This is a fundamental problem that needs to be addressed for general research, but the need is even more pressing for research on vaccine and treatment development for emerging infections and bioterrorism threats.<sup>128</sup> We need to identify more precisely the differences in practice that increase local research subject protection and abandon variations in practice that are merely bureaucratic. The tighter time frame, potentially widespread devastating effects of an unchecked outbreak, or poor timing with an expected seasonal outbreak justify a review process that minimizes redundancies that are not tied to increasing the ethical oversight of such research or experimental treatment. Increasingly, as with other areas of clinical research, research studies on emerging infections and biodefense are not conducted at a single institution but at multiple institutions.<sup>129</sup> Numerous IRBs may review a single proposal where the efforts are largely redundant and even contradictory.<sup>130</sup> We lack studies demonstrating whether variation across IRBs increases subject protection. However, there is mounting empirical evidence to show that a significant portion of variation is due to arbitrary differences across institutions regarding the interpretation of the federal requirements and concerns about institutional liability.<sup>131</sup> The particular challenge for oversight of biodefense and emerging in-

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<sup>127</sup> OFFICE OF INSPECTOR GEN., U.S. DEP'T OF HEALTH & HUMAN SERVICES, PUB. NO. OEI-97-00193, INSTITUTIONAL REVIEW BOARDS: A TIME FOR REFORM (1998); Kathleen Dziak et al., *IRBs and Multisite Studies: Variations among Institutional Review Board Reviews in a Multisite Health Services Research Study*, 40 H.S.R. 279, 287 (2005); Rita McWilliams et al., *Problematic Variation in Local Institutional Review of a Multicenter Genetic Epidemiology Study*, 290 J.A.M.A. 360 (2003).

<sup>128</sup> Penelope M. Jester et al., *Regulatory Challenges: Lessons Learned from Recent West Nile Virus Trials in the United States*, 27 CONTEMPORARY CLINICAL TRIALS 254 (2006); William Burman et al., *The Effects of Local Review on Informed Consent Documents from a Multicenter Clinical Trials Consortium*, 24 CONTROLLED CLINICAL TRIALS 245 (2003); Kurt D. Reed et al., *The Detection of Monkeypox in Humans in the Western Hemisphere*, 350 N. ENGL. J. MED. 342 (2004); Susan M. Poutanen et al., *Identification of Severe Acute Respiratory Syndrome in Canada*, 348 N. ENGL. J. MED. 20 (2003).

<sup>129</sup> M.C. Christian et al., *A Central Institutional Review Board for Multi-Institutional Trials*, 346 N. ENGL. J. MED. 1405 (2002).

<sup>130</sup> *Id.*

<sup>131</sup> OFFICE OF INSPECTOR GEN., U.S. DEP'T OF HEALTH & HUMAN SERVICES, PUB. NO. OEI-97-00193, INSTITUTIONAL REVIEW BOARDS: A TIME FOR REFORM 11 (1998).

fections research is to streamline the review process without sacrificing human subject protections and public safety. It is important not to characterize the problem as a simple trade-off between human subjects protection and stemming a public health threat. Data showing instances where research is delayed or derailed as a result of the IRB process reveal the important connection between efficiency and the potential benefits of research to individuals and the public.<sup>132</sup> For this reason, the principles of ethical human subjects research in an emergency, or in preparation for an emergency, need to be optimized alongside other important values, such as the benefits and risks of fast-tracked vaccines or treatments, and the individual, social, and economic costs of a wide-spread outbreak without fully tested treatments.

*Inadequate mechanisms for professional deliberation on recurring ethical problems.* Most of the professional deliberation on recurring ethical problems in research occurs at the level of national political and professional organizations as well as in research ethics literature. While these efforts have advanced debates over topics such as conflicts of interest, protection of vulnerable subjects, the ethics of population studies, informed consent in emergency research, and numerous other recurrent problems, individual researchers and local IRB members typically do not have the time or resources to reflect on and apply these recommendations meaningfully and consistently across studies, over time, and across even regional institutions.<sup>133</sup> Mechanisms that facilitate shared knowledge of recurrent ethical problems in emerging infections and biodefense research would help already overburdened IRB members and investigators to efficiently access shared wisdom on problems such as the application of the two animal rule, informed consent with a countermeasure or vaccine that

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<sup>132</sup> William J. Burman et al., *Breaking the Camel's Back: Multicenter Clinical Trials and Local Institutional Review Boards*, 134 ANN. INTERN. MED. 152 (2001); Penelope M. Jester et al., *Regulatory Challenges: Lessons Learned from Recent West Nile Virus Trials in the United States*, 27 CONTEMPORARY CLINICAL TRIALS 254 (2006); Kathleen Dziak et al., *IRBs and Multisite Studies: Variations among Institutional Review Board Reviews in a Multisite Health Services Research Study*, 40 H.S.R. 279 (2005); Rita McWilliams et al., *Problematic Variation in Local Institutional Review of a Multicenter Genetic Epidemiology Study*, 290 JAMA 360 (2003); Thomas O. Stair et al., *Variation in Institutional Review Board Responses to a Standard Protocol for a Multicenter Clinical Trial*, 8 ACAD. EMERG. MED. 636 (2001).

<sup>133</sup> Ezekiel J. Emanuel et al., *Oversight of Human Participants Research: Identifying Problems to Evaluate Reform Proposals*, 141 ANN. INTERN. MED. 282, 282–86 (2004).

has not yet been tested in humans, community consultation, and other issues prevalent in this particular research community.

***Lack of expertise on IRBs.*** Another general criticism of local IRBs is the lack of relevant scientific knowledge and research ethics expertise among IRB membership.<sup>134</sup> Again, this is an important problem in the review of all clinical research that needs to be addressed, but there is added reason for addressing this concern quickly in the context of emerging infection and biodefense research. Both the quality and efficiency of the review can be adversely affected if IRB membership is not trained to evaluate the special public health, subject safety, and epidemiological aspects of this research. Reviewers of these proposals must have a working knowledge in a number of health-related areas, such as epidemiology and infectious disease, general public health, as well as an understanding of the ethical and legal issues confronting investigators and research coordinators when dealing with subject recruitment and protection in this research context.

***Inappropriate emphasis on informed consent forms.*** Review time would be better spent discussing the difficult substantive issues of consent in biodefense and emerging infections than editing informed consent forms. One of the factors cited in time-consuming variation among local IRBs is the time spent fine-tuning consent forms.<sup>135</sup> Given that informed consent should ideally be a process of communication among research coordinators, investigators, and research subjects, it has yet to be shown how more detailed, multi-paged consent forms improve this process. Much of the time spent on refining forms seems to have more to do with ensuring the correct documentation of research regulations governing informed consent rather than attention to changes that are specifically aimed at improving subjects' understanding.<sup>136</sup> Attention to language in consent documents is of great ethical importance in overcoming barriers to under-

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<sup>134</sup> *Id.* at 286.

<sup>135</sup> Rita McWilliams et al., *Problematic Variation in Local Institutional Review of a Multicenter Genetic Epidemiology Study*, 290 JAMA 360 (2003); Thomas O. Stair et al., *Variation in Institutional Review Board Responses to a Standard Protocol for a Multicenter Clinical Trial*, 8 ACAD. EMERG. MED. 636 (2001); William Burman et al., *The Effects of Local Review on Informed Consent Documents from a Multicenter Clinical Trials Consortium*, 24 CONTROLLED CLINICAL TRIALS 245 (2003).

<sup>136</sup> William Burman et al., *The Effects of Local Review on Informed Consent Documents from a Multicenter Clinical Trials Consortium*, 24 CONTROLLED CLINICAL TRIALS 245 (2003).

standing, especially in vulnerable populations and in addressing the problem of therapeutic misconception in early-phase trials.<sup>137</sup> However, once instruments have been tested and data gathered on effective language and wording, these forms can be shared across research groups. Attempts to standardize forms across institutions may help minimize some unnecessary time that IRBs spend on reviewing consent forms. There should then be less need for an IRB to revisit the same questions in subsequent study reviews. This is another aspect of the review process that suffers from inadequate mechanisms for sharing materials, insights, and data on these important but recurrent ethical review problems.

*Different analysis needed for risk and benefit.* Review of human subjects research in the context of a public health threat also requires a shift in thinking about risk and benefit. Those charged with reviewing such protocols ought to have a good sense of what risk-benefit ratio will ethically justify approval of the research. For example, what would constitute “minimal risk” when reviewing a human study to develop a possible vaccine for an emerging pandemic like Avian Flu? Should the risk threshold itself be altered in the context of a public health threat, or can it be justifiably overridden if the potential harms are great enough or sufficiently widespread? Determining this ratio in a way that is sensitive to the broader context of a public health threat requires us to factor in the scientific basis and ethical principles as applied to public health. As we have discussed above, under the “two animal rule,” some interventions may be approved for human use under emergency circumstances with minimal human data to predict possible risks and efficacy. In addition to assessing risks to subjects associated with adverse effects of an experimental vaccine, the overall risk to public health needs to be taken into account, and guidance is needed on the best way to convey such public risks and benefits to potential study participants.

*Insufficient attention to informed consent in the public health context.* Informed consent to participate in research on vaccines or treatments for an emerging infection or an outbreak caused by a terrorist attack raises several issues that deserve expert attention in the review process. Politics and the very nature of infectious disease and

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<sup>137</sup> J. Kimmelman & N. Palmour, *Therapeutic Optimism in the Consent Forms of Phase I Gene Transfer Trials: An Empirical Analysis*, 31 J. MED. ETHICS 209 (2005).

bioterrorist threats, with rapid onset and insidious spread, create a sense of emergency even in day-to-day research on vaccines and treatments. It is important in this context to be aware of the fundamental trade-off in public health ethics between civil liberties and public goods (or minimizing public harms). Human subject protection is no less important in the context of a disease outbreak or threatened outbreak, but introduces an added dimension in the evaluation of the research intervention. In general research, investigators are ethically required to assess and ensure participants' understanding and appreciation of the risks and benefits associated with the experimental intervention and the risks and benefits associated with foregoing the experimental intervention.

In human subjects research on emerging infections or biodefense, should patients also be expected to understand and appreciate the broader public risks associated with a disease threat? What role might fear play in consenting to the use of available experimental vaccines or treatments when citizens may be generally fearful about the possibility of an outbreak or terrorist attack? Investigators need more guidance on the presentation of information regarding public risks and benefits, as well as presenting to patients less information about possible therapeutic benefits and possible side effects. Guidelines for review in this context should also include a detailed discussion of handling informed refusals, since refusals in the context of a public health emergency may be accompanied by consequences such as quarantine. There is a predictable element of strong persuasion, if not coercion, inherent in the informed consent process in the context of a serious disease outbreak.<sup>138</sup> The standard normative reasoning in public health emergencies is that the consequences of a serious disease outbreak may outweigh appeals to individual rights.<sup>139</sup> In the ideal review process for public health interventions there should be more precise guidance on what level of public risk justifies what level of strong persuasion and even coercion with potential research subjects. It will also be important to determine the best way to inform the public and potential participants of this threshold.

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<sup>138</sup> Onora O'Neill, *Informed Consent and Public Health*, 359 PHIL. TRANS. R. SOC. LOND. 1133, 1135 (2004).

<sup>139</sup> *Id.*

### RECOMMENDATIONS FOR PROCEDURAL REFORM: FACILITATED EXPERT REVIEW

We raise the above concerns in part to encourage debate on these important questions but also to motivate further empirical work on possible remedies for each of these problems. Some of the problems clearly overlap with oversight of clinical research generally and can be addressed in the ongoing debate about oversight reforms. However, we have attempted to highlight important differences between the key problems in general research and the problems that are either unique or compounded in the context of biodefense and emerging infections research. These important differences signal a need to examine both the procedure and substance of the ethical review as it pertains to this area of research. Because the inefficiencies of the current review structure pose serious barriers to both timely and ethical research and pose immediate public health concerns, we propose changes in the review structure that will begin to address many of the concerns raised here, while being compatible with the current regulatory framework. This more pragmatic approach would allow the research and research ethics communities to make concrete improvements without overhauling the present system (or waiting for the present system to be overhauled before addressing the serious ethical and public health concerns). The proposed restructuring, drawing on the review model used for multi-center trials,<sup>140</sup> addresses the central concerns about duplication of effort and the need for scientific and ethical expertise, while maintaining current rigorous standards of ethical human subjects protection.

We appreciate the Institute of Medicine's insight of a need for institutional and systemic flexibility in providing ethical oversight in complex areas of research; emerging infections and biodefense research are both scientifically and ethically complex.<sup>141</sup> Our proposal sacrifices overall elegance and simplicity for the sake of optimizing greater efficiency at the study-level (timely review of research pro-

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<sup>140</sup> M.C. Christian et al., *A Central Institutional Review Board for Multi-Institutional Trials*, 346 N. ENGL. J. MED. 1405 (2002).

<sup>141</sup> INST. OF MED., *RESPONSIBLE RESEARCH: A SYSTEMS APPROACH TO PROTECTING RESEARCH PARTICIPANTS* 2-3, 8 (2002); *See generally* Kendall Powell, *Call for Clinical Trial Reform Leaves Critics Unmoved*, 419 NATURE 546, 546 (2002) (discussing the Institute of Medicine's report calling for change in clinical review systems).

posals) with uncompromised protection of research subjects. There are scientifically and ethically significant differences between study types, and a one-size-fits-all approach will not likely lead to greater efficiency in complex areas of research.<sup>142</sup> There are three different types of human subjects studies within the broader category of emerging infections and biodefense research, and we propose slightly different review processes for each: 1) large, federally-funded vaccine trials of national scope, 2) regional, multi-site vaccine or treatment studies, and 3) single-site studies, typically early-phase trials with less than ten subjects. In this case, model review mechanisms are already in place. Our main aim is not to propose unnecessary additional oversight but to suggest as a first step the more efficient use of the current oversight institutions and mechanisms to better harness clinical and ethical resources. This model does not envision creation of a national oversight model similar to the Recombinant DNA Advisory Committee (RAC) for genetic research,<sup>143</sup> in this case tailored to biodefense issues. Instead, our proposal (*infra*) for a Centralized Expert Review Board (CERB) will serve a similar function, providing a locus for shared information and guidance on the ethical issues associated with this type of research while being sensitive to regional and local ethical concerns.

### **(1) Large, federally funded trials of national scope**

The most significant streamlining of the present process for human subjects protection review is needed in trials extending over large geographic areas, as these trials may involve epidemiology, treatment, vaccine studies, or treatment trials of national scope. Regional, national, and global outbreaks can have a widespread and devastating impact on the lives and health of individuals and communities, and can deal a serious blow to the health and security of political and economic institutions.<sup>144</sup> The potential benefit of such studies to the overall public health, coupled with the constrained timeframe for responding quickly to imminent outbreaks or predict-

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<sup>142</sup> See INST. OF MED., *supra* note 141.

<sup>143</sup> Recombinant DNA Advisory Committee, <http://www4.od.nih.gov/oba/rac/aboutrdagt.htm> (2004).

<sup>144</sup> Michael T. Osterholm, *Preparing for the Next Pandemic*, FOREIGN AFF., Jul.-Aug. 2005, at 24.



able seasonal outbreaks, make revisions in the review process necessary.<sup>145</sup> We recommend a facilitated central review for such studies, relying on the existing institutions and expert staff at the National Institute of Allergy and Infectious Diseases (NIAID) and/or the Centers for Disease Control (CDC). The review mechanisms would be almost identical to the model piloted by the National Cancer Institute (NCI) in consultation with the Office for Human Research Protections (OHRP).<sup>146</sup> The Central IRB Initiative at NCI is designed to offer clinically, scientifically, and ethically specialized human subjects review while reducing redundancies at the level of the local IRBs and investigators through facilitated review.<sup>147</sup> Institutions throughout the country conducting biodefense or emerging infections research could choose to participate in a central review conducted by the CERB for Biodefense and Emerging Infections. (See Figure 1). Protocols and informed consent documents would be submitted for central review by the specialized board. Applying the CERB model to the context of biodefense research would not require the creation and staffing of an entirely new CERB since NIAID and CDC already have functioning IRBs in place with expertise in the areas of infectious disease, ethics, and public health. Although some additional resources might be necessary to address protocol-specific needs and ongoing administrative support, we anticipate that such resources would only marginally increase the costs involved because we propose using already functioning review groups. Once the protocol is approved, investigators at participating institutions can apply for facilitated review by downloading the application and all review documents from the CERB for BD and EI website.<sup>148</sup> In the facilitated review model, local IRBs retain responsibility to assure local context issues related to the protocol and consent are satisfied and also provide oversight over local performance of research activities such as review of local serious

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<sup>145</sup> Penelope M. Jester et al., *Regulatory Challenges: Lessons from Recent West Nile Virus Trials in the United States*, 27 CONTEMPORARY CLINICAL TRIALS 254 (2006).

<sup>146</sup> NAT'L CANCER INST., THE CENTRAL INSTITUTIONAL REVIEW BOARD INITIATIVE, <http://www.ncicirb.org> (last visited Mar. 11, 2008).

<sup>147</sup> NAT'L CANCER INST., HOW THE CIRB PROCESS WORKS - A SYNOPSIS, [http://www.ncicirb.org/CIRB\\_Howworks.asp](http://www.ncicirb.org/CIRB_Howworks.asp) (last visited March 17, 2008).

<sup>148</sup> *Id.*

adverse events and unanticipated problems with the study.<sup>149</sup> The central IRB is the IRB of record and is responsible for reviewing all adverse events associated with the study.<sup>150</sup> Use of this model may have some mitigating effect on potential liability for local IRBs since the central IRB is the IRB of record.

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<sup>149</sup> *Id.*

<sup>150</sup> *Id.*

**(1) For Federally Funded Studies of National Scope:  
Existing NIAID or CDC IRBs with facilitated review by  
sites**

**EXAMPLE: West Nile Virus Studies**

**CIRB for Biodefense & Emerging Infections**

- Central Institutional Review Board staffed by trained clinicians and public health experts at NIAID or CDC.
- Receives applications, protocols, and informed consent documents from cooperating institutions.
- Approves or disapproves of study and communicates directly with investigators for information.
- Makes review available online for participating IRBs at each site.
- Maintains shared database for adverse events.



**Local IRBs at Sites**

- Once a protocol has been approved by the CIRB for BD and EI, local investigators at participating institutions may decide to enroll subjects via facilitated CIRB review.
- The investigator downloads the application.
- The local IRB convenes to review for local context-sensitive issues (e.g., Local IRB may recommend minor changes in the consent process to address concerns of a particular research subject community).
- Where feasible in larger centers, an IRB may create a specially trained subcommittee charged only with offering expedited review of BD and EI proposals for context-sensitive revision.
- Data on adverse events stored in nationally accessible database.
- Individual sites can draw on shared database that includes guidance on ethical issues such as informed consent, including model consent forms.

Primary and continuing review of the protocols will be handled directly by the CERB for biodefense and emerging infections in direct contact with investigators. On this proposed model, responsibility for local human protections rests with the institution and the investigator(s). The CERB is responsible for the overall IRB review of a multi-site study. A detailed process for communication between CERB and the participating institution(s) will be crucial. Sending the proposal to the local IRB for local review may be important for meeting both human subjects protection regulations and important ethical requirements for local context review, such as taking into account community values as well as local cultures and language, especially in the informed consent process.<sup>151</sup> The greater importance of the generalized knowledge to be gained from public health research of this nature demands a shift in thinking about study context; preparing for potential public health emergencies requires us to think of the research context as being at the very least regional, if not national or global. Such potentially widespread consequences justify sacrificing some autonomy by local IRBs and support a review model that more adequately reflects a more holistic, larger, even global perspective in dealing with threats such as Avian Flu and HIV. Limited institutional responsibility for review may be a virtue in this context, while avoiding the added bureaucratic layers of multiple reviews.

The proposed streamlining of the review process is driven both by a need for optimizing human subject protection and by the potential benefits of efficiently delivered, safe and effective vaccines and treatments.<sup>152</sup> One way to strike this balance is to aim for consistency in process and consistency in ethical guidance and oversight. Shared, centralized ethical information such as including model "points to consider," informed consent forms and interview questions, can help diminish some of the unnecessary time spent on redundant activities.

## **(2) Regional, multi-site vaccine or treatment studies**

The national review model would not be appropriate for all stud-

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<sup>151</sup> Memorandum from J. Thomas Puglisi, Dir., U.S. Dep't of Health & Human Services, Division of Human Subject Protections, Office for Protection from Research Risks, IRB Knowledge of Local Research Context (Aug. 27, 1998), available at <http://www.hhs.gov/ohrp/humansubjects/guidance/local.htm>.

<sup>152</sup> See INST. OF MED., *supra* note 141, at 5.

ies. Multi-site studies, particularly those for novel treatments or vaccines, may be effectively accomplished using only a few institutional collaborators but would further benefit from cooperative IRB review arrangements or from a single, independent IRB review governing all participating institutions. These models are already represented through arrangements such as the Multicenter Academic Cooperative Review Organization (MACRO)<sup>153</sup> and the Western IRB.<sup>154</sup> We envision a collaborative facilitated review model as particularly suitable for clinical research studies emanating from institutions comprising regional centers for excellence for bioterrorism and emerging infectious disease research (RCEs).<sup>155</sup> (See Figure 2). Currently, there are ten RCEs nationally, each comprised of five to eight primary institutions and additional affiliated institutions.<sup>156</sup> One participating institution could serve as the lead institution for human subjects review on which the other institutions would rely. The central review duties could be located permanently at one participating institution or rotated among institutions as per a stipulated agreement.

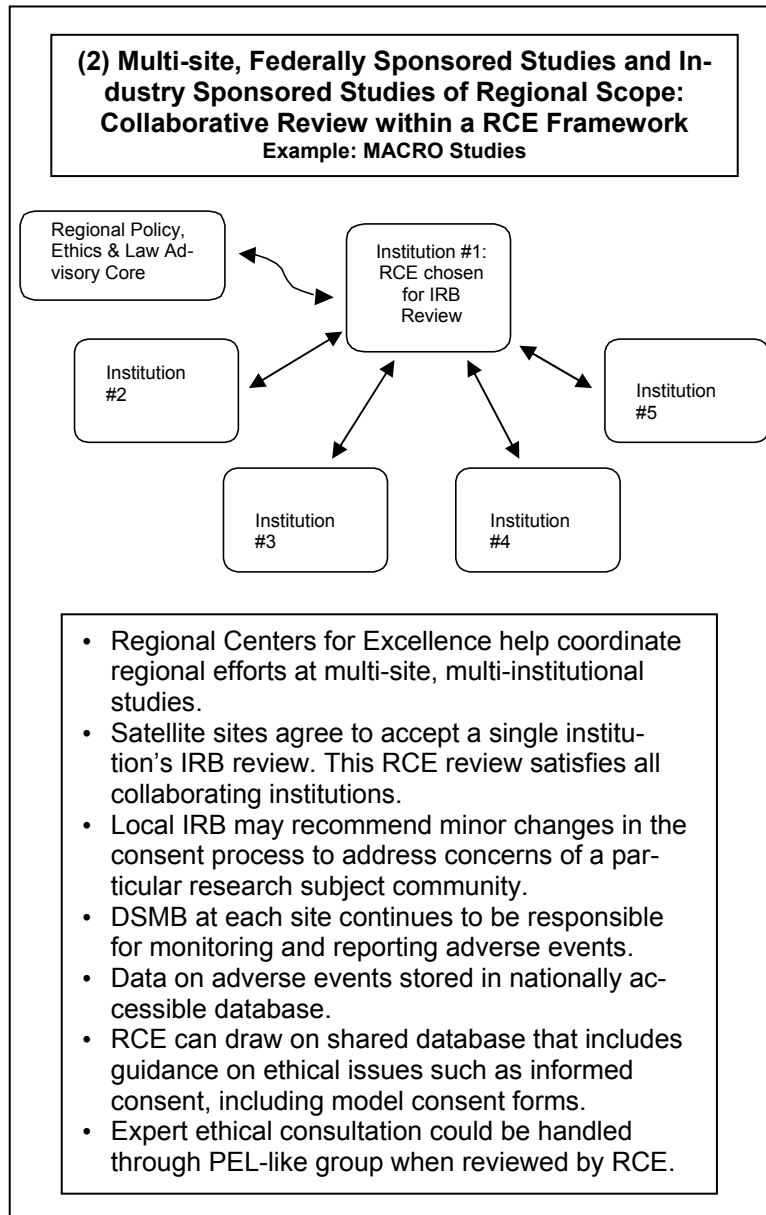
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<sup>153</sup> Multicenter Academic Clinical Research Org., <http://www.med.upenn.edu/ohr/about-macro.html> (last visited Mar. 11, 2008).

<sup>154</sup> Western Institutional Review Board, History of WIRB, [http://www.wirb.com/content/about\\_history.aspx](http://www.wirb.com/content/about_history.aspx) (last visited Mar. 11, 2008).

<sup>155</sup> See Nat'l Inst. Of Allergy and Infectious Diseases, Regional Center of Excellence for Biodefense and Emerging Infectious Diseases, <http://www3.niaid.nih.gov/research/resources/rce/introduction.htm> (last visited Mar. 11, 2008).

<sup>156</sup> *Id.*



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To further address the need for specialized knowledge in public health and ethics in this novel research arena, we see a potential role for the use of a regional Policy, Ethics, and Law advisory group (PEL) attached to the RCEs. As research evolves into the clinical arena, questions pertaining to ethical testing in human research participants will arise.<sup>158</sup> A PEL is ideally positioned to serve a useful consultative role by performing ethical review of these projects and providing valuable feedback and recommendations to the prospective clinical investigators.<sup>159</sup> Moreover, these reviews could be appended to IRB submissions and could provide valuable assistance to IRBs in their review of research protocols in this new field of research.

This proposal for ethical review arises as an extension of our experience with the PEL associated with the Southeast Regional Center for Excellence in Bioterrorism and Emerging Infections (SERCEB).<sup>160</sup> Taking advantage of PEL's membership qualifications based in ethics, science, and law and its consultative and educational functions, the SERCEB steering committee refers fundable research proposals to PEL for evaluation of potential dual-use concerns.<sup>161</sup> Investigators are forwarded comments and questions from the PEL by the steering committee and asked to address them prior to an award.<sup>162</sup> Analogously, PEL review of proposed clinical research could be a benefit to both investigators and IRBs by identifying potential problematic ethical issues for consideration early in research development. With accumulated experience of proposed clinical research for bioterrorism, an educational benefit may arise with the production of specialized materials relating to bioterrorism research, such as guidance on informed consent, biosafety, and ethical management of conflicts of interests. Realization of such benefits could improve overall protection of human research participants.

In summary, we propose generally that clinical research proposals submitted for funding through RCEs be referred to PELs for re-

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<sup>158</sup> Southeast Regional Center of Excellence for Emerging Infections and Biodefense, Core Services: Policy, Ethics and Law Core, <http://www3.niaid.nih.gov/research/resources/rce/sites.htm> (last visited Mar. 11, 2008).

<sup>159</sup> *Id.*

<sup>160</sup> *Id.*

<sup>161</sup> *Id.*

<sup>162</sup> *Id.*

view of ethical issues related to the research. The PEL comments and questions can be referred back to the investigators by the RCE steering committee. The investigators can then respond to the PEL review before receiving an award, and use this review for IRB submission, as well. With experience, the RCE will be able to gather materials related to the important ethical considerations in clinical research in bioterrorism to share as an educational resource for investigation based on the accumulated experience with PEL review. This pooling of resources and experience will further the goal of ethical and procedural consistency in the review process while most likely enhancing the quality of human subjects protection.

### 3) Small, single-site studies, typically early phase trials

Finally, it is important to distinguish the smaller, early-phase treatment or vaccine trials from the larger multi-center or national studies. There is no need to go through national or regional review mechanisms with single-institution studies.<sup>163</sup> We have in mind, for example, a Phase One study of a new anthrax vaccine, where one institution might recruit six to eight patients for the study. For these smaller scale studies, local IRB review should be sufficient, but individual institutions may still benefit from PEL review through the funding application mechanisms outlined in the previous section on multi-site review. (See Figure 3). To address the concerns about specialized research ethics training for public health studies, we would encourage local IRBs to seek consultation from the nearest regional PEL or download guidance and materials from the regional database. Again, sharing of materials, expertise, and specific informed consent instruments may help achieve ethical consistency across institutions while minimizing the need to reinvent the wheel when individual institutions find themselves facing recurrent ethical issues. These local IRBs will also be encouraged to contribute to the regional or national pools of information on these questions. Given the special nature of the risk associated with an experimental vaccine or treatment tested under the two animal rule,<sup>164</sup> we recommend IRBs send two or three

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<sup>163</sup> M.C. Christian et al., *A Central Institutional Review Board for Multi-Institutional Trials*, 346 N. ENGL. J. MED. 1405 (2002).

<sup>164</sup> 21 C.F.R. § 314.600 (2002); 21 C.F.R. § 601.90 (2002).



members through a specialized educational module, designed to address the special problems in assessing risk and benefit and communicating that to potential research subjects. We will offer more specific guidance on these substantive questions in our final section.

**(3) Single Site, Smaller Studies:  
Local IRB review with PEL consultation available for  
RCE institutions**

**EXAMPLE: Phase I study of new anthrax vaccine, 6-8 patients**

**Local IRB Only**

- Standard review track through an institution's IRB.
- Recommend bringing in members with expert training.
- IRB may choose to seek an ethics consultation from a PEL-like group from a RCE institution.
- Local IRB members may also rely on the shared national database containing data on adverse events and guidance on informed consent, conflicts of interest, and other ethical issues.

## CONCLUSION

We have attempted to address two of the fundamental flaws in the current oversight system as applied to human subjects research on emerging infections and biodefense with an eye to maintaining or improving human subjects protection: (1) lack of expertise on the specific clinical and ethical issues surrounding biodefense and emerging infections research, and (2) reduction of redundancies while maintaining or improving human subjects protection. Members from the NIAID or CDC asked to staff the national review of the large-scale national studies, and members of RCEs in the various regions, will naturally bring highly relevant public health expertise to

bear on the review process. PEL advisory groups will contribute ethical and legal expertise at the regional and local levels through consultation and the pooling of resources.

In addition, at the institutional level, we would recommend targeted training for bioterrorism and emerging infections, including guidance for reviewing informed consent procedures and the determination of risk-benefit ratios in the context of public health research of this nature. In situations where there is a strong likelihood of an outbreak or a seasonal outbreak may be reliably predicted, relying on the model of community consultation used in emergency research and population genetics research, may be valuable in conveying information about available experimental vaccines and treatments, along with the associated risks and benefits, to the relevant community or region.<sup>165</sup> This model is an effective way to convey information about available experimental vaccines and treatments, along with the associated risks and benefits, to the relevant community or region. Such a model relies on community leaders to coordinate the dissemination of reliable, accurate information and to offer a conduit for public questions and concerns about ongoing research in their communities.<sup>166</sup> The community consultation approach is often offered as a substitute for individual informed consent in the context of emergency research.<sup>167</sup> It will be important to offer criteria for distinguishing between emergency research (e.g., in response to an immediate outbreak or attack) and research in anticipation of an emergency. In the context of biodefense research, the community consultation model may also offer critical checks and balances against the tendency to decrease public transparency in security-sensitive research.<sup>168</sup> At this time of rapid change in response to real

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<sup>165</sup> Katherine A. McCarthy et al., *Informed Consent and Subject Motivation to Participate in a Large, Population Based Genomics Study: The Marshfield Clinic Personalized Medicine Project*, in 10 *COMMUNITY GENETICS*, 2-9 (2007); Sandra C. Quinn, *Protecting Human Subjects: The Role of Community Advisory Boards*, 94 *AM. J. PUBLIC HEALTH* 918, 919 (2004); Charles Contant et al., *Community Consultation in Emergency Research*, 34 *CRIT. CARE MED.* 2049, 2049 (2006); Lynne D. Richardson et al., *Communicating with Communities About Emergency Research*, 12 *ACAD. EMERG. MED.* 1064, 1065 (2005).

<sup>166</sup> Quinn, *supra* note 165, at 920.

<sup>167</sup> Charles Contant et al., *Community Consultation in Emergency Research*, 34 *CRIT. CARE MED.* 2049, 2049 (2006); Richardson et al., *supra* note 165, at 1065.

<sup>168</sup> James B. Petro & David A. Relman, *Understanding Threats to Scientific Openness*, 302 *SCIENCE*

and anticipated public health emergencies, it is especially important not to lose sight of the central ethical justification of research regulation: institutional protections and review were put in place to protect human subjects, and to provide a check against the tendency to trump the rights of subjects for sake of a greater good.<sup>169</sup>

On the level of individual consent, investigators need to strike a delicate balance between presenting the information in a way that does not unduly frighten citizens into a refusal of potentially beneficial intervention but, at the same time, does not exploit heightened community fears to secure agreement by exaggerating the public health threat. Sometimes alarm may be justified, but it will require clinical and ethical wisdom to know the difference and to be sensitive to the added complexities of decision-making when facing a possible or actual public health threat. The institutional checks and balances proposed here would potentially offer a mechanism for safeguarding against potential distortion of information regarding the threat, risks, and benefits of potential vaccines or treatment interventions. The process of individual informed consent when recruiting individual subjects in a community or regional trial may be qualitatively improved by prior community outreach.<sup>170</sup> Public health officials can thereby encourage and facilitate informed public discussion about the broader public health concerns associated with the disease threat and the available experimental interventions in advance of an outbreak, in addition to addressing such concerns in clinician-patient conversations in the midst of an outbreak.

Whether at the community or individual level, consultation and consent must address important ethical issues. In emerging infections and biodefense research, individual subjects are being asked to bear the shared public cost of the risks associated with the development of a new vaccine against the benefits of an expected public good, name-

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1898 (2003); NAT'L ACAD. OF SCIENCES, BIOTECHNOLOGY RESEARCH IN AN AGE OF TERRORISM: CONFRONTING THE 'DUAL USE' DILEMMA (Nat'l Academies Press 2003); JULIE E. FISCHER, DUAL-USE TECHNOLOGIES: INEXORABLE PROGRESS, INSEPARABLE PERIL (Ctr. for Strategic and Int'l Studies Press 2005).

<sup>169</sup> H.K. Beecher, *Ethics of Clinical Research*, 274 N. ENG. J. MED 1354, 1354-60 (1966); J. KATZ, EXPERIMENTATION WITH HUMAN BEINGS (Russell Sage Foundation 1972); G. ANNAS AND M. GRODIN, THE NAZI DOCTORS AND THE NUREMBERG CODE (Oxford Univ. Press 1992); R. J. LEVINE, ETHICS AND REGULATION OF CLINICAL RESEARCH (Yale Univ. Press 1988).

<sup>170</sup> Quinn, *supra* note 165, at 920.

ly minimizing the threat of a spreading infectious disease. In thinking about how best to convey this to citizens, we can draw wisdom from our discussions about informed consent with non-therapeutic Phase-I trials.<sup>171</sup> There we find a similar appeal to participating for the sake of furthering a public good, such as “contributing to scientific progress,” or “ensuring that no other person suffers from this disease,” or “that a cure is found for others.”<sup>172</sup> Such benefits should then be conveyed to individual subjects in a way that goes beyond the standard attempts to ensure a patient’s understanding, appreciation, and willingness to volunteer regarding an intervention that will primarily affect the subject. Researchers and communities should be especially sensitive to the history of biodefense research and other controversial public health research, such as Tuskegee or the U.S. Radiation Experiments.<sup>173</sup> When scientific and clinical studies have been co-opted or heavily driven by political agendas, there is an increased risk that human subjects’ protections may be compromised in the name of the greater public good.<sup>174</sup> The pluralistic review model offered here, including a variety of institutions, while streamlining those redundancies that are morally arbitrary (or stand in the way of life-saving treatments or vaccines), maintains the means for public and multi-institutional scrutiny on the science and process of ethical review. In all research, the scientific community must contend with some lack of trust among the public, particularly in communities that have historically been given good reason to mistrust scientific and medical institutions.<sup>175</sup> While some level of mistrust is healthy in a liberal society, cultivating or regaining warranted trust between science and citizens is essential to the well-being of both.<sup>176</sup> Establishing public trust may

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<sup>171</sup> W. Glannon, *Phase I Oncology Trials: Why the Therapeutic Misconception Will Not Go Away*, J. MED ETHICS, May 2006, at 252–55; Gail E. Henderson et al., *Therapeutic misconception in early phase gene transfer trials*, 62 SOC. SCI. & MED. 239 (2006).

<sup>172</sup> W.M. Kong, *Legitimate Requests and Indecent Proposals: Matters of Justice in the Ethical Assessment of Phase I Trials Involving Competent Patients*, 31 J. MED. ETHICS 205 (2005); Gail E. Henderson et al., *Uncertain Benefit: Investigators’ Views and Communications in Early Phase Gene Transfer Trials*, 10 MOLECULAR THERAPY 225, 225–32 (2004).

<sup>173</sup> JAMES JONES, *BAD BLOOD: THE TUSKEGEE SYPHILIS EXPERIMENT* (1993); ADVISORY COMMITTEE ON HUMAN RADIATION EXPERIMENTS, *THE HUMAN RADIATION EXPERIMENTS* (1996).

<sup>174</sup> *Id.*

<sup>175</sup> *Id.*

<sup>176</sup> Petro & Relman, *supra* note 168; Daniel Kevles, *Biotech’s Big Chill*, TECH. REV., July 2003, at

also play an important role in effectively managing disease outbreaks when they happen.<sup>177</sup> These concerns give us good reason to optimize public transparency of research, to encourage public discussions and awareness of possible outbreaks and current experimental interventions.

It will take time to address the deeper structural, procedural, and substantive problems in the current system of human subjects research oversight. In fact, it should take time, as we gather more precise data about the efficacy of proposed alternative models of review. While we are beginning to see more systematic information on the shortcomings of local IRBs, it would be helpful to know what local IRBs are doing well.<sup>178</sup> Such data can confirm or deny the widespread intuition that local IRBs are better situated and equipped to monitor the safety of research subjects and to be more sensitive to variations in local research communities. It is also essential to gather data on the performance of central and regional institutional review boards. As the national and professional debate on research oversight reform continues, we offer a pragmatic and ethically-motivated proposal for immediate reform within the current regulatory framework. One virtue of this approach is that it may be implemented while the important public discussion over more fundamental changes continues. In addition, we hope the proposal will further the discussion about how best to reform human subjects review with an eye to the special challenges raised in emerging infection and biodefense research.

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<sup>177</sup> Pamela L. Sankar, Susan Coffin & Cynthia Schairer, *Public Mistrust: The Unrecognized Risk of the CDC Smallpox Vaccination Program*, AM. J. BIOETHICS, Nov. 2003, at W22–W25.

<sup>178</sup> William J. Burman et al., *Breaking the Camel's Back: Multicenter Clinical Trials and Local Institutional Review Boards*, 134 ANN. INTERN. MED. 152–53 (2001).