EBOLA and FDA: reviewing the response to the 2014 outbreak, to find lessons for the future

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ABSTRACT

In 2014, West Africa confronted the most severe outbreak of Ebola virus disease (EVD) in history. At the onset of the outbreak—as now—there were no therapies approved by the U.S. Food and Drug Administration (FDA) for prevention of, post-exposure prophylaxis against, or treatment of EVD. As a result, the outbreak spurred interest in developing novel treatments, sparked calls to use experimental interventions in the field, and highlighted challenges to the standard approach to FDA approval of new drugs. Although the outbreak was geographically centered in West Africa, it showcased FDA’s global role in drug development, approval, and access. FDA’s response to EVD highlights the panoply of agency powers and demonstrates the flexibility of FDA’s regulatory framework. This paper evaluates the strengths and weaknesses of FDA’s response and makes policy recommendations regarding how FDA should respond to new and re-emerging public health threats. In particular, it argues that greater emphasis should be placed on drug development in interoutbreak periods and on assuring access to approved products. The current pandemic of Zika virus infection...
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is but one example of an emerging health threat that will require FDA involvement in order to achieve a successful response.

**KEYWORDS:** Ebola, ethics, food and drug law, public health

In 2014, West Africa confronted ‘the largest, most severe, most complex outbreak of Ebola virus disease (EVD) in history’.\(^1\) By early 2016, the total number of probable, confirmed, and suspected Ebola cases tallied since the onset of the outbreak exceeded 28,600, with 11,300 deaths.\(^2\) The outbreak, declared a ‘public health emergency of international concern’ (PHEIC) by the World Health Organization (WHO),\(^3\) was difficult to bring under control owing to high infectivity, weak health systems, rampant fear and mistrust among the affected population, and fluid cross-border movement of peoples.\(^4\)

Although the outbreak was centered on three countries—Guinea, Liberia, and Sierra Leone—it riveted the attention worldwide of clinicians, virologists, public health experts, industry, regulators, and the lay public alike.\(^5\)

While there are many lenses through which one might examine and critique the unfolding of and response to the 2014 Ebola outbreak, this paper adopts the lens of food and drug law and focuses on the significant role assumed by the U.S. Food and Drug Administration (FDA). Because there were no FDA-approved therapies for prevention of, post-exposure prophylaxis against, or treatment of EVD, the outbreak spurred interest in developing novel treatments, sparked calls to use experimental interventions in the field, thrust the need for human subjects research in the midst of a disaster—with the attendant practical, ethical, and methodological concerns—into the spotlight, and prompted concern about whether the worst off would ultimately have access to approved drugs and vaccines. Though geographically centered in West Africa, the EVD outbreak showcased FDA’s global role in drug development, approval, and access. Additionally, the outbreak permitted valuable lessons to be drawn regarding what FDA can do to better promote and protect public health in emergencies—whether caused by new or reemerging threats—going forward.

This is the first law review article to systematically explore the role played by the FDA during the 2014 Ebola outbreak by focusing on what the FDA did in ushering new

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1. World Health Organization (WHO), Ethical Considerations for Use of Unregistered Interventions for Ebola Viral Disease: Report of an Advisory Panel to WHO, [http://www.who.int/csr/resources/publications/ebola/ethical-considerations/en/](http://www.who.int/csr/resources/publications/ebola/ethical-considerations/en/) (last accessed August 30, 2016).

2. WHO, WHO: EBOLA SITUATION REPORT, Jan. 6, 2016, [http://apps.who.int/ebola/current-situation/ebola-situation-report-6-january-2016](http://apps.who.int/ebola/current-situation/ebola-situation-report-6-january-2016) (last accessed August 30, 2016).

3. WHO, WHO STATEMENT ON THE MEETING OF THE INTERNATIONAL HEALTH REGULATIONS EMERGENCY COMMITTEE REGARDING THE 2014 EBOLA OUTBREAK IN WEST AFRICA, Aug. 8, 2014, [http://www.who.int/mediacentre/news/statements/2014/ebola-20140808/en/](http://www.who.int/mediacentre/news/statements/2014/ebola-20140808/en/) (last accessed August 30, 2016). It is worth noting that this is only the third time in the agency’s history that the WHO has declared a public health emergency of international concern. Isaac Bogoch et al., *Assessment of the Potential for International Dissemination of Ebola Virus Via Commercial Air Travel During the 2014 West African Outbreak*, 385 LANCET 29, 29 (2015).

4. Mit Philips & Áine Markham, *Ebola: A Failure of International Collective Action*, 384 LANCET 1181 (2014); Margaret Chan, *Ebola Virus Disease in West Africa—No Early End to the Outbreak*, 371 NEW ENG. J. MED. 1183, 1183–84 (2014).

5. For a popular account of another Ebola outbreak that captured the public imagination, see generally, Richard Preston, *The Hot Zone: The Terrifying True Story of the Origins of the Ebola Virus* (1995).
medical countermeasures (MCMs), particularly drugs, to market. Section I provides background on Ebola, generally; the 2014 Ebola outbreak, specifically; and the state of vaccines against and treatments for EVD when the outbreak commenced. Section II discusses the calls that were made for use of experimental Ebola interventions in the field and outlines both the need for accreting evidence of their safety and efficacy as well as the ethical mandate to conduct rigorous human subjects research in the midst of a public health emergency. Section III briefly reviews the standard FDA-approval process and highlights challenges to the arc of development, approval, and access created by public health emergencies. Next, Section IV examines how FDA responded to those challenges in the 2014 outbreak. FDA’s response illustrates the panoply of tools at the agency’s disposal and its regulatory flexibility. Yet, it also reveals limitations and weaknesses. Therefore, Section IV draws lessons for the inevitable future outbreaks of emerging and re-emerging conditions—like Zika virus—for which diagnostic, prophylactic, and therapeutic interventions are inadequate.

I. EVD AND THE 2014 OUTBREAK
This section offers general background on EVD, on the 2014 West African outbreak, and on the interventions available at the time of the outbreak for prevention, post-exposure prophylaxis, and treatment of EVD. An appreciation of these three strands—and how they were interwoven—is essential to understanding the calls made by prominent actors, including WHO, for use of innovative therapies in the field, discussed at length in Section II, as well as the important role played by FDA, despite its geographical removal from the outbreak’s epicenter, as discussed in Sections II and IV.

A. Ebola virus disease
EVD was originally identified in 1976 in Zaire (now the Democratic Republic of Congo) and South Sudan. It is a severe hemorrhagic fever caused by an RNA virus in the filovirus family. Signs and symptoms of Ebola—which appear anywhere from 2 to 21 days after exposure—include fever, headache, diarrhea, vomiting, muscle pain, stomach pain, and unexplained bleeding or bruising. EVD is associated with a case fatality rate between 30% and 90%. Diagnosis of EVD may initially be difficult, as the

6 ‘Medical countermeasures, or MCMs, are FDA-regulated products (biologics, drugs, devices) that may be used in the event of a potential public health emergency stemming from a terrorist attack with a biological, chemical, or radiological/nuclear material, a naturally occurring emerging disease, or a natural disaster’. U.S. Food and Drug Administration (FDA), What are Medical Countermeasures?, http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/AboutMCMi/ucm431268.htm (last accessed April 13, 2016).
7 Anthony S. Fauci, Ebola—Underscoring the Global Disparities in Health Care Resources, 371 NEW ENG. J. MED. 1084, 1084 (2014).
8 Id. ‘Ebola’ encompasses five separate species—Zaire ebolavirus, Bundibugyo ebolavirus, Tai Forest ebolavirus, Sudan ebolavirus, and Reston ebolavirus. Id. Virologic investigation identified Zaire ebolavirus as the causative agent in the 2014 outbreak. Sylvain Baize et al., Emergence of Zaire Ebola Virus Disease in Guinea, 371 NEW ENG. J. MED. 1418, 1418 (2014).
9 U.S. Centers for Disease Control and Prevention (CDC), Questions and Answers on Ebola, Aug. 28, 2014, http://www.cdc.gov/vhf/ebola/outbreaks/guinea/qa.html (last accessed August 31, 2016); see also WHO Ebola Response Team, Ebola Virus Disease in West Africa—The First 9 Months of the Epidemic and Forward Projections, 371 NEW ENG. J. MED. 1481, 1482 (2014).
10 Baize et al., supra note 8, at 1418 (noting that the case fatality rate depends on the virus species). The Zaire ebolavirus strain has historically resulted in the highest mortality (90%). Fauci, supra note 7, at 1084.
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Symptoms are nonspecific and can be confused with those of diseases more common in Equatorial Africa. The most useful tests for confirming an Ebola diagnosis—reverse transcriptase polymerase chain reaction and antigen detection by enzyme linked immunosorbent assay—are only available in referral centers or national reference laboratories.

Outbreaks are thought to originate from an animal reservoir, most likely a fruit bat, although that linkage has not been confirmed. Person-to-person infection occurs through direct contact with infected bodily fluids—usually blood, feces, or vomit. As a result, most cases occur in individuals who provide direct patient care, such as family members or clinicians. Implementation of strict barrier and droplet precautions and use of personal protective equipment are necessary to control an outbreak. When patients pass away, the body must be handled with extreme caution, and incineration is recommended.

Dr. Anthony Fauci, Director of the National Institute of Allergy and Infectious Disease (NIAID), one of the institutes of the National Institutes of Health (NIH), has advised that ‘[a] high index of suspicion, proper infection-control practices and epidemiologic investigations should quickly limit the spread of the virus’.

B. The 2014 outbreak

The 2014 outbreak began in December 2013 in Guinea. The initial source of the outbreak has been identified as the village of Meliandou in Guéckédou Prefecture. A young boy named Emile Ouamouno, now considered patient zero, came down with symptoms of EVD and died on December 28, 2013. Members of his family, a nurse, a physician, and other healthcare workers died shortly thereafter. In the following week, members of Emile’s extended family also fell sick and died. On January 24, 2014, ‘the head of the Meliandou health post informed district health officials of five cases of severe diarrhea with a rapidly fatal outcome.’ This prompted

11 Carlos del Rio et al., Ebola Hemorrhagic Fever in 2014: The Tale of an Evolving Epidemic, 161 ANNAALS INTERN. MED. 746, 746 (2014).  
12 Id.  
13 Fauci, supra note 7, at 1085.  
14 Id.  
15 Id.  
16 del Rio et al., supra note 12, at 746.  
17 Id. at 746, 747. See generally National Library of Medicine, Isolation Precautions, http://www.nlm.nih.gov/medlineplus/ency/patientinstructions/000446.htm (last accessed August 31, 2016) (explaining the different types of isolation precautions).  
18 Id. (noting that incineration is rarely available in the field and is not usual practice in Africa).  
19 Fauci, supra note 7, at 1085.  
20 Derek Gatherer, The 2014 Ebola Virus Disease Outbreak in West Africa, 95 J. GEN. VIROL. 1619, 1619 (2014).  
21 Id.  
22 Kevin Sack et al., How Ebola Roared Back, THE NEW YORK TIMES, Dec. 29, 2014, http://www.nytimes.com/2014/12/30/health/how-ebola-roared-back.html (last accessed February 29, 2016) (describing how 1-year-old ‘Emile had taken ill in late December with fever, vomiting and bloody stool’). Many sources describe Emile as a 2-year-old child. For example, Gatherer, supra note 20, at 1621. According to WHO, he was 18 months old. WHO, Ebola in West Africa: 12 Months On, Jan. 15, 2015, http://www.who.int/mediacentre/news/notes/2015/ebola-one-year-on/en/ (last accessed May 20, 2016).  
23 WHO, supra note 22, at n.p. Prior to the onset of symptoms, Emile was seen playing in his backyard near a tree heavily infested with bats. Id.  
24 For example, Sack et al., supra note 22, at n.p.  
25 WHO, supra note 22, at n.p.  
26 Id.
an investigation by a small team of local health officials.\textsuperscript{27} Although the investigation was inconclusive, the reported symptoms—including diarrhea, vomiting, and severe dehydration—‘appeared similar to those of cholera, one of the area’s many endemic infectious diseases’.\textsuperscript{28} A second, larger investigation also supported the conclusion that the unknown disease was likely cholera.\textsuperscript{29}

An infected member of Emile’s family carried the Ebola virus to the Guinean capital, Conakry, on February 1, 2014.\textsuperscript{30} He died there, 4 days later, in a hospital.\textsuperscript{31} No measures had been taken to protect either the hospital’s staff or its other patients, as doctors had no reason to suspect the man was infected with Ebola.\textsuperscript{32} As the month of February progressed, cases of EVD spread to additional prefectures—Macenta, Baladou, Nzerekore, and Farako—as well as to villages and cities en route to these destinations.\textsuperscript{33}

The Ministry of Health of Guinea issued its first alert to the unidentified disease on March 13, 2014.\textsuperscript{34} A team sent by the Ministry of Health arrived in Guéckédou the next day.\textsuperscript{35} On March 18, a team sent by Médecins sans Frontières (MSF), or Doctors without Borders, arrived.\textsuperscript{36} Epidemiologic investigation began, and blood samples were collected and sent to laboratories in France and Germany for virologic analysis.\textsuperscript{37} Ebola was identified on March 21.\textsuperscript{38} The WHO issued its first communiqué on a new outbreak of EVD on March 23, 2014.\textsuperscript{39}

In what has been called ‘some of the worst luck in epidemiological history’,\textsuperscript{40} this Ebola outbreak—the 25th known outbreak of EVD\textsuperscript{41}—occurred at the intersection of Liberia, Guinea, and Sierra Leone, three of the world’s poorest, least developed countries. An editorial in the prestigious \textit{New England Journal of Medicine} concluded that the vast scale of the outbreak was ‘likely to be a result of the combination of dysfunctional health systems, international indifference, high population mobility, local customs, densely populated capitals, and lack of trust in authorities after years of armed conflict’.\textsuperscript{42} The editorialists succinctly (and damningly) enumerated the barriers and shortcomings that made the West African Ebola outbreak difficult to control; however, those barriers and shortcomings deserve some further elaboration here.

\begin{itemize}
  \item \textsuperscript{27} Id.
  \item \textsuperscript{28} Id.
  \item \textsuperscript{29} Id. Cholera is an acute diarrheal infection ‘that can kill within hours if left untreated’. See generally WHO, \textit{Cholera Fact Sheet No. 107}, \url{http://www.who.int/mediacentre/factsheets/fs107/en/} (last accessed July 29, 2016).
  \item \textsuperscript{30} WHO, \textit{supra} note 22, at n.p.
  \item \textsuperscript{31} Id.
  \item \textsuperscript{32} Id.
  \item \textsuperscript{33} Id.
  \item \textsuperscript{34} Id. (‘On that same day, staff at WHO’s Regional Office for Africa (AFRO) formally opened an Emergency Management System event for a disease suspected to be Lassa fever.’).
  \item \textsuperscript{35} Baize et al., \textit{supra} note 8, at 1418, 1419.
  \item \textsuperscript{36} Id.
  \item \textsuperscript{37} Id. at 1419.
  \item \textsuperscript{38} WHO, \textit{supra} note 22, at n.p.
  \item \textsuperscript{39} WHO, \textit{Ebola Virus Disease in Guinea}, Mar. 23, 2014, \url{http://www.who.int/csr/don/2014_03_23_ebola/en/} (last accessed August 31, 2016).
  \item \textsuperscript{40} Sack et al., \textit{supra} note 22, at n.p.
  \item \textsuperscript{41} Jeremy J. Farrar and Peter Piot, \textit{The Ebola Emergency—Immediate Action, Ongoing Strategy}, 371 NEW ENG. J. MED. 1545, 1545 (2014).
  \item \textsuperscript{42} Id.
\end{itemize}
This is a region where doctors are ‘rarer than paved roads’.\textsuperscript{43} Liberia and Sierra Leone have some of the worst physician-patient ratios in West Africa.\textsuperscript{44} The initially meager healthcare workforce was further diminished by the ‘unprecedented’ number of healthcare workers infected with the Ebola virus.\textsuperscript{45} Nearly 700 healthcare workers were infected by the end of 2014, and more than half of these died.\textsuperscript{46} When the outbreak began, hospitals and clinics lacked essentials like running water, soap, and personal protective equipment.\textsuperscript{47} Guinea, Sierra Leone, and Liberia were already coping with major health challenges, including malaria and other endemic diseases.\textsuperscript{48} Moreover, this was the first major outbreak of Ebola in West Africa, and ‘the affected countries had weak capacity and structures for epidemic preparedness and response, particularly for viral hemorrhagic fever’.\textsuperscript{49} Additionally, international health workers had largely pulled out of West Africa in the 1990s, when civil wars devastated Liberia and Sierra Leone.\textsuperscript{50} As a result, it took more than three months to diagnose Ebola as the cause of the outbreak; a public health emergency was not declared until five months later, and it was nearly two more months before a humanitarian response was put into place.\textsuperscript{51}

A homogenous community with shared sociocultural roots lives along the borders of Guinea, Liberia, and Sierra Leone,\textsuperscript{52} and individuals move easily across the porous national borders.\textsuperscript{53} The extensive cross-border movement of people facilitated the rapid spread of Ebola virus across West Africa.\textsuperscript{54} Such movement also complicated tracking and follow-up of contacts.\textsuperscript{55} Moreover, as the situation improved in one country, patients seeking unoccupied treatment beds were drawn from neighboring countries, a practice which reignited transmission chains.\textsuperscript{56} Although roads were unpaved, villagers

\textsuperscript{43} Sacket et al., supra note 22, at n.p. (‘Liberia, for instance, had fewer than 250 physicians for 4 million people’).
\textsuperscript{44} del Rio et al., supra note 12, at 746 (explaining that there are ‘more than 86 000 patients per physician in Liberia and 45 000 patients per physician in Sierra Leone’).
\textsuperscript{45} WHO, supra note 22, at n.p.
\textsuperscript{46} Id.; see also WHO, Health Worker Ebola Infections in Guinea, Liberia, and Sierra Leone, May 21, 2015, http://www.who.int/hrh/documents/21may2015_web_final.pdf (last accessed February 29, 2016). There are concerns that the loss of healthcare workers attributable to the 2014 Ebola outbreak will have a staggering effect on non-Ebola mortality even after the countries are declared Ebola-free. See generally David K. Evans, Markus Goldstein & Anna Popova, Health-care Worker Mortality and the Legacy of the Ebola Epidemic, 3 THE LANCET GLOBAL HEALTH e439 (2015).
\textsuperscript{47} Fauci, supra note 7, at 1085.
\textsuperscript{48} Id.
\textsuperscript{49} WHO, Ebola Virus Disease, West Africa—update, July 3, 2014, http://www.who.int/csr/don/2014_07_03_ ebola/en/ (last accessed August 31, 2016) see also del Rio et al., supra note 12, at 746 (explaining that the most useful tests for diagnosing Ebola have not been readily available in the remote areas of Africa where most outbreaks have occurred).
\textsuperscript{50} Sacket et al., supra note 22, at n.p.
\textsuperscript{51} Farrar & Piot, supra note 41, at 1545, 1546. The NEW YORK TIMES Editorial Board called the WHO’s handling of the Ebola outbreak ‘anemic’ and asserted that the agency’s lapses have rightly been blamed on poor leadership in Geneva and in the WHO’s regional office in Africa. The Board noted that the office in Africa was ‘slow to respond, partly because it was staffed by politically appointed people of little competence and partly because it feared that declaring a widespread emergency would tarnish the regulation and international trade of afflicted countries’. The Editorial Board, Reform After the Ebola Debacle, THE NEW YORK TIMES, Feb. 10, 2015.
\textsuperscript{52} WHO, supra note 49, at n.p.
\textsuperscript{53} WHO, supra note 22, at n.p.
\textsuperscript{54} WHO, supra note 49, at n.p.
\textsuperscript{55} Id.
\textsuperscript{56} WHO, supra note 22, at n.p.
could ride motorcycles into densely populated cities. In West Africa, cities became ‘epicenters of intense virus transmission’. The spread of EVD into cities further complicated contact tracing.

Additional challenges arose because distrust of government ran high due to decades of conflict. Many West Africans had to be convinced that EVD was real and reacted with indignation to outsiders demanding that they stop providing hands-on care to their sick relatives and friends. Although governments sought to educate the public that Ebola was spread through contact with feces, vomit, and blood and that bodies remained highly contagious even after death, people continued to care for the living and to wash the dead, a step which they ‘considered essential to a dignified burial and a contended afterlife’, in a manner that promoted spread of the virus. These high-risk cultural practices led to extensive exposures to Ebola virus in the community, and facilitated the virus’s transmission. Reliance on traditional healers, lack of compliance with advice to seek early medical care, and stigma surrounding Ebola also disrupted control efforts.

57 Sacketal., supra note 22, at n.p.; see also Dina F. Maron, Motorcycling to Ebola Treatment Could Spread the Infection, SCIENTIFIC AMERICAN, Sept. 17, 2014 (‘During the journey a weak patient, clinging to the [motorcycle taxi] driver, may expel diarrhea and literally drape herself over the driver even as her bodily fluids permeate the seat. In the process the driver may get infected.’); Larisa Epatko, WHO: ‘Many Thousands of New Cases’ of Ebola Expected in Liberia, PBS NEWSHOUR, Sept. 8, 2014 (‘In a way, the use of motorcycles is a sign of how convoluted the struggle with Ebola has become. In early September, the [WHO] donated two dozen motorcycles to the Ministry of Health in Guinea, one of the countries hit hardest by the Ebola virus. A week later, WHO said motorbikes used as taxis were one of the ways Ebola was spreading in Liberia.’).

58 WHO, supra note 22, at n.p.

59 Fauci, supra note 7, at 1085.

60 See eg Caelainn Hogan, There Is No Such Thing as Ebola, THE WASHINGTON POST, July 18, 2014, https://www.washingtonpost.com/news/morning-mix/wp/2014/07/18/there-is-no-such-thing-as-ebola/ (last accessed March 4, 2016) (‘[A man from a rural part of Sierra Leone] was adamant, like many others in his community, that “there is no such thing as Ebola.”’).

61 Sacketal., supra note 22, at n.p.

62 See Helene Cooper, Ebola’s Cultural Casualty: Hugs in Hands-On Liberia, THE NEW YORK TIMES, Oct. 4, 2014, http://www.nytimes.com/2014/10/05/world/africa/ebolas-cultural-casualty-hugs-in-hands-on-liberia.html (last accessed March 4, 2016) (describing a mother caring for her 2-year-old daughter who was ‘feverish, vomiting blood and in pain’); see also Norimitsu Onishi, For a Liberian Family, Ebola Turns Loving Care Into Deadly Risk, THE NEW YORK TIMES, Nov. 13, 2014, http://www.nytimes.com/2014/11/14/world/africa/in-ebola-outbreak-in-liberia-a-familys-strength-can-be-its-fatal-flaw.html?_r=0 (last accessed March 4, 2016) (‘[M]any victims in the region are still being treated within the family, a place of succor—and a font of contagion.’).

63 Sack et al., supra note 22, at n.p. During previous Ebola outbreaks, adherence to ancestral funeral and burial rites was singled out as fueling large explosions of new cases. WHO, supra note 22, at n.p. However, medical anthropologists have described the funeral and burial practices in West Africa as exceptionally high risk. Id. (describing burial practices).

64 WHO, supra note 49, at n.p.

65 WHO, supra note 22, at n.p. See eg United Nations Population Fund, Ebola Survivors Facing Stigma, Unemployment, Exclusion, Feb. 3, 2015, http://www.unfpa.org/news/ebola-survivors-facing-stigma-unemployment-exclusion (last accessed March 4, 2016) (‘Many [survivors in Liberia] say they are encountering hostility, exclusion and unemployment when they return to their communities.’); Helene Cooper, They Helped Erase Ebola in Liberia. Now Liberia Is Erasing Them, THE NEW YORK TIMES, Dec. 9, 2015, http://www.nytimes.com/2015/12/10/world/africa/they-helped-erase-ebola-in-liberia-now-liberia-is-erasing-them.html?_r=0 (‘Still, they [those who helped cremate bodies] are largely shunned by Liberian society.’).
Cases of EVD were subsequently confirmed in Senegal, first in a young man who traveled to Dakar, from his home in Guinea, by car, and in Mali, first in a 2-year-old from Guinea. Many commentators were quick to note that the unprecedented Ebola epidemic in West Africa occurred ‘in an age when air travel brings us together like never before’. Early in 2014, Dr. Fauci presciently predicted that ‘global air transit could, and most likely will, allow an infected person to board a plane and unknowingly carry Ebola virus’. The virus flew into Lagos, Nigeria on July 20, 2014 and into Dallas, Texas on September 30, 2014. These were the first times that the virus entered a new country via air travel. Both imported and locally acquired cases were eventually reported in the United States and in other countries outside of West Africa.

The majority of Ebola ‘cases and deaths were reported between August and December 2014, after which time case incidence began to decline as a result of the rapid scale-up of treatment, isolation, and safe burial capacity in’ Guinea, Liberia, and Sierra Leone. In January 2016, WHO declared an end to the Ebola outbreak, the deadliest on record. WHO’s announcement ‘mark[ed] the first time since the start of the epidemic … that Guinea, Liberia, and Sierra Leone — the three countries that were hardest hit by the virus — had reported zero cases for at least 42 days, or two incubation periods of the virus’. Although the outbreak has been ‘stopped’, WHO continues to caution that future flare-ups of EVD are to be expected.

C. The state of vaccines and treatments in 2014

At the time the West African Ebola outbreak began no vaccine or medication was proven effective in humans against Ebola. Even today, there are no ‘FDA-approved

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67 WHO, supra note 22, at n.p. The first case in Senegal was confirmed on Aug. 29, and the first case in Mali was confirmed on Oct. 23. Id.
68 del Rio et al., supra note 12, at 747.
69 Fauci, supra note 7, at 1085.
70 The virus entered Lagos by way of a symptomatic air traveler, Patrick Sawyer, whose sister, Princess, had just died from Ebola in Liberia. Michael Daly, He Could Have Brought Ebola Here: Minnesota Widow on Her Husband, THE DAILY BEAST, July 30, 2014, http://www.thedailybeast.com/articles/2014/07/30/minnesota-widow-on-her-husband-he-could-have-brought-ebola-here.html (last accessed August 31, 2016). Sawyer told the hospital staff he had malaria, and as malaria is not transmitted person to person, healthcare workers did not take protective precautions. WHO, supra note 22, at n.p.
71 WHO, supra note 22, at n.p.
72 Id. On Feb. 19, 2016, it was announced that the USA is ‘no longer conducting enhanced entry screening for Ebola’ for travelers coming to the United States. CDC, 2014 Ebola Outbreak in West Africa, http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/ (last accessed February 29, 2016).
73 CDC, Cases of Ebola Diagnosed in the United States, http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/united-states-imported-case.html (last accessed April 1, 2016).
74 Health Maps, 2014 Ebola Outbreaks, http://www.healthmap.org/ebola/#timeline (last accessed April 13, 2015).
75 WHO, WHO: EBOLA SITUATION REPORT, Jan. 6, 2016, http://apps.who.int/ebola/current-situation/ebola-situation-report-6-january-2016 (last accessed April 15, 2016).
76 Dionne Searcey, Nick C.-Bruce & Clair MacDougall, Deadliest Ebola Outbreak on Record is Over, W.H.O. Says, THE NEW YORK TIMES, Jan. 14, 2016, http://www.nytimes.com/2016/01/15/world/africa/ebola-who.html (last accessed April 15, 2016).
77 Id.
78 WHO, Latest Ebola Outbreak Over in Liberia; West Africa is at Zero, But New Flare-Ups are Likely to Occur, http://www.who.int/mediacentre/news/releases/2016/ebola-zero-liberia/en/ (last accessed February 26, 2016).
79 Id.
vaccines or therapeutics available for prevention, post-exposure, or treatment for EVD.\textsuperscript{80} Treatment consists of supportive care, providing oral rehydration and/or IV fluids with electrolytes, and treating complications.\textsuperscript{81} Notably, the standard of care for treatment of hemorrhagic fevers, of which EVD is one, ‘has not changed appreciably since the 1950s’.\textsuperscript{82}

1. A neglected disease

Until 2014, fewer than 2400 cases of Ebola—of which more than 1500 were fatal—had been reported since 1976, when EVD was first identified.\textsuperscript{83} The sheer rarity of Ebola and the unpredictability of outbreaks doubtless slowed the development of targeted vaccines and treatments.\textsuperscript{84} The fact that Ebola is solely endemic to Africa has likely also played a role. It has been lamented, for example, that ‘a vaccine would probably exist today if Ebola affected a large number of people in high-income countries, making research and development financially attractive to drug companies’.\textsuperscript{85} Given that development of drugs and vaccines is both expensive and cumbersome,\textsuperscript{86} and that the people who would most benefit from the development of Ebola therapies live in extreme poverty, it is difficult to attract investors.\textsuperscript{87} Those affected by Ebola are widely seen as a vulnerable population whose health needs have not been met by the market economy.\textsuperscript{88}

While explanations for lags in drug development are typically in the wheelhouse of ethicists, economists, and health policy experts, the satirical news outlet \textit{The Onion} published an article titled \textit{Experts: Ebola Vaccine At Least 50 White People Away}.\textsuperscript{89} The article states, ‘[W]aiting more than 50 white people for an effective prevention measure [is] something the world would simply not allow’.\textsuperscript{90} The thrust of the article is that if

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\textsuperscript{80} CDC, \textit{Ebola Virus Disease (EVD) Information for Clinicians in U.S. Healthcare Settings}, \url{http://www.cdc.gov/vhf/ebola/healthcare-us/preparing/clinicians.html} (last accessed January 6, 2016).  \\
\textsuperscript{81} WHO, \textit{supra} note 22, at n.p.  \\
\textsuperscript{82} del Rio et al, \textit{supra} note 12, at 747 (emphasis added) (citing Joseph E. Smadel, \textit{Epidemic Hemorrhagic Fever}, 43 \textit{AM. J. PUB. HEALTH} 1327 (1953). Even in the absence of effective treatments, an outbreak can be controlled by taking steps such as isolating patients, placing contacts under fever surveillance, isolating the febrile until a diagnosis is made, and educating the community on minimizing the risks of infection. François Lamontagne et al., \textit{Doing Today’s Work Superbly Well—Treating Ebola with Current Tools}, 371 \textit{NEW ENG. J. MED.} 1565, 1566 (2014).  \\
\textsuperscript{83} Tracy Hampton, \textit{Largest-Ever Outbreak of Ebola Virus Disease Thrusts Experimental Therapies, Vaccines into Spotlight}, 312 \textit{JAMA} 987, 987 (2014); see also WHO, \textit{Ebola Virus Disease}, \textit{Fact Sheet No. 103}, \url{http://www.who.int/mediacentre/factsheets/fs103/en/} (last accessed April 15, 2016).  \\
\textsuperscript{84} Cf. Emily A. Largent & Steven D. Pearson, \textit{Which Orphans Will Find a Home? The Rule of Rescue in Resource Allocation for Rare Diseases}, 42 \textit{HASTINGS CENTER REP.} 27 (2012).  \\
\textsuperscript{85} Philips & Markham, \textit{supra} note 4, at 637; see also Sara Reardon, \textit{Ebola Treatments Caught in Limbo}, \textit{S11 NATURE} 520 (2014).  \\
\textsuperscript{86} Rick Mullin, \textit{Cost to Develop New Pharmaceutical Drug Now Exceeds $2.5B}, \textit{SCIENTIFIC AMERICAN}, \url{http://www.scientificamerican.com/article/cost-to-develop-new-pharmaceutical-drug-now-exceeds-2-5b/} (last accessed March 1, 2016).  \\
\textsuperscript{87} Justine Calma, \textit{Ebola Drug Killed by Congressional Inaction Less than Two Years Before Outbreak}, NOVA, Oct. 14, 2015, \url{http://www.pbs.org/wgbh/nova/next/body/ebola-drug-halted/} (last accessed March 1, 2016).  \\
\textsuperscript{88} Cf. Liviu Oprea, Annette Braunack-Mayer, & Christian A. Gericke, \textit{Ethical Issues in Funding Research and Development of Drugs for Neglected Tropical Diseases}, 35 \textit{J. MED. ETHICS} 310 (2009).  \\
\textsuperscript{89} \textit{Experts: Ebola Vaccine At Least 50 White People Away}, \textit{THE ONION}, July 30, 2014, \url{http://www.theonion.com/article/experts-ebola-vaccine-at-least-50-white-people-awa-36580} (last accessed April 7, 2016).  \\
\textsuperscript{90} Id.
\end{flushright}
white people, rather than black people, were the primary victims of the Ebola virus, there would already be a vaccine. Race was a lens through which some viewed and critiqued the outbreak and the subsequent response, though the factors were complex.\(^91\)

Although EVD is not on WHO’s list of neglected tropical diseases (NTDs), ‘a diverse group of [17] communicable diseases that prevail in tropical and sub-tropical conditions … [and] mainly affect populations living in poverty’,\(^92\) comparisons have been drawn between EVD and the ‘classic’ NTDs.\(^93\) Between 1975 and 2000, ‘only 10% of global research and development resources were allocated for neglected diseases’\(^94\) despite their pernicious impact on the ‘bottom billion’, those individuals living in the world’s most impoverished conditions.\(^95\) Almost everyone in the bottom billion has at least one NTD, and the NTDs serve to reinforce their poverty.\(^96\) While the overall burden of disease due to EVD is dwarfed in comparison to the classic NTDs, when ‘examined from a bottom billion viewpoint, there are multiple factors supporting the notion that [the] disease, and particularly outbreaks, are components of impoverished conditions’.\(^97\)

When existing or emerging viruses that cause diseases like EVD are neglected, that neglect exacerbates global health inequalities and directly implicates questions of distributive justice.\(^98\) Thus, there is a moral and ethical dimension to the 2014 EVD outbreak—and to the lack of vaccines and therapies that, in part, allowed the virus to spread. Complicating this analysis, however, is the fact that, due to concerns over the potential use of Ebola as a biological weapon,\(^99\) the US government and others have provided substantial funding for Ebola research.\(^100\) Since 2003, for instance, the Defense Threat Reduction Agency, an agency within the U.S. Department of Defense

\(^{91}\) See eg Susan Dwyer, *The Not-So-Experimental Ethics of Ebola*, ALJAZEERA AMERICA, Aug. 13, 2014, http://america.aljazeera.com/opinions/2014/8/the-not-so-experimentalethicsofebola.html (last accessed August 1, 2016); Wendy Orent, *West Africans are Key to Fighting Ebola*, LOS ANGELES TIMES, Sept. 25, 2014, http://www.latimes.com/opinion/op-ed/la-oe-orent-ebola-sierra-leone-20140926-story.html (last accessed August 1, 2016) (‘In the view of many Africans, the West has let native doctors and nurses die of Ebola, while evacuating afflicted Western volunteers for treatment in Europe and the United States’).

\(^{92}\) WHO, *Neglected Tropical Diseases*, http://www.who.int/neglected_diseases/diseases/en/ (last accessed February 29, 2016).

\(^{93}\) For example, Adam MacNeil & Pierre E. Rollin, *Ebola and Marburg Hemorrhagic Fevers: Neglected Tropical Diseases*, 6 PLoS NEGL. TROP. DIS. e1546 (2012).

\(^{94}\) Ripudaman Bains, *A Ticking Time Bomb? Ebola and The Neglected Tropical Diseases*, BIOCENTRAL, Nov. 27, 2014, http://blogs.biomedcentral.com/on-biology/2014/11/27/a-ticking-time-bomb-ebola-and-the-neglected-tropical-diseases/ (last accessed March 5, 2016).

\(^{95}\) MacNeil & Rollin, supra note 93, at n.p.

\(^{96}\) Peter J. Jotez et al., *Rescuing the Bottom Billion Through Control of Neglected Tropical Diseases*, 373 LANCET 1570, 1570 (2009).

\(^{97}\) MacNeil & Rollin, supra note 93, at n.p.

\(^{98}\) Cf. C.A. Gericke, A. Riesberg, & R. Busse, *Ethical Issues in Funding Orphan Drug Research and Development*, 31 J. MED. ETHICS 164 (2005); Oprea et al., supra note 88.

\(^{99}\) See generally Calma, supra note 87, at n.p. (‘Ebola has been classified as a Category A bioterrorism threat by the U.S. Centers for Disease Control and Prevention (CDC) since at least 2004’); Dina F. Maron, *Weaponized Ebola: Is It Really a Bioterror Threat?*, SCIENTIFIC AMERICAN, Sept. 25, 2014, http://www.scientificamerican.com/article/weaponized-ebola-is-it-really-a-bioterror-threat/ (last accessed February 29, 2016).

\(^{100}\) See eg Rick Noack, *Why Ebola Worries the Defense Department*, THE WASHINGTON POST, Aug. 5, 2015, https://www.washingtonpost.com/news/worldviews/wp/2014/08/05/why-ebola-worries-defense-department/ (last accessed February 29, 2016).
that supports efforts to combat weapons of mass destruction,\textsuperscript{101} ‘has invested more than $300 million to develop MCMs against hemorrhagic fever viruses’ including Ebola.\textsuperscript{102} In 2013, NIAID spent more than $42 million on Ebola research.\textsuperscript{103}

In fact, some suggest that ‘disproportionate resources’ have been deployed for Ebola research and control as compared to other neglected diseases.\textsuperscript{104} As a result of this investment, progress was made in understanding the Ebola virus and in developing potential therapies.\textsuperscript{105} Nevertheless, writing in 2012 on the eve of the 2014 outbreak, two clinicians from the U.S. Centers for Disease Control and Prevention (CDC) observed that ‘from the perspective of those most at risk of [EVD], … progress has not been experienced.’\textsuperscript{106}

2. Experimental interventions, repurposing and off-label use

When the 2014 EVD outbreak began, several Ebola-specific drugs and vaccines were already under development.\textsuperscript{107} The most promising of these—most prominently, perhaps, ZMapp, a combination of three different monoclonal antibodies, developed by Mapp Biopharmaceutical Inc.\textsuperscript{108} — ‘all [had] roots in programs run by the Department of Defense’.\textsuperscript{109} Yet, Dr. Luciana Borio of FDA noted at the time that

\[\text{the experimental vaccines and treatments in development are in the earliest investigational stages and have not been fully tested for safety or efficacy. Only small amounts of some experimental products have been manufactured for testing, which means few courses, if any, are available.}\textsuperscript{110}

In addition to these investigational Ebola-specific vaccines and treatments, there was also interest in repurposing FDA-approved drugs—that is, drugs previously approved by the FDA for other indications—as treatments for EVD.\textsuperscript{111} Repurposing is the process by which a drug that is patented and FDA-approved for treating one

\textsuperscript{101} Defense Threat Reduction Agency, \textit{Who We Are}, \url{http://www.dtra.mil/About/WhoWeAre.aspx} (last accessed February 29, 2016).

\textsuperscript{102} Cheryl Pellerin, \textit{DTRA Medical Countermeasures Help Western African Ebola Crisis}, \url{http://www.defense.gov/News-Article-View/Article/603806} (last accessed February 29, 2016) (’[T]hose efforts are paying off today in potential new ways to fight Ebola virus disease.’)

\textsuperscript{103} Zoë Schlanger & Elijah Wolfson, \textit{The U.S. Is Sitting On Promising Ebola Vaccines}, \textit{Newsweek}, Aug. 4, 2014, \url{http://www.newsweek.com/2014/08/15/us-sitting-promising-ebola-vaccines-262870.html} (last accessed March 7, 2016).

\textsuperscript{104} David H. Molyneux, ‘Neglected’ Diseases But Unrecognised Successes—Challenges and Opportunities for Infectious Diseases Control, \textit{364 LANCET} 380, 380 (2004).

\textsuperscript{105} MacNeil & Rollin, \textit{supra} note 93, at e1546.

\textsuperscript{106} Id.

\textsuperscript{107} Id.

\textsuperscript{108} CDC, \textit{Questions and Answers on Experimental Treatments and Vaccines for Ebola}, Aug. 29, 2014, \url{http://www.cdc.gov/vhf/ebola/outbreaks/guinea/qa-experimental-treatments.html} (last accessed March 8, 2016).

\textsuperscript{109} See generally Calma, \textit{supra} note 87, at n.p.

\textsuperscript{110} Luciana Borio, \textit{FDA Works to Mitigate the West Africa Ebola Outbreak}, Aug. 22, 2014, \url{http://blogs.fda.gov/fdavoice/index.php/tag/emergency-investigational-new-drug-eind/#sthash.DU5oGuVB.dpuf} (last accessed January 8, 2015).

\textsuperscript{111} Sean Ekins & Megan Coffee, \textit{FDA Approved Drugs as Potential Ebola Treatments}, \textit{F1000 RESEARCH} (2015), \url{http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4358410/pdf/f1000research-4-6644.pdf} (last accessed August 31, 2016).
disease is further developed for the purpose of treating another disease.\textsuperscript{112} Drugs could also be used ‘off-label’. Off-label use is the prescribing of a drug or biological agent for a treatment regimen not specified in the FDA-approved labeling or package insert.\textsuperscript{113}

The legislative history of the Federal Food, Drug, and Cosmetic [(FD&C) Act indicates that Congress did not intend FDA to interfere with the practice of medicine. Once a drug is approved for marketing, FDA does not generally regulate how, and for what uses, physicians prescribe that drug. A physician may prescribe a drug for uses or in treatment regimens or patient populations that are not listed in the FDA-approved labeling.\textsuperscript{114}

While concerns may arise when existing drugs are repurposed or prescribed off-label in a public health emergency, given the lack of alternatives, many felt repurposing and off-label prescribing were worth trying.\textsuperscript{115}

\section*{II. CALLS FOR THE USE OF EXPERIMENTAL INTERVENTIONS IN THE 2014 OUTBREAK}

As established above, at the onset of the 2014 EVD outbreak—the deadliest on record—the standard of care for hemorrhagic fevers, including EVD, had not progressed appreciably beyond supportive care since the 1950s. Due, however, to investments made by the U.S. Department of Defense and others, several candidate vaccines and treatments were in the works. Given the relative dearth of treatment options and a case fatality rate reported to be between 53\% and 60\%,\textsuperscript{116} calls were made for the use of experimental interventions in the field.\textsuperscript{117} In late August 2014, for instance, a panel convened by WHO concluded that an ethical imperative existed ‘to offer the available experimental interventions that have shown promising results in the laboratory and in relevant animal models to patients and people at high risk of developing [Ebola]’ as long as ethical criteria guided the provision of such interventions.\textsuperscript{118}

Using experimental interventions—particularly in the midst of an outbreak difficult to bring under control for the host of social, political, and economic reasons discussed in

\begin{footnotes}
\item[112] Daniel S. Sem, Repurposing—Finding New Uses for Old (and Patented) Drugs: Bridging the ‘Valley of Death,’ to Translate Academic Research into New Medicines, 18 MARQ. INTELL. PROP. L. REV. 143, 143–44 (2014).
\item[113] See generally Emily A. Largent, Franklin G. Miller & Steven D. Pearson, Going Off-label Without Venturing Off Course, 169 ARCH. INTERN. MED. 1745 (2009).
\item[114] William B. Schultz, Statement Before the Senate Committee on Labor and Human Resources, Feb. 22, 1996, http://www.fda.gov/newsevents/testimony/ucm115098.htm (last accessed February 29, 2016).
\item[115] For example, Fast-tracking Treatments: The Hunt for Ebola Medicines is Being Accelerated, THE ECONOMIST, http://www.economist.com/news/science-and-technology/21616888-hunt-ebola-medicines-being-accelerated-fast-tracking-treatments (last accessed February 29, 2016); see also Peter B. Madrid et al., A Systematic Screen of FDA-Approved Drugs for Inhibitors of Biological Threat Agents, 8 PLOS ONE e60579 (2013) (discussing advantages of off-label use, such as the known safety and pharmacokinetic profiles, as well as existing manufacturing and distribution networks).
\item[116] WHO Ebola Response Team, supra note 9, at 1.
\item[117] See eg Hampton, supra note 83, at 987, 989; Thomas R. Frieden et al., Ebola 2014—New Challenges, New Global Response and Responsibility, 371 NEW ENG. J. MED. 1177 (2014); Erika C. Hayden & Sara Reardon, Should Experimental Drugs Be Used in the Ebola Outbreak?, NATURE, Aug. 12, 2014, doi:10.1038/nature.2014.15698, http://www.nature.com/news/should-experimental-drugs-be-used-in-the-ebola-outbreak.1.15698 (last accessed March 1, 2016).
\item[118] WHO, ETHICAL CONSIDERATIONS FOR USE OF UNREGISTERED INTERVENTIONS FOR EBOLA VIRAL DISEASE: REPORT OF AN ADVISORY PANEL TO WHO.
\end{footnotes}
Section I above—poses practical and ethical challenges.\footnote{See eg, Annette Rid & Ezekiel J. Emanuel, Ethical Considerations of Experimental Interventions in the Ebola Outbreak, 384 LANCET 1896 (2014); Carl H. Coleman, Control Groups on Trial: The Ethics of Testing Experimental Ebola Treatments, 7 J. BIOSEC. BIOSAFETY & BIODEF. L. 3–24 (2016) (discussing the ethics of randomized controlled trials in an epidemic); see also Emily A. Largent, Recently Proposed Changes to Legal and Ethical Guidelines Governing Human Subjects Research, 3 J. L. & BIOSCI., 206–16 (2016) (discussing proposed changes to the Council for International Organizations of Medical Sciences (CIOMS) Ethical Guidelines for Biomedical Research, particularly Proposed Guideline 20, Research in Disaster Situations).} A challenge of particular relevance to FDA—and therefore a focus of this article—is that of gathering high-quality evidence to prove that a novel drug or vaccine is both safe and effective when used in humans. Before a vaccine or drug can be approved by FDA for marketing, it must be rigorously evaluated for quality, safety, and efficacy.\footnote{Michelle Meadows, Promoting Safe and Effective Drugs for 100 Years, FDA CONSUMER MAGAZINE, Jan.–Feb. 2006, http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/PromotingSafeandEffectiveDrugsfor100Years/ (last accessed February 29, 2016). Between the passage of the Federal Food, Drug, and Cosmetic Act in 1938 (Public Law 75-717) and the adoption of the 1962 Kefauver-Harris Drug Amendments (Public Law 87-781), drug manufacturers were required to show only that their drugs were safe. The 1962 amendments included a provision requiring manufacturers to establish a drug’s effectiveness by ‘substantial evidence’.}

Given the history of investment by the U.S. Department of Defense in Ebola-related interventions, specifically those that were thought in 2014 to be most promising, and the likely role of the U.S. government as an eventual buyer of these interventions, calls to use experimental interventions in the field directly implicated FDA. Although Ebola is not endemic in the United States, if an intervention will be stockpiled and/or used by the American military, as Ebola drugs and vaccines likely would be, ‘all critical functions in the development and acquisition … lead to and through FDA’.\footnote{Richard A. Rettig & Jennifer Brower with Orlie Yaniv, The Acquisition of Drugs and Biologics for Chemical and Biological Warfare Defense: Department of Defense Interactions with the Food and Drug Administration 2 (RAND 2003) (‘At the heart of the DoD [Department of Defense] acquisition process for drugs and biologics, then, are FDA requirements that must be met … This reality creates for DoD a dependence on FDA, another government agency, in meeting its national security requirements for CBW [chemical and biological warfare] defense.’).}

Additionally, although national regulatory authority (NRA) officials in any Ebola-affected country are ultimately responsible for determining whether an MCM for Ebola should be approved for use within the nation’s borders,

[a]pproval from a stringent regulatory authority such as the US [FDA] … can expedite another country’s NRA review, given that such approval signifies to international medical and regulatory communities that the data have been thoroughly examined and … meet[] performance and manufacturing standards.\footnote{Wellcome TRUST & CENTER FOR INFECTIOUS DISEASE RESEARCH AND POLICY (CIDRAP) AT UNIVERSITY OF MINNESOTA, Plotting the Course of Ebola Vaccines: Challenges and Unanswered Questions (2016), http://www.cidrap.umn.edu/sites/default/files/public/downloads/ebola_team_b_report_2-033116-final.pdf (last accessed April 12, 2016).}

Drug and vaccine manufacturers therefore had several clear incentives to work with FDA in the West African outbreak despite FDA’s geographic remove.

The particulars of FDA’s response to the 2014 outbreak are the focus of Sections III and IV. In this section, I provide general background on the distinction between clinical research and clinical care and then advance an argument, which is both practically and
normatively grounded, that, even in the midst of an Ebola outbreak, it is essential to deliver innovative therapies in the course of randomized controlled research rather than in the course of clinical care if at all possible. Understanding why robust research is essential helps to position my evaluation of FDA’s response to the 2014 outbreak, as well as my recommendations for future outbreaks.

A. The research-care distinction

Gathering evidence that a drug is safe and effective for use in humans requires the systematic conduct of human subjects research, research in which human beings (‘as opposed to animals, atoms, or asteroids’) are the subjects of study. Clinical research, a type of human subjects research, explores new ways to prevent, detect, or treat illness in order to improve human health and well-being.

Clinical research has long been distinguished from clinical care. Clinical care refers to interventions ‘designed solely to enhance the well-being of an individual patient … and that have a reasonable expectation of success. The purpose of medical … practice is to provide diagnosis, preventive treatment, or therapy to particular individuals’. By contrast, research is ‘designed to test an hypothesis, permit conclusions to be drawn, and thereby develop or contribute to generalizable knowledge … . Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective’.

Central to the distinction between research and care is the idea that the purpose of clinical research is fundamentally different from that of clinical medicine: whereas medical care focuses on providing optimal care to individual patients, clinical research is primarily concerned with producing knowledge for the benefit of future patients. Other characteristics of research include use of distinctive methods—such as randomization, placebo controls, and blinding—that sacrifice personalization of care in favor of scientific validity and the inclusion of procedures that hold no prospect of medical benefit for the research participant but which are justified in light of their scientific value.

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123 David Wendler, The Ethics of Clinical Research, THE STANFORD ENCYCLOPEDIA OF PHILOSOPHY (Fall 2012 Edition) (Edward N. Zalta, ed.) http://plato.stanford.edu/archives/fall2012/entries/clinical-research/ (last accessed January 4, 2016).

124 Id.; see generally NIH, Clinical Research Trials and You: The Basics, http://www.nih.gov/health-information/nih-clinical-research-trials-you/basics (last accessed March 1, 2016).

125 There have been influential calls to integrate research and care. The integration of research and care within so-called learning healthcare systems holds the potential to advance socially valuable research, to yield health benefits for current and future patients, and to improve the quality of care while lowering. INSTITUTE OF MEDICINE (IOM), BEST CARE AT LOWER COST: THE PATH TO CONTINUOUSLY LEARNING HEALTH CARE IN AMERICA (2012). Yet, even as research and care are routinely and systematically integrated, the normative importance of the research-care distinction remains. Emily A. Largent, Steven Joffe & Franklin G. Miller, Can Research and Care Be Ethically Integrated?, 41 HASTINGS CENTER REP. 37 (2011).

126 The Nat’l Comm’n for the Protection of Human Subjects of Biomedical and Behavioral Research, The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (1979).

127 Id.; see also 45 CFR § 46.102(d) (2005) (‘Research is ‘a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge’.’).

128 Largent et al., supra note 125, at 37.

129 Id. at 37, 38.
One consequence of the research-care distinction is that research ethics and medical ethics have long been considered distinct sets of normative commitments. Clinical research and clinical care are also regulated differently. Human subjects research is governed by ‘a series of international codes, national legislation, and agency regulations’. FDA, for instance, requires ‘adherence to the principles of good clinical practices (GCPs), including adequate human subject protection’, regardless of the funding source, in studies used to support an application to FDA for research or marketing permits for products regulated by FDA. The International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines—also known as ICH GCP (E6)—is ‘an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects’.

FDA does not, by contrast, regulate the practice of medicine. Rather, long-standing congressional and FDA policies respect the regulatory role of states. The FD&C Act explicitly states, ‘[N]othing... shall be construed to limit or interfere with the authority of a healthcare practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate healthcare practitioner-patient relationship’. This has been interpreted to mean that

[i]f a physician determines that the use of a device is appropriate for their patient, as long as they’re not studying the safety and effectiveness of that device, they may use the device under practice of medicine. Under practice of medicine, the physician should be well-informed about the product, and use firm scientific rationale and sound medical evidence to determine whether they should use the device.

While FDA advises physicians to use ‘firm scientific rationale and sound medical evidence’ to guide their care, including off-label use, ‘physicians failing to do so would not be answerable to FDA but rather to their state medical practice licensing boards and to plaintiffs in state medical malpractice suits’. The distinction between research and care is of fundamental importance because, once calls were made for the use of experimental interventions in the midst of the 2014 EVD epidemic, I will argue that the need for research was unavoidable. Because

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130 Emily A. Largent, Steven Joffe & Franklin G. Miller, A Prescription for Ethical Learning, 43 HASTINGS CENTER REP. S28 (2013).
131 ERIN D. WILLIAMS, CONGRESSIONAL RESEARCH SERVICE, FEDERAL PROTECTION FOR HUMAN RESEARCH SUBJECTS: AN ANALYSIS OF THE COMMON RULE AND ITS INTERACTIONS WITH FDA REGULATIONS AND THE HIPAA PRIVACY RULE, CRS-12 (2005).
132 FDA, Clinical Trials and Human Subject Protection, http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ (last accessed March 1, 2016).
133 HHS, Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance, http://www.fda.gov/downloads/Drugs/.../Guidances/ucm073122.pdf (last accessed August 31, 2016). This guidance provides ‘a unified standard for the European Union, Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in those jurisdictions’. Id.
134 Barbara J. Evans, The Limits of FDA’s Authority to Regulate Clinical Research Involving High-Throughput DNA Sequencing, 70 FOOD & DRUG L. J. 259, 260 (2015).
135 21 U.S.C., Chapter 9, Subchapter X, § 396 (2011).
136 Soma Kalb, IDE Basics—Transcript, http://www.fda.gov/Training/CDRHLearn/ucm426001.htm (last accessed April 7, 2016).
137 Id.
138 Evans, supra note 134, at 265.
research and care are distinct, calls for use of experimental interventions also entailed adherence to distinct ethical and regulatory commitments that became a field for contestation.

B. The potential benefits of research to current patient-participants
Participation in research may or may not offer potential benefits to individual research participants.\(^{139}\) Offering such benefits is not a criterion of ethically acceptable research.\(^{140}\) In practice, institutional review boards (IRBs), the administrative bodies ‘established to protect the rights and welfare of human research subjects recruited to participate in research activities’,\(^{141}\) are required to determine that the risks to individual participants have been minimized and that any residual risks are offset or outweighed by either the prospect of individual benefit or the social value of the knowledge to be gained. Thus, if the social value is sufficiently high (and all clinical research must have social value to be ethical), research may be IRB-approved even if it offers no potential benefit to research participants.\(^{142}\)

A prevailing though contested ethical perspective on clinical trials does, however, hold that ‘clinical equipoise’ is necessary for research to be ethically acceptable.\(^{143}\) Clinical equipoise exists when the medical profession as a whole has not yet reached consensus that one arm of a clinical trial—whether the control or the experimental intervention—offers a therapeutic benefit over the other arm(s).\(^{144}\) Accordingly, if there is genuine uncertainty that any of the arms is superior, it is ethical for the trial to proceed; individuals cannot, however, ethically be assigned to an arm that is, ex ante, known to be worse for them than the others. One implication of this position is that it rules out a placebo-controlled trial whenever a proven-effective treatment exists for a disorder.\(^{145}\) Critically, ‘ensuring that equipoise exists is not the same as establishing a reasonable chance of benefit’.\(^{146}\)

Significantly, clinical research can provide care for an individual that is good, or even optimal, depending on the alternatives available to the patient as well as on the design of the trial.\(^{147}\) Nevertheless, it is important to appreciate that some aspects of research participation may not be in an individual’s best interest due to the loss of personalization and the inclusion of research-related procedures. For instance, a study protocol may include a research blood draw (eg to test the level of drug in an individual’s

\(^{139}\) For a helpful taxonomy of benefits, see Nancy M.P. King, Defining and Describing Benefit Appropriately in Clinical Trials, 28 J. L. MED. & ETHICS 332 (2000).

\(^{140}\) See generally Ezekiel J. Emanuel, David Wendler & Christine Grady, What Makes Clinical Research Ethical?, 283 JAMA 2701 (2000); see also, Ezekiel J. Emanuel et al., What Makes Clinical Research in Developing Countries Ethical? The Benchmarks of Ethical Research, 189 J. INFECT. DIS. 930 (2004).

\(^{141}\) H.H.S. DEP’T OF HEALTH AND HUMAN SERVICES, INSTITUTIONAL REVIEW BOARD GUIDEBOOK (1993).

\(^{142}\) In such cases, participation is reasonable, and research participants may be altruistically motivated.

\(^{143}\) For example, Paul B. Miller & Charles Weijer, Rehabilitating Equipoise, 13 KENNEDY INST. ETHICS J. 93 (2003); but see Franklin G. Miller & Howard Brody, A Critique of Clinical Equipoise: Therapeutic Misconception and the Ethics of Clinical Trials, 33 HASTINGS CENTER REP. 19 (2003) (arguing this perspective is flawed because it confuses the ethics of research and of care).

\(^{144}\) Miller & Brody, supra note 143, at 19.

\(^{145}\) Id. at 20 (pointing out the practical and ‘theoretical incoherence’ that IRBs routinely approve placebo-controlled trials).

\(^{146}\) King, supra note 139, at 337 (emphasis added).

\(^{147}\) Largent et al., supra note 125, at 38.
bloodstream) that offers no potential for personal benefit (eg treatment wouldn’t change on the basis of that blood level; it is simply for researchers to develop an idea of how quickly the drug is metabolized). While a research blood draw is relatively low risk, one could imagine progressively riskier procedures that offer no prospect of personal medical benefit but which are important for the scientific validity of a study. Such procedures, while justified, illustrate the potential tension between patients’ individual interests and the aim of research to promote the greater good.

C. The benefits of research for future patients
Determining whether experimental interventions to prevent or treat EVD—or drugs repurposed or used off-label for EVD—are safe and effective for use in humans can only be accomplished by testing them in people exposed to or infected with the Ebola virus.\textsuperscript{148} It would be unethical intentionally to expose healthy research participants to the highly lethal Ebola virus. Therefore, research conducted during outbreaks of EVD is likely to be the primary, if not sole, means of establishing the safety and efficacy of novel interventions. That is, it will be essential to systematically conduct human subjects research in the midst of an Ebola outbreak to secure the body of socially valuable generalizable knowledge needed to benefit those affected by future Ebola outbreaks.

There can, however, be discomfort with conducting clinical research—which, as discussed above, entails different normative commitments than clinical care—in a public health emergency laden with human suffering. Assuming that the status quo (ie treatment consisting of supportive care) is not acceptable, an alternative to robust research would be compassionate use, the use of an experimental intervention outside of a clinical trial. In the 2014 Ebola outbreak, some advocated for compassionate use. They maintained that compassionate use was more desirable than rigorous data collection because compassionate use offered ‘hope for survival despite the fact that the efficacy and adverse effects of the [experimental] drug are unknown’.\textsuperscript{149} Although compassionate use is theoretically compatible with learning about a drug’s safety and efficacy, without well-designed research, it would be difficult to establish the evidence base needed to move the standard of care appreciably beyond where it currently stands.\textsuperscript{150}

Thus, a compassion-knowledge trade-off arises. The tradeoff can affect both the current patient—who receives a dose of hope from what is at bottom an unproven intervention—and future patients—who, going forward, will not benefit from a largely absent body of generalizable knowledge. The tradeoff can also adversely affect third parties if compassionate use consumes scarce healthcare resources for uncertain clinical benefits.\textsuperscript{151} Emphasis needs to be placed on research to validate the safety and efficacy of experimental interventions because outcomes for patients collectively are optimized when the practice of medicine is based on current knowledge.

Of course, there is understandable reluctance to deny anyone presenting with a life-threatening condition like EVD access to a potentially beneficial intervention, to hope.

\textsuperscript{148} Daniel G. Bausch et al, Treatment of Marburg and Ebola Hemorrhagic Fevers: A Strategy for Testing New Drugs and Vaccines Under Outbreak Conditions, 78 ANTIVIRAL RES. 150 (2008).

\textsuperscript{149} Morenike Folayan et al, Compassionate Use of the Experimental Drugs in the Ebola Outbreak, 384 LANCET 1843, 1843 (2014).

\textsuperscript{150} Steven Joffe, Evaluating Novel Therapies During the Ebola Epidemic, 312 JAMA 1299, 1299 (2014).

\textsuperscript{151} Annette Ridd & Ezekiel J. Emanuel, Compassionate Use of Experimental Drugs in the Ebola Outbreak—Authors’ Reply, 384 LANCET 1844, 1844 (2014).
This reluctance is, however, a misguided moral impulse and should not guide policy. The dilemma posed by compassionate use can be analogized to difficulties related to how scarce resources should be allocated between identified and statistical lives. The preference for identifiable lives—individuals currently known to us—over statistical lives—individuals who are as yet unknown or possibly not yet in existence—has been criticized as mistaken by many bioethicists. One argument made in favor of saving identifiable lives, the ‘symbolic value argument’, is that by rescuing identifiable lives, a society demonstrates the value it places on human life, thereby promoting social utility. Yet, ‘[i]t is unclear why showing respect for identified lives better captures this symbolic value of life; indeed, one might think it is statistical lives that captures the notion that all lives are equal and of the same value’. The implication of this argument is not that identifiable lives do not matter. The implication is that they do not deserve any ‘preference over the equivalent number of statistical lives’. Gains for future patients should not be sacrificed in order to offer a benefit as ephemeral as hope to current patients—particularly when hope is conditioned on receipt of an admittedly unproven intervention. In such circumstances, clinical research rather than compassionate use is the appropriate response.

Rigorous research was ethically appropriate—whether or not one recognizes a role within research ethics for clinical equipoise—because the 2014 Ebola outbreak was characterized by genuine uncertainty. Moreover, research was necessary because the outbreak was likely the sole opportunity, at least until the next outbreak, ethically to conduct research and, hopefully as a result, to have FDA approved treatments available in future Ebola epidemics. Even if one accepted, however, that it was both ethically acceptable and imperative to conduct research in the midst of an EVD epidemic, open questions remained about what kind of research should be conducted—that is, how the research should be designed and executed. That is the focus of the next subsection.

D. An argument for randomized placebo-controlled trials

Studies conducted in the midst of a public health emergency ‘raise difficult ethical, scientific, and practical questions about how best to design and conduct research’. One such question is whether it is ethically acceptable to conduct a randomized placebo-controlled trial. This question was highly divisive in the 2014 Ebola outbreak. While some felt that randomized placebo-controlled trials were the optimal means of

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152 I. Glenn Cohen, *Rationing Legal Services*, 5 J. LEGAL ANALYSIS 221, 252 (2013) (listing ethicists who have taken this position).
153 Largent & Pearson, supra note 84, at 30.
154 Cohen, supra note 152, at 252.
155 Id. at 254.
156 PRESIDENTIAL COMMISSION FOR THE STUDY OF BIOETHICAL ISSUES (PRESIDENTIAL COMMISSION), ETHICS AND EBOLA: PUBLIC HEALTH PLANNING AND RESPONSE, at 33 (2015).
157 Id.
158 See Joffe, supra note 150, at 1300 (‘Investigators should instead move directly to randomized trials that compare best supportive care plus an experimental agent with best supportive care alone.’); Jon Cohen & Kai Kupferschmidt, *Ebola Vaccine Trials Raise Ethical Issues*, 346 SCIENCE 289, 289 (2014) (‘At a consultation held by the World Health Organization (WHO) on 29 to 30 September, . . . there was unexpectedly broad support for the RCT design’); but see Coleman, supra note 119, at 6 (identifying groups who refused to participate in placebo-controlled trials).
efficiently identifying safe and effective interventions for EVD, others argued for providing access to potentially beneficial experimental interventions as widely as possible and, therefore, advocated for use of alternative trial designs that did not incorporate randomization to placebo controls.

The debate surrounding randomized placebo-controlled trials had two primary strains. On the one hand, there were questions about whether alternative trial designs were sufficiently methodologically rigorous to yield valid results; on the other, there were questions about whether it was ethical in the context of the 2014 EVD outbreak to randomize individuals to a control arm and deny them the opportunity to benefit from an experimental intervention. I consider each of these in turn and argue that those in favor of randomized placebo-controlled trials held the superior position; here, I bracket off discussion of prevention trials, as treatment and prevention can raise quite different issues.

1. Validity of results

Randomized controlled trials (RCTs) are the gold standard means of assessing whether a potential treatment is efficacious. In the preapproval stage at FDA, ‘RCTs are regarded as fulfilling the statutory requirement of “adequate and well-controlled” studies to support a marketing claim’.\(^\text{159}\) Randomization ensures that individuals who receive the experimental intervention do not systematically differ from the control group along observable or unobservable dimensions.\(^\text{160}\) This allows valid (ie causal) inferences to be drawn about the safety and efficacy of the novel intervention.\(^\text{161}\)

A central fear of those opposed to alternative trial designs was that such designs might lack validity and yield biased conclusions. While conceding that ‘[u]ncontrolled trials can give accurate answers when certain stringent conditions are met, including preliminary evidence of large effect sizes and the availability of data from historical cohorts that permit valid comparisons’,\(^\text{162}\) they argued that those opposing RCTs had failed to demonstrate those conditions could be met in the West African epidemic.\(^\text{163}\)

\(^{159}\) COMMITTEE ON ETHICAL AND SCIENTIFIC ISSUES IN STUDYING THE SAFETY OF APPROVED DRUGS, BOARD ON POPULATION HEALTH AND PUBLIC HEALTH PRACTICE, INSTITUTE OF MEDICINE, EVIDENCE AND DECISION-MAKING, in ETHICAL AND SCIENTIFIC ISSUES IN STUDYING THE SAFETY OF APPROVED DRUGS (2012) (noting that although ‘observational studies are a major source of evidence related to drug safety and are playing an increasing role in FDA’s oversight of drug safety[, s]uch designs play a relatively minor role in establishing drug safety in the preapproval stage’). Controversially, the proposed 21st Century Cures Act could change this. Jerry Avorn & Aaron S. Kesselheim, THE 21ST CENTURY CURES ACT—WILL IT TAKE US BACK IN TIME? 372 NEW ENG. J. MED. 2473 (2015) (‘[A]s introduced, the 21st Century Cures Act instructs the FDA to consider nontraditional study designs and methods of data analysis to further speed approvals. Adaptive trial designs and the use of Bayesian methods hold promise in some kinds of evaluations, particularly in oncology. However, more problematic proposals include encouraging the use of ‘shorter or smaller clinical trials’ for devices and the request that the FDA develop criteria for relying on ‘evidence from clinical experience,’ including ‘observational studies, registries, and therapeutic use’ instead of randomized, controlled trials for approving new uses for existing drugs. Although such data can provide important information about drug utilization and safety once a medication is in use, there is considerable evidence that these approaches are not as rigorous or valid as randomized trials in assessing efficacy.’)

\(^{160}\) Joffe, supra note 150, at 1300.

\(^{161}\) Id.

\(^{162}\) Id. (internal citations omitted).

\(^{163}\) Id.
It is ethically concerning if research participants are exposed to research-related risks and burdens that cannot be justified because a study is not scientifically valid. Moreover, a real concern was that misleading results from an uncontrolled study could have negative ramifications for many stakeholders in a high-stakes situation.

Mistakenly determining a benefit or missing a potential harm can directly hurt research participants as well as individuals who use the intervention if implemented, and can impose substantial economic costs on communities and societies [by misdirecting scarce healthcare resources]. In contrast, failing to detect a modest but meaningful level of clinical effectiveness might deprive those in need of an intervention that can reduce suffering or improve chances of survival.

Proponents of RCTs argued that a randomized placebo-controlled trial would increase confidence in the accuracy of research findings. As mentioned above, there is understandable reluctance to deny anyone with a life-threatening condition access to a promising experimental intervention, for example, by screening them out of a clinical trial via inclusion and exclusion criteria or by randomizing them to a placebo-control arm. However, if only RCTs can provide reliable information about safety and efficacy, then alternative trial designs unacceptably favor current patients at the expense of future patients—a position which is not ethically tenable. A moral impulse to offer a potential benefit to current patients cannot overcome concerns about the validity of research results.

A practical concern that informed the debate about validity of results was that, as mentioned above, only small amounts of experimental interventions had been manufactured at the time of the 2014 outbreak. This meant that few courses were available for use in research. This point was made by those opposed to RCTs. Of course, if insufficient amounts were available to allow for the conduct of scientifically valid studies, then RCTs should not be performed. To do so would unacceptably expose research participants to research-related risks that could not be justified. Yet, the possibility of misleading results due to too small sample sizes is also an argument against conducting non-randomized or uncontrolled studies because the requirements of social value and scientific validity are universal. Therefore, the argument from small quantities risked proving too much.

Even accepting that it is possible for alternative trial designs to yield valid results that constitute a sufficiently robust basis for both clinical practice and health policy, it is necessary to concede that in any particular circumstances, as a threshold matter, methodologists must determine that alternative trial designs are appropriate. In the 2014 outbreak, the position in favor of alternative designs did not secure sufficient consensus among methodologists to justify moving away from the gold standard of RCTs. Therefore, it was essential to answer the outstanding normative question: whether research participants can ethically be randomized to a placebo control.

164 Emanuel et al., supra note 140, at 2704.
165 RESIDENTIAL COMMISSION, supra note 156, at 35.
166 Steven Joffe, Ethical Testing of Experimental Ebola Treatments—Letter to the Editor, 313 JAMA 422, 422 (2015).
167 Emanuel et al., supra note 140, at 2703, 2704.
168 Joffe, supra note 166, at 422.
2. Randomization to a control arm

A primary objection made to the conduct of RCTs in the 2014 outbreak was that it was unethical to randomize individuals to a control arm—that is, not to give them access to a promising experimental intervention—given the high case fatality rate of Ebola.169

For example, a prominent editorial in the *Lancet* asserted, ‘When conventional care means such a high probability of death, it is problematic to insist on randomising patients to [conventional (i.e., supportive) care] when the intervention arm holds out at least the possibility of benefit’.170 I will argue, however, that proponents of this position are mistaken. Use of controls, including placebo controls, would be ethical.

First, as the editorial acknowledged, in an RCT evaluating an experimental intervention for EVD, research participants would likely be randomized to receive either (i) the experimental intervention in conjunction with the necessary supportive care or (ii) supportive care only or, possibly, supportive care plus a placebo.171 It is essential to underscore that in such trials, receiving a placebo or being assigned to the control arm is not equivalent to *no care*. Supportive care was not available to many people in West Africa during the 2014 outbreak.172 Therefore, being enrolled in a study that provided supportive care could, in and of itself, be an improvement over an individual’s status quo at baseline. While this fact is regrettable, it also weakens the argument made against controls.

Second, a mere 10% of drugs that are developed make it to clinical trials, and of those, just one in five is ultimately made available to the public.173 While there may be several explanations for this, one is that clinical research may reveal that a drug is not safe, not effective, or neither safe nor effective. Therefore, it is incorrect to assume—as some opponents of controls implicitly seem to do—that individuals are necessarily disadvantaged when they do not receive an experimental intervention. They seemingly overestimate the possibility of benefit. Although there was promising evidence from animal models—for instance, ZMapp was 100% effective in studies with rhesus macaques174 but had not finished typical animal safety testing175—there must be caution when inferring the implications for humans from animal data. There is no guaranteed benefit. Moreover, the risks are uncertain. There is a possibility that experimental interventions can make people not just no better off but materially *worse off*, which also appears to be underplayed by those who reject controls.

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169 For example, Clement Adebamowo et al., *Randomised Controlled Trials for Ebola: Practical and Ethical Issues*, 384 LANCET 1423, 1423 (2014); Morenike O. Folayan, Bridget Haire & Kristin Peterson, *Ethical Testing of Experimental Ebola Treatments—Letter to the Editor*, 313 JAMA 421, 421 (2015).

170 Adebamowo et al., supra note 169, at 1423.

171 CDC, supra note 108, at n.p.

172 Jon Cohen, *Issues Continue to Dog the Testing of Ebola Drugs and Vaccines*, SCIENCE, Oct. 16, 2014, http://www.sciencemag.org/news/2014/10/issues-continue-dog-testing-ebola-drugs-and-vaccines (last accessed April 7, 2016).

173 Lindsay M. Boyd, *Ebola, The 'Right to Try,' And Why We Should Care*, FORBES, Aug. 12, 2014, http://www.forbes.com/sites/realspin/2014/08/12/ebola-the-right-to-try-and-why-we-should-care/#35aee4958f (last accessed March 3, 2016).

174 Xiangguo Qui et al., *Reversion of Advanced Ebola Virus Disease in Nonhuman Primates with ZMapp*, 514 NATURE 47, 47 (2014).

175 Andrew Pollack, *Ebola Drug Could Save a Few Lives, But Whose?*, THE NEW YORK TIMES, Aug. 8, 2014, http://www.nytimes.com/2014/08/09/health/in-ebola-outbreak-who-should-get-experimental-drug.html?r=1 (last accessed April 7, 2016).
It may be argued in response that when a condition has as high a case fatality rate as EVD, surely, the risks associated with taking an experimental drug cannot be any worse than the risks of having EVD and receiving the standard of care and may, in fact, be better. I concede that reasonable people may—and likely would—prefer to try an apparently promising experimental intervention under such circumstances. Yet, the reported case fatality rate in the 2014 outbreak hovered around 50%, and it is arbitrary line drawing to say that this is the point where it is ethically superior to provide access to an experimental intervention despite the genuine uncertainty about the attendant risks and benefits.

Fourth, individuals do not have a right to access experimental interventions outside of clinical research, nor do they have a right to those interventions conditional on participating in clinical research. Investigators do not have a therapeutic obligation to research participants. Recall, the purpose of research is to produce generalizable knowledge for the benefit of future patients.

[T]he point of medical trials is not to provide the intervention that’s medically best for the research subject. It’s to establish something that’s important—and this point is crucial—for a far larger population and to prevent human catastrophe.

Just as clinical research may justifiably require exposing research participants to procedures that hold no prospect of medical benefit for them personally, research may require randomizing some individuals to a control group. The burdens and risks randomization imposes on individuals are justified by their social and scientific value. To claim that individuals have a right to a promising experimental intervention is to confuse the ethics of research and care.

An argument can be made that Ebola-ravaged populations have a right to healthcare. It is indisputably unfortunate that existing healthcare systems in countries like Guinea, Liberia, and Sierra Leone cannot meet the pressing need for even the most basic healthcare. It is not, however, the obligation of researchers to fulfill this right. Conditional on engaging in clinical research, researchers may assume obligations to provide ancillary care, to provide a high standard of care to research participants, and also

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176 Cf. Abigail Alliance for Better Access to Developmental Drugs v. Von Eschenbach, 495 F.3d 695 (DC Cir. 2007) (cert denied) (holding that terminally ill adult patients had no fundamental right protected by Due Process Clause to have access to investigational drugs).

177 I concede that there may be reasons to think that participants should have post-trial access if a drug proves to be safe and effective.

178 Franklin G. Miller & Howard Brody, A Critique of Clinical Equipoise: Therapeutic Misconception in the Ethics of Clinical Trials, 33 HASTINGS CENTER REP. 19, 25 (2003).

179 Cohen, supra note 172, at n.p. (quoting Nir Eyal).

180 For example, the WHO Constitution enshrines ‘the highest attainable standard of health as a fundamental right of every human being’.

181 See generally Henry S. Richardson & Leah Belsky, The Ancillary-Care Responsibilities of Medical Researchers: An Ethical Framework for Thinking about the Clinical Care that Researchers Owe Their Subjects, 34 HASTINGS CENTER REP. 25 (2004).

182 It is an open debate whether researchers can provide the ‘local’ standard of care or whether they should provide the ‘best’ standard of care. See eg Marcia Angell, The Ethics of Clinical Research in the Third World, 337 NEW ENG. J. MED. 847 (1997).
to provide post-trial access to beneficial interventions.\textsuperscript{183} It would be wrong, however, to claim that researchers exploit research participants when clinical research offers fair benefits—even if potential research participants’ background situation is an unfair one and even if that background situation leads them to feel they have no alternative but to participate in research.\textsuperscript{184} The desire to provide clinical benefit to everyone affected by EVD should be realized by strengthening health systems, not by prohibiting controls.\textsuperscript{185} Research and strengthening of healthcare systems must be pursued simultaneously.

Finally, when a resource—like an EVD treatment—is scarce, clinicians and policymakers face the difficult task of determining how to allocate it among the many individuals who might benefit. Inevitably, rationing will be necessary, and by definition, not everyone who might benefit will be able to have access. It follows from this that there is a real possibility promising experimental interventions might be allocated unfairly. Randomization offers a means to allocate a scarce resource fairly.\textsuperscript{186} This is preferable to alternate rationing approaches that seem facially to be fair but have disparate impacts on lesser-resourced groups in practice.

To choose but one example, well-off and well-connected patients should not be further privileged in a public health emergency by being prioritized to receive a promising albeit unproven intervention.\textsuperscript{187} This would be unfair and could undermine the perceived legitimacy of the public health response to the outbreak. This is not idle speculation. For example, initially, there was only enough ZMapp for seven patients.\textsuperscript{188} Many were critical of the fact that two white Americans aid workers, Nancy Writebol and Dr. Kent Brantly, received ZMapp when comparably sick Africans did not.\textsuperscript{189} It was reported that Brantly and Writebol’s employer, Samaritan’s Purse, only requested two doses of ZMapp, despite the fact that they were treating about 17 other Ebola patients in their Liberian clinic.\textsuperscript{190} Although, Mapp Biopharmaceutical Inc., the company that makes ZMapp, says that it filled requests for ZMapp on a first-come, first-served

\textsuperscript{183} See generally Christine Grady, The Challenge of Assuring Continued Post-Trial Access to Beneficial Treatment, S YALE J. HEALTH POL’Y L. & ETHICS 425 (2005) (describing the controversy over post-trial benefits).

\textsuperscript{184} Cf. Christine Pace, Franklin G. Miller & Marion Danis, Enrolling the Uninsured in Clinical Trials: An Ethical Perspective, 31 CRIT. CARE MED. S121 (2003).

\textsuperscript{185} Cf. Rid & Emanuel, supra note 151, at 1844.

\textsuperscript{186} \textit{Id.}

\textsuperscript{187} \textit{Id.}

\textsuperscript{188} Andrew Pollack, U.S. Will Increase Production of the Ebola Drug ZMapp, but May Not Meet Demand, THE NEW YORK TIMES, Oct. 1, 2014, \url{http://www.nytimes.com/2014/10/02/world/us-to-increase-production-of-experimental-drug-but-may-not-meet-demand.html?_r=0} (last accessed March 3, 2016) (‘[T]he federal official said it was expected to produce only about 10 to 20 treatment courses by the end of the year, and the same amount every month going forward.’).

\textsuperscript{189} See eg Kwei Quartey, Ebola’s Racial Disparity: The Most Effective Treatment for Ebola Might be Having White Skin, FOREIGN POLICY IN FOCUS, Nov. 26, 2014, \url{http://fpif.org/ebolas-racial-disparity/} (last accessed April 7, 2016).

\textsuperscript{190} Beth Skwarecki, Ethical Dilemmas of Giving Ebola Drugs to the People Who Need them Most, PLOS BLOGS, Sept. 12, 2014, \url{http://blogs.plos.org/publichealth/2014/09/12/last-big-ebola-outbreak/} (last accessed April 7, 2016).
basis, that Writebol and Brantley received the drug served as potent evidence to some that ‘the life of an African is less valuable’.

First-come, first-served—the allocation method favored by many advocates of alternative trial design—may superficially seem like a fair way of distributing a scarce resource, but on further reflection, it is abundantly clear that such an allocation scheme inherently favors the privileged—for example, those who know where to go and have the means to get there—while ignoring other relevant considerations. Randomization within an ethically conducted RCT offers an alternative way to allocate the scarce resource—a drug with the potential (not the promise) to offer an advantage over standard care—fairly among individuals who meet a study’s eligibility criteria and who agree to contribute to the social good achieved by answering the crucial question: is this intervention beneficial, neutral, or harmful?

WHO has cautioned that flare-ups of EVD are to be expected in the wake of the 2014 outbreak, and experts expect that there will be other EVD outbreaks in the future. Additionally, we can assume that public health emergencies will arise from other threats like Zika virus. It is, therefore, essential to balance individual patient needs and preferences with broader public health considerations. For the reasons outlined above, it is both ethical and necessary to conduct research, including randomized placebo-controlled trials as the opportunity arises, to develop and identify safe and effective drugs and vaccines for use in future outbreaks.

From a research ethics perspective, conducting randomized placebo-controlled trials in the midst of a public health emergency can be justified. Now, let us turn to the formal laws that govern the situation to see how they can advance the goals of drug development, approval, and access in a public health emergency.

### III. DEVELOPMENT, APPROVAL, AND ACCESS

A primary reason for FDA involvement in the West African Ebola outbreak was that any drug, device, or biologic must be reviewed by FDA’s Center for Drug Evaluation and Research (CDER) and deemed safe and effective before it is marketed in the United States. In this section, I will briefly review the standard process for drug and vaccine development, approval, and marketing/access—the process by which experimental interventions progress from the lab into the hands of consumers—and highlight challenges that arose in 2014–2015.

#### A. The standard model

The standard model has three phases: drug development, drug approval, and finally, drug access.

191 Skwarecki, supra note 190, at n.p.
192 Pollack, supra note 175, at n.p. (but also quoting an African researcher as saying ‘It would have been the front-page screaming headline: Africans used as guinea pigs for American drug company’s medicine’ if ZMapp had been tested in Africans first).
193 Cf. Govind Persad, Alan Wertheimer & Ezekiel J. Emanuel, Principles for Allocation of Scarce Medical Interventions, 373 LANCET 423, 424 (2009).
194 WHO, supra note 79, at n.p.
195 Meera Senthilingham, Are We Ready for the Next Global Epidemic?, CNN.com, http://www.cnn.com/2015/02/13/health/are-we-ready-for-global-outbreak/ (last accessed March 3, 2016).
1. Development

The costs of developing a new drug are often estimated to exceed $1 billion, and it takes an average of 10 years to complete the journey from bench to bedside. This expensive and lengthy process begins with the identification of potential biological targets, or structures in the body that will react with a drug compound to produce the desired clinical effect, such as treating EVD. Typically, after starting with thousands of candidate drug compounds, the field is narrowed to one or more ‘lead compounds’, ‘promising molecule[s] that could influence the target and, potentially, become a medicine’. Pre-clinical testing is used to identify those lead compounds that will advance to clinical trials.

Clinical research is part of the drug development process, as FDA does not test the safety or efficacy of drugs itself but instead relies on data supplied by the pharmaceutical company seeking to market the drug. If a company wishes to test a drug, device, or biologic it has developed within the United States, it is first required to contact FDA in order to obtain an Investigational New Drug (IND) application. An IND details the results of preclinical work, including a list of potential side effects indicated by preclinical studies, and provides a detailed clinical trial plan, outlining how, where, and by whom clinical studies will be conducted. While the full safety profile of a novel drug is obviously not known when the company seeks an IND, the company must provide data gathered in laboratory and animal testing to support the claim that the drug is safe enough to give to humans. FDA’s ‘primary concern [w]hen reviewing an original IND submission or planning for a pre-IND meeting … is the safety of the subjects who will receive the drug during the proposed clinical trial’. As discussed above, CDER requires companies to adhere with GCPs.

An IND becomes effective 30 days after the application is submitted, unless FDA imposes a clinical hold. Only after the company has an IND in hand can it begin a multi-phase clinical trial to establish safety (phase I), to establish efficacy (phase 2), and

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196 See generally Joseph A. DiMasi, Henry G. Grabowski & Ronald W. Hansen, Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs, 47 J. HEALTH ECON. 20 (2016).
197 PhRMA, BIOPHARMACEUTICAL RESEARCH & DEVELOPMENT: THE PROCESS BEHIND NEW MEDICINES 1 (2015).
198 Id. at 4.
199 Id.
200 Id.
201 FDA describes Clinical Research as Step 3 in the Drug Development Process. FDA, The Drug Development Process, http://www.fda.gov/ForPatients/Approvals/Drugs/default.htm (last accessed July 28, 2016).
202 FDA, How Drugs are Developed and Approved, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ (last accessed January 7, 2016).
203 See FDA, The FDA’s Drug Review Process: Ensuring Drugs are Safe and Effective, http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm (last accessed January 7, 2016).
204 PhRMA, supra note 197, at 11.
205 FDA, supra note 203, at n.p.
206 Jennifer S. Bard, A Taxonomy for Analysing Legal and Ethical Issues Arising When Conducting Human Subject Research Outside the Borders of One’s Own Country, 37 Hous. J. INT’L L. 1, 32–33 (2015).
207 21 CFR 312.40.
to compare the new treatment to the current standard of care in a larger study population (phase 3). Clinical trials take, on average, 6 to 7 years to complete.

Clinical trials that take place outside the United States—as Ebola trials likely would—do not, by contrast, require an IND, although a sponsor may choose to conduct a foreign clinical study under an IND. Companies can, therefore, avoid any kind of preliminary review regarding the adequacy of human subjects protections. However, should a company subsequently seek to market a drug in the United States, ‘FDA has the legal authority to require sponsors to certify that the data they are using was obtained under the same human subjects protections as would be applicable in the United States’. The GCP requirements help to ensure that non-IND foreign studies are conducted in a manner comparable to that required for IND studies.

2. Approval

Once clinical trials have been completed, companies then submit a new drug application (NDA) to FDA. A team from CDER—consisting of physicians, statisticians, chemists, pharmacologists, and other scientists—will review the NDA, which contains data from the clinical trials as well as the proposed labeling and which can run 100,000 pages or more. The 1992 Prescription Drug User Fee Act established two tiers of review: standard and priority. Drugs that offer major advances in treatment or provide a treatment where none previously existed—as would be the case for therapies targeted at Ebola—are designated for priority review. The goal for completing a priority review is 6 months. The target for standard review is 10 months.

3. Access

If the NDA is approved, the product may be marketed in the United States. The delay between the NDA and the grant of marketing authorization has been identified as a preliminary barrier to patient access to new drugs. Yet, access to FDA-approved drugs will depend, in the United States—as elsewhere—on formulary placement,

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208 Clinical trials typically are conducted in a series of phases, each designed to answer a distinct research question. Phase 1 studies aim to determine how a drug is metabolized and excreted, establish a safe dosage range, and identify the most frequent side effects. They are usually conducted as one-arm trials in healthy volunteers. While the emphasis in phase 1 is on safety, the emphasis in phase 2 is on efficacy. Researchers aim to obtain data on whether the drug works in individuals with the disease or condition of interest. Sometimes, clinical trial phases may be combined (eg phase 1/2) to allow faster development of a new intervention and/or to minimize risks to research participants. National Institutes of Health, What Are Clinical Trial Phases?, 18 Apr. 2008, http://www.nlm.nih.gov/services/ctphases.html (last accessed April 15, 2016).

209 PhRMA, supra note 197, at 1.

210 21 C.F.R. part 312 (2016).

211 Bard, supra note 206, at 33.

212 21 C.F.R. 312.120 (2016); 21 C.F.R. 314.106 (2016) (governing marketing approval of a new drug based solely on foreign clinical data).

213 FDA, How Drugs are Developed and Approved, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/default.htm (last accessed January 8, 2016).

214 PhRMA, supra note 197, at 14.

215 FDA, Frequently Asked Questions about the FDA Drug Approval Process, http://www.fda.gov/Drugs/ResourcesForYou/SpecialFeatures/ucm279676.htm (last accessed January 8, 2016).

216 See generally Joshua Cohen et al., Comparing Patient Access to Pharmaceuticals in the UK and US, 5 APPL. HEALTH ECON. HEALTH POL’Y 177 (2006).
cost-sharing, and conditions of reimbursement. Coverage may not be evenly spread over the population.

B. Challenges to the standard model in the 2014 outbreak

The standard model, just outlined, has significant limitations in public health emergencies like the West African EVD outbreak. As just described, developing a new drug and getting FDA approval is time consuming. Companies may spend years—or even decades—developing a drug and ushering it through clinical trials before they send an NDA to FDA for review, which then takes 6 months or more. While this is true of all drugs, there are two key implications in a public health emergency.

First, it is exceedingly unlikely that an entirely new treatment will or even can be developed from scratch during an epidemic. Rather, promising compounds must already be far along the development pipeline if they are to have an impact in the near term. EVD might be relatively unique among public health threats in that there had already been significant investment in basic research and drug development before the 2014 outbreak in light of concerns the Ebola virus might be used in bioterrorism. Promising compounds are unlikely to be at the ready if a public health emergency is the result of a NTD or comparable illness that is not commercially attractive to pharmaceutical companies or if it is the result of an emerging threat with which clinicians and researchers have yet to become familiar. Second, even if a drug has already been developed, including the completion of clinical trials, if it is not yet FDA approved, it is unlikely that FDA will be able to approve it in time to meet the most pressing patient demands in an outbreak. Taken together, these two considerations suggest that it is extremely important to prioritize drug development and approval of drugs addressing public health threats in interoutbreak periods to the greatest extent possible, granting that the ‘greatest extent possible’ might be quite limited.

Further challenges to drug development, approval, and access arose in the 2014 outbreak and are likely to recur in future public health emergencies. First, as mentioned in Section II, it was necessary to conduct clinical trials in the midst of the outbreak because it is unethical intentionally to expose healthy research participants to the Ebola virus. Yet, conducting research in the midst of an outbreak raised contentious ethical and methodological questions, and people had widely divergent views on how best to proceed. Furthermore, conditions on the ground, discussed in Section I, made both the delivery of care and the conduct of research extremely difficult from a practical perspective. Although the particular challenges that will be confronted on the ground in any given public health emergency cannot be anticipated in advance, there are ethical, methodological, and practical considerations that can and should be anticipated and addressed as part of pre-planning for clinical trials that will transpire in such circumstances.

Second, there were few doses of experimental interventions available for conducting clinical trials, and as the outbreak receded and the number of EVD cases waned, the epidemiological trajectory made it increasingly difficult to conduct RCTs,

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217 Id.; see also Henry Grabowski, Medicaid Patients’ Access to New Drugs, 7 Health Aff. 102 (1988).
218 Although it is beyond the scope of FDA’s role, I think that it is essential that efforts are made to address weak health systems to safeguard public health.
to show efficacy.\textsuperscript{219} Even if an experimental intervention had successfully passed through clinical trials, however, FDA and other regulatory agencies were likely to confront relatively limited data on safety and efficacy in light of the small size of the patient population. Thus, it is necessary to consider whether alternative approval pathways are appropriate, how data collection standards might be compromised in an epidemic to achieve the appropriate balance between speeding approval and protecting drug consumers, and what, if any, post-marketing trials should be required.

Finally, the prospect of FDA approval raises important questions about who should have access to FDA-approved therapies in a public health emergency and how this will be accomplished. MSF, for example, worried that there was no mechanism to ensure that West African patients would have access to EVD treatments. An FDA-approved drug is of little value if it does not get into the hands of those who need it because, for example, they cannot afford it or because it cannot be manufactured in sufficient quantities. Although there are independent normative arguments for why global health inequalities should be addressed, in a public health emergency—particularly in an age when global air transit brings us together and exposes us more widely to health risks—there are additional self-interested reasons to ensure broad access.

In order for FDA’s response to any public health emergency to be maximally effective, the agency must anticipate and address barriers to development, approval, and access. Here, I have made preliminary, broad recommendations for how this might be accomplished. In the next section, I will look at how FDA in fact used its flexible regulatory framework to respond to these challenges in the 2014 outbreak and make more granular recommendations for how FDA might better respond to future public health emergencies.

**IV. FDA AND THE 2014 OUTBREAK**

During the 2014 Ebola outbreak, FDA worked to ‘help expedite the development and availability of medical products—such as treatments, vaccines, diagnostic tests, and personal protective equipment—with the potential to help bring the Ebola epidemic in West Africa under control as quickly as possible’.\textsuperscript{220} FDA’s response to the 2014 Ebola outbreak showcases the agency’s panoply of powers and its regulatory flexibility, which enabled it to move relatively rapidly in the context of a public health emergency. Yet, if one considers the response along the dimensions of development, approval, and access, it is clear that there is room for substantial improvement in the response to future public health emergencies.

Unfortunately, more public health emergencies are inevitable. Threats may come from reemerging or from new diseases. The recent pandemic of Zika virus infection in South America, Central America, and the Caribbean is but one example.\textsuperscript{221} On

\textsuperscript{219} Lisa Schnirring, CENTER FOR INFECTIOUS DISEASE RESEARCH AND POLICY (CIDRAP), Experts Weigh Challenges, Options for Ebola Vaccine Clearance, CIDRAP News, May 12, 2015, http://www.cidrap.umn.edu/news-perspective/2015/05/experts-weigh-challenges-options-ebola-vaccine-clearance (last accessed March 4, 2016).

\textsuperscript{220} FDA, Ebola Response Updates from FDA, http://www.fda.gov/ EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/ucm410308.htm (last accessed January 7, 2016).

\textsuperscript{221} Anthony S. Fauci & David M. Morens, Zika Virus in the Americas—Yet Another Arbovirus Threat, 374 NEW ENG. J. MED. 601, 601 (2016).
February 1, 2016, WHO declared Zika virus a PHEIC.222 Although Zika was first discovered in 1947,223 the present clusters of microcephaly cases and other neurological disorders have occurred in areas newly infected with Zika virus.224 Presently, neither vaccines nor treatments for Zika are in advanced stages of development.225 Moreover, ‘[t]here are no commercially available diagnostic tests cleared by the FDA for the detection of Zika virus’.226

The response to the 2014 EVD outbreak therefore serves as a useful case study from a health policy perspective because it allows us to understand FDA’s response to a particular public health emergency and to draw lessons for moving forward. I focus on describing and evaluating six steps taken and one not taken by FDA. Some of my suggestions would simply require FDA to assume a broader role in coordination and planning in interemergency periods; others, however, would require congressional action to alter or expand the scope of FDA’s powers. While one could imagine a range of policy interventions by a broad array of actors—both domestic and international—that would yield improvements along the dimensions of development, approval, and access, this section focuses more narrowly on what FDA in particular is able to do and how FDA’s capacity to respond could be further strengthened.

A. Offering development incentives

During the 2014 outbreak, FDA actively used drug development programs to encourage the pursuit of Ebola vaccines and treatments.227 As discussed in Section I above, many, including the [Director-General of WHO Dr.] Margaret Chan, have criticized the pharmaceutical industry’s lack of investment in investigational treatments for [EVD], saying many companies had likely determined the return on any investment for an Ebola treatment was not worth the development cost’.228 Development incentives are intended to overcome entrenched reluctance to invest in neglected diseases. Unfortunately, the two development incentives at FDA’s disposal—the Orphan Drug Act and vouchers for priority review—had clear shortcomings when used in the context of EVD.

1. Orphan Drug Act

The Orphan Drug Act of 1983 was passed to counterbalance market forces and incentivize development of drugs defined by statute as affecting fewer than 200,000 people in
the United States. The act offers pharmaceutical companies a variety of incentives, including market exclusivity, tax credits, and research grants. These are ‘push’ and ‘pull’ incentives for drug development. Whereas ‘push’ is focused on the cost side of the profit equation, ‘pull’ is focused on the revenue side: ‘push’ incentives serve to lower the logistical and financial barriers to entry, while ‘pull’ incentives increase the likelihood that there will be a sufficient return on investment once products reach market. In 2014, FDA granted orphan designation to products being developed to treat EVD, including ZMapp.

The Department of Health and Human Services (HHS) has previously concluded that the Orphan Drug Act ‘unquestionably stimulated the development [of drugs] for rare diseases’, particularly for rare genetic diseases affecting Americans. This success is partially attributable to the surprising profitability of orphan drugs. Eighteen blockbuster drugs—those with global annual sales of greater than $1 billion—were approved solely as orphan drugs within the United States. The profitability of orphan drugs has been ‘driven [in part] by a strong disposition among healthcare purchasers in high-income countries to pay for these drugs at high prices’. These drugs can be prohibitively costly for patients without means. The effect of the Orphan Drug Act on the development of drugs for NTDs and other neglected public health threats has been markedly less impressive. Some have concluded that the act’s generous subsidies ‘are not enough when prospective gains from commercialization are poor’.

With respect to the Orphan Drug Act, the pharmaceutical industry has consistently identified the 7-year marketing exclusivity provision as the act’s most important ‘pull’ lever. This fact led some to advocate during the 2014 EVD outbreak for extending the marketing exclusivity period from 7 to 10 years to further strengthen incentives for development of Ebola drugs. Extending the marketing exclusivity period, which would...

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229 FDA, THE ORPHAN DRUG ACT (as amended), http://www.fda.gov/orphan/oda.htm (last accessed August 31, 2016).
230 Id.
231 Christopher-Paul Miline & Joyce Tait, Evolution Along the Government-Governance Continuum: FDA’s Orphan Products and Fast Track Programs As Exemplars of ‘What Works’ for Innovation and Regulation, 64 FOOD & DRUG L.J. 733, 737 (2009).
232 Jason Millman, Why the Drug Industry Hasn’t Come up with An Ebola Cure, THE WASHINGTON POST, Aug. 13, 2014, https://www.washingtonpost.com/news/wonk/wp/2014/08/13/why-the-drug-industry-hasnt-come-up-with-an-ebola-cure/ (last accessed March 4, 2016).
233 OFFICE OF INSPECTOR GENERAL, HHS, THE ORPHAN DRUG ACT IMPLEMENTATION AND IMPACT, at 7 (2001). See also FDA, CDER Approved Many Innovative Drugs in 2014, http://blogs.fda.gov/fdavoice/index.php/2015/01/cder-approved-many-innovative-drugs-in-2014/ (last accessed January 8, 2016) (noting that 17 of the 41 novel new drugs were approved to treat rare diseases).
234 Arnold & Pogge, infra note 247, at 225.
235 M. Ian Phillips, Big Pharma’s New Model in Orphan Drugs and Rare Diseases, 1 EXPERT OPINION ON ORPHAN DRUGS 1, 2 (2012).
236 Arnold & Pogge, infra note 247, at 225.
237 Id.
238 Id.
239 Gilbert Grimm & Len M. Nichols, Ebola Crisis of 2014: Are Current Strategies Enough to Meet the Long-Run Challenges Ahead?, 105 AM. J. PUB. HEALTH e8, e9 (2015).
240 Id.
require an act of Congress, would, in theory, create some additional ‘pull’. Yet, it is unclear that this amendment to the Orphan Drug Act would make any meaningful difference with respect to current or future public health threats because, ‘[f]or things like Ebola, there is no clear buyer other than the government’. Beyond the government, the market for EVD treatments was both small and likely unable to pay for any saleable product. Under the circumstances, it would be more effective for Congress to introduce advanced market commitments (AMCs). AMCs have not been used for NTDs but they could incentivize development by setting a minimum price and quantity for purchase, for example, conditioned on receipt of orphan drug designation and FDA approval.

In the case of NTDs and other public health threats, it is doubtful that orphan drug designation currently offers sufficient ‘push’ incentives for the development of interventions to address public health threats either. Additional ‘push’ solutions need to be identified. While FDA could potentially administer these, for example, by deepening the tax credits and research grants tied to orphan drug designation, it would be preferable to look beyond FDA and increase federal research funds to support development of vaccines and treatments for public health threats—for instance, to look to NIH and the Biomedical Advanced Research and Development Authority (BARDA). Given its first-hand knowledge of the shortcomings of orphan designation, FDA should advocate for these changes as a complement to its own efforts.

2. PRV program

On December 16, 2014, President Obama signed the Adding Ebola to the FDA Priority Review Voucher Program Act into law. This was an amendment to the FDAAA, which was intended to provide incentives to companies to invest in NTDs. The FDAAA added new section 524 to the FD&C Act, which authorizes FDA to award PRVs to, sponsors of certain tropical disease product applications that meet the criteria specified by the Act.

241 Brendan Greeley & Caroline Chen, How the U.S. Screwed Up in the Fight Against Ebola, BLOOMBERG BUSINESS WEEK, Sept. 24, 2014, http://www.bloomberg.com/news/articles/2014-09-24/ebola-drug-zmappsd-development-delayed-by-pentagon-agency (last accessed April 12, 2016).

242 Sarika Bansal, How Pharmaceutical Companies Can Help Take the ‘Neglected’ Out of Neglected Tropical Diseases (NTDs), FORBES, Nov. 9, 2011, http://www.forbes.com/sites/sarikabansal/2011/11/09/ neglected-tropical-disease-pharmaceutical-companies/2/#2bfc6d326fd1 (last accessed April 14, 2016).

243 As discussed above, NIAID, the Department of Defense, and the Biomedical Advanced Research and Development Authority, within HHS, have supported research relevant to Ebola; this includes basic research as well as getting drugs into clinical trials. However, funding has been erratic, which has led to ‘delays in many programs critical to biodefense’. JAMES J. CARAFANO, CHARLOTTE FLORANCE & DANIEL KANIEWSKI, THE EBOLA OUTBREAK OF 2013&2014: AN ASSESSMENT OF U.S. ACTIONS, THE HERITAGE FOUNDATION 22 (2015). Appropriations for the development of medical countermeasures need to be larger as well as more consistent. When no effective market exists, government contracting may constitute ‘a necessary complementary incentive’ to intellectual property. Henry G. Grabowski, Joseph A. DiMasi & Genia Long, The Roles of Patents and Research And Development Incentives in Biopharmaceutical Innovation, 34 HEALTH AFF. 302, 308 (2015). Furthermore, there needs to be coordination between the various arms of the federal government working to address these problems so as to avoid inefficiencies.

244 Alexander Gaffney, Obama Signs Special Ebola Incentive Program into Law, http://www.raps.org/Regulatory-Focus/News/2014/12/18/20999/Obama-Signs-Special-Ebola-Incentive-Program-Into-Law/ (last accessed March 4, 2016).

245 FDA, Guidance for Industry: Tropical Disease Priority Review Vouchers (Draft Guidance Oct. 2008), http://www.fda.gov/downloads/Drugs/.../Guidances/UCM080599.pdf (last accessed August 31, 2016).
An ex post reward for developers, the PRV is a transferable voucher for future priority review on a subsequent drug or biologic brought before FDA. The PRV program seeks to ‘incentivize the development of tropical disease products without burdening taxpayers or delaying generic entry’. Compared to the Orphan Drug Act,

which significantly subsidizes the inputs of innovation (‘push’), the [PRV] program rewards only the successful outputs of the pharmaceutical R&D process. The vouchers, therefore, serve exclusively as a pull mechanism to stimulate the development of drugs that might not otherwise be brought to market due to insufficient sales potential.

PRVs provide a significant advantage to drug manufacturers, as they entitle their holder to a 6-month priority review by FDA, rather than the standard 10-month review. It has been estimated that a PRV ‘would be worth more than $300 million for a potential blockbuster drug’ because the drug reaps the benefit of entering the market significantly earlier. Alternatively, a PRV may be transferred or sold to another sponsor, which can also be lucrative. For instance, Sanofi paid $245 million for a PRV in 2015.

EVD was initially omitted from the FDAAA because FDA consulted with WHO’s Department of Control of Neglected Tropical Diseases when drafting its initial list of eligible NTDs in 2006–07, and WHO does not recognize EVD as an NTD because of its historically low morbidity and mortality. Ebola serves as a potent reminder that the PRV program is too narrow as currently written to address burgeoning public health threats, which may not be ‘classic’ NTDs, the characteristics of which were addressed at some length in Section I. It has been suggested that the PRV program should be expanded to include biodefense products, a category that would include Ebola, and could also be relevant to some future public health emergencies. While potentially beneficial, such an eligibility expansion is an incomplete solution at best.

The delayed expansion of the PRV program to include Ebola could be characterized as needlessly hampering FDA’s ability to incentivize EVD research. Incentivizing research with PRVs only after the outbreak began was unlikely to make any meaningful difference in the short term—that is, the lifecycle of the 2014 outbreak. The failure to

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246 Lesley Hamming, *The Promise of Priority Review Vouchers As A Legislative Tool to Encourage Drugs for Neglected Diseases*, 11 DUKE L. & TECH. REV. 390, 394 (2013).

247 Cameron G. Arnold & Thomas Pogge, *Improving the Incentives of the FDA Voucher Program for Neglected Tropical Diseases*, 21 BROWN J. WORLD AFF. 223, 225 (2014–2015).

248 GAO Highlights, *Rare Diseases: Too Early to Gauge Effectiveness of FDA’s Pediatric Voucher Program*, Mar. 2016, http://www.gao.gov/assets/680/675544.pdf (last accessed March 4, 2016), at 1.

249 Hamming, *supra* note 246, at 398, 399.

250 FDA, *supra* note 245, at 1

251 PMLIVE, *Sanofi Pays $245m for FDA Priority Review Voucher*, May 28, 2015, http://www.pmlive.com/pharma_news/sanofi_pays_245m_for_fda_priority_review_voucher_744940 (last accessed March 4, 2016) (‘This is the third time a PRV has changed hands and, with their value escalating each time, the deals clearly illustrate the competitive benefits that can accrue from even a small lead in the marketplace’.)

252 Arnold & Pogge, *supra* note 247, at 228.

253 INSTITUTE OF MEDICINE (IOM) FORUM ON MEDICAL AND PUBLIC HEALTH PREPAREDNESS FOR CATASTROPHIC EVENTS & IOM FORUM ON DRUG DISCOVERY, DEVELOPMENT, AND TRANSLATION, THE PUBLIC HEALTH EMERGENCY MEDICAL COUNTERMEASURES ENTERPRISE: INNOVATIVE STRATEGIES TO ENHANCE PRODUCTS FROM DISCOVERY THROUGH APPROVAL: WORKSHOP SUMMARY (2010).
include EVD in the original FDAAA was faulted for stalling ‘auspicious early research’ into EVD drugs and vaccine candidates due to a lack of interest from the private sector.\textsuperscript{254} Yet, given the low overall number of people affected by EVD before the 2014 outbreak began, this is probably overstating the effect that more timely PRVs would have had. A PRV would effectively have been the lone commercial reward for any Ebola-specific product developed because there was, in reality, no market for such products. The approximately $300 million value of the PRV would likely have been insufficient on its own for pharmaceutical companies, given that the costs of developing a new drug or vaccine are often estimated to exceed $1 billion.

More broadly, PRVs have been criticized as ‘an inefficient and potentially dangerous way of encouraging research into [neglected] tropical diseases’.\textsuperscript{255} For large pharmaceutical companies, PRVs do not ‘directly connect the incentive with the innovation … [because] the voucher’s value depends on the success of potential ‘blockbuster’ drugs that are currently in their pipelines, which is far from assured’.\textsuperscript{256} Small companies, which conduct the majority of tropical disease research, will often be unable to use their vouchers themselves,\textsuperscript{257} though it can, as just mentioned, be lucrative to sell them.

A further challenge of ‘pull’ funding instruments like PRVs is that they assume that a drug or vaccine developer has the funds available up-front to invest in initial R&D and clinical development.\textsuperscript{258} Yet, that will not always be the case, particularly given the role for small companies, just mentioned. ‘Push’ mechanisms—like funding of clinical trials—will also be needed to provide an urgently needed infusion of funds.\textsuperscript{259} Thus, the PRV program should be understood not as a stand-alone solution to the problem of NTDs but as a complement to other mechanisms for encouraging drug development.

Even if we assume, however, that (i) the lure of PRVs is sufficient to drive the development of new drugs for NTDs, EVD, or other public health threats that might be added to the PRV program and (ii) companies have or can obtain the necessary up-front funds, this can be viewed as only a first step in providing a drug to combat a public health threat. The mere existence of a drug or drugs does not ensure that those who need them will have access. In order to receive a PRV, a company must only get FDA approval for its new drug. The company is not required to facilitate access to the drug for those who need it.\textsuperscript{260} In practice, sustainable access to drugs that have earned their developers PRVs has not been achieved in developing countries.\textsuperscript{261} Experience prompted MSF to describe the addition of EVD to the PRV program as ‘much-welcome’ but simultaneously to express concern that there was still no ‘way to ensure that patients,

\begin{thebibliography}{9}
\bibitem{254} Arnold & Pogge, supra note 247, at 229.
\bibitem{255} Aaron S. Kesselheim, Drug Development for Neglected Diseases—The Trouble with FDA Review Vouchers, 359 NEW ENG. J. MED. 1981, 1981 (2008); but see Jeffrey Moe, Henry Grabowski & David Ridley, Correspondence: FDA Review Vouchers, 360 NEW ENG. J. MED. 837 (2009) (replying to Kesselheim).
\bibitem{256} Kesselheim, supra note 255, at 1981.
\bibitem{257} Id. (noting the lack of transparency in these transactions is undesirable).
\bibitem{258} See Peter J. Hotez, Maria Elena Bottazzi & Ulrich Strych, New Vaccines for the World’s Poorest People, 67 ANNU. REV. MED. 405, 412–13 (2016).
\bibitem{259} Id. at 413.
\bibitem{260} Arnold & Pogge, supra note 247, at 227, 228.
\bibitem{261} Id. at 228.
\end{thebibliography}
governments and treatment providers like MSF, will have affordable and appropriate access to the potential resulting Ebola medicines and vaccines.\(^{262}\)

FDA has already—and for unrelated reasons—asked for changes to the PRV program.\(^{263}\) It should request further changes in the program to enhance the response to future public health emergencies. In particular, Congress should make explicit demands that companies seeking a PRV demonstrate that reasonable efforts have been made to facilitate access to any new drug.\(^{264}\) This could be accomplished by having the developer manufacture and market the drug itself at an affordable price or by licensing the drug to another manufacturer to achieve the same result.\(^{265}\) Such changes to the legislation would further align the economic incentives of drug developers with broader public health needs.

### B. Granting fast track status

Fast Track is ‘a process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need’.\(^{266}\) Fast Track programs have previously been used to address bioterror threats, pandemic threats, and neglected diseases.\(^{267}\) FDA granted Fast Track status to several Ebola treatments, including TKM-Ebola in 2014\(^ {268}\) and ZMapp in 2015.\(^ {269}\)

A drug company must request Fast Track designation. FDA reviews the request and makes a decision within 60 days. A drug that receives Fast Track designation is eligible for more frequent meetings with FDA to discuss the drug’s development plan; more frequent communication from FDA; accelerated approval and priority review, if certain criteria are met; and rolling review.\(^ {270}\) By opening the lines of communication between the drug company and FDA, Fast Track designation ‘assures that questions and issues are resolved quickly, often leading to earlier drug approval and access by patients’.\(^ {271}\)

Although development times are comparable to other newly approved drugs and biologics, Fast Track-designated products have shorter median approval times.\(^ {272}\)

Due to the challenges associated with developing a drug or vaccine to address a public health emergency, the need for frequent consultation with FDA is likely. Formalizing this process—that is, getting Fast Track designation—can be an ‘important

\(^{262}\) MSF, Ebola to Be Added to List of Neglected Diseases Eligible for US Government Research and Development Incentive, http://www.msfaccess.org/our-work/neglected-diseases/article/2341 (last accessed March 4, 2016).

\(^{263}\) John Carroll, That Priority Review Voucher Program? The FDA Hates It, FIERCE BIOTECH, Mar. 3, 2016, http://www.fiercebiotech.com/story/priority-review-voucher-program-fda-hates-it/2016-03-03 (last accessed March 4, 2016) (‘FDAsaysit’sbeena bust, forcing regulatorstoprioritize drugs that neither are focused on a key health issue nor offer all that much in terms of added safety or efficacy. It’s also a chore to keep up with the mandate.’).

\(^{264}\) Arnold & Pogge, supra note 247, at 230, 231.

\(^{265}\) Id.

\(^{266}\) FDA, Fast Track, http://www.fda.gov/ForPatients/Approvals/Fast/ucm405399.htm (last accessed March 8, 2016).

\(^{267}\) Miline & Tait, supra note 231, at 747.

\(^{268}\) Anna Prior, FDA Fast Tracks Tekmira’s Ebola Drug, THE WALL STREET JOURNAL, Mar. 5, 2014.

\(^{269}\) Debra Goldschmidt, Experimental Ebola Drug ZMapp Gets Fast Track Status from FDA, CNN, Sept. 17, 2015.

\(^{270}\) FDA, supra note 266, at n.p.

\(^{271}\) Id.

\(^{272}\) Miline & Tait, supra note 231, at 741.
milestone’ for a company.\textsuperscript{273} This is not merely a formality. While orphan designation, just addressed, fosters innovation directly, Fast Track designation ‘arguably does so indirectly.’\textsuperscript{274}

An econometric analysis of Fast Track suggests that shortening the arduous path from lab bench to pharmacy shelf can have the following effects: (i) earlier access to cash returns; (ii) cuts in development costs; (iii) allowing a sponsor to gain first mover advantage, ie gender brand loyalty resulting in higher and longer market share; and (iv) earlier launch, and thus longer effective patent life or period of market exclusivity protection.\textsuperscript{275}

Unsurprisingly, Fast Track status is often pursued in conjunction with other development incentives, like orphan drug designation and PRVs.\textsuperscript{276}

The Fast Track process is beneficial to speeding FDA approval, which is a necessary though not sufficient condition for access, and will work best when public health goals are clear. Obviously, such clarity may be difficult to achieve when emerging threats are broadly anticipated but the particulars are unknown. Nevertheless, looking forward, it is important that FDA clearly communicate with drug developers during inter-epidemic periods and suggest they apply for Fast Track designation in order to direct efforts towards advanced planning for accelerating the development and testing of promising interventions when epidemic situations arise.\textsuperscript{277} During the 2014 outbreak it was said that

several vaccines and drugs … have shown promise in animal studies, and some are so far along that human clinical trials could probably have begun at any time in the past several years …. Some of these vaccines have been stuck in this position for 10 years.\textsuperscript{278}

FDA should work closely with sponsors to ensure that promising products are not ‘stuck’ when opportunity knocks. Fast Track designation offers one existing, but thus far underutilized, means of achieving this.

**C. Collaborating with international partners**

In September 2014, the International Coalition of Medicines Regulatory Authorities (ICMRA), of which FDA is a member, issued a statement pledging that regulators would ‘work together internationally to find innovative solutions to facilitate evaluation of and access to potential new medicines to counter Ebola outbreaks’.\textsuperscript{279} ICMRA

\textsuperscript{273} Maggie Fox, \textit{FDA Fast-Tracks Experimental Ebola Drug ZMapp}, NBC News, Sept. 21, 2015, \url{http://www.nbcnews.com/storyline/ebola-virus-outbreak/ebola-drug-zmapp-gets-fda-fast-track-n429156} (last accessed April 14, 2016).

\textsuperscript{274} Milne & Tait, \textit{supra} note 231, at 744.

\textsuperscript{275} \textit{Id.} at 741.

\textsuperscript{276} Cf. Fox, \textit{supra} note 273, at n.p.

\textsuperscript{277} Farrar & Piot, \textit{supra} note 41, at 1545.

\textsuperscript{278} Schlanger & Wolfson, \textit{supra} note 103, at n.p. (internal quotation marks omitted).

\textsuperscript{279} International Coalition of Medicines Regulatory Authorities (ICMRA), \textit{International Coalition of Medicines Regulatory Authorities (ICMRA)—Statement}, Sept. 4, 2014, \url{http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/ucm412785.htm} (last accessed July 28, 2016).
is a relatively new body that brings together heads of NRAs from around the world to enable a shared strategic leadership to address current and emerging global regulatory challenges and to better leverage resources in ways that expand global regulatory reach.

In light of the realization that PHEICs present global regulatory challenges, FDA and others should continue to collaborate in order to identify emerging public health threats that implicate NRAs in a timely fashion, foster synergies and efficiencies between NRAs, reduce duplicative efforts, and, ultimately, regulate within a complex domain in a manner that improves availability of and access to safe and effective medicines. ICMRA has already pledged to support WHO in countering the Zika outbreak by working together and ‘building on ICMRA’s collaborative work on Ebola’. Longer term, ICMRA has stated a goal of establishing a global architecture to support enhanced communication, information-sharing and crisis response. ICMRA will also focus on strengthening regulatory systems and capacity, and increasing awareness of and appreciation for the importance of strong regulatory systems and functions within national, sub-regional, and global contexts.

Such high-level efforts would be beneficial when confronting new and re-emerging public health threats.

During the 2014 EVD outbreak, FDA also worked collaboratively with WHO and its international regulatory counterparts, such as the European Medicines Agency (EMA) and Health Canada, to share information. For instance, FDA entered into a variety of cooperative arrangements. These included international confidentiality commitments (CCs) between FDA and the Ministry of Public Health and Hygiene of Guinea, the Pharmacy Board of Sierra Leone, and the Liberian Medicines and Health Products

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280 ICMRA, International Coalition of Medicines Regulatory Authorities (ICMRA)—Fact Sheet, http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/11/WC500177574.pdf (last accessed July 28, 2016) (discussing origins of ICMRA).
281 John Skierritt et al., Regulatory Collaboration: The International Coalition of Medicines Regulatory Authorities (ICMRA), 29 WHO Drug Info. 3, 4 (2015).
282 Cf. Skierritt et al., supra note 281, passim.
283 ICMRA, International Coalition of Medicines Regulatory Authorities (ICMRA) Statement of Zika Virus, Feb. 9, 2016, http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMIssues/ucm485546.htm (last accessed July 28, 2016).
284 Skierritt et al., supra note 281, at 5.
285 Luciana Borio, Statement Before the Subcommittee on Health: Examining Medical Product Development in the Wake of the Ebola Epidemic, Nov. 19, 2014, http://www.fda.gov/NewsEvents/Testimony/ucm432735.htm (last accessed July 28, 2016).
286 FDA and Ministry of Public Health and Hygiene of Guinea, Statement of Authority and Confidentiality Commitment, Sept. 1, 2015, http://www.fda.gov/downloads/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/UCM461832.pdf (last accessed July 28, 2016).
287 FDA and Pharmacy Board of Sierra Leone, Statement of Authority and Confidentiality Commitment, Mar. 18, 2015, http://www.fda.gov/downloads/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/UCM441396.pdf (last accessed July 28, 2016).
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Regulatory Authority, as well as WHO. A CC is a document that establishes a legal framework for FDA ‘to share certain kinds of non-public information with FDA counterparts in foreign countries and international organizations as part of cooperative law enforcement or regulatory activities’. Such collaborations are intended to support regulatory collaboration, accelerate product development, and contribute to the approval of medical products in the United States and abroad. Bilateral statements of cooperation are already part of the response to Zika.

Additionally, FDA participated in WHO-sponsored consultations ‘with representatives of the international public health community and medical product sponsors, to discuss leading investigational treatments and vaccines for Ebola and key considerations for deployment in West Africa’. And, building on a long-standing collaboration, FDA has encouraged developers of EVD medicines to submit applications for orphan designation to FDA and to the EMA simultaneously so that the agencies can work collaboratively and speed the development process.

Collaborative efforts are and should continue to be an important part of FDA’s response to PHEICs. Working with FDA’s international colleagues both to build the architecture for broad regulatory collaboration and to execute cooperative arrangements in response to particular threats should harmonize and accelerate drug development and approval at home and abroad.

D. Providing general guidance on trial design

As a result of its unique regulatory role, FDA is positioned to identify drug development issues and gaps in drug development processes, and it has employed various means to address such challenges over the years. FDA has, for example, become

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288 FDA and Liberian Medicines and Health Products Regulatory Authority, Statement of Authority and Confidentiality Commitment, Feb. 3, 2015, http://www.fda.gov/downloads/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/UCM441392.pdf (last accessed July 28, 2016).

289 FDA and WHO, Mutual Confidentiality Arrangement and Commitment Not to Disclose Non-Public Information, Aug. 25, 2014, http://www.fda.gov/downloads/InternationalPrograms/Agreements/ConfidentialityCommitments/UCM411602.pdf (last accessed July 28, 2016).

290 FDA, Confidentiality Commitments, http://www.fda.gov/InternationalPrograms/Agreements/ConfidentialityCommitments/ucm2016756.htm (last accessed July 28, 2016).

291 Borio, supra note 285, at n.p.

292 For example, FDA and Brazilian Health Regulatory Agency, Statement of Continued Cooperation Between FDA and ANVISA—Zika Virus Disease, Apr. 11, 2016, http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/ucm495211.htm (last accessed July 28, 2016).

293 Luciana Borio, Statement Before the House Energy and Commerce Committee Subcommittee on Oversight and Investigations: Examining the U.S. Public Health Response to the Ebola Outbreak, Oct. 16, 2014, http://www.fda.gov/NewsEvents/Testimony/ucm422169.htm (last accessed July 28, 2016).

294 FDA, Ebola Response Updates from FDA, http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/ucm410308.htm (last accessed July 28, 2016); see also European Medicines Agency (EMA), Ebola, http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000624.jsp (last accessed July 28, 2016) (containing nearly identical language to FDA website regarding how the agencies collaborate).

295 Ameeta Parekh et al., Catalyzing the Critical Path Initiative: FDA’s Progress in Drug Development Activities, 97 CLIN. PHARMACOL. & THER. 221, 222 (2015).

296 See generally id. (describing FDA’s efforts to modernize its regulatory processes to address challenges in the drug development sector and facilitate drug development).
increasingly involved in designing clinical trials, which ‘reflect[s] the view that the public, the industry, and the FDA are poorly served by drug development efforts that are poorly designed or inadequate and that therefore waste resources and delay availability of therapy’.

FDA acknowledged that the EVD ‘epidemic has highlighted the importance of being able to rapidly evaluate investigational products during a public health emergency, including in resource limited settings’. In an important piece of advocacy, particularly given the ethical and methodological controversies surrounding trial design described in Section II.D above, officials at FDA made the case for RCTs when evaluating Ebola therapies in the *New England Journal of Medicine* in December 2014. Agency officials also outlined the FDA perspective on evaluating medical products for EVD—separating out considerations for vaccines and therapeutic products—in an article in *Clinical Trials*. The officials underscored the need for ‘scientifically valid studies that are ethically acceptable and well conducted to provide timely, interpretable data’.

Additionally, in November 2015, FDA held a workshop in partnership with NIAID, CDC, and the HHS Office of the Assistant Secretary for Preparedness and Response to discuss ‘the scientific, ethical, and practical issues considered in the choice of specific trial designs, and the generalizability of these designs for other types of emerging infectious diseases’. FDA is working to develop ‘a flexible, innovative and adaptive clinical trial protocol that will provide a mechanism for product sponsors and investigators to evaluate multiple investigational products under a common protocol’. I welcome such efforts and encourage FDA to continue to pursue them beyond the 2014 Ebola outbreak.

‘Platform trials’—clinical trials with a master protocol in which multiple treatments are evaluated simultaneously—have been planned and/or implemented in a variety of diseases, including Ebola. Platform trials have the advantage of allowing for standardized data collection and providing for a common statistical analysis plan. As a result, they ‘can find beneficial treatments with fewer patients, fewer patient failures, 297

297 Suzanne White Junod, *FDA and Clinical Drug Trials: A Short History* (2008), [http://www.fda.gov/AboutFDA/WhatWeDo/History/Overviews/ucm304485.htm](http://www.fda.gov/AboutFDA/WhatWeDo/History/Overviews/ucm304485.htm) (last accessed July 29, 2016) (quoting Robert Temple). This reflects a change in the Agency’s prior thinking that ‘too much participation by FDA staff in the development process would leave the Agency unable to be properly neutral and analytical when the resulting data were submitted as part of an NDA’. Id.

298 FDA, *Public Workshop—Clinical Trial Designs for Emerging Infectious Diseases*, [http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/AboutMCMi/ucm466153.htm](http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/AboutMCMi/ucm466153.htm) (last accessed March 7, 2016).

299 Edward Cox, Luciana Borio & Robert Temple, *Evaluating Ebola Therapies—The Case for RCTs*, 371 New Eng. J. Med. 2350 (2014); see also FDA Officials Call for Ebola RCTs, 22 No. 5 GUIDE TO GOOD CLINICAL PRACTICE NEWSL. at 16 (2014).

300 Estelle Russek-Cohen et al., *A US Food and Drug Administration Perspective on Evaluating Medical Products for Ebola*, 13 CLIN. TRIALS 105, 105 (2016).

301 Id.

302 Id.

303 Luciana Borio, *Examining Medical Product Development in the Wake of the Ebola Epidemic*, [www.hhs.gov/asl/testify/2014/11/t20141119b.html](http://www.hhs.gov/asl/testify/2014/11/t20141119b.html) (last accessed April 12, 2016).

304 Benjamin R. Saville & Scott M. Berry, *Efficiencies of Platform Clinical Trials: A Vision of the Future*, 13 CLIN. TRIALS 358, 366 (2016).

305 Id. at 7.
less time, and with greater probability of success than a traditional two-arm strategy’. Moreover, it is easier to show the comparative effectiveness of different experimental interventions in platform trials. Such trials have the additional advantage of having only one control group with numerous experimental arms, which satisfies the need for methodological rigor while also minimizing randomization to control arms, both of which were addressed in Section II, above. A potential drawback to platform trials is that they ‘require considerable coordination of efforts that may be difficult to achieve during an outbreak’. Additionally, pharmaceutical companies might not naturally gravitate to such a trial design because the approach is inherently cooperative, while their industry is inherently competitive. It is important that FDA lend its weight to such a plan and serve as a hub, coordinating between sponsors and investigators.

Furthermore, FDA must continue to collaborate with NRAs and WHO to come up with broad-based solutions that are acceptable to all stakeholders. FDA can and should use the interepidemic period to address transparently the practical, scientific, and ethical issues presented by such a trial design—many of which were addressed in Section II—and build consensus behind its choices. I stress that the process of consensus-building will require FDA to examine and synthesize the emerging literature on conducting research in public health emergencies. Understandably, a number of concerns were raised about researchers’ ability to adhere to ethical principles while conducting research in the midst of the 2014 Ebola outbreak. The urgent demand for use of experimental interventions coupled with the complex dynamics of the outbreak itself made it difficult to be confident that standard subject protections were in place. Such concerns are particularly potent when the potential population of research subjects is inherently vulnerable, such as patients in resource-limited settings.

306 Id.
307 Judy Stone, *Are Placebos Ethical In Ebola Trials?*, Forbes, Dec. 30, 2014, http://www.forbes.com/sites/judystone/2014/12/30/are-placebos-ethical-in-ebola-trials/#14a3361945e5 (last accessed April 12, 2016).
308 Lori E. Dodd et al., *Design of a Randomized Controlled Trial for Ebola Virus Disease Medical Countermeasures: PREVAIL II, The Ebola MCM Study*, 213 J. INFECT. DIS. 1906, 1913 (2016).
309 For example, Philippe Calain et al., *Research Ethics and International Epidemic Response: The Case of Ebola and Marburg Hemorrhagic Fevers*, PUBLIC HEALTH ETHICS (2009); Bausch et al., supra note 148; CIOMS, *REVISION OF CIOMS 2002 INTERNATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS: DRAFT GUIDELINES* (2015), http://www.cioms.ch/images/stories/guidelines_demo/AllGuidelines-1-25.pdf (last accessed January 4, 2016) (Proposed Guideline 20, Research in Disaster Situations).
310 Ebola was discussed at Meeting Twenty of the Presidential Commission for the Study of Bioethical Issues. *PRESIDENTIAL COMMISSION FOR THE STUDY OF BIOETHICAL ISSUES, Ebola*, Feb. 5, 2015, http://www.bioethics.gov/taxonomy/term/213 (last accessed August 31, 2016). Laura Seay, *Ebola, Research Ethics, and the ZMapp Serum*, The Washington Post, Aug. 6, 2014, http://www.washingtonpost.com/blogs/monkey-cage/wp/2014/08/06/ebola-research-ethics-and-the-zmapp-serum/ (last accessed July 28, 2016); Andrew Hantel & Christopher O. Olopade, *Drug and Vaccine Access in the Ebola Epidemic: Advising Caution in Compassionate Use*, 162 ANN. INTERN. MED. 141, 141 (2015) (‘The belief that informed consent is understood by patients naive to advanced health care, especially in an epidemic, is cavalier’); Arthur Caplan, *Bioethicist: Experimental Ebola Treatment Endorsed, but Who Gets It?*, NBC News, Aug. 12, 2014, http://www.nbcnews.com/storyline/ebola-virus-outbreak/bioethicist-experimental-ebola-treatment-endorsed-who-gets-it-n178691 (last accessed July 28, 2016) (asking if third parties can consent for children, persons with poor education, prisoners, or others who might wish to try or be eligible for unapproved drugs); Tracy Hampton, *Largest-Ever Outbreak of Ebola Virus Disease Thrusts Experimental Therapies, Vaccines into Spotlight*, JAMA (2014) (noting that ‘obtaining adequate informed consent would be a [sic] challenging in resource-limited settings’).
participants is vulnerable, and the perceived legitimacy of clinical research may affect
the uptake of clinical care.311

FDA can—and must—continue to play an active role in ensuring adequate protec-
tions for research participants in public health emergencies. While it has the power
to require adherence to GCPs in domestic and foreign trials used for getting FDA ap-
proval, additional constraints on clinical research conducted in public health emergen-
cies should be considered. While it is beyond the scope of this paper to elaborate on
such protections, I will offer some initial comments. First, it may be necessary to more
rigorously distinguish research regarding treatment from research pertaining to pre-
vention in outbreak situations.312 Furthermore, EVD is a public health emergency that
can be controlled—and must be addressed—through public health measures. In de-
developed countries, the use of local infrastructure and human resources by research studies
generally does not interfere with the provision of healthcare; however, this may not be
true in developing countries. For instance, research activities might take up space in
a local clinic or require the staff’s time and attention, thereby reducing the availability
of clinical care. This can be of particular concern in a public health emergency in de-
developed countries, where a disease outbreak places additional burdens on the already
strained local healthcare infrastructure.313 Research should be allowed only when it will
not make research subjects or the host community prospectively worse off.314 If clinical
research takes place, it must be conducted in parallel with the components of outbreak
control.315

Additionally, FDA must confront the ethical challenges that surround the inclusion
of special populations in clinical research conducted during public health emergencies.
For example, pregnant women—and by extension their fetuses—should be enrolled in
Zika-related drug and vaccine trials. A pregnant woman can pass Zika virus to her fe-
tus, and CDC has concluded that Zika is a definitive cause of birth defects.316 Yet, it
has rightly been observed that there is no broadly accepted ethical framework for the
inclusion of pregnant women in clinical research, and this has had a ‘chilling effect’ on
academic and industry-led research in pregnancy.317 The inclusion of pregnant women
introduces legal and ethical wrinkles into trial design that should be resolved proactively
and transparently.

311 For example, Pollack, supra note 175, at n.p.
312 See Angus J. Dawson, Ebola: What It Tells Us About Medical Ethics, 41 J. MED. ETHICS 107, 108 (2014) (cri-
tiquing WHO for treating ‘drugs and vaccines as though they can be considered as a single issue, for treatment
and prevention actually raise quite different questions’).
313 See eg Hantel & Olopade, supra note 310, at 141.
314 David Wendler, Ezekiel J. Emanuel & Reidar K. Lie, The Standard of Care Debate: Can Research in Developing
Countries Be Both Ethical and Responsive to Those Countries’ Health Needs?, 94 AM. J. PUB. HEALTH 923 (2004).
315 See generally, Bausch et al., supra note 148.
316 Liz Szabo, Study: Zika May Affect Babies Even in Later Stages of Pregnancy, USA TODAY, Apr. 14,
2016, http://www.usatoday.com/story/news/2016/04/13/study-zika-may-affect-babies-even-later-stages-
pregnancy/82987460/ (last accessed April 14, 2016).
317 Saad B. Omer & Richard H. Beigi, Pregnancy in the Time of Zika: Addressing Barriers for Developing Vaccines
and Other Measures for Pregnant Women, 315 JAMA 1227, 1227 (2016); see generally Mary C. Blehar et al.,
Enrolling Pregnant Women: Issues in Clinical Research, 23 WOMEN’S HEALTH ISSUES e39 (2013) (providing
historical background of pregnant women’s exclusion from clinical research).
E. Considering alternative approval pathways

FDA considered use of alternative drug efficacy testing pathways as it became apparent that conducting RCTs would be infeasible due to the epidemiological trajectory of the 2014 outbreak.318 If conditions do not allow phase 3 trials to proceed, FDA has two other licensing pathways: accelerated approval319 and the ‘animal rule’.320

FDA’s power to grant accelerated approval comes out of the

Food and Drug Administration Safety Innovations Act (FDASIA) [of 2012]. Section 901 of FDASIA amends the [FD&C] Act … to allow the FDA to base accelerated approval for drugs for serious conditions that fill an unmet medical need on whether the drug has an effect on a surrogate or an intermediate clinical endpoint.321

Like traditional approval, accelerated approval has ‘the same requirements for demonstration of safety and consistency of manufacture’.322

The Animal Efficacy Rule or ‘Animal Rule’ was introduced in the wake of the 9/11 attacks.323 Though concerns about bioterrorism constituted the original impetus for the rule, the final guidance, issued in October 2015, clarifies that products intended to address threats from emerging infectious pathogens would also be eligible.324 Use of the animal rule as a regulatory pathway to approval is intended for drugs developed to ameliorate or prevent serious or life-threatening conditions caused by chemical, biological, radiological, or nuclear substances regardless of whether the substances are considered potential threat agents for deliberate exposure (e.g., nerve agent, Bacillus anthracis) or threats to individuals’ health from accidental exposure (e.g., emerging infectious pathogens, snake venom, industrial chemicals), provided that human efficacy studies are not ethical and field trials to study effectiveness of the drug are not feasible.325

318 For example, the Agency’s Vaccines and Related Biological Products Advisory Committee (VRBPAC) considered ‘whether, if an Ebola vaccine was approved through an alternative pathway, what approaches post-marketing studies would need to show vaccine benefits’. Schnirring, supra note 219, at n.p.

319 21 CFR 601.40–41 (2016) (biologics).

320 21 CFR 314. 600–650 (2016) (drugs); 21 CFR 601.90–91 (2016) (biologics).

321 FDA, Accelerated Approval, http://www.fda.gov/ForPatients/Approvals/Fast/ucm405447.htm (last accessed March 4, 2016) A surrogate endpoint used for accelerated approval is a marker - a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. Likewise, an intermediate clinical endpoint is a measure of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on irreversible morbidity and mortality (IMM).

322 Doran L. Fink, Approaches to Demonstrating Effectiveness: Considerations for Ebola Vaccines, May 12, 2015, at 3, http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM451561.pdf (last accessed March 4, 2016).

323 Elie Dolgin, Animal Rule for Drug Approval Creates a Jungle of Confusion, 19 NAT. MED. 118, 118 (2013).

324 HHS, FDA, Product Development Under the Animal Rule: Guidance for Industry (Oct. 2015), http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm399217.pdf (last accessed August 30, 2016).

325 Id.
For FDA to apply the animal rule, the agency would first have to determine that approval is not possible through traditional or accelerated approval. Use of the animal rule can be considered on a product-by-product basis.

The Animal Rule pathway is best understood as a compromise: the investigational product is tested in humans under existing requirements for establishing the safety of new drugs, while determinations of efficacy are based on ‘animal efficacy studies when the results of those studies establish that the drug is reasonably likely to produce clinical benefit in humans’. The Animal Rule was not intended to make FDA approval for novel MCMs easier to obtain. To the contrary, investigators may need to ‘develop, test and validate animal models, in addition to determining the efficacy and optimal dose of their countermeasures’, and testing in multiple animal species is usually required.

Before the animal rule, licensure was often not possible for therapies responsive to emerging, sporadically occurring diseases. FDA has, to date, approved only a handful of products under this pathway, which suggests that its effect has—in practice—been modest. There was, however, an increase in Animal Rule-based approvals beginning in 2012, suggesting ‘FDA’s growing appreciation of the real threats to the U.S. population from infectious disease outbreaks’. Several Ebola treatments were developed under the Animal Rule. For example, in July 2016, RedHill Biopharma announced its collaboration with NIH to evaluate an experimental therapy for EVD; RedHill explained that it expected to gather data to pursue FDA approval under the animal

326 WELLCOME TRUST & CIDRAP, supra note 122, at 12.
327 Id.
328 FDA, supra note 325, at 2.
329 Gigi K. Gronvall et al. on behalf of the Alliance for Biosecurity, The FDA Animal Efficacy Rule and Biodefense, 25 NAT. BIOTECHNOL. 1084, 1085 (2007).
330 Id. at 1084.
331 Id. at 1084.
332 Alexander Gaffney, FDA Grants Approval to New Drug Under Rarely Used Animal Rule Pathway, RAPS, May 11, 2015, http://www.raps.org/Regulatory-Focus/News/2015/05/11/22135/FDA-Grants-Approval-to-New-Drug-Under-Rarely-Used-Animal-Rule-Pathway/ (last accessed July 28, 2016).
333 Gail H. Javitt, What Does the Future Hold for the Animal Rule? Examining FDA’s Final Guidance, PHARMTECH.COM, Feb. 3, 2016, http://www.pharmtech.com/what-does-future-hold-animal-rule-examining-fdas-final-guidance (last accessed July 28, 2016).
334 FDA, supra note 325, at 4; see also GAVI, Report to the Board 10–11 June 2015: Ebola Vaccine and Mitigation Plan, http://www.gavi.org/about/governance/gavi-board/minutes/2015/10-june/minutes/14—ebola-vaccine-and-mitigation-plan/ (last accessed July 28, 2016) (observing that use of the animal rule was a ‘subject of considerable debate . . . as immune correlates of protection have not been unambiguously identified, animal models have not been validated[,] and the perceived risk-benefit balance . . . keeps shifting with the further waning of the epidemic’).
335 In the case of vaccines, there is ‘[n]o scientifically well-established immunologic marker that predicts protection’ against EVD. Fink, supra note 322, at 5.
336 Stephen Strauss, Biotech Drugs Too Little, Too Late for Ebola Outbreak, 32 NAT. BIOTECHNOL. 849, 850 (2014) (‘Thus far, the Mapp, Tekmira and BioProtection Systems products have been approved for emergency use through the FDA’s animal rule.’).
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At present, drugs and vaccines for EVD remain at the stage of investigational products, which will be inadequate if another Ebola outbreak occurs. The animal rule may represent the best chance to develop MCMs before they are needed, despite the fact that it will not be possible to be certain a drug will actually work when it is needed. Recognizing that sporadic outbreaks, uncertain epidemiological trajectories, small patient populations, and clinical uncertainty may make it difficult to collect data in epidemics, FDA should be transparent about the conditions under which alternative pathways will be considered and what the tradeoffs are between certainty and access.

FDA can further improve its response by actively building scientific consensus around animal models for specific disease threats, if possible; there are no well-characterized animal models for many potential threats to public health. Moreover, companies will need FDA to provide guidance for modeling special populations that may be affected by new and re-emerging threats to public health, such as children and the elderly.

Various offices within FDA use the animal rule, which could lead to divergent interpretations. Processes should be put into place to ensure consistent interpretation of the animal rule within the agency. Ideally, requirements and expectations for non-traditional approval pathways would be harmonized across NRAs. More drugs might be in the pipeline if the rules were clearer. Nevertheless, use of the animal rule will entail a complex and iterative process. As a result, communication between developers and FDA should be frequent and ongoing.

Finally, approval under either accelerated approval or the animal rule pathway would require that post-licensure studies be conducted in the future to verify and describe clinical benefit. FDA—in conjunction with others—should offer guidance to companies preparing these studies.

F. Authorizing compassionate use of drug products

‘Compassionate use’, or expanded access, ‘is the use of investigational new drug products outside of clinical trials to treat patients with serious or immediately life-threatening diseases or conditions when there are no comparable or satisfactory alternative treatment options’. FDA has mechanisms for allowing expanded access to

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337 RedHill Biopharma, RedHill Announces Research Collaboration with NIH for Potential Ebola Treatment, July 13, 2016, http://ir.redhillbio.com/releasedetail.cfm?releaseid=979304 (last accessed July 28, 2016).
338 Id.
339 Gronval et al., supra note 331, at 1085, 1086.
340 Id. at 1085.
341 Id. at 1086.
342 WELLCOMETRUST & CIDRAP, supra note 122, at 23.
343 Dolgin, supra note 323, at 119.
344 WELLCOMETRUST & CIDRAP, supra note 122, at 12.
345 Gronval et al., supra note 331, at 1085.
346 FDA, IND Applications for Clinical Treatment (Expanded Access): Overview, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm351748.htm (last accessed January 8, 2016). See also 21 CFR 312 Subpart I (2016).
individuals, intermediate-size patient populations, and widespread populations.\textsuperscript{347} During the Ebola outbreak, the focus was on expanding individual access.

A physician can request to use an investigational product for a single patient via an Emergency Investigational New Drug (EIND) application.\textsuperscript{348} An EIND may be granted if the ‘physician considers the product may be urgently needed for the patient’s serious or life-threatening condition; no satisfactory alternative therapy is available; and the patient cannot receive the product through any existing clinical trials or expanded access protocols’.\textsuperscript{349} An EIND request can be authorized by the agency ‘within a very short period of time, depending on the urgency of the situation and the nature of the available information’.\textsuperscript{350} FDA cannot, however, compel a drug company to give a patient access to an experimental drug; the company that produces the drug must agree to provide it.

In 2014, EINDs were granted for several investigational therapeutic candidates, such as ZMapp, TKM-Ebola, and Brincidofovir.\textsuperscript{351} As discussed in Section II, compassionate use is potentially at odds with conducting socially valuable, scientifically rigorous research to benefit future patients. For example, two American aid workers, Brantly and Writebol, were transferred from West Africa to Emory University Hospital in Atlanta, Georgia, where they received ZMapp under a compassionate use exemption

\textsuperscript{347} FDA, Expanded Access: Information for Patients, http://www.fda.gov/ForPatients/Other/ExpandedAccess/ucm2004176.htm#different-types (last accessed March 4, 2016).

\textsuperscript{348} In Feb. 2015, FDA released a draft guidance document, Individual Patient Expanded Access Applications: Form 3926, announcing a move toward a ‘streamlined alternative’ for submitting individual patient expanded access applications. FDA estimated that the new form, ‘when finalized, will require only eight elements of information and a single attachment. We estimate that physicians will be able to complete the finalized version of the form in just 45 minutes, as compared to the 100 hours listed on the previous form’. Alexander Gaffney, From 100 Hours to 1: FDA Dramatically Simplifies its Compassionate Use Process, Feb. 4, 2015, http://www.raps.org/Regulatory-Focus/News/2015/02/04/21243/From-100-Hours-to-1-FDA-Dramatically-Simplifies-its-Compassionate-Use-Process/ (last accessed March 4, 2016).

\textsuperscript{349} FDA, Emergency Investigational New Drug (EIND) Applications for Antiviral Products, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm090039.htm (last accessed January 8, 2016).

\textsuperscript{350} Alexander Gaffney, Regulatory Explainer: What You Need to Know About the Regulation of Ebola Treatments, Aug. 7, 2014, http://www.raps.org/Regulatory-Focus/News/2014/08/07/19977/Regulatory-Explainer-What-You-Need-to-Know-About-the-Regulation-of-Ebola-Treatments/ (last accessed March 7, 2016).

\textsuperscript{351} FACTSHEET: Update on the Ebola Response, Dec. 2, 2014, https://www.whitehouse.gov/the-press-office/2014/12/02/fact-sheet-update-ebola-response (last accessed January 8, 2016). There were concerns that, due to the high-profile nature of the Ebola outbreak, Brantly, Whitebol, and others were able to circumvent the mandated process quickly. Boyd, supra note 173, at n.p. The Goldwater Institute, a libertarian think tank which developed the model for ‘Right-to-Try’ legislation adopted in several states, filed a Freedom of Information Act request with FDA seeking information about the internal decision-making process used by FDA to allow Brantly and Whitebol access to ZMapp. FDA Denies FOIA Request on Use of Experimental Ebola Drug, 22 No. 3 GUIDE TO GOOD CLINICAL PRACTICE NEWSL. at 9. Significantly, the Institute ‘never objected to the fact that the missionaries received the medication, but has questioned whether the agency provided favorable treatment and sought to obtain FDA records about the ZMapp decision’. Ed Silverman, Think Tank Sues FDA for Compassionate Use Documents for an Ebola Drug, THE WALL STREET JOURNAL, June 10, 2015, http://blogs.wsj.com/pharmalot/2015/06/10/think-tank-sues-fda-for-compassionate-use-documents-for-an-ebola-drug/ (last accessed March 3, 2016). The agency denied the request, saying that release of the information would violate trade secrets. Id.
from FDA. Brantly and Writebol ultimately recovered. While their recoveries were encouraging, it was not possible to reach a sound conclusion about ZMapp’s safety or efficacy on the basis of Brantley’s and Writebol’s experiences alone. At the time, Dr. Bruce Ribner, director of Emory’s Infectious Disease Unit acknowledged, ‘There is no prior experience with [ZMapp], and frankly, we do not know whether it helped them, whether it made no difference, or even, theoretically if it delayed their recovery.’

Compassionate use provided no clear evidence that experimental interventions like ZMapp were actually superior to supportive care, nor did compassionate use foreclose the possibility that they were inferior. Yet, in the 2014 outbreak, quantitates of experimental interventions were extremely limited. For instance, by August 2014, supplies of ZMapp had been exhausted. Given that it was not possible to conduct a valid RCT with so few doses, compassionate use was not necessarily inappropriate, though it still raised questions about fairness in the allocation of a scarce resource, an issue addressed above.

The decision to allow compassionate use during the 2014 EVD outbreak was further complicated by the reality confronted by researchers on the ground: ‘the same volatile mix of skepticism, fear, false rumor, and understandable mistrust that helped spread Ebola in the first place.’ Many argued that West African communities would require some degree of demonstrated efficacy in humans to alleviate their ‘significant suspicion of outbreak response teams, including researchers.’ Moreover, as ‘there hadn’t been human trials, no one wanted to appear to be experimenting on an African.’ It was decided, for example, not to give Dr. Sheik Humarr Khan, a Sierra Leonean physician who

352 CBS News, ‘Miraculous day’: American Ebola Patients Discharged From Atlanta Hospital, Aug. 21, 2014, 11:12 am, http://www.cbsnews.com/news/ebola-patients-kent-brantly-and-nancy-writebol-discharged-from-hospital/ (last accessed January 6, 2015).

353 Id.

354 Jesse L. Goodman, Studying ‘Secret Serums’—Toward Safe, Effective Ebola Treatments, 371 NEW ENG. J. MED. 1086, 1087 (2014).

355 Maggie Fox, What Cured Ebola Patients Kent Brantly and Nancy Writebol?, NBC NEWS, Aug. 21, 2014, http://www.nbcnews.com/storyline/ebola-virus-outbreak/what-cured-ebola-patients-kent-brantly-nancy-writebol-n186131 (last accessed January 9, 2016). Underscoring Dr. Ribner’s point, a Spanish priest and a Liberian doctor who also received ZMapp subsequently died. Donald G. McNeil, Jr., Liberian Doctor Treated With an Experimental Drug Dies From Ebola, THE NEW YORK TIMES, Aug. 25, 2014, http://www.nytimes.com/2014/08/26/world/africa/liberian-doctor-treated-with-an-experimental-drug-dies-from-ebola.html (last accessed January 9, 2016).

356 WHO, Anecdotal Evidence About Experimental Ebola Therapies, Aug. 21, 2014, http://who.int/mediacentre/news/ebola/21-august-2014/en/ (last accessed March 4, 2016).

357 Cf. Dywer, supra note 91, at n.p. (‘A large quantity of a safe and effective Ebola drug preferentially withheld from black African nonprofessionals would constitute a grave injustice, but that is not what has happened, because there is simply not much of anything to be withheld.’).

358 Norimitsu Onishi & Sheri Fink, Vaccines Face Same Mistrust That Fed Ebola, THE NEW YORK TIMES, Mar. 13, 2015, http://www.nytimes.com/2015/03/14/world/af rica/ebola-vaccine-researchers-fight-to-overcome-public-skepticism-in-west-africa.html?_r=0 (last accessed August 1, 2016) (noting also the layer of mistrust directed at governments, which are important research partners).

359 Bausch et al., supra note 148, at 156; see also Jenna McLaughlin, Ebola’s Legacy: A Potentially Horrifying Measles Outbreak in West Africa, MOTHER JONES, Mar. 12, 2015, http://www.motherjones.com/politics/2015/03/ebola-measles-vaccination-study-west-africa (last accessed August 1, 2016).

360 Orent, supra note 91, at n.p. In the midst of the EVD outbreak, an African scientist wrote, ‘[D]isease outbreaks in Africa have become opportunities for foreign researchers to fine-tune their skills, enabling them to solve African problems, doing for Africa what African scientists should be doing for Africa’; he noted that African
contracted Ebola after caring for more than 100 Ebola patients, the first experimental dose of ZMapp. Shortly after Dr. Kahn’s death, Writebol and Brantley were treated with ZMapp and survived. While some research was ultimately conducted in West Africa, a great deal of effort was required to build public trust and convince people that it was safe to enroll. For example, several Liberian doctors invited local news media to film them being vaccinated with a new Ebola vaccine.

In future public health emergencies, should exemptions be offered for compassionate use, ‘distribution of scarce interventions must be conducted with careful ethical guidance and regulatory review’. However, if sufficient doses are available, use should generally be limited to clinical trials. Efforts should be made in interepidemic periods to ensure that sufficient doses are available for clinical research when the opportunity arises. While this is beyond the current powers of FDA, some of the ‘push’ incentives and pre-planning described above could be aimed at stockpiling doses for use in future clinical investigations. This is part of making sure that promising drugs are not ‘stuck’ when opportunity knocks.

Although the focus was on expanding access for single patients in the EVD outbreak, group-level expanded access to unapproved drugs should also be considered in future public health emergencies. This would not be an alternative but rather an adjunct to clinical trials. While FDA has permitted almost all expanded access requests, practical challenges pose barriers to widespread implementation of expanded access programs. These challenges include administrative and financial burdens to industry, as well as liability exposure and possible negative effects on ongoing development and regulatory approval efforts. Regulatory policy should be examined to remove such obstacles.

G. Addressing repurposing and off-label use of approved drugs
As described in Section I, there was interest in the repurposing and off-label prescribing of FDA-approved drugs in the 2014 EVD outbreak because there was a dearth of other treatment options. Repurposing and off-label use hold the potential to address concerns about development, approval, and accessibility and should not be overlooked as vital tools in the effort to combat new and reemerging public health threats. Although they were not a significant part of FDA’s response to EVD, they should be harnessed going forward.

1. Repurposing
Repurposing is the further development of a drug that is already FDA approved for a wholly new indication. Repurposing is ‘a far “easier lift”’ for drug developers than

\[\text{scientists were ‘reduced to mere sample collectors and impotent contributers’. Oyewale Tomori, Will Africa’s Future Epidemic Ride on Forgotten Lessons from the Ebola Epidemic?, 13 BMC MED. 116, 119 (2015).}\]
\[\text{Id.}\]
\[\text{Id.}\]
\[\text{Onishi & Fink, supra note 358, at n.p.}\]
\[\text{Fauci, supra note 7, at 1086.}\]
\[\text{See generally, Jonathan J. Darrow et al., Practical, Legal, and Ethical Issues in Expanded Access to Investigational Drugs, 372 NEW ENG. J. MED. 279 (2015); Jess Rabourn, Creating A Landscape for Patient Engagement, CLINICALTRIALSARENA, July 14, 2016, http://www.clinicaltrialsarena.com/news/operations/creating-a-landscape-for-patient-engagement-4950337 (last accessed August 1, 2016).}\]
\[\text{Darrow et al., supra note 365, passim.}\]
beginning with a wholly new compound because these drugs “have already been subjected to pre-clinical … testing and are already deemed to be pharmacologically active, effective and safe in some clinical context”.\textsuperscript{367} Moreover, results from the clinical trials sometimes indicate that the drug may have effects on similar conditions or viruses transmitted via similar mechanisms. Repurposing speeds development, which hopefully translates to approval and availability sooner than would otherwise be possible. It is thus a means of filling in gaps in our drug arsenal that is beneficial to pharmaceutical companies and consumers alike. How might FDA promote this practice for public health threats?

In 2010, FDA launched an orphan drug disease development database to encourage manufacturers to develop drugs for rare diseases by identifying products that have already received FDA approval and that have potential to treat rare diseases through added indications’.\textsuperscript{368} This database, the Rare Disease Repurposing Database (RDRD), is still in its Beta version.\textsuperscript{369} In future iterations, it should be expanded to include products that have potential to treat NTDs and other public health threats, which may not be rare diseases as statutorily defined in the Orphan Drug Act but which need to be addressed nonetheless. Such a database may help with the identification and development of promising compounds during interemergency periods, and as has been repeatedly stressed above, would allow for the advanced planning that is needed if clinical research can only be practicably and/or ethically conducted during an outbreak. FDA could also urge companies to move forward with particularly promising compounds, as it has said it will do for rare diseases.\textsuperscript{370}

Some have criticized the RDRD because it failed to address the need to incentivize manufacturers to incur the cost of repurposing.\textsuperscript{371} Yet, such a database would be complemented by other ‘push’ and ‘pull’ incentives, such as orphan drug designation, PRVs, and fast-track approval.

2. Off-label use

FDA does not regulate the practice of medicine, and doctors can prescribe FDA-approved drugs for treatment regimens or patient populations that are not listed in the FDA-approved labeling.\textsuperscript{372} It is, therefore, unsurprising that FDA did not vigorously address off-label use as part of its response to the 2014 outbreak. In anticipation of future public health emergencies, however, FDA should do more to promote research into off-label uses, and ideally, work to expand product labeling so that safe and effective off-label uses are included in FDA-approved labeling.

\textsuperscript{367} Shannon Gibson & Barbara von Tigerstrom, *Orphan Drug Incentives in the Pharmacogenomic Context: Policy Responses in the US and Canada*, 2 J LAW BIOSCI. 263, 282 n.139 (2015) (quoting FDA, A Valuable Resource for Drug Developers: The Rare Disease Repurposing Database (RDRD)).

\textsuperscript{368} Tim Mackey & Byan A. Liang, *Off-Label Promotion Reform: A Legislative Proposal Addressing Vulnerable Patient Drug Access and Limiting Inappropriate Pharmaceutical Marketing*, 45 U. MICH. J. L. REFORM 1, 15 (2011).

\textsuperscript{369} FDA, supra note 367, at n.p.

\textsuperscript{370} Amy D. Marcus, *FDA Database Aims to Spark Orphan-Disease Drug Development*, WALL STREET JOURNAL, June 18, 2010, http://blogs.wsj.com/health/2010/06/18/fda-database-aims-to-spark-orphan-disease-drug-development/ (last accessed April 13, 2016).

\textsuperscript{371} Mackey & Liang, supra note 368, at 15.

\textsuperscript{372} See generally FDA, *Off-Label’ and Investigational Use of Marketed Drugs, Biologics, and Medical Devices—Information Sheet*, http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm (last accessed March 7, 2016).
Many of the arguments made in Section II in favor of research regarding experimental interventions apply with equal force to off-label uses. Research is important because any given off-label use may not be beneficial and could, in fact, be harmful. Truly novel off-label uses are ‘unlikely to be supported by strong evidence regarding efficacy and safety, even if the drug itself has been on the market for more than 3 to 5 years.’ In the 2014 EVD outbreak, for example, concerns were specifically raised about the risks, like organ failure, of using statins off-label to treat complications of EVD.374 Elsewhere, I have argued that when an off-label use has a very low certainty of net benefit, it generally should be limited to the context of research protocols.375 This research does not necessarily need to be conducted by drug companies, and information about off-label uses can be disseminated through medical journals.376 It is important, at a minimum, that FDA champion such research.

FDA could also consider incentivizing pursuit of FDA approval for a new indication on an already approved drug. Adding ‘additional indications for an already approved medication requires the proprietor to file a supplemental drug application, and, even if eventually approved, revenues for the new indication may not offset the expense and effort of obtaining approval’.377 First, the effective patent life of a drug may be expired or near expiration by the time a manufacturer could benefit from a successful supplemental NDA.378 Second, a manufacturer is generally able to profit from off-label prescriptions whether or not it pursues a labeling change.379 If a drug is already off patent, there may be inadequate funding for generic medications to pursue FDA approval.380 Thus, ‘push’ and ‘pull’ mechanisms should be considered to allow for the immediate repurposing of existing FDA-drugs while also incentivizing the accretion of socially valuable knowledge. Changes to FDA-approved labeling are not, however, necessary as long as high-quality information about off-label uses is being pursued and disseminated along other channels.

FDA’s response to the 2014 EVD outbreak highlights the agency’s panoply of powers and demonstrates the flexibility of its regulatory framework. While I have just evaluated FDA’s response in terms of its constituent parts and suggested ways in which each could be further strengthened, the overall package of responses must also be evaluated in terms of how it met the three overarching goals of drug development, approval, and accessibility. Although some view FDA approval as the bottleneck, this misconstrues

373 Largent et al., supra note 113, at 1745 (internal citations omitted) (giving the example of Fen-Phen).
374 Fast-tracking Treatments: The Hunt for Ebola Medicines is Being Accelerated, THE ECONOMIST, http://www.economist.com/news/science-and-technology/21616888-hunt-ebola-medicines-being- accelerated-fast-tracking-treatments (last accessed February 29, 2016).
375 Largent et al., supra note 113, at 1746.
376 This implicates a larger literature on publication bias and first amendment issues for off-label promotion, which I will not touch upon here.
377 Christopher M. Wittich, Christopher M. Burkle & William L. Lanier, Ten Common Questions (And Their Answers) About Off-Label Drug Use, 87 MAYO CLIN. PROC. 982, 986 (2012). According to 21 C.F.R. 312.2(b)(1), the clinical investigation of a marketed drug or biologic does not require submission of an IND if six conditions are met.
378 Mitchell Oates, Facilitating Informed Medical Treatment Through Production And Disclosure of Research Into Off-Label Uses of Pharmaceuticals, 80 N.Y.U. L. REV. 1272, 1285 (2005).
379 Id.
380 Id.
the problem. The two biggest problems within the purview of FDA to address are drug development—that is, drugs are not being developed and must pass through clinical trials before FDA can approve them—and post-approval access—once drugs are approved, there is no guarantee they will go where they are most needed. These are the areas in which, viewing the response as a whole, there are the greatest deficiencies and the greatest possibilities for improvement.

Meeting these goals is not the sole responsibility of FDA, and, in fact, I have suggested above that FDA is not always the actor best positioned to address these problems. The primary locus of the federal government’s mission to develop drugs is, for instance, elsewhere: particularly at NIH and BARDA. Nevertheless, it is possible for FDA to work both alone and in concert with others to further each of these ends. Given FDA’s stature nationally and internationally, the agency has the potential to be a powerful advocate for change, and congressional action could further strengthen its position.

CONCLUSION
The 2014 Ebola outbreak in West Africa constituted a public health emergency of international concern. FDA was one of the crucial players in the aftermath of the outbreak because there was a need for and emphasis on developing experimental therapies to supplement the current standard of care. As this paper has emphasized, FDA employed a wide swath of the regulatory mechanisms available to it to protect and promote the public health. This entailed collaboration with the medical and scientific community, industry, international organizations, and other regulators. Considering that FDA in meaningful ways started from behind as the Ebola outbreak unfolded, the end result was a generally effective response. Even now, however, there are no FDA-approved vaccines or drugs for prevention or treatment of Ebola. Moreover, there are concerns about other emerging and re-emerging diseases. The challenges FDA encountered to drug development, approval, and access in the midst of the 2014 outbreak will be encountered again, repeatedly. Looking forward, FDA will have ongoing opportunities to take a leadership role in public health emergencies nationally and internationally. Lessons drawn from the 2014 outbreak should be used to adapt accordingly.

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