

Untested Drugs to Treat Ebola: A Case of Uncompassionate Compassionate Use?

STACEY B. LEE, J.D.*

This Article examines the FDA's Expanded Access or, as they are commonly referred to, "compassionate use" regulations. The purpose of these regulations is to provide access to promising unapproved drugs without exposing patients to unnecessary risk, jeopardizing on-going clinical trials, or delaying the development of new medication for marketing approval. However, since their enactment over thirty years ago, Expanded Access regulations have been a continual source of criticism from patients, pharmaceutical manufacturers, and physicians alike. In response, the FDA has repeatedly tried to find the appropriate balance between authorizing access to experimental treatments and ensuring the integrity of the drug approval process. Beginning with the recent Ebola outbreak and then continuing the discussion to include other practical and legal issues central to Expanded Access debate, this Article posits that, in large part, the FDA's balancing efforts have failed. Next, this Article sets forth an Expanded Access regulatory framework that reconciles a patient's desire to access experimental therapies and society's interest in the efficient development of new drugs to treat life-threatening conditions while protecting vulnerable patients from unnecessary risks. In doing so, this Article concludes by striking that elusive balance.

I. INTRODUCTION

In August 2014, the Ebola viral disease ("EVD") epidemic that ravaged West Africa was featured prominently in U.S. news after two American humanitarian workers, Dr. Kent Brantly and missionary Nancy Writebol, contracted the disease.¹ In an effort to save their lives, the doctor and missionary received ZMapp, an unapproved experimental monoclonal antibody derived from mice.² In the weeks and months that followed, the media chronicled Brantly and Writebol's treatment and attributed their

* Stacey B. Lee is an assistant professor at the Johns Hopkins Carey Business School in Baltimore, Maryland. She can be contacted at staceyb.lee@jhu.edu.

1. Sheri Fink, *3 Liberian Health Workers with Ebola Receive Scarce Drug After Appeals to the U.S.*, N.Y. TIMES (Aug. 16, 2014), <http://www.nytimes.com/2014/08/17/world/africa/three-liberian-health-workers-get-experimental-ebola-drug.html>.

2. *Id.*; Jacque Wilson & Danielle Dellorto, *9 Questions About This New Ebola Drug*, CNN (Aug. 5, 2014, 8:20 PM), <http://www.cnn.com/2014/08/04/health/ebola-drug-questions/>.

healthy recovery to the availability of experimental drugs through “Expanded Access,” commonly referred to as “Compassionate Use” type protocols.³

By early 2015, U.S. coverage of the Ebola outbreak had largely faded from public view.⁴ Content that the possibility of an Ebola epidemic in North America was unlikely and amid reports that the handful of U.S. cases were successfully treated, the virus and the regulatory protocols used to fight Ebola ceased to be a headline news item or public priority.⁵ However, among patients with life-threatening diseases, drug manufacturers, and physicians, the prominence that experimental drugs played in the U.S. response to the Ebola outbreak has had the lasting effect of renewing the focus and debate on the Expanded Access protocols.⁶

Through Expanded Access protocols, the Food and Drug Administration (“FDA”) authorizes the use of untested experimental drugs.⁷ Substantially revised in 2009, this program allows patients with serious or immediately life-threatening diseases to access unapproved drugs outside the clinical trial setting when no satisfactory alternative treatment is available.⁸ The 2009 regulations, and 2013 FDA draft guidance, aim to strike the appropriate balance between facilitating patient access to experimental treatments and ensuring such access does not jeopardize ongoing pre-approved clinical trials.⁹

The 1980s onset of the Acquired Immune Deficiency Syndrome (“AIDS”) epidemic is, in large part, responsible for creating regulatory pathways for patient access to experimental medications.¹⁰ Advocating on behalf of desperately ill victims of the disease, patient activists called for expanding treatment options to include incompletely evaluated

3. Dr. Sanjay Gupta & Danielle Dellorto, *Experimental Drug Likely Saved American Patients*, CNN (Aug. 5, 2014, 8:22 PM), <http://www.cnn.com/2014/08/04/health/experimental-ebola-serum/>; James Hamblin, *The Recovering Americans and the ‘Top Secret’ Ebola Treatment*, THE ATLANTIC (Aug. 5, 2014), <http://www.theatlantic.com/health/archive/2014/08/the-secret-ebola-treatment/375525/>; *Expanded Access (Compassionate Use)*, FDA, <http://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm> (last visited Mar. 1, 2016).

4. See Dr. Joanne Liu, *Attention, World: The Ebola Fight Isn’t Over*, TIME (Aug. 12, 2015), <http://time.com/3994353/ebola-epidemic-msf/>.

5. Abigail Chmielecki, *The Status of Expanded Access in Light of the 2014 Ebola Outbreak Introduction*, 11 J. HEALTH & BIOMEDICAL L. 25, 51-52 (2015).

6. *Id.* at 26-27.

7. *Id.* at 26.

8. 21 C.F.R. § 312.305 (2015).

9. U.S. DEP’T OF HEALTH AND HUMAN SERV., GUIDANCE FOR INDUSTRY: EXPANDED ACCESS TO INVESTIGATIONAL DRUGS FOR TREATMENT USE—QS & AS 1 (2013) [hereinafter GUIDANCE FOR INDUSTRY].

10. Michael D. Greenberg, *AIDS, Experimental Drug Approval, and the FDA New Drug Screening Process*, 3 N.Y.U. J. LEGIS. & PUB. POL’Y 295, 296 (2000).

medications.¹¹ Proponents argued that, for patients facing imminent death, even the most remote probabilities offered by unapproved drugs for improvement might generate enormous benefits.¹² In 2003, the Abigail Alliance for Better Access to Developmental Drugs (“Abigail Alliance”) added a constitutional dimension to the Expanded Access debate by suing the FDA under the Fifth Amendment.¹³ According to the Abigail Alliance, FDA policies limiting patients’ access to experimental drugs violated “their constitutional guarantee against deprivation of life without due process.”¹⁴ Essentially, the alliance argued that terminally ill patients have a fundamental right of access to purchase investigational drugs.¹⁵

On the other side of the debate are researchers and manufacturers who, whether medically or financially minded, have a primary interest in evaluating experimental drugs through clinical trials to garner FDA approval and make them available to the public.¹⁶ These groups argue that Expanded Access can jeopardize the clinical trial process and ultimately the availability of these drugs ever making it to the public.¹⁷ Expanded Access makes experimental drugs available to critically ill patients outside of the clinical trial setting, which is a less controlled environment.¹⁸ A chief concern of drug manufacturers in these cases is that Expanded Access could increase the possibility of “adverse reactions that might raise difficult to resolve but spurious safety concerns.”¹⁹ Critics also warn that Expanded Access programs compete with formal clinical studies for patients.²⁰ Small manufacturers and physicians caution that the administrative demands of complying with Expanded Access protocols could adversely affect the

11. See Hans-Georg Eichler et al., *The Risks of Risk Aversion in Drug Regulation*, 12 NATURE REV. DRUG DISCOVERY 907, 907 (2013).

12. See *id.* at 907-08, 911.

13. *Abigail Alliance for Better Access to Developmental Drugs v. Eschenbach*, 495 F.3d 695, 700-01 (D.C. Cir. 2007).

14. Complaint at 1, *Abigail Alliance for Better Access to Developmental Drugs v. McClellan*, 495 F.3d 695 (D.C. Cir. 2007) (No. 04-5350).

15. *Id.*

16. *FDA Gives NewLink Genetics Approval to Proceed to Phase 1 Clinical Studies of Their Ebola Vaccine*, NEWLINK GENETICS (Sept. 4, 2014), <http://investors.linkp.com/releasedetail.cfm?releaseid=869082> (“We are pleased to have received FDA permission to proceed with human clinical trials . . . Our goal is to empower our research partners to conduct scientifically sound and ethically appropriate first in human studies.”) (quoting Dr. Charles Link, CEO and Chief Scientific Officer of NewLink Genetics); Denise Grady, *2 New Ebola Vaccines Pass Important Early Test, Researchers Say*, N.Y. TIMES (Apr. 8, 2015), http://www.nytimes.com/2015/04/09/health/2-new-ebola-vaccines-pass-important-early-test-researchers-say.html?_r=1; Steven Joffe, *Evaluating Novel Therapies During the Ebola Epidemic*, 312 J. AM. MED. ASS’N 1299, 1299 (2014).

17. *Availability of Investigational Drugs for Compassionate Use, Statement of Robert J. Temple, before the House Committee on Gov’t Reform*, FDA.GOV (June 20, 2001), <http://www.fda.gov/NewsEvents/Testimony/ucm115209.htm> [hereinafter *Statement of Robert J. Temple*].

18. *Id.*

19. *Id.*

20. *Id.*

staffing of ongoing clinical trials.²¹ The FDA acknowledges that, in the past, complying with Expanded Access administrative protocols required more than 120 hours to complete.²² The Agency recently created a new proposal to address this concern.²³

The EVD outbreak provides a compelling backdrop for re-examination of the controversial role of the Expanded Access program. These recent events also provide a persuasive invitation to find the appropriate regulatory balance between patients' desires to make their own decisions about their healthcare and society's need for the development of marketable drugs.²⁴ Part II traces the evolution of the FDA's Expanded Access regulatory framework.²⁵ This section examines the history of the Agency's informal practice of permitting patient access to experimental drugs for treatment outside of clinical trials, beginning in 1962.²⁶ In 1987, this informal practice became part of the FDA Investigational New Drug ("IND") regulations.²⁷ In response to criticism from patients, physicians, and manufacturers alike, the FDA has amended the Expanded Access protocols.²⁸ Part II highlights these changes and concludes with a brief overview of the Agency's recent Expanded Access to Investigational Drugs for Treatment Use—Q&As draft guidance.²⁹

Part III discusses the role of Expanded Access during the recent EVD outbreak within the U.S. and also highlights treatment outside of the U.S.³⁰ In Part IV, the Article analyzes the FDA's Expanded Access protocols used during that outbreak.³¹ Here, the Article assesses lessons learned in terms of the short and long-term impact of Expanded Access regulations in response

21. *Id.*; see also Arthur Caplan and Kenneth Moch, *Rescue Me: The Challenge of Compassionate Use in the Social Media Era*, HEALTH AFF. BLOG (Aug. 27, 2014), <http://healthaffairs.org/blog/2014/08/27/rescue-me-the-challenge-of-compassionate-use-in-the-social-media-era/>.

22. Expanded Access to Investigational Drugs for Treatment Use, 74 Fed. Reg. 40900, 40937 (Aug. 13, 2009) (to be codified at 21 C.F.R. pt. 312 and 316); Johnathan J. Darrow et al., *Practical, Legal, and Ethical Issues in Expanded Access to Investigational Drugs*, 372 NEW ENG. J. MED. 279, 280-81 (2015).

23. Alexander Gaffney, *From 100 Hours to 1: FDA Dramatically Simplifies its Compassionate Use Process*, REG. AFF. PROF. SOC'Y (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/>; see generally Expanded Access to Investigational Drugs for Treatment Use, 74 Fed. Reg. 40900.

24. Expanded Access to Investigational Drugs for Treatment Use, 71 Fed. Reg. 75,147, 75,150 (proposed Dec. 14, 2006) (to be codified at 21 C.F.R. pt. 312) [hereinafter Proposed FDA Rule].

25. See *infra* Part II.

26. See *id.*

27. Proposed FDA Rule, 71 Fed. Reg. at 75,147, 75,148.

28. See Gaffney, *supra* note 23.

29. See *infra* Part II.

30. See *infra* Part III.

31. See *infra* Part IV.

to EVD.³² Specifically, this section examines the deficiencies in the regulations and their corresponding effect on patients and clinical trials.³³

Part V broadens the Expanded Access discussion to address regulatory deficiencies beyond those central to the recent Ebola outbreak.³⁴ Section A focuses on the role of drug manufacturers in the Expanded Access process.³⁵ While manufacturers' willingness was not an obstacle in the recent outbreak, this section explores how that is not always the case.³⁶ Section B examines how state "Right-to-Try" legislation and proposed informed consent changes alter the Expanded Access debate.³⁷ Finally, Part VI articulates a regulatory framework that is properly calibrated to strike the elusive balance allowing patients access to promising treatments while guarding against undue risk and safeguarding the clinical trial process.³⁸

II. OVERVIEW OF THE EXPERIMENTAL DRUG APPROVAL PROCESS

The FDA is charged with "protecting the public health by assuring the safety, efficacy, and security" of consumer products.³⁹ As such, the FDA is responsible for the "most highly regulated system ever created to ensure a safe drug market."⁴⁰ In carrying out that responsibility, the FDA has two specific functions: to review and approve new products that may improve public health and to protect the public from unsafe or ineffective products.⁴¹ Within these functions, however, tension exists as to the proper balance between ensuring the safety and efficacy of drugs and promoting a drug industry that can prolong or save the lives of seriously ill patients.⁴² To appreciate the positions that undergird tension, a brief overview of the FDA's traditional approval process for investigational drugs, followed by a fuller examination of exceptions to that process in the form Expanded Access protocols is required.

32. *See id.*

33. *See id.*

34. *See infra* Part V.

35. *See infra* Part V.A.

36. *See id.*

37. *See infra* Part V.B.

38. *See infra* Part VI.

39. *What We Do*, FDA.GOV.D, <http://www.fda.gov/AboutFDA/WhatWeDo/> (last visited Feb. 25, 2016).

40. John Patrick Dillman, *Prescription Drug Approval and Terminal Diseases: Desperate Times Require Desperate Measures*, 44 VAND. L. REV. 925, 927 (1991) (citing R. Cooper, *Remarks at the Symposium for the 75th Anniversary of the 1906 Pure Food & Drugs Act and the Meat Inspection Act*, in 37 FOOD DRUG COSM. L. J. 49, 59 (1982)).

41. *See* Food and Drug Admin. v. Brown & Williamson Tobacco Corp., 529 U.S. 120, 133-34 (2000); 21 C.F.R. § 314.2 (2007) (stating that the overarching purpose of FDA's drug approval process is to efficiently and thoroughly "facilitate the approval of new drugs shown to be safe and effective" and "ensure the disapproval of drugs not shown to be safe and effective").

42. *Abigail Alliance*, 495 F.3d at 700.

A. Brief Overview of Traditional Investigational New Drug Approval Process

The traditional drug approval process in the United States begins with the drug's sponsor submitting an IND application to the FDA.⁴³ The IND includes results from animal and in vitro studies establishing that human testing for the drug is appropriate.⁴⁴ It may take a sponsor as long as three and one-half years to complete the necessary preclinical investigations and assemble all the data required for the IND.⁴⁵ If the FDA approves the IND, the sponsor then begins the first of three phases of clinical investigations to establish the safety and efficacy of the drug in human populations.⁴⁶

During Phase 1, a small number of healthy human volunteers receive low doses of the drug.⁴⁷ These tests determine the drug's effect on human subjects, side effects associated with specific doses, and evidence of the drug's effectiveness.⁴⁸ Researchers obtain toxicity and pharmacology information that allows them to clarify dosage requirements, evaluate the drug's actual therapeutic effects, and compare the new drug's effects with those of currently existing drugs.⁴⁹ In Phase 2, researchers conduct controlled studies on a small group of human volunteers, which typically includes patients who suffer from the disease or condition that the drug is designed to treat.⁵⁰ If the data from the first two phases offer reasonable assurance that the drug is safe, effective, and the potential benefits of the drug outweigh the risks of a large-scale clinical trial, the sponsor proceeds to Phase 3.⁵¹

Phase 3 is the most time-consuming and intensive phase of clinical investigations, as thousands of volunteers participate in double-blind, randomized, and controlled clinical trials designed to collect additional information on dose-response relationships, safety and effectiveness, and data for proper labeling and instructions.⁵² The average length of the three phases of clinical trial evaluation is seven and one-half years and the entire

43. 21 C.F.R. § 312.23 (2015).

44. *Id.*

45. James L. Zelenay, Jr., *The Prescription Drug User Fee Act: Is A Faster Food and Drug Administration Always a Better Food and Drug Administration?*, 60 FOOD & DRUG. L. J 261, 267 (2005).

46. 21 C.F.R. § 312.21 (2015).

47. *Id.* at § 312.21(a).

48. *Id.*

49. *Id.*

50. *Id.* at § 312.21(b).

51. *See* 21 C.F.R. § 312.21(a)-(c).

52. *Id.*; AYLIN SERTKAYA ET AL., EXAMINATION OF CLINICAL TRIAL COSTS AND BARRIERS FOR DRUG DEVELOPMENT 1-2 (2014), https://aspe.hhs.gov/sites/default/files/pdf/77166/rpt_erg.pdf.

drug development often costs the pharmaceutical manufacturer over a billion dollars.⁵³

In response to the amount of time required to develop and assess data about experimental drugs to determine their safety and effectiveness, the FDA created regulatory exceptions to the standard approval process for new drugs.⁵⁴ These exceptions generally fall into one of two categories: expedited review and Expanded Access.⁵⁵ Expedited review involves shortening the review process and is beyond the scope of this paper.⁵⁶ Expanded Access involves providing critically ill patients access to investigational drugs prior to formal product approval.⁵⁷ Treatment INDs (commonly referred to as “Compassionate Use”) are the primary mechanism for Expanded Access protocols.⁵⁸

B. *The Evolution of Expanded Access Protocols*

The FDA created the multi-phase clinical trial framework to ensure that there is “substantial evidence” of a new drug’s safety and effectiveness before approving it for the public.⁵⁹ Notwithstanding the FDCA’s prohibition against “interstate distribution of any new drug” unless approved by the FDA, the Agency has a long history of authorizing experimental drugs for treatment outside of clinical trials.⁶⁰ For example, the FDA has authorized the use of investigational orphan drugs under INDs for several years.⁶¹ This informal practice continued throughout the 1970s, when several thousand patients received an experimental cardio selective

53. SERTKAYA ET AL., *supra* note 52, at ix, 4-1.

54. *See id.* at 4-14.

55. Peter M. Currie, *Restricting Access to Unapproved Drugs: A Compelling Government Interest*, 20 J. L. & HEALTH 309, 313-14 (2007).

56. Subpart E of Title 21 of the Code of Federal Regulations created a variety of measures to expedite review of new drugs for serious diseases. 21 C.F.R. § 312.80 (2015). These measures included early and repeated FDA consultation with pharmaceutical developers to accelerate the clinical trial process, consolidation of Phase 2 and Phase 3 clinical testing, and increased Phase 4 post marketing trials to postpone the burden of additional safety research. *See* 21 C.F.R. §312.82 (2015) (early consultation between FDA and drug sponsors); 21 C.F.R. § 312.87 (2015) (FDA involvement in clinical trials); 21 C.F.R. §312.85 (2015) (discussing Phase 4 post-marketing trials).

57. 21 C.F.R. § 312.310 (2015).

58. *Expanded Access*, *supra* note 3; C. R. Horsburgh, Jr. et al., *Compassionate Use of and Expanded Access to New Drugs for Drug-Resistant Tuberculosis*, 17 INT’L J. TUBERCULOSIS. & LUNG DISEASE 146, 147 (2012).

59. 21 U.S.C.A. § 355(d) (West 2015).

60. *United States v. Rutherford*, 422 U.S. 544, 546 (1979); Greenberg, *supra* note 10, at 304.

61. Orphan Drug Act of 1983, Pub. L. No. 97-414, 96 Stat. 2049. (codified at 21 U.S.C. § 360aa-ee (2006)); Michelle Meadows, *Promoting Safe and Effective Drugs for 100 Years*, 40 FDA CONSUMER 14, 18 (2006).

beta blocker under a treatment protocol outside the clinical trial process.⁶² In the mid-1970s, the FDA, in conjunction with the National Cancer Institute, also created a system that used treatment protocols to distribute promising Group C cancer drugs to patients in need.⁶³

In response to political pressure arising out of the AIDS epidemic, the FDA amended its IND regulations to include the Treatment IND in 1987.⁶⁴ Under these regulations, the FDA authorized the use of investigational drugs under an IND protocol provided that:

- (1) The drug is intended to treat a serious or immediately life-threatening disease;
- (2) there is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population;
- (3) the drug is under investigation in a controlled clinical trial under an IND in effect for the trial, or all clinical trials have been completed; and
- (4) the sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence.⁶⁵

After meeting the above criteria, the FDA typically approved a treatment IND for seriously ill patients as early as during Phase 3 clinical trials and for terminally ill patients as early as Phase 2 trials.⁶⁶ For purposes of the regulations, “immediately life-threatening” was defined as “a stage of the disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.”⁶⁷ In such circumstances, the standard for treatment was that “the available scientific evidence, taken as a whole . . . provide[d] a reasonable basis for concluding that the drug may be effective . . . or would not expose the patients . . . to an unreasonable and significant additional risk of illness or injury.”⁶⁸

By 1994, seriously ill patients gained access to more than thirty experimental drugs and biologics through IND treatment use protocols.⁶⁹

62. See Frank E. Young et. al., *The FDA's New Procedure for the Use of Investigational Drugs and Treatment*, 259 J. AM. MED. ASS'N 2267, 2267 (1988) (Describing practices of investigational drugs dating back to 1976).

63. *Id.* at 2268.

64. Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Treatment Use and Sale, 52 Fed. Reg. 19466, 19466, 19467 (May 22, 1987) (codified at 21 C.F.R pt. 312).

65. *Id.*

66. *Id.*

67. *Id.*

68. MARSHALL S. SHAPO, EXPERIMENTING WITH THE CONSUMER: THE MASS TESTING OF RISKY PRODUCTS ON THE AMERICAN PUBLIC 37 (2009); Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Treatment Use and Sale, 52 Fed. Reg. at 19476.

69. Lois K. Perrin, *The Catch-22 for Persons with AIDS: To Have or Not to Have Easy Access to Experimental Therapies and Early Approval for New Drugs*, 69. S. CAL. L. REV. 105, 140 (1995).

Despite the expanded regulatory mechanisms for access, the FDA continued to receive criticism regarding its Expanded Access program.⁷⁰ Chief deficiencies identified in the protocols included inconsistent application of policies and an absence of regulatory criteria regarding different types of Expanded Access pathways.⁷¹ For example, while IND regulations implicitly acknowledged the existence of Expanded Access for individual patients, this program was not included in the IND regulations.⁷² Moreover, even the broad population IND specifically identified in the regulation lacked adequate definition and accompanying criteria governing FDA's decisions to allow access to treatment in a variety of situations.⁷³ In response to these concerns, Congress enacted the FDA Modernization Act ("FDAMA") in 1973, which revised the Agency's statutory mandate for Expanded Access regulations.⁷⁴

Noteworthy aspects of the FDAMA included the grant of specific statutory authority for IND use for individual patients⁷⁵ and emergency situations.⁷⁶ Notwithstanding those additions, the amendments did little to resolve the confusing landscape of FDA regulations and policy in this area.⁷⁷ Accordingly, in 2006, the FDA proposed a rule to "further address the concerns that motivated Congress" to include Expanded Access provisions in the FDAMA.⁷⁸ In 2009—after vociferous public comment from persons with life threatening diseases, healthcare professionals, pharmaceutical and biotechnology companies, hospitals, and insurance companies—the FDA published the final rule revising the Expanded Access regulations.⁷⁹

In pertinent part, the regulations attempt to cure prior deficiencies by amending general expanded access requirements and creating specific protocols for treatment INDs for individuals in emergent and non-emergent

70. *Id.*

71. *See* Expanded Access to Investigational Drugs for Treatment Use, 71 Fed. Reg. at 75149

72. *See id.*

73. *See id.*

74. *Food and Drug Administration Modernization Act (FDAMA) of 1997*, FDA.GOV (Nov. 23, 2015), <http://www.fda.gov/RegulatoryInformation/Legislation/SignificantAmendmentstotheFDCA/FDAMA/default.htm>.

75. H. R. REP. NO. 105-399, at Sec. 402 (1997).

76. 21 U.S.C.A. § 360bbb (West 2015).

77. *See, e.g.*, Tim Mackey & Bryan 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 7 (2011).

78. Expanded Access to Investigational Drugs for Treatment Use, 71 Fed. Reg. at 75149.

79. *Final Rules for Expanded Access to Investigational Drugs for Treatment Use and Charging for Investigational Drugs*, FDA.GOV (Dec. 17, 2014), <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm172492.htm>; Expanded Access to Investigational Drugs for Treatment Use, 74 Fed. Reg. 40900, 40901 (proposed Aug. 13, 2009) (to be codified at 21 C.F.R. pt. 312 and 316) [hereinafter Proposed FDA rule II].

situations and intermediate size population.⁸⁰ Accordingly, the revised regulation provided:

- (1) The patient or patients to be treated have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;
- (2) The potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated; and
- (3) Providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use.⁸¹

The final rule reflects a recalibration in the Agency's approach by including patient safety measures and clinical trial protections as part of all Expanded Access protocols.⁸² The previous regulatory framework did not require any analysis of whether the potential patient benefit of receiving the unapproved drug justified the potential risk.⁸³ Nor did the prior framework require an analysis into whether providing the unapproved drug would jeopardize the continued development of drugs in the clinical trial process.⁸⁴ The 2009 revisions to the Expanded Access protocols attempt to appropriately balance the three-legged stool of authorizing access to promising new drugs for treatment use, protecting patient safety, and avoiding interference with the development of investigational drugs for marketing under approved applications.⁸⁵

According to the FDA, the design of the revised protocols also addressed the fundamental problem of incomplete or ambiguous regulatory protocols.⁸⁶ However, amid unresolved provider, patient, and industry confusion regarding what expanded access is, when it can be used, what information must accompany a request, and what role the FDA plays in determining the appropriateness of the request, the FDA issued draft guidance addressing these issues in 2013.⁸⁷

80. *Id.*

81. 21 C.F.R. § 312.305(a).

82. *See id.*

83. *See generally* Currie, *supra* note 55.

84. *See* Proposed FDA rule II, 74 Fed. Reg. at 40900.

85. *See id.*

86. *Id.*

87. *See* GUIDANCE FOR INDUSTRY, *supra* note 9, at 1.

The resulting regulations and guidance provides patients a wide swath of access to investigational drugs.⁸⁸ The FDA established criteria for access intended to “reconcile individual patients’ desires to make their own decisions about their health care with society’s need for drugs to be developed for marketing.”⁸⁹ Noting that these interests cannot always be reconciled, the FDA conceded that the Expanded Access regulations “may not be satisfactory to all.”⁹⁰ Using the recent Ebola outbreak as a lens, the next section explores what the regulations lack and how those deficiencies compromise the FDA’s ability to ensure patient safety and the integrity of the clinical trial process.⁹¹

III. EXPANDED ACCESS DURING THE U.S. EBOLA OUTBREAK

The Ebola virus, formally known as the Ebola hemorrhagic fever, is a virulent and often deadly infectious disease.⁹² The Ebola virus originated in the Democratic Republic of Congo (formerly Zaire) in 1976.⁹³ The recent outbreak began in West Africa, quickly spread to Senegal, and arrived in the United States in September 2015.⁹⁴ To date, the virus has infected more than 27,000 people and claimed more than 11,000 lives.⁹⁵ It is the largest and most severe outbreak of the virus in history.⁹⁶

A. *The U.S. Response to Its Ebola Outbreak*

As of April 2015, there were eleven confirmed cases in the U.S. of hospitals using experimental drugs to treat Ebola patients.⁹⁷ The first

88. Proposed FDA rule II, 74 Fed. Reg. at 40932.

89. SHAPO, *supra* note 68, at 48.

90. Proposed FDA rule II, 74 Fed. Reg. at 40902.

91. *See infra* Part III.

92. *See Ebola virus disease*, WORLD HEALTH ORG. (Jan. 2016), <http://www.who.int/mediacentre/factsheets/fs103/en/> (Ebola is transmitted to humans through close contact with blood, secretion, or other bodily fluids of infected animals including monkeys and antelope. Ebola is passed from human to human by direct contact through abrasions in the skin or mucous membranes, with the blood, secretion, or other bodily fluids of those already infected with Ebola.).

93. *See id.*

94. *Ebola Fast Facts*, CNN (Feb. 11, 2016, 4:47 PM), <http://www.cnn.com/2014/04/11/health/ebola-fast-facts/>.

95. *Ebola in Africa: The End of a Tragedy?*, THE ECONOMIST (Jan. 14, 2016), <http://www.economist.com/blogs/graphicdetail/2016/01/daily-chart-12?page=3&fsrc=rss>.

96. *Outbreaks Chronology: Ebola Virus Disease*, CTR. FOR DISEASE CONTROL & PREVENTION (Feb. 17, 2016), <http://www.cdc.gov/vhf/ebola/outbreaks/history/chronology.html>.

97. *See Ebola Virus Disease (EVD) Information for Clinicians in U.S. Healthcare Settings*, CTR. FOR DISEASE CONTROL & PREVENTION (Feb. 22, 2016), <http://www.cdc.gov/vhf/ebola/healthcare-us/preparing/clinicians.html> (confirming that from August 2014 to April 2015 a total of eleven EVD cases were treated in U.S. hospitals); Lauren Raab & Kurtis Lee, *With Ian Crozier’s Reveal, Here Are the 10 Ebola Patients Treated in the U.S.*, L.A. TIMES (Dec. 8, 2014), <http://www.latimes.com/nation/nationnow/la-na-nn-ebola-patients-us-20141208-story.html>; *see also* Kimberly Leonard, *How We*

reported laboratory case of Ebola contracted in the United States, where the patient received treatment under Expanded Access protocols, occurred in October 2014 and involved a Texas healthcare worker.⁹⁸ The Centers for Disease Control (“CDC”) confirmed two other cases involving healthcare workers, one in Texas and one in New York, where patients received experimental treatment under the Expanded Access program.⁹⁹ In addition, the National Health Institute (“NIH”) reported several cases of healthcare workers exposed to Ebola in West Africa who were repatriated to the United States for similar experimental treatment.¹⁰⁰

The conventional post-exposure treatment of Ebola consists of addressing dehydration with volume repletion, maintaining blood pressure and oxygen levels, treating secondary bacterial infections, and receiving nutritional support.¹⁰¹ In the United States, however, the standard course of treatment used to treat patients involved investigational drugs including TKM-Ebola, an experimental drug that prevents the replication of the Ebola virus by triggering an immune response;¹⁰² Brincidofovir, a broad-spectrum antiviral;¹⁰³ ZMapp; and mAPC2.¹⁰⁴ From the information available on the NIH database of clinical trials, it does not appear that any of these individuals received treatment as part of a United States Ebola-related clinical trial.¹⁰⁵ Accordingly, the treatment protocol for Ebola patients in

are Treating Ebola, U.S. NEWS & WORLD REP. (Oct. 27, 2014, 5:34 PM), <http://www.usnews.com/news/articles/2014/10/27/how-we-are-treating-ebola>.

98. *First to Contract Ebola in US: CDC Confirms Texas Health Care Worker’s Diagnosis*, RT (Oct. 13, 2014, 2:54 PM), <https://www.rt.com/usa/195260-texas-ebola-health-care/>. This healthcare worker was treating a male who contracted Ebola in Liberia and travelled to Texas. *Id.* The man was sent home the first time he asked for treatment in the hospital. *Id.* Returning a second time, the hospital realized he had Ebola and administered the experimental drug brincidofovir, but he died soon after. *Id.*

99. *Cases of Ebola Diagnosed in the United States*, CTR FOR DISEASE CONTROL & PREVENTION (Dec. 16, 2014), <http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/united-states-imported-case.html>.

100. Laura Stephenson Carter, *NIH Ebola Response: Ebola-Infected Nurse Discharged*, NIH CATALYST, <http://irp.nih.gov/catalyst/v22i6/nih-ebola-response> (last visited Feb. 27, 2016).

101. *Ebola Virus Disease (EVD) Information for Clinicians in U.S. Healthcare Settings*, *supra* note 97.

102. K.K. Rebecca Lai, *Treating Ebola: The Hunt for a Drug*, N.Y. TIMES (Oct. 23, 2014), <http://www.nytimes.com/interactive/2014/10/23/world/africa/ebola-drugs.html>.

103. *Ebola Epidemic Shines Light on Expanded Access*, AEGIS (Nov. 24, 2014), <http://aegiscreative.com/blog/ebola-epidemic-shines-light-expanded-access/>.

104. Christin Melton, *Governments and Companies Working to End Ebola Epidemic*, RARE DISEASE REP. (Dec. 13, 2014), <http://www.raredr.com/news/Governments-Companies-Ebola-Epidemic>.

105. Raab & Lee, *supra* note 97. The Ebola cases treated in the United States, in chronological order of treatment, are as follows: Dr. Kent Brantly was treated with ZMapp in Atlanta after contracting Ebola in Liberia. *Id.* After recovering, he donated his blood to several other patients in the hopes of helping them. *Id.* Nancy Writebol received ZMapp in the United States under Expanded Access protocols, temporarily depleting the supply. *Id.* Dr. Rick Sacra, treated under Expanded Access protocols, received blood plasma from Brantly and the experimental drug TKM-Ebola. *Id.* Dr. Ian Crozier contracted Ebola while treating patients in Sierra Leone. Raab & Lee, *supra* note 97. He received treatment at Emory University Hospital in Atlanta, but how he was treated is not publically

the United States consisted of experimental drugs made available through Expanded Access and not in a clinical trial setting.¹⁰⁶ Outside of the Expanded Access arena, there are currently fourteen ongoing Ebola virus studies in the United States.¹⁰⁷ All but three of the studies evaluating investigational vaccines for the prevention of Ebola are Phase I trials.¹⁰⁸

available. *Id.* Thomas Duncan, the first person diagnosed with Ebola in the United States, was treated under Expanded Access protocols with brincidofovir. *Id.* He later died at the hospital. *Id.* Ashoka Mukpo, an NBC cameraman, contracted the virus in Liberia. *Id.* His treatment included a blood plasma transfusion from Brantly and brincidofovir, the same drug administered to Duncan. Raab & Lee, *supra* note 97. Mukpo recovered from the illness. *Id.* Nina Pham, an American nurse received treatment at NIH. *Id.* She recovered, but no information is available on her course of treatment. *Id.* Amber Vinson, a nurse who treated Duncan, received care at Emory University Hospital after her Ebola diagnosis. *Id.* No information is publically available regarding her course of treatment. Raab & Lee, *supra* note 97. Dr. Craig Spencer contracted Ebola while working in Guinea. *Id.* Spencer received treatment at Bellvue Hospital Center in New York and recovered. *Id.* Similar to Pham and Vinson, no information is publically available regarding his course of treatment. *Id.* Dr. Martin Salia contracted Ebola in Sierra Leone. *Id.* He was treated at Nebraska Medical Center with ZMapp under Expanded Access protocols, but he died. Raab & Lee, *supra* note 97.

106. *Id.*; UPDATE: *American Healthcare Worker with Ebola Virus Disease Arrives Safely at NIH Clinical Center*, NAT'L INST. OF HEALTH (Mar. 15, 2015), <http://www.nih.gov/news/health/mar2015/nih-13.htm>.

107. List, CLINICALTRIALS.GOV, <https://clinicaltrials.gov/ct2/results?term=ebola&cntryl=NA%3AUS&pg=1> (last visited Feb. 27, 2016).

108. *Placebo Controlled, Dose Response, Safety and Immunogenicity Study of VSV Ebola Vaccine in Healthy Adults*, CLINICALTRIALS.GOV (May 12, 2015), <https://clinicaltrials.gov/ct2/show/NCT02314923?term=ebola&cntryl=NA%3AUS&rank=1> (Phase I trial); *Safety, Tolerability, and Immunogenicity of the Ebola Chimpanzee Adenovirus Vector Vaccine (cAd3-EBO), VRC-EBOADC069-00-VP, in Healthy Adults*, CLINICALTRIALS.GOV (Aug. 27, 2015), <https://clinicaltrials.gov/ct2/show?term=ebola&cntryl=NA%3AUS&rank=2> (Phase I trial); *VRC 208: Dose, Safety and Immunogenicity of a Recombinant Modified Vaccinia Virus Ankara Ebola Vaccine, VRC-EBOMVA079-00-VP (MVA-EbolaZ), Administered Alone or as a Boost to cAd3-Ebola Vaccine in Healthy Adults*, CLINICALTRIALS.GOV (Dec. 8, 2015), <https://clinicaltrials.gov/ct2/show?term=ebola&cntryl=NA%3AUS&rank=3> (Phase I trial); *A Study to Evaluate a Range of Dose Levels of Ad26.ZEBOV and MVA-BN-Filo in Healthy Adult Participants*, CLINICALTRIALS.GOV (Jan. 20, 2016), <https://clinicaltrials.gov/ct2/show?term=ebola&cntryl=NA%3AUS&rank=4> (Phase III trial); *A Study to Evaluate the Immunogenicity, Safety and Tolerability of Ad26.ZEBOV and MVA-BN-Filo in Healthy Adult Participants*, CLINICALTRIALS.GOV (Jan. 20, 2016), <https://clinicaltrials.gov/ct2/show?term=ebola&cntryl=NA%3AUS&rank=5> (Phase III trial); *A Prospective, Open Label, Phase I Safety Study of Passive Immune Therapy During Acute Ebola Virus Disease Using Transfusion of INTERCEPT Plasma Prepared from Volunteer Donors Who Have Recovered from Ebola Virus Disease*, CLINICALTRIALS.GOV (Jan. 5, 2016), <https://clinicaltrials.gov/ct2/show?term=ebola&cntryl=NA%3AUS&rank=6> (Phase I trial); *Open-Label Study of INO-4212 With or Without INO-9012, Administered IM or ID Followed by Electroporation in Healthy Volunteers*, CLINICALTRIALS.GOV (Oct. 16, 2015), <https://clinicaltrials.gov/ct2/show?term=ebola&cntryl=NA%3AUS&rank=7> (Phase I trial); *Safety, Tolerability and Immunogenicity Study of 2 Prime-boost Regimens for Ebola Vaccines Ad26.ZEBOV/MVA-BN-Filo*, CLINICALTRIALS.GOV (Feb. 2, 2016), <https://clinicaltrials.gov/ct2/show?term=ebola&cntryl=NA%3AUS&rank=8> (Phase II trial); *Putative Investigational Therapeutics in the Treatment of Patients With Known Ebola Infection*, CLINICALTRIALS.GOV (Jan. 22, 2016), <https://clinicaltrials.gov/ct2/show?term=ebola&cntryl=NA%3AUS&rank=10> (Phase I trial); *Safety and Immunogenicity of Prime-Boost VSV Ebola Vaccine in Healthy Adults*, CLINICALTRIALS.GOV (Jan. 31, 2015), <https://clinicaltrials.gov/ct2/show?term=ebola&cntryl=NA%3AUS&rank=13> (Phase I trial); *Vaccine Treatment for Ebola Virus in Healthy Adults*, CLINICALTRIALS.GOV (Jan. 31, 2015), <https://clinicaltrials.gov/ct2/show?term=ebola&cntryl=NA%3AUS&rank=15> (Phase I trial); *Evaluating the Safety of and Immune Response to a Human Parainfluenza Virus Type 3 Ebola Virus Vaccine*

B. Ebola Treatments Outside of the United States

Unlike the approach used in the United States, health workers in West Africa primarily relied on a two-prong approach of volume replacement of fluids, isolation of infected individuals, and measures to reduce infection through bodily contact.¹⁰⁹ Due in part to limited drug availability and few modern healthcare facilities, the ethical issue of whether to treat large populations outside of the United States with unapproved drugs through Expanded Access protocols was moot.¹¹⁰ In fact, any alternative to conventional treatments used in previous outbreaks was not an option until clinical trials opened some ten months after the initial outbreak.¹¹¹ In January 2015, NIH, in collaboration with Glaxo-Smith Kline and Merck, opened clinical trials in Liberia and Sierra Leone.¹¹² Shortly thereafter, the pharmaceutical company Chimerix launched open-label clinical trials in Liberia to test the World Health Organization (“WHO”) approved experiment drug Brincidofovir.¹¹³

By February 2015, health workers sustained efforts to isolate Ebola patients and instituted practices that reduced bodily contact with Ebola-infected bodily fluids, resulting in a steady decline in the number of new Ebola cases in West Africa.¹¹⁴ In the wake of fewer cases, Chimerix

(HPIV3-EbovZ GP) in Healthy Adults, CLINICALTRIALS.GOV (Sep. 29, 2015), <https://clinicaltrials.gov/ct2/show?term=ebola&cntry1=NA%3AUS&rank=16> (Phase I trial); *A Safety and Immunogenicity Study of Heterologous and Homologous Prime-Boost Ebola Vaccine Regimens in Healthy Participants*, CLINICALTRIALS.GOV (Jan. 8, 2016), <https://clinicaltrials.gov/ct2/show?term=ebola&cntry1=NA%3AUS&rank=21> (Phase I trial); *Safety and Pharmacokinetics of a Single ZMapp™ Administration in Healthy Adult Volunteers*, CLINICALTRIALS.GOV (Aug. 8, 2015), <https://clinicaltrials.gov/ct2/show?term=ebola&cntry1=NA%3AUS&rank=22> (Phase I trial).

109. *Prevention*, CTR. FOR DISEASE CONTROL & PREVENTION (July 22, 2015), <http://www.cdc.gov/vhf/ebola/prevention/index.html>; *Treatment*, CTR. FOR DISEASE CONTROL & PREVENTION (July 22, 2015), <http://www.cdc.gov/vhf/ebola/treatment/>.

110. *How is Ebola being treated on the ground?*, BBC NEWS (Oct. 10, 2014), <http://www.bbc.com/news/world-africa-29537156>; Sarah Boseley, *Ebola: Experimental Drug Trials to Go Ahead in West Africa*, THE GUARDIAN (Nov. 13, 2014, 1:29 PM), <http://www.theguardian.com/world/2014/nov/13/ebola-drug-trials-liberia-guinea>.

111. See Boseley, *supra* note 110.

112. Thomas M. Burton, *NIH to Start Ebola Vaccine Study With Glaxo, Merck; Research will be Conducted on Thousands Living Near Liberia’s Capital*, WALL ST. J. (Jan. 23, 2015), <http://www.wsj.com/articles/nih-to-start-ebola-vaccine-study-with-glaxo-merck-1421963499>; Thomas M. Burton, *NIH Expands Testing of Ebola Drugs and Vaccines into New Countries; Move into Sierra Leone, Guinea Increases Chances of getting Definitive Results from Clinical Studies*, WALL ST. J. (June 23, 2015), <http://www.wsj.com/articles/nih-expands-ebola-research-into-new-countries-in-search-for-vaccine-1435093932> [hereinafter Burton, *NIH Expands Testing*].

113. See Burton, *NIH Expands Testing*, *supra* note 112.

114. See John Murawski, *Chimerix Withdrawing from Ebola Clinical Trials*, NEWS & OBSERVER (Feb. 2, 2015, 11:00 AM), <http://www.newsobserver.com/news/business/article10245149.html>; *How is Ebola being Treated on the Ground?*, *supra* note 110.

withdrew funding for its clinical trials.¹¹⁵ Tekmira Pharmaceuticals also terminated its clinical trial of the experimental drug TKM-Ebola.¹¹⁶ According to Tekmira Pharmaceuticals, it decided to terminate the trial because results indicated that the experimental drug was “not likely to demonstrate an overall therapeutic benefit.”¹¹⁷ Notwithstanding these setbacks, in August 2015 scientists published a study on the efficacy of an Ebola vaccine in Guinea.¹¹⁸ According to the results, the vaccine is *100 percent effective* at protecting humans against Ebola.¹¹⁹ Given that effectiveness rate, Doctors Without Borders recommended that patients receive the vaccine immediately after exposure.¹²⁰ While promising, the results and the scientific methods used in the study have renewed debate within the research community about using experimental treatments without appropriate scientific protocols to support their regulatory approval.¹²¹ In large part, this study suffers from the same problem as data derived from cases where Ebola patients received Expanded Access experimental drugs in the United States.¹²² The FDA is historically reluctant to consider data from Expanded Access uses as evidence of efficacy for drug approval.¹²³ The FDA issued a critique of the Guinea vaccine study and concluded that the trial methods did not meet scientific standards and the data failed to produce statistically significant results.¹²⁴ Accordingly, none of the data from the Guinea study met the FDA efficacy standards for drug approval.¹²⁵ Similarly, despite “[s]everal investigational drugs and convalescent plasma from recovered Ebola virus disease patients [that] have been used to treat patients with EVD during the outbreak,” data from these controlled clinical

115. David Kroll, *Chimerix Ends Brincidofovir Ebola Trials to Focus on Adenovirus and CMV*, FORBES (Jan. 31, 2015), <http://www.forbes.com/sites/davidkroll/2015/01/31/chimerix-ends-brincidofovir-ebola-trials-to-focus-on-adenovirus-and-cmv/>.

116. Andrew Pollack, *Clinical Trial of Experimental Ebola Drug Is Halted*, N.Y. TIMES (June 19, 2015), http://www.nytimes.com/2015/06/20/health/clinical-trial-of-experimental-ebola-drug-is-halted.html?_r=0 (referring to lack of results as the reason for discontinuing clinical trial).

117. *Id.*

118. Philip R. Krause, *Interim Results from a Phase 3 Ebola Vaccine Study in Guinea*, 386 THE LANCET 831, 831 (2015).

119. *Id.* (emphasis added).

120. Laura Smith-Spark, *WHO: Trials Show New Ebola Vaccine is ‘Highly Effective’*, CNN (Aug. 3, 2015, 12:33 PM), <http://www.cnn.com/2015/07/31/health/guinea-ebola-vaccine/>.

121. John-Arne Røttingen, *Ebola vaccine trial in Guinea*, 385 THE LANCET 2459, 2460 (2015).

122. *See supra* Part III.A.

123. *See* Tom Murphy, *Some Caution with the Good News about an Ebola Vaccine*, HUMANOSPHERE (Aug. 10, 2015), <http://www.humanosphere.org/global-health/2015/08/some-cautiously-good-news-about-an-ebola-vaccine/>.

124. *See* Krause, *supra* note 118, at 831.

125. *Expanded Access: Information for Patients*, FDA.GOV (Feb. 5, 2015), <http://www.fda.gov/ForPatients/Other?expandedAccess/ucm20041768.htm>; Murphy, *supra* note 123.

trials are unavailable.¹²⁶ Accordingly, there is no data on the safety and effectiveness on any experimental drugs for the treatment of patients with Ebola to inform clinical management.¹²⁷

After fourteen months, the Ebola epidemic is winding down.¹²⁸ The WHO has declared Liberia virus-free.¹²⁹ There has not been a case of Ebola contracted in the United States since October 2014.¹³⁰ Similar to the twelve prior Ebola epidemics, the outbreak ended without an approved vaccine or drug.¹³¹ Isolation, rehydration, and increased vigilance regarding hygiene and burial rites remain the only medically accepted and most effective tools in treating the virus.¹³²

IV. WHAT THE EBOLA OUTBREAK REVEALED ABOUT EXPANDED USE REGULATORY DEFICIENCIES

The Ebola outbreak and the responses of the FDA, research community, and pharmaceutical manufacturers to the virus have changed the Expanded Access debate. This section explores what we have learned about the utility of Expanded Access protocols in the wake of the Ebola epidemic. In doing so, this section reveals how regulatory deficiencies permitted immediate access to experimental drugs that may have come at the expense of clinical trials, which were designed to provide society with an FDA-approved treatment.

A. Lack of Clarity and Transparency in the Risk Analysis Requirements

Before making a drug available for Expanded Access, the FDA must determine that the possible risk of providing the unapproved drug outweighs the risk posed to the patient.¹³³ Expanded Access protocols played a critical

126. *Ebola Virus Disease (EVD) Information for Clinicians in U.S. Healthcare Settings*, *supra* note 97.

127. *Id.*

128. Monte Morin, *New Ebola Cases Are Declining: Why That's Bad News For A Cure*, L.A. TIMES (March 9, 2015, 1:39 PM), <http://www.latimes.com/science/la-sci-ebola-drug-trials-20150309-story.html> [hereinafter Morin, *New Ebola Cases Are Declining*].

129. Henry Karmo, *Liberia: WHO Declares Liberia Ebola Virus Free for Third Time*, ALLAFRICA (Jan. 15, 2016), <http://allafrica.com/stories/201601150976.html>.

130. *See Ebola Fast Facts*, *supra* note 94.

131. Krause, *supra* note 118 (In August 2015, the Lancet published the results of a 7651 person phase 3 randomized trial of an Ebola virus. Referred to as the Guinean Ebola Ring Vaccine Trial, the results show early promise in beginning an effective vaccine against the deadly virus.).

132. *Prevention*, *supra* note 108; *Treatment*, *supra* note 109.

133. *See* Monte Morin, *Use of Experimental Ebola Drug Raises Red Flags Among Medical Experts*, L.A. TIMES (Aug. 5, 2014, 9:30 PM), <http://www.latimes.com/science/la-sci-ebola-virus-ethics-20140806-story.html> [hereinafter Morin, *Use of Experimental Ebola Drug Raises Red Flags*].

role in treating Ebola patients in the United States.¹³⁴ What is less clear, however, is the analysis used to determine whether ZMapp, the first unapproved drug administered in the United States to treat Ebola, met the Expanded Access criteria.¹³⁵ Compounding this inquiry is the lack of information the FDA made publically available regarding its analysis.

Beginning with the first Ebola patients treated in the United States and throughout the outbreak, there have been several instances where the government declined to make the patient's course of treatment, or the role Expanded Access protocols played in the patient's recovery, publically available.¹³⁶ For example, in the highly publicized cases of Dr. Brantly and Ms. Writebol, the FDA would not confirm what role Expanded Use protocols played in their recovery.¹³⁷ Although these individuals received follow-up care in Georgia, they received ZMapp in Liberia, outside of United States jurisdiction.¹³⁸ Presumably, the FDA was involved in making the drug available in Liberia; however, the Agency's regulatory steps are not available to the public.¹³⁹ The FDA denied a Freedom of Information Act ("FOIA") request regarding the internal decision-making process used by the Agency to allow the doctor and missionary access to the experimental drug.¹⁴⁰ However, the Agency acknowledged, "[it] can authorize access to potentially promising products through other mechanisms, such as through an emergency Investigational New Drug (IND) application."¹⁴¹ The lack of FDA transparency prompted the Goldwater Institute to file suit against the U.S. Department of Health and Human Services.¹⁴² The suit seeks to compel the FDA to disclose:

134. See *Examining Medical Product Development in the Wake of the Ebola Epidemic* Before the Comm. on Energy and Com., House of Representative COM., (2014) (Statement of Luciana Borio, Assistant Comm'r for Counterterrorism Pol'y, Dir., Off. of Counterterrorism and Emerging Threats, Deputy Chief Scientist (Acting)).

135. Debra Goldschmidt, *Experimental Ebola Drug ZMapp Gets First Track Status from FDA*, CNN (Sept. 17, 2015, 5:57 PM), <http://www.cnn.com/2015/09/17/health/zmapp-status-fast-tracked/>.

136. See Morin, *Use of Experimental Ebola Drug Raises Red Flags*, *supra* note 133.

137. *Id.*

138. See Gupta & Dellorlo, *supra* note 3.

139. See Morin, *Use of Experimental Ebola Drug Raises Red Flags*, *supra* note 133.

140. Starlee Coleman, *Goldwater Institute Asks About Experimental Treatment for Ebola Patients*, PRESCOTT NEWS (Oct. 13, 2014), <http://www.prescottnews.com/index.php/news/current-news/item/24317-goldwater-institute-asks-about-experimental-treatment-for-ebola-patients> (The FDA denied the request on the basis that complying would violate the drug maker's trade secrets).

141. Alexander Gaffney, *Think Tank Seeks Ebola Info from FDA, Calling It a Test Case for Compassionate Use System*, REG. AFF. PROF. SOC'Y (Oct. 9, 2014), <http://www.raps.org/Regulatory-Focus/News/2014/10/09/20534/Think-Tank-Seeks-Ebola-Info-From-FDA-Calling-it-a-Test-Case-for-Compassionate-Use-System/>.

142. Complaint at 1, *Goldwater Inst. v. U.S. Dep't of Health and Human Serv.*, No. 2:2015cv01055 (D. Ariz. June 9, 2015).

Any and all records that indicate the approval process, deliberations made during that process, and final approval records regarding . . . [the] approval of the drug and serum ‘ZMapp’ . . . [that was] administered to Dr. Kent Brantly and Ms. Nancy Writebol, or any other individuals suspected to be infected with the Ebola virus, under the ‘compassionate use’ process or any other approval process at the FDA.¹⁴³

At the time Brantly and Writebol received ZMapp, it had only been tested on monkeys.¹⁴⁴ In the study, eighteen Ebola-infected monkeys received three doses of the drug.¹⁴⁵ In addition, the Ebola strain used in the study was not the same as the one causing the current outbreak.¹⁴⁶ Neither the FDA nor Expanded Access regulations provide insight into the evaluation process that was used to determine whether this data was sufficient to justify treating patients with the unapproved ZMapp.¹⁴⁷ Such analysis is vital given the vulnerability of the patient, the experimental nature of the drug, and the fact that the regulation’s risk analysis criteria does not include an accompanying minimum evidentiary standard.¹⁴⁸

The FDA concedes that the evidentiary standard for the Expanded Access risk analysis is quite low.¹⁴⁹ The regulations require the FDA and a physician to determine: (1) the investigational drug will not cause more harm than the disease, and (2) the potential benefit justifies the potential risk to the patient.¹⁵⁰ In terms of evidentiary support to make that analysis, the FDA has indicated that “little, if any, clinical evidence to suggest the potential benefit or possibly only animal data to support safety of the use” is sufficient.¹⁵¹ Given this exceedingly low evidentiary bar, the FDA admits that it is likely that some drugs used to treat patients ultimately will have no therapeutic value and, in fact, may cause harm.¹⁵²

143. *Id.* at 3.

144. Erika Check Hayden, *Ebola Drug Saves Infected Monkeys* (Aug. 29, 2014), <http://www.nature.com/news/ebola-drug-saves-infected-monkeys-1.15793> (To date seven people were treated with ZMapp. Two of the patients died.).

145. *Id.*

146. *Id.*

147. CATEGORIZATION AND PRIORITIZATION OF DRUGS FOR CONSIDERATION FOR TESTING FOR USE IN PATIENTS INFECTED WITH EBOLA, WORLD HEALTH ORG. (Feb. 18, 2015), http://www.who.int/medicines/ebola-treatment/2015-0218_tables_of_ebola_drugs_updated.pdf.

148. Nicholas J. Plionis, *The Right to Access Experimental Drugs: Why the FDA Should Not Deprive The Terminally Ill of a Chance to Live*, 16 WM. & MARY BILL OF RTS J. 901, 923 (2008).

149. Expanded Access to Investigational Drug for Treatment, Fed. Reg. at 40911.

150. 21 C.F.R. §312.310(a)(1).

151. Expanded Access to Investigational Drugs for Treatment, 71 Fed. Reg. 75147, 75153 (proposed Dec. 14, 2006) (codified at 21 C.F.R. pt. 312).

152. Expanded Access to Investigational Drug for Treatment, 74 Fed. Reg. at 40911.

Of the patients treated with ZMapp in the United States under Expanded Access provisions, nine lived and two died.¹⁵³ Internationally, NIH commenced a clinical trial to test ZMapp's effectiveness.¹⁵⁴ The trial enrolled approximately sixty participants in a trial in which randomly assigned Ebola patients received "supportive care—the standard treatment—or supportive care plus ZMapp."¹⁵⁵ In the wake of declining Ebola cases, the trial's Data Safety and Monitoring Board did not have enough data to determine whether the ZMapp offered statistically better treatment than supportive care.¹⁵⁶

TKM-Ebola, an experimental drug used to treat patients outside of the clinical trial setting, offers a slightly different insight into the Expanded Access risk analysis process.¹⁵⁷ In August 2014, the FDA lifted the clinical hold that it had placed on the study, based on the adverse reaction experienced in twenty-eight healthy adults.¹⁵⁸ Shortly thereafter, two Americans contracted Ebola in West Africa and received ZMapp treatments in the United States.¹⁵⁹ The Agency did not publically disclose a detailed analysis substantiating the validity of removing the hold, nor was the Agency's evidentiary threshold used to determine whether, in the patients' weakened condition, the experimental drug would do more harm than good.¹⁶⁰ While both survived, "[i]n one of the patients, TKM-Ebola, was discontinued after six days because his condition worsened."¹⁶¹ Further, because both patients also received blood transfusions from Ebola survivors, doctors could not determine if the drug contributed to their recovery.¹⁶² Further, "the doctors could not say if the drug contributed to the severity of symptoms reported."¹⁶³ Without a clear and transparent understanding of the risk analysis benefit, FDA authorizations for

153. Hayden, *supra* note 144.

154. Helen Branswell, *With Ebola Cases Petering Out, Will Trial of the Drug ZMapp Run Out of Time?*, CTV NEWS (Aug. 13 2015, 6:23 PM), <http://www.ctvnews.ca/health/with-ebola-cases-petering-out-will-trial-of-the-drug-ZMapp-run-out-of-time-1.2515992>.

155. *Id.*

156. *Id.*

157. *FDA Lifts Hold on Experimental Ebola Drug from Tekmira*, CBS NEWS (Aug. 8 2014, 10:36 AM), <http://www.cbsnews.com/news/fda-lifts-hold-on-experimental-ebola-drug-tekmira>.

158. *Id.*

159. *Id.*

160. *See generally id.*

161. *Trial of Canadian Ebola Drug Stopped after No Overall Benefit Shown*, GLOBE & MAIL (June 19, 2015, 9:58 AM), <http://www.theglobeandmail.com/news/national/trial-of-canadian-ebola-drug-stopped-no-overall-benefit-shown-from-tkm-ebola/article25035127/>.

162. *Id.*

163. *Id.* (Phase II clinical trials for TKM-Ebola-Guinea began in Sierra Leone, March 2015, but were halted because early trial results indicated that it is "unlikely to demonstrate an overall therapeutic benefit to patients").

unapproved drugs under expanded use are suspect. Furthermore, it calls into question the validity of informed consent derived from this process.

B. No Regulatory Provision to Address Drug Shortages

During the outbreak, the ZMapp manufacturer exhausted its supply of the drug after treating two patients.¹⁶⁴ What the outbreak highlighted was that approval to access drugs under Expanded Access protocols contains no assurance that an adequate supply of the drug exists.¹⁶⁵ As discussed, one of the goals of the Expanded Access program is to increase the availability of experimental drugs to patients with life-threatening illnesses.¹⁶⁶ In some cases, this increased demand can create supply constraints and threaten the completion of clinical studies.¹⁶⁷ The regulations contain no guidance to ensure fair and equitable access in such situations where there is inadequate supply to meet the demand.¹⁶⁸

The FDA agrees that there needs to be a mechanism to allocate limited drug supplies to at least some people who could benefit from them.¹⁶⁹ However, the Agency does not believe it is necessary to provide any regulatory guidance to stipulate what that “fair and equitable distribution mechanisms” should be.¹⁷⁰ Instead, the FDA relies on the IRB requirement that selection of subjects under Expanded Access is equitable.¹⁷¹ In doing so, the FDA seems to imply that hallmarks of an equitable distribution mechanism should be case-specific, require unification of threshold clinical parameters for possible access, and include a way to randomly select those who meet the parameters.¹⁷² According to the FDA, this will require disease advocacy organizations to devise the most appropriate mechanism for allocating a limited drug supply in a specific situation or collaboration between the sponsor and relevant patient.¹⁷³ However, the FDA makes clear that even if such steps are taken, the Agency “has no authority to compel sponsors to participate in that collaboration or make their investigational products available for treatment use.”¹⁷⁴

164. Steven Ross Johnson, *Ebola Drug Supply Exhausted after Shipments to Africa, Company Says*, MOD. HEALTHCARE (Aug. 12, 2014), <http://www.modernhealthcare.com/article/20140812/NEWS/308129965>.

165. Expanded Access to Investigational Drugs for Treatment, 74 Fed. Reg. at 40904.

166. *Id.* at 40908.

167. *Id.* at 40904.

168. *Id.*

169. *Id.*

170. Expanded Access to Investigational Drugs for Treatment, 74 Fed. Reg. at 40904.

171. 21 C.F.R. 56.111(a)(3) (2015).

172. Expanded Access to Investigational Drugs for Treatment, 74 Fed. Reg. at 40904-05.

173. *Id.*

174. *Id.* at 40905.

At best, Expanded Access provisions offer patients a way to access potentially life-saving drugs.¹⁷⁵ At worst, the provisions offer nothing more than an illusion of access to a product over which the FDA has no control over its supply.¹⁷⁶ Further, the regulations fail to provide meaningful guidance when the number of approved Expanded Access patients exceed the supply of investigational treatment.¹⁷⁷

C. *Inadequate Regulatory Requirements to Safeguard Clinical Trials*

As previously noted, the U.S. response to the Ebola outbreak consisted of treating patients with experimental drugs outside of a systematic clinical trial process.¹⁷⁸ Critics of that approach posit that while these treatments may provide short-term gains for patients infected with Ebola, in the end it undermines scientists' ability to determine whether these drugs are safe and effective in battling the virus.¹⁷⁹

A key requirement of Expanded Access protocols is that the drug will not interfere with the initiation and completion of clinical trials, and drug development generally.¹⁸⁰ Specifically, the regulations are intended to guard against increased access that would create the domino effect of decreased enrollment in clinical trials, create less rigorous trial protocols, generate less useful data, and ultimately decrease the amount of safety and efficiency information on approved drugs.¹⁸¹ Many of these concerns played out during the recent outbreak.

None of the data from treatment administered through Expanded Access or similar protocols can be used to support the efficacy of an approved treatment or vaccine.¹⁸² With the number of Ebola cases dwindling and clinical trials closing, Expanded Access data will not aid in the ultimate goal of evaluating investigational drugs for FDA marketing approval.¹⁸³ The FDA has repeatedly emphasized "that the evidentiary standards for [Expanded Access] treatment . . . are not the functional equivalent of the amount and type of data needed for marketing approval."¹⁸⁴ By utilizing

175. *See id.* at 40900.

176. *See, e.g.,* Peter D. Jacobson & Wendy E. Parmet, *A New Era of Unapproved Drugs: The Case of Abigail Alliance v. Von Eschenbach*, 297 J. AM. MED. ASS'N 205, 207 (2007).

177. *See* Expanded Access to Investigational Drugs for Treatment, 74 Fed. Reg. at 40904-05.

178. *See* Annette Rid & Ezekiel J. Emanuel, *Ethical Considerations of Experimental Interventions in the Ebola Outbreak*, THE LANCET (Aug. 22, 2014), [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(14\)61315-5/fulltext?rss=yes](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(14)61315-5/fulltext?rss=yes).

179. *Dispute Emerges over Ebola Drug Trials*, MANICAPOST (May 15, 2015), <http://www.manicapost.com/disputes-emerge-over-ebola-drug-trials/>

180. 21 C.F.R. § 312.305.

181. Expanded Access to Investigational Drugs for Treatment, 74 Fed. Reg. at 40901, 40913.

182. *See Dispute Emerges*, *supra* note 179.

183. *See* Expanded Access to Investigational Drugs for Treatment, 74 Fed. Reg. at 40914.

184. *Id.* at 40914.

these treatments outside of the clinical trial setting, researchers lost the opportunity to use that data to evaluate the safety and efficiency of Ebola treatments.¹⁸⁵ Not only is that data not being considered in helping to devise a cure, but data derived through Expanded Access impedes clinical trials in other ways.¹⁸⁶ As noted by Ezekiel Emanuel, when using experimental drugs outside of the clinical trial process, there should be minimum transparency regarding the data points and patient reactions.¹⁸⁷ In the case of ZMapp, researchers refused to release detailed information about patients' reactions to the drug for fear that they would not be able to publish the cases.¹⁸⁸ In addition, the pharmaceutical manufacturer, Chimerix, will not reveal why it withdrew support for its experimental drug after treating four patients.¹⁸⁹

During the recent outbreak, patients requested access to experimental drugs before clinical trials.¹⁹⁰ In such cases, the FDA acknowledged that it was important for the Agency to closely monitor these patients, the implications of Expanded Access, and the impact it could have on the ability to enroll patients into a clinical trial and other clinical development milestones.¹⁹¹ In terms of what analysis that requires, the regulations provide no guidance and the FDA has not made its thought process publicly available.

Another deficiency that Expanded Access protocols laid bare during the outbreak was the lack of explicit criteria for determining how access to the investigational drug will not detrimentally affect clinical trials.¹⁹² For example, the regulations fail to require the FDA to seek specific assurances from the manufacturer that the treatment would not interfere with enrolling patients in a trial.¹⁹³ The FDA is also under no requirement to request, from the sponsor, a comprehensive investigational plan with a timetable and milestones to allow the Agency to periodically assess the treatment's effect on the pace of clinical development.¹⁹⁴ Given the rate of the virus' initial progression, many researchers assumed that there would be no shortage of

185. Tammy Kim et al., *U.S. Food and Drug Administration Efforts to Facilitate the Use of Expanded Access Programs*, J. CLINICAL ONCOLOGY 1, 1 (2015).

186. See Erika Check Hayden, *Ebola Teaches Tough Lessons about Rapid Research*, NATURE (May 27, 2015), <http://www.nature.com/news/ebola-teaches-tough-lessons-about-rapid-research-1.17623> [hereinafter Hayden, *Ebola Teaches Tough Lessons*].

187. Rabiya S. Tuma, *Expanded-Access Programs: Little Heard Views from the Industry*, ONCOLOGY TIMES 19, 23 (2008).

188. Hayden, *Ebola Teaches Tough Lessons*, *supra* note 186.

189. *Id.*

190. See Tracy Hampton, *Largest-Ever Outbreak of Ebola Virus Disease Thrusts Experimental Therapies, Vaccines Into Spotlight*, 312 J. AM. MED. ASS'N 987, 987-88 (2014).

191. See 21 C.F.R. § 312.315 (2016).

192. See Hayden, *Ebola Teaches Tough Lessons*, *supra* note 186.

193. See 21 C.F.R. § 312.315.

194. See 21 C.F.R. § 312.305.

potential patients.¹⁹⁵ That assumption, however, was incorrect.¹⁹⁶ Consequently, researchers were left with a depleted patient pool; and patients received carte blanche access to experimental treatments under protocols that could not be included in New Drug Applications.¹⁹⁷

During the outbreak, the FDA interpreted Expanded Access protocols in a way that tipped the balance in favor of the short-term gain of immediate availability and away from proper evaluation of the investigation drug in a clinical setting.¹⁹⁸ The FDA acknowledges that Expanded Access has a greater ability to impede development when granted for a drug that is in the early stages of development.¹⁹⁹ Similarly, Expanded Access for orphan diseases can impede development because of the relatively smaller pool from which to draw clinical trial subjects.²⁰⁰ In response to these deficiencies, the FDA maintains that it must carefully evaluate any Expanded Access submission for early stage or orphan drugs to ensure that access will not jeopardize gathering data needed to support product approval.²⁰¹ Whether or how the Agency did this during the Ebola outbreak is unknown. Further, the regulations provide no guidance regarding what criteria or standards that inquiry would include.

D. Ethical Implications of Expanded Access on Clinical Trials

The Ebola outbreak raised ethical questions about whether it is even appropriate to use Expanded Access protocols when dealing with epidemics.²⁰² Again, because the FDA does not consider data derived through Expanded Access treatments when evaluating New Drug Applications for approval, many in the scientific community posit that the protocols should not be used.²⁰³ Proponents of this position state that the goal of research is to develop safe and effective products for approval.²⁰⁴ The best way to do that is through properly structured clinical trials.²⁰⁵

195. Morin, *New Ebola cases are declining*, *supra* note 128.

196. *Id.*

197. Fiona Fleck, *Tough Challenges for Testing Ebola Therapeutics*, 93 BULL. WORLD HEALTH ORG. 70, 70-71 (2015).

198. *See Dispute Emerges*, *supra* note 179.

199. Expanded Access to Investigational Drugs for Treatment, 74 Fed. Reg. at 40916.

200. *Id.*

201. *Id.*

202. *See* Laura Seay, *Ebola, Research Ethics, and the ZMapp Serum*, WASH. POST (Aug. 6, 2014), <http://www.washingtonpost.com/blogs/monkey-cage/wp/2014/08/06/ebola-research-ethics-and-the-zmapp-serum>.

203. *See id.*

204. Expanded Access to Investigational Drugs for Treatment, 74 Fed. Reg. at 40906.

205. *See* REVIEWING CLINICAL TRIALS: A GUIDE FOR THE ETHICS COMMITTEE 55 (John P.E. Karlberg & Marjone A. Speers eds., 2010).

The characteristics of the disease, “including the fact that outbreaks are sporadic and unpredictable and the disease does not occur naturally in the United States, all combine to make it not feasible to conduct standard clinical trials in the United States.”²⁰⁶ For diseases such as this, researchers generally conduct studies under the FDA’s animal efficiency rule.²⁰⁷ The recent epidemic, however, presented a rare opportunity to conduct human clinical trials and evaluate the effectiveness of investigatory treatments in the United States.²⁰⁸

The outbreak revealed that Expanded Access protocols are not adaptable enough to collect data that can be used for FDA approval.²⁰⁹ Specifically, because of the way the experimental drugs were administered under the Expanded Access program—outside of a clinical trial setting, without a control group, and to a small group of people—it is impossible to determine what role they play in a patient’s recovery.²¹⁰ For example, in the case of ZMapp, Dr. Brantly received blood transfusions from a teenager who survived Ebola.²¹¹ As noted by Dr. Anthony Fauci, Head of the National Institute of Allergy and Infectious Diseases, there was no way to tell whether the drug actually effected Dr. Brantly’s health and thus, at the end of the day, the only certainty was “that the drug didn’t kill [him].”²¹²

To the extent that clinical trials utilize Expanded Access protocols, several researchers advocate using these protocols only as part of a randomized, controlled, and double-blind trial.²¹³ This approach randomly assigns patients to groups that receive either the experimental drug or a placebo, and neither the physicians nor the patients know who received what.²¹⁴ Referred to as the “gold standard,” the scientific community agrees that this method generally produces the fastest and most compelling answers in FDA approvals.²¹⁵ As pointed out by U.S. Health and Human Services assistant secretary for preparedness and response, Nicole Lurie, “We recognise [sic] the need for compassion and quick access to effective

206. Laurie Scudder & Luciana Borio, *Responding to Ebola: The View from the FDA*, MEDSCAPE (Aug. 20, 2014), <http://www.medscape.com/viewarticle/830142>.

207. Scudder & Borio, *supra* note 206fs.

208. See Jon Cohen & Martin Enserink, *Special Report: Ebola’s Thin Harvest*, SCI. (Dec. 31, 2015, 6:00 AM), <http://www.sciencemag.org/news/2015/12/special-report-ebolas-thin-harvest>.

209. See 21 C.F.R. § 312.20 (2016); see Scudder & Borio, *supra* note 206.

210. See *Dispute Emerges*, *supra* note 179.

211. Liz Szabo, *Cameraman with Ebola gets Blood Transfusion*, USA TODAY (Oct. 8, 2014, 1:04 PM), <http://www.usatoday.com/story/news/nation/2014/10/08/cameraman-ebola-transfusion/16906983>.

212. Morin, *Use of Experimental Ebola Drug Raises Red Flags*, *supra* note 133.

213. Ronald Waldman & Phillip Nieburg, *Thoughts on Alternative Designs for Clinical Trials for Ebola Treatment Research*, 15 AM. J. BIOETHICS 38, 38 (2015).

214. *Id.* at 38.

215. Jon Cohen & Kai Kupferschmidt, *Ebola Vaccine Trials Raise Ethical Issues: Randomized Studies May Offer Fastest Answer*, 346 SCI. 289, 289 (2014); but see Waldman & Nieburg, *supra* note 213, at 38.

drugs for those in need . . . but history has taught that the best approach is to conduct rigorous controlled trials to determine both safety and effectiveness.”²¹⁶

Researchers on the other side of the ethical debate also advocate for adaptability in the Expanded Access protocols so data can support FDA approval, but as part of alternative non-randomized trials.²¹⁷ In these studies, all eligible patients who want the medication receive it.²¹⁸ While these researchers concede that this approach has some limitations, they counter that—in the midst of an epidemic that has more than a fifty percent mortality rate—this approach is more consistent with research ethics.²¹⁹ They also note that trials routinely use this type of design “to provide early indications of drug safety and efficacy, particularly in conditions with high case fatality and no existing effective treatments.”²²⁰ For these members of the research community, obtaining evidence of the effectiveness of experimental drugs in the midst of an epidemic is not high science; it is “the art of the possible.”²²¹

The appropriate role for Expanded Access treatments in clinical trials has raised a host of ethical issues.²²² Those seeking to include the protocols in placebo-controlled clinical trials justify their approach by making an analogous argument to scarcity.²²³ They contend:

When there is a scarcity of agents to be tested, the intervention cannot be given to all those who seek it. Randomization to placebo is therefore no worse, and they argue, ethically more appropriate, than alternative ways of prioritizing access to novel agents such as “first come first served,” sickest first, lottery, or ease of delivery. . . [In response, opponents argue that w]hen available conventional care means a high probability of death and a novel intervention holds some possibility of benefit due to promising prior if limited

216. *Dispute Emerges*, *supra* note 179.

217. See Annette Rid, *The Goals of Research During an Epidemic*, 15 AM. J. BIOETHICS 47, 48 (2015).

218. Peter Horby, *Nonrandomized Trials Could Minimize Deaths of Ebola in West Africa*, N.Y. TIMES (Dec. 2, 2014, 10:54 AM), <http://www.nytimes.com/roomfordebate/2014/12/01/experimental-drugs-and-the-ethics-of-fighting-ebola/nonrandomized-trials-would-minimize-deaths-of-ebola-in-west-africa>.

219. Chris Degeling et al., *Impure Politics and Pure Science: Efficacious Ebola Medications Are Only A Palliation and Not A Cure For Structural Disadvantage*, 15 AM. J. BIOETHICS 43, 44 (2015); *Ebola Virus Disease*, WORLD HEALTH ORG. (Jan. 2016), <http://www.who.int/mediacentre/factsheets/fs103/en/>.

220. Horby, *supra* note 218.

221. *Id.*

222. Darrow et al., *supra* note 22, at 283-84.

223. Arthur L. Caplan et al., *Selecting the Right Tool For the Job*, 15 AM. J. BIOETHICS 4, 6 (2015).

use in humans, animal studies, or simply theoretical plausibility, it is morally problematic to insist on randomizing patients to a control arm in the context of an ineffective standard of care.²²⁴

While the full range of these ethical issues is beyond the scope of this Article, the increased use of Expanded Access protocols casts a large shadow.

V. BROADER EXPANDED ACCESS ISSUES

The recent Ebola epidemic shed light on several key issues in the Expanded Access debate.²²⁵ The public health aspect of the crisis, however, shifted focus away from other central issues: (1) the role of drug manufacturers, legislative, and social media pressures to extend Expanded Access, and (2) the lack of accompanying patient protections offered by Expanded Access informed consent protections.

A. *Manufacturers' Expanded Access Concerns*

The availability of drugs under Expanded Access depends on the willingness of drug manufacturers to provide them.²²⁶ The dynamics involved in the regulatory drug approval and development process, however, makes providing experimental drugs a potentially risky course of action for drug manufacturers.²²⁷ Manufacturers fear that providing access to the experimental drugs could adversely affect new drug development as a whole.²²⁸ Historically, there has been a shortage of available and qualified subjects willing to participate in trials.²²⁹ Currently, less than five percent of cancer patients enroll in U.S. clinical trials.²³⁰ Given the choice, patients would most likely choose access to drugs outside of a clinical study in order to avoid the possibility of receiving a placebo in a double-blind randomized trial.²³¹ In addition, if patients can access these drugs locally from their doctors, patients have less incentive to travel to sites to participate in clinical trials.²³²

224. *Id.*

225. *See* Darrow et al., *supra* note 22, at 279.

226. *Id.* at 280-81.

227. *See id.*

228. *Id.* at 281.

229. Rebecca Dresser, *Subversive Subjects: Rule-Breaking and Deception in Clinical Trials*, 41 J. L. MED. & ETHICS 829, 837 (2013).

230. Cameron Scott, *Trials for New Cancer Treatments Reach Only a Tiny Fraction of Patients*, HEALTHLINE (Sept. 4, 2014), <http://www.healthline.com/health/cancer/trials-for-new-treatments-reach-few-patients>.

231. *See* George J. Annas, *Cancer and the Constitution — choice at life's end*, 357 NEW ENG. J. MED. 408, 408. (2007).

232. *See id.* at 411.

Manufacturers expressed further concern regarding the effect of Expanded Access on the development of their clinical trials.²³³ Researchers collect limited data on Expanded Access and “the FDA recognize[s] that such data may not be collected in a systemized fashion and therefore may not be useful.”²³⁴ Accordingly, the FDA makes it clear that the Agency does not consider this data evidence of a drug’s efficacy.²³⁵ However, the FDA does consider Expanded Access data to evaluate a drug’s safety.²³⁶ All manufacturers must submit reports regarding all adverse events that occur in any patient receiving a drug during its pre-approval stage.²³⁷ “Patients receiving treatment under Expanded Access protocols are often sicker than clinical trial participants.”²³⁸ Manufacturers indicate that possible complications or issues that may arise with terminally ill patients could later jeopardize FDA evaluation and approval.²³⁹ Moreover, manufacturers note that since these experimental drugs do not occur in a controlled or regulated environment, outcomes (either beneficial or adverse) could be misleading.²⁴⁰ In addition, public sentiment to adverse reactions of drugs outside clinical trials could unfairly interfere with the results of an ongoing trial, possibly prompting the FDA to get involved prior to a manufacturer’s submission of a new drug application.²⁴¹

Another factor influencing manufacturers’ unwillingness to participate in Expanded Access protocols is the administrative burden.²⁴² Though recently streamlined, the FDA estimated that Expanded Access protocols required 120 hours of human effort to complete.²⁴³ This burden:

[M]ay weigh particularly heavily on smaller manufacturers [with limited personnel]. Even if manufacturers are willing to devote the necessary time, production capacity may not be sufficient to meet demand for both [Expanded Access] and ongoing clinical trials.²⁴⁴

233. See Jessica McDiarmid, *Cobourg Patient Drew the ‘Short Straw’ in Cancer Drug Trial*, TORONTO STAR. (Feb. 7, 2014), http://www.thestar.com/news/gta/2014/02/07/cobourg_woman_34_faces_death_from_melanoma_without_access_to_trial_drug.html.

234. Darrow et al., *supra* note 22, at 281.

235. Perrin, *supra* note 69, at 133.

236. *Id.*

237. Darrow et al., *supra* note 22, at 281.

238. *Id.*

239. *Id.*

240. See Morin, *Use of Experimental Ebola Drug raises Red Flags*, *supra* note 133.

241. Ashley Ochs, Comment, *A Study in Futility: Abigail Alliance for Better Access to Developmental Drugs Will Not Expand Access to Experimental Drugs for The Terminally Ill*, 39 SETON HALL L. REV. 559, 587 (2009).

242. Darrow et al., *supra* note 22, at 280.

243. *Id.*

244. *Id.* at 281.

In addition to administrative burdens, manufacturers indicate that Expand Access protocols raise financial concerns.²⁴⁵ In 2009, the FDA amended Expanded Access protocols to permit companies to charge the direct costs of Expanded Access programs to patients or their insurers.²⁴⁶ However, manufacturers have discovered the downside of this move:

Charging direct costs . . . can lead to adverse publicity because these costs will be far less than the price of a drug when it is ultimately approved by the FDA, a price that sometimes exceeds \$1000 per pill or \$200,000 per patient per year. [As a result,] manufacturers . . . guard cost information carefully, even if it means forgoing the modest revenue that might be obtained through this [regulatory] pathway.²⁴⁷

Further, patients may pressure manufacturers to waive costs instead of imposing charges because Medicare, Medicaid, and private insurers do not pay for experimental Phase 1 treatments.²⁴⁸ In addition to the lack of insurance to compensate for experimental treatments, if the manufacturer finds it necessary to track and monitor these drugs, the additional costs above research and development in clinical trials may be too high to make access feasible.²⁴⁹

B. The Influence of Social Media and Right-to-Try Legislation on the Expanded Access Debate

Social media is exerting greater influence on the availability of drugs through Expanded Access.²⁵⁰ Increasingly, patients, their parents, and patient advocacy groups use social media to pressure manufacturers to make experimental drugs available.²⁵¹ Most recently, Chimerix, the company that manufactures Brincidofovir, found itself in the throes of the social media crisis surrounding the family of a seven-year-old boy, Josh Hardy.²⁵² Josh developed a life-threatening adenovirus infection.²⁵³ His mother posted a letter on Facebook seeking to identify someone who could influence the

245. *Id.* at 281.

246. GUIDANCE FOR INDUSTRY, *supra* note 9, at 3.

247. Darrow et al., *supra* note 22, at 281.

248. *Id.*

249. *Id.*

250. Arthur L. Caplan & Alison Bateman-House, *Should Patients in Need be Given Access to Experimental Drugs?*, 16 EXPERT OPINION ON PHARMACOTHERAPY 1275, 1277 (2015).

251. *See id.*

252. David Kroll, *Chimerix CEO Out In Wake of Josh Hardy Compassionate Use Media Frenzy*, FORBES (Apr. 10, 2014, 9:33 AM), <http://www.forbes.com/sites/davidkroll/2014/04/10/chimerix-ceo-out-in-wake-of-josh-hardy-compassionate-use-media-frenzy/>.

253. *Id.*

company to provide Expanded Access to Brincidofovir.²⁵⁴ Within hours, people flooded the company with Facebook and Twitter requests to provide the drug for Josh.²⁵⁵ Additionally, local and national media outlets picked up the story overnight.²⁵⁶ Following a CNN report covering the family's plight, the company's CEO met with the FDA to discuss ways to provide access without compromising ongoing clinical trials.²⁵⁷ Ultimately, the Hardy family accessed the drug not through Expanded Access, but through an open-label investigational trial.²⁵⁸ After the announcement, the company replaced both the CEO and Chief Medical Officer and the company's stock rose over fifty percent.²⁵⁹

In response to public pressure to increase Expanded Access, more than twenty states have introduced Right-to-Try bills since early 2014.²⁶⁰ Modeled loosely after Expanded Access protocols, these bills contain provisions that are designed to make it faster and easier for patients to obtain experimental therapies.²⁶¹ While patients and patient advocacy groups welcome the increased access provisions, critics cite several state provisions that, in their opinion, not only undermine the FDA approval process, but also potentially jeopardize patient safety.²⁶² For example, legislation in Colorado, Louisiana, and Missouri allow manufacturers to provide experimental medicines without FDA authorization.²⁶³ These laws simply require that a treating physician recommend experimental treatment.²⁶⁴ The laws further contain language that shields "physicians from professional discipline and negligence [causes of action] for making good faith recommendations; Colorado and Missouri also extend limited

254. *Id.*

255. *Id.*

256. See Alice Gomstyn, *Josh Hardy's Health Improving after Social Media Push to Get Him Experimental Drug*, BABBLE, <http://www.babble.com/mom/josh-hardys-health-improving-after-social-media-push-to-get-him-experimental-drug/> (last visited Feb. 27, 2016).

257. Kroll, *supra* note 252.

258. *Id.*

259. Arthur Caplan & Kenneth Moch, *Rescue Me: The Challenge of Compassionate Use In The Social Media Era*, HEALTH AFFAIRS BLOG, <http://healthaffairs.org/blog/2014/08/27/rescue-me-the-challenge-of-compassionate-use-in-the-social-media-era/> (last visited Feb. 19, 2016).

260. David Gorski, *As in 2014, "Right-to-Try" Laws Continue To Metastasize in 2015*, SCI-BASED MED. (May 18, 2015), <https://www.sciencebasedmedicine.org/the-con-game-that-is-right-to-try-legislation-continues-to-metastasize/>.

261. Alexander Gaffney, *'Right to Try' Legislation Tracker*, REG. AFF. PROF. SOC'Y (June 24, 2015), <http://www.raps.org/Regulatory-Focus/News/Databases/2015/06/24/21133/Right-to-Try-Legislation-Tracker/>.

262. David Farber et al., *How State Right to Try laws Create False Expectations*, HEALTH AFFAIRS BLOG (May 22, 2015), <http://healthaffairs.org/blog/2015/05/22/how-state-right-to-try-laws-create-false-expectations/>.

263. Darrow et al., *supra* note 22, at 283.

264. *Id.* (Colorado and Louisiana require further that the physician state that the FDA approved medication is inadequate).

civil immunity to manufacturers related to harms of experimental drugs may cause.”²⁶⁵

While these laws appear to give patients hope, they cannot compel manufacturers and insurers to supply or pay for experimental treatments.²⁶⁶ They also cannot prevent the federal government from taking drug enforcement action against physicians who prescribe experimental drugs independent of the FDA.²⁶⁷ Of the various state legislation, “[o]nly Colorado requires eligible patients to have been unable to participate in a clinical trial ‘within one hundred miles of the patient’s home address’ or not to have been ‘accepted to the clinical trial within one week of the completion of the clinical trial process.’”²⁶⁸

Manufacturers are reluctant to embrace pathways to provide experimental drugs outside of federal requirements.²⁶⁹ Pharmaceutical Research and Manufacturers of America (“PhRMA”) representatives note that they “have serious concerns with any approach to make investigational medicines available that seeks to bypass the oversight of the FDA and clinical trial process[.]”²⁷⁰ In addition, critics indicate that, if challenged, Right-To-Try laws are likely to be held unconstitutional based on preemption grounds.²⁷¹ The Supreme Court’s long-standing deference to federal law in this case would likely find a conflict limiting the reach to patients with terminal illness.²⁷²

Notwithstanding the questionable legal footing of Right-to-Try legislation, these efforts call attention to the inadequacy of Expanded Access informed consent protection.²⁷³ The Michigan Right-to-Try informed consent provisions require patients to waive liability for harm resulting from Expanded Access treatment, including acts of providers.²⁷⁴ Expanded Access informed consent provisions prohibit any such requirement.²⁷⁵ Unfortunately, in terms of Expanded Access, the informed consent provisions provide little more. The FDA has promulgated no guidance regarding how to obtain informed consent from patients who are candidates to receive treatment under Expanded Access.²⁷⁶ While the

265. *Id.*

266. *Statement of Robert J. Temple, supra* note 17.

267. Darrow et al., *supra* note 22, at 283.

268. *Id.* (quoting H.R. 1281, Gen. Assemb., Reg. Sess. (Colo. 2014)).

269. See Carol Gentry, ‘Right to Try’ May Be Hard to Implement, WUSF NEWS (July 1, 2015), <http://wusfnews.wusf.usf.edu/post/right-try-may-be-hard-implement#stream/0>.

270. *Id.*

271. Darrow et al., *supra* note 22, at 283.

272. *Id.*

273. See *id.* at 284.

274. See Gorski, *supra* note 260.

275. Darrow et al., *supra* note 22, at 283.

276. See Expanded Access to Investigational Drugs for Treatment Use, 74 Fed. Reg. at 40920.

Agency encourages submission of informed consent documents for the Agency's review, it is not required.²⁷⁷ More troubling, the provision prohibiting such waivers is located in a regulatory section that, on its face, does not appear to apply to Expanded Access.²⁷⁸ The informed consent procedure used in Expanded Access treatment is contained in section 50.20 of the Code of Federal Regulations.²⁷⁹ However, Expanded Access does not technically involve "research" or a "clinical investigation."²⁸⁰ Accordingly, "the requirements and principles for obtaining the informed consent of subjects participating in clinical investigations . . . may not adequately address the range of issues that would arise in obtaining the informed consent of patients receiving investigational drugs" under Expanded Access.²⁸¹

VI. A NEW APPROACH

Recent events, such as the FDA's response to the Ebola outbreak and state efforts to usurp federal pathways for patient access to experimental drugs, suggest that current Expanded Access protocols are ill-suited to balance the increasingly disparate needs of patients and those conducting clinical trials.²⁸² This section proposes a regulatory framework properly calibrated to achieve the FDA's goal of affording patients a reasonable and meaningful measure of the economy over their healthcare decisions while simultaneously preserving the integrity of the drug approval process and protecting patient safety.

The recent outbreak strongly suggests a need for the FDA to reconsider its historical reluctance to regard data from Expanded Access treatments as evidence of efficacy in New Drug Applications.²⁸³ In part, this reluctance has served as a disincentive for some manufacturers to make experimental drug products available.²⁸⁴ In the past, the FDA has agreed "that there should be efforts to optimize the information obtained from expanded access exposures with an eye toward detecting any unexpected outcomes or events."²⁸⁵ Building on that, the Agency should revise the regulations to inform sponsors, patients, and investigators that both safety and efficacy

277. *See id.*

278. *See generally* 21 C.F.R. § 50.23.

279. 21 C.F.R. § 50.20 (2016).

280. Expanded Access to Investigational Drugs for Treatment Use, 74 Fed. Reg. at 40920.

281. *Id.*

282. Patricia J. Zettler, *Compassionate Use of Experimental Therapies: Who Should Decide?*, EMBO MOLECULAR MED. (2015), http://readingroom.law.gsu.edu/cgi/viewcontent.cgi?article=3074&context=faculty_pub.

283. *Id.*

284. Expanded Access to Investigational Drugs for Treatment Use, 74 Fed. Reg. at 40905.

285. *Id.* at 40906.

data collected in Expanded Access is a required part of initial New Drug Applications.²⁸⁶

In addition, to make the most out of Expanded Access data, the FDA should compile a database of evidence derived from Expanded Access used by patients, clinicians, manufacturers, and researchers to help pursue new treatments and remedies.²⁸⁷ That information should be publicly available to avoid the lack of transparency that has surrounded the results of experimental treatments used in the most recent outbreak.

The regulations must provide evidentiary standards regarding the risk/benefit analysis.²⁸⁸ While the FDA maintains a need for flexibility, a minimum evidentiary threshold is necessary.²⁸⁹ Otherwise, the possibility of exposing patients to drugs that “may not improve [their] condition, and in some cases, increase [their] suffering and hasten death” increases.²⁹⁰ For example, in the absence of a minimum evidentiary standard, over 30,000 women with advanced breast cancer received autologous bone marrow transplants “before it was established that such treatment did more harm than good and that, as a result, some of the women who received this treatment had increased suffering and shortened lives.”²⁹¹ There should be at least preliminary clinical evidence, such as Phase 1 safety testing prior to allowing patients to undergo Expanded Access.²⁹²

At a minimum, to reduce patient risk when using experimental drugs, the FDA should provide Expanded Access “only under a defined protocol, by a qualified investigator, with defined dosage range, and adverse event monitoring procedures, and with specified time intervals for assessing response.”²⁹³ These procedures closely align with clinical trial protocols and increase the suitability of data for efficacy evaluations for New Drug Applications.²⁹⁴ In addition, the regulation should require the physician who offers a drug under Expanded Access to provide the manufacturer with information about any subsequent adverse events.²⁹⁵

286. *Id.* at 40905 (A comment received by the FDA suggested “that FDA revise the proposed rule to explicitly inform sponsors, investigators, patients, and patient representatives that any safety and efficacy data collected in expanded access are expected to be reported in the initial NDA seeking approval for the drug or biological product.”).

287. *Id.* at 40906 (“FDA received several comments advocating more systematic collection of data on outcomes of expanded access programs, including adverse events.”).

288. *Id.* at 40910.

289. Expanded Access to Investigational Drugs for Treatment Use, 74 Fed. Reg. at 40911.

290. *Id.*

291. *Id.*

292. *Id.* at 40910.

293. *Id.* at 40911.

294. See U.S. DEP’T OF HEALTH AND HUMAN SERV., GUIDANCE FOR CLINICAL TRIAL SPONSORS, ESTABLISHMENT AND OPERATION OF CLINICAL TRIAL DATA MONITORING COMMITTEES 25 (2015).

295. Expanded Access to Investigational Drugs for Treatment Use, 74 Fed. Reg. at 40919.

Furthermore, the protocol should include explicit criteria for determining that Expanded Access does not detrimentally affect clinical trials.²⁹⁶ Sponsors should “seek specific assurances from the sponsor that [Expanded Access] will not interfere with the accrual of patients in the clinical trial” and “request that the sponsor submit a comprehensive investigational plan with a timetable and milestones.”²⁹⁷

Expanded Access provisions need to include mechanisms to allocate equitably limited drug supply.²⁹⁸ In the past, the FDA indicated that while it favored collaboration between patient advocacy groups and sponsors, it did not have the authority to require such relationships.²⁹⁹ The Agency could, however, publish industry guidance to indicate scarcity of a collaborative framework. For example, the Hastings Center has developed guidance to allocate scarce life-saving resources for a flu pandemic.³⁰⁰ The eight ethical principles that the Hastings Center suggests for policymakers consider during a rationing plan is an excellent start.³⁰¹ Additionally, the WHO has guidance on allocating resources to scarcity.³⁰²

Finally, the regulations need to include informed consent requirements specifically tailored to Expanded Access.³⁰³ The vulnerability of a patient with a life-threatening disease and the investigatory nature of the drugs requires a more detailed and nuanced informed consent discussion than is afforded in section 50.20 of the Code of Federal Regulations.³⁰⁴ As a starting point, the FDA could require IRBs “to establish special criteria to ensure that physicians have discussed all treatment options with patients as part of the informed consent process”³⁰⁵ Next, consent requirements need to ensure “that patients and their families fully understand the experimental and investigational nature of a drug or other therapy, the types and degrees of unknown risks, and the potential positive and negative health outcomes.”³⁰⁶

296. Tamy Kim et al., *US Food and Drug Administration Efforts to Facilitate the Use of Expanded Access Programs*, J. OF CLINICAL ONCOLOGY 1, 1 (2015).

297. Expanded Access to Investigational Drugs for Treatment Use, 74 Fed. Reg. at 40904.

298. *Id.*

299. *Id.* at 40905.

300. The Hastings Center, *Flu Pandemic and the Fair Allocation of Scarce Life-Saving Resources: How Can We Make the Hardest of Choices?*, BIOETHICS BACKGROUNDER, http://www.thehastingscenter.org/pdf/avian_flu_backgrounder.pdf (last visited Mar. 2, 2016).

301. *Id.*

302. See generally Joseph Kutzin, *Health Financing for Universal Coverage and Health System Performance: Concepts and Implications for Policy*, 91 BULL. WORLD HEALTH ORG. 602, 602, 605-06 (2013).

303. Expanded Access to Investigational Drugs for Treatment Use, 74 Fed. Reg. at 40920.

304. *Id.* at 40907 (quoting 21 C.F.R. § 50.20).

305. *Id.* at 40920.

306. *Id.*

VII. CONCLUSION

Reconciling critically ill patients' desires to access promising experimental drugs and the FDA's regulatory responsibility to evaluate the safety and effectiveness of drugs for market approval is a difficult task.³⁰⁷ In response, the FDA has created a set of permissive and ambiguous Expanded Access protocols that provide access not only at the expense of a patient's safety, but also at the expense of the clinical trial process.³⁰⁸

Expanded Access increases the treatment options for critically ill patients.³⁰⁹ Given the vulnerability of these patients, regulatory pathways to provide investigational treatments must contain appropriate safeguards.³¹⁰ Chief among these protections are adequate informed consent procedures that are specifically tailored to the Expanded Access procedure.³¹¹ In addition, Expanded Access protocols need to contain adequate risk/benefit criteria for patients to determine, in their weakened condition, whether treatment with investigational drugs is appropriate.³¹² As part of that determination, Agency transparency and minimum evidentiary standards are necessary.

The increased use of experimental treatments is giving rising to valuable data that the FDA historically refused to recognize as part of New Drug Applications.³¹³ The proposed regulatory framework recasts collections protocols within the clinical trial setting. By removing the unnecessary tension between the clinical trial process and Expanded Access protocols, manufacturers have made more investigation treatments available. There is no need for access to come at the expense of patient safety or the integrity of the clinical trial process. The proposed Expanded Access regulatory framework strikes a balance that allows for both.

307. See Plionis, *supra* note 148, at 923.

308. Expanded Access to Investigational Drugs for Treatment Use, 74 Fed. Reg. at 40907, 40915.

309. See Darrow et al., *supra* note 22, at 279.

310. See *id.*

311. Expanded Access to Investigational Drugs for Treatment Use, 74 Fed. Reg. at 40920.

312. See *id.* at 40910.

313. See *id.* at 40905.