



AMERICAN UNIVERSITY | WASHINGTON COLLEGE OF LAW

# HEALTH LAW & POLICY BRIEF

VOLUME 18 • ISSUE 2 • SPRING 2024

## ARTICLES

FUNKY MUSHROOMS AND GROOVY PLANTS: A REJUVENATION OF  
PSYCHEDELIC TREATMENT..... *Devin Auriana*

INCREASING GLOBALIZATION OF PHARMACEUTICAL CLINICAL TRIALS:  
BENEFITS, DRAWBACKS, AND CONCRETE  
SOLUTIONS..... *Alexa C. Chronister*

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*Acknowledgements:*

We would like to thank our advisor, Maya Manian, for her support.

We are also grateful to the American University Washington  
College of Law for providing a legal education that empowers us  
to champion what matters.

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TREATMENT

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2023 – 2024

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## LETTER FROM THE EDITORS

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Dear Reader:

On behalf of the Editorial Board and Staff, we proudly present Volume 18, Issue 2 of the *Health Law & Policy Brief*. Since its formation in 2007, the Brief has published articles on an array of topics in health law, food and drug law, and emerging health technologies. In this issue, our authors discuss facets of substance use, treatment, and regulation in the United States. Volume 18.2 features two articles: one examining the federal government's response to emerging treatments involving psychedelic substances, and one discusses the value in using generic biologics to increase access to medicine.

Our first article, by Devin Auriana, a third-year law student at the Elisabeth Haub School of Law at Pace University and a non-commissioned officer in the United States Army Reserve, discusses state and federal policies regarding innovative mental health treatments involving psychedelic substances. Mr. Auriana analyzes the latest reform measures and legal hinderances that states have encountered to inform his recommendations for a federal response. Our second article, by Alexa C. Chronister, a third-year law student at Duke University School of Law highlights the failures of current regulations to adequately protect participants in foreign clinical trials. Ms. Chronister contextualizes this issue in the broader field of global health policy to highlight specific areas of concern and argue for more comprehensive regulation of foreign clinical trials by the Food and Drug Administration, noting the importance of ensuring diversity in clinical trials.

We would like to thank the authors for their insight, creativity, and cooperation in producing these pieces. We would also like to thank the *Health Law & Policy Brief's* article editors and staff members who worked so diligently on this issue.

To all our readers, we hope you enjoy this issue, that the never-ending complexities of this area of law inspire your own scholarship, and that you continue to anticipate and scrutinize the inevitable challenges that our healthcare system continues to withstand.

Sincerely,

Devyn Malouf  
*Editor-in-Chief*

Kimia Khatibi  
*Executive Editor*



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# FUNKY MUSHROOMS AND GROOVY PLANTS: A REJUVENATION OF PSYCHEDELIC TREATMENT

*Devin Auriana\**

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\*I am a third-year student at the Elisabeth Haub School of Law at Pace University, set to graduate in May 2024. Upon graduation, I will be joining the New York County District Attorney's office as an Assistant District Attorney. Beyond my legal pursuits, I also serve as a Civil Affairs Non-Commissioned Officer in the United States Army Reserve. My path to law was inspired by my previous work with a non-profit organization dedicated to assisting veterans. Witnessing firsthand the challenges veterans face, I became intrigued by the potential of psychedelics in addressing some of these issues. My legal interests lie in criminal law and procedure, as well as health law and policy.

## INTRODUCTION

As part of the War on Drugs campaign, President Richard Nixon signed the Federal Comprehensive Drug Abuse Prevention and Control Act of 1970,<sup>1</sup> more commonly known as the Controlled Substances Act (“CSA”).<sup>2</sup> The CSA became effective on May 1, 1971.<sup>3</sup> Its primary purpose was to “improve the manufacturing, importation and exportation, distribution, and dispensing of controlled substances.”<sup>4</sup> The CSA gave the Drug Enforcement Agency (“DEA”) the means to control or decontrol the scheduling of substances.<sup>5</sup> According to the DEA, “[d]rugs, substances, and certain chemicals used to make drugs are classified into five distinct categories or schedules depending on the drug’s acceptable medical use and the drug’s abuse or dependency potential,”<sup>6</sup> with “the abuse rate is a determinate factor in the scheduling of the drug.”<sup>7</sup>

Psychedelic drugs are classified as Schedule I drugs under the CSA and are heavily regulated by the DEA.<sup>8</sup> With a surge in clinical research studies focusing on the effectiveness of psychedelic substances, there is a dual aim: (1) understanding the efficacy of psychedelic substances, and (2) pioneering new

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<sup>1</sup> 21 U.S.C. § 811 (1970).

<sup>2</sup> See Michael Gabay, *The Federal Controlled Substances Act: Schedules and Pharmacy Registration*, HOSP. PHARM., June 2013, at 473.

<sup>3</sup> *Id.*

<sup>4</sup> *Id.*

<sup>5</sup> See 21 U.S.C. § 811(a) (2011).

<sup>6</sup> Drug Enforcement Agency (DEA), Drug Scheduling (Nov. 1-29, 2022), <https://www.dea.gov/drug-information/drug-scheduling>.

<sup>7</sup> *Id.*

<sup>8</sup> See *id.*

treatments for a broader spectrum of psychiatric and behavioral disorders.<sup>9</sup> Psychedelic substances are being used to “treat[] illnesses such as posttraumatic stress disorder [(“PTSD”)], anxiety, depression, and addiction,” indicating high levels of medical value.<sup>10</sup> This newfound interest in using psychedelic substances for medical treatments is rejuvenating after fifty years of psychedelic substances being categorized as ‘drugs of abuse.’<sup>11</sup> For many years, these ‘drugs of abuse’ were believed to have the potential to be very harmful and were heavily stigmatized.<sup>12</sup> However, most cases of abuse were from people taking such substances in “unsupervised nonmedical contexts.”<sup>13</sup> A new approach is underway to eradicate such stigma. Clinicians are focusing on a paradigm that will facilitate healing experiences and positive outcomes.<sup>14</sup> The tenets of the paradigm include “the importance of set (i.e., psychological expectations),

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<sup>9</sup> See, e.g., *Psychedelics Research and Psilocybin Therapy*, JOHNS HOPKINS MED., <https://www.hopkinsmedicine.org/psychiatry/research/psychedelics-research> (last visited Apr. 9, 2024) (providing a timeline of psychedelic research); see also *First Day Psilocybin Wellness Retreat: Coral Cave Wellness Resort in Jamaica. EARLY BIRD PRICING FOR FIRST 4 BOOKINGS*, SILO WELLNESS [hereinafter SILO WELLNESS], <https://retreats.silowellness.com/products/five-day-psilocybin-wellness-retreat-coral-cove-wellness-resort-in-jamaica-early-bird-pricing-for-first-4-bookings> (last visited Apr. 9, 2024) (discussing the inclusions in the retreat to Jamaica: four nights in luxury accommodation, five days immersed in natural beauty, two psilocybin ceremonies, once micro dosing activity, 1:1 intake calls with a team and pharmacologist, three healthy meals a day, nature immersive excursion, journaling & meditation, three group preparation meetings, four on-site group meetings, one 1:1 on-site meeting, and three post-retreat group meetings).

<sup>10</sup> Kenneth W. Tupper et al., *Psychedelic Medicine: A Re-Emerging Therapeutic Paradigm*, 187 CAN. MED. J. ASS’N 1054, 1054 (2015).

<sup>11</sup> *Id.*

<sup>12</sup> Kaitlin Puccio, *The Stigma of Psychedelics*, PYSCH. TODAY (March 3, 2023), <https://www.psychologytoday.com/us/blog/from-obscurity/202303/the-stigma-of-psychedelics>.

<sup>13</sup> Tupper et al., *supra* note 10, at 1054.

<sup>14</sup> *Id.*

setting (i.e., physical environment), and the therapeutic clinician-patient relationship as critical elements.”<sup>15</sup>

With this newfound interest in finding differing treatment options to use in conjunction with the more traditional psychotherapy or counseling, reform is happening at both the federal and state levels. For instance, at the federal level, the Department of Veterans Affairs (“VA”) has developed clinical trials for clinicians to administer psychedelic substances to veterans for a whole host of mental health issues.<sup>16</sup> Such clinics are able to receive approval to administer psychedelic substances by getting a breakthrough therapy designation from the Federal Food & Drug Administration (“FDA”).<sup>17</sup> At the state level, multiple states are passing legislation that decriminalizes possession of psychedelic substances or creates programs to supervise administration of such substances.<sup>18</sup> Previous cannabis legalization on the state level has contributed to paving the way for psychedelic reform to enter society, but many legal obstacles could

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<sup>15</sup> *Id.*

<sup>16</sup> See Ernesto Londono, *After Six-Decade Hiatus, Experimental Psychedelic Therapy Returns to the V.A.*, N.Y.

TIMES (June 24, 2022), <https://www.nytimes.com/2022/06/24/us/politics/psychedelic-therapy-veterans.html> (discussing the resurgence of psychedelic research since the 1960s).

<sup>17</sup> *Breakthrough Therapy*, U.S. FOOD & DRUG ADMIN. (Oct. 29, 2022),

<https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy>.

<sup>18</sup> See, e.g., Thomas Salazar, *Trip or Treat: Psychedelic Drug Reform in California*, 53 U. PAC. L. REV. 321 (2022) (discussing California’s recent psychedelic legalization efforts). Colorado Proposition 122, the Decriminalization, Regulated Distribution, and Therapy Program for Certain Hallucinogenic Plants and Fungi Initiative was recently passed, creating a natural medicine services program for the supervised administration of various psychedelic substances. Prop. 122, Gen. Assemb. (Colo. 2022). It also created a framework for regulating the growth, distribution, and sale of such substances to permitted entities. *Id.*

hinder the progress such reform seeks to produce.<sup>19</sup>

Part I of this Article will focus on the regulation of psychedelic substances at the federal level and how clinics can receive special designation under the FDA.<sup>20</sup> Specifically, Part I will focus on the response the federal government should have towards growing trends of reform.<sup>21</sup> Part II will examine the latest reform measures passed at the state level and the legal hindrances they encounter. Further, Part II will emphasize what states can do to prevent a federal response that diminishes progress.<sup>22</sup> Part III will provide a model legislative framework that states should consider implementing in order to provide meaningful care to people seeking treatment.<sup>23</sup> Part IV will discuss additional considerations to contemplate when implementing these treatment options, including the possibility of commercializing and patenting psychedelics, as well as accounting for the associated costs of these treatment options.<sup>24</sup> Ultimately, this Article will argue that the utilization of psychedelic substances can offer a viable alternative for addressing mental health concerns, and that this type of legal reform is imperative for enhancing treatment

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<sup>19</sup> *See infra* Part D (stating that “psychedelic reform can ride on the proverbial coattails of the cannabis movement and follow a similar path where more states can enact legislation without much federal response”).

<sup>20</sup> *See infra* Part I.

<sup>21</sup> *See infra* Part I.

<sup>22</sup> *See infra* Part II.

<sup>23</sup> *See infra* Part III.

<sup>24</sup> *See infra* Part IV.

accessibility for individuals grappling with mental illnesses.<sup>25</sup>

## I. THE USE AND REGULATION OF PSYCHEDELICS AT THE FEDERAL LEVEL

As more states recognize the need for varying approaches to mental health treatment, and as reform measures are developed, one major concern is the federal government. Given that psychedelics, such as psilocybin, are still categorized as Schedule I, this makes legislation at the state level to be in direct conflict with federal law.<sup>26</sup> Yet, there is a gradual acknowledgment within Congress that support for psychedelic treatments is gaining momentum. This is demonstrated by bipartisan provisions within the 2024 National Defense Authorization Act, requiring that the Department of Defense establish a process under which military service members with PTSD or TBIs can participate in clinical trials involving psychedelics....<sup>27</sup> However, the federal government has the ability, through various means, to support these state measures and help be a catalyst in the psychedelic movement.

### A. *Breakthrough Therapy: Pathway for Clinical Trials*

Typically, it takes years of approval to be given by the federal

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<sup>25</sup> See *infra* Part V.

<sup>26</sup> *Drug Fact Sheet—Psilocybin*, DRUG ENF'T AGENCY (Oct. 2022), <https://www.dea.gov/sites/default/files/2023-04/Psilocybin%202022%20Drug%20Fact%20Sheet.pdf>.

<sup>27</sup> Hillary Campbell, *et. al.*, *Defending Psychedelics: Congress Includes Psychedelic Provisions in Defense Authorization Act*, *The Nat'l L. Rev.*, Jan. 3, 2024, <https://natlawreview.com/article/defending-psychedelics-congress-includes-psychedelic-provisions-defense> (last visited Apr. 17, 2024).

government before a drug becomes available. However, Breakthrough Therapy Designation (“BTD”) under the FDA’s Drug and Device Approvals is one tool that allows public access as rapidly as possible.<sup>28</sup> Breakthrough therapy was signed into law with the approval of the FDA’s Safety and Innovation Act of 2012.<sup>29</sup> According to the FDA, BTD “is a process designed to expedite the development and review of drugs that are intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s).”<sup>30</sup> A drug demonstrates a substantial improvement if “the preliminary clinical evidence . . . show[s] a clear advantage over available therapy.”<sup>31</sup> Clinical trials, such as the one being developed by the VA, demonstrate how psychedelic substances can be used under the breakthrough therapy umbrella.<sup>32</sup>

The Health Services Research & Development Department of the VA is one organization that started these clinical trials after realizing the need for alternative approaches to mental health care. The VA’s clinical trials have been a

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<sup>28</sup> See *Breakthrough Therapy*, *supra* note **Error! Bookmark not defined.** (stating that there are other ways for rapid approval which include priority review, accelerated approval, and fast track).

<sup>29</sup> Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, 126 Stat. 993; *Breakthrough Therapy*, *supra* note **Error! Bookmark not defined.**

<sup>30</sup> *Id.*

<sup>31</sup> *Id.*

<sup>32</sup> See Londono, *supra* note **Error! Bookmark not defined.** (stating that psilocybin has been designated as a “breakthrough therapy,” which is a label regulators give to drugs where studies have shown that the drug may be more effective than traditional treatments for serious conditions).



significant step toward understanding the potential therapeutic value of psychedelic drugs.<sup>33</sup> Moreover, President Biden signed a defense bill that earmarks ten million dollars for clinical trials studying psychedelic drugs.<sup>34</sup> Active duty servicemembers will be allowed to participate in such trials.<sup>35</sup> Additionally, the VA has provided funding for new research opportunities where VA researchers can study the efficacy of psychedelic substances in treating mental health issues such as PTSD.<sup>36</sup> The results of these trials and the research obtained can further advance the goals of destigmatizing psychedelics and providing alternative treatment methods for those suffering from various mental health issues.

### ***B. Change at the Administrative Level***

The Attorney General could also propose a change at the administrative level. This can be done if the Secretary of Health and Human Services (“HHS”) petitions for a change in scheduling or opens a scientific and medical review of a

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<sup>33</sup> See *id.* (noting that preliminary psychedelic studies have shown the effectiveness of these drugs).

<sup>34</sup> See Robert Johnson, *Legal Psychedelic Therapy is Coming For Veterans—But How Long Will They Have to Wait?*, ROLLING STONE (Feb. 21, 2024), <https://www.rollingstone.com/culture-council/articles/legal-psychedelic-therapy-coming-veterans-but-how-long-will-they-have-wait.html> (stating the bill is the “first-ever federal legislation signed into law that mandates psychedelic clinical trials”).

<sup>35</sup> See *id.* (noting tht the legislation “requires the Department of Defense to establish a system that allows active-duty service member to participate in these trials within 180 days”).

<sup>36</sup> See Press Release, *Veterans Affairs, To Improve Care for Veterans, VA to Fund Studies on New Therapies for Treating Mental Health Conditions*, VA NEWS (Jan. 5, 2024, 1:00 PM), <https://news.va.gov/press-room/to-improve-care-for-veterans-va-to-fund-studies-on-new-therapies-for-treating-mental-health-conditions> (announcing the VA’s request for research study funding applications “to study the use of certain psychedelic compounds in treating posttraumatic stress disorder (PTSD) and depression”).

controlled substance.<sup>37</sup> Once the HHS Secretary files the petition, the Attorney General receives and reviews the petition.<sup>38</sup> Many factors are considered when determining to control or remove a substance from a particular schedule.<sup>39</sup>

In making any finding under subsection (a) of this section [factors determinative of control or removal from schedules] or under subsection (b) of section 812 of this title, the Attorney General shall consider the following factors with respect to each drug or other substance proposed to be controlled or removed from the schedules:

- (1) Its actual or relative potential for abuse.
- (2) Scientific evidence of its pharmacological effect, if known.
- (3) The state of current scientific knowledge regarding the drug or other substance.
- (4) Its history and current pattern of abuse.
- (5) The scope, duration, and significance of abuse.
- (6) What, if any, risk there is to the public health.
- (7) Its psychic or physiological dependence liability.
- (8) Whether the substance is an immediate precursor of a substance already controlled under this subchapter.<sup>40</sup>

The factors outlined in the statute serve as the basis for the Attorney General's decisions regarding the addition or reclassification of drugs within schedules. Additionally, it grants the authority to remove any drug or substance from the schedules if it's found not to meet the criteria for inclusion in any schedule.<sup>41</sup> Depending on the HHS findings by the Secretary, the Secretary will

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<sup>37</sup> 21 U.S.C. § 811(a)(2), (b)–(c).

<sup>38</sup> *Id.* § 811(b).

<sup>39</sup> *See id.* § 811(c) (stating eight factors to be considered).

<sup>40</sup> *Id.*

<sup>41</sup> *Id.* § 811(b); *see also id.* §§ 812(a)–(b) (discussing the five schedules and how controlled substances should be categorized).

recommend the drug or substance be either controlled or not controlled.<sup>42</sup> If the recommendation is for the drug to not be controlled, the Attorney General is bound by the decision to not control the drug or substance; if the recommendation is controlled, additional steps are required.<sup>43</sup> The Attorney General will initiate rulemaking proceedings for control, transfer between schedules, or removal.<sup>44</sup> Unfortunately, this process seems unrealistic in the psychedelic reform movement. It would likely be too laborious to get the Attorney General and the HHS Secretary to undergo the requisite steps to reschedule or repeal measures already in place.<sup>45</sup> Consequently, states are striving to address this federal government inaction since there have been no efforts made to repeal such legislation.

### *C. Federal Preemption Limiting State Psychedelic Reform*

The federal government is seen as a hindrance to the widespread use of psychedelic substances. The influence of federal legislation makes it nearly

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<sup>42</sup> *Id.* § 811(b).

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

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

<sup>45</sup> *See, e.g.,* John Hudak & Grace Wallack, *How to Reschedule Marijuana, and Why it's Unlikely Anytime Soon*, BROOKINGS INST. (Feb. 13, 2015), <https://www.brookings.edu/articles/how-to-reschedule-marijuana-and-why-its-unlikely-anytime-soon> (discussing the attempts to reschedule Marijuana from a Schedule I drug by Congress and President Obama). A drug may be rescheduled through Congressional legislation or administrative rulemaking process as dictated by the Administrative Procedures Act, 5 U.S.C. § 551, followed by a review of the Office Management and Budget's Office of Information and Regulatory affairs. Hudak & Wallack, *supra*.

impossible to repeal or narrow the scheduling of controlled substances.<sup>46</sup> Since states provide a narrower pathway to legalization than federal action allows for, proponents in favor of allowing psychedelic use at the federal level need to understand the implications of the doctrine of preemption. This was of important concern when state cannabis laws were enacted, especially because cannabis is still a Schedule I substance under the CSA.<sup>47</sup>

Under the Supremacy Clause,<sup>48</sup> federal law takes precedence over state law.<sup>49</sup> As such, states are prohibited from interfering with the federal government's exercise of its constitutional powers.<sup>50</sup> State law is preempted when it conflicts with federal law, and when examining controlled substances, two fundamental types of conflict emerge: (1) direct conflicts, and (2) obstacle conflicts.<sup>51</sup> A direct conflict arises when it is physically impossible to comply with both state and federal law."<sup>52</sup> Contrast that with an obstacle conflict, which "arises anytime state law 'stands as an obstacle to the accomplishment and

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<sup>46</sup> See generally Robert A. Mikos, *Observations on 25 Years of Cannabis Law Reforms and Their Implications for the Psychedelic Renaissance in the United States*, 18 ANN. REV. L. & SOC. SCI. 155, 155–67 (2022) (discussing legalization reform methods for federally illegal drugs through Congressional action, court action, and state action).

<sup>47</sup> See DEA, *supra* note **Error! Bookmark not defined.** (stating that cannabis is still a Schedule I substance).

<sup>48</sup> U.S. CONST. art. VI, § 2.

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

<sup>50</sup> See *id.*

<sup>51</sup> Robert A. Mikos, *Preemption Under the Controlled Substances Act*, 16 J. HEALTH CARE L. & POL'Y 5, 10 (2013) [hereinafter Mikos, *Preemption*].

<sup>52</sup> *Id.*

execution of the full purposes and objectives of Congress.”<sup>53</sup>

Considering the enactment of cannabis laws, an examination of Congress’s intent regarding preemptive measures under the CSA has left ambiguity regarding whether state decriminalization and legalization of controlled substances are overridden by federal law.<sup>54</sup> An example of a state cannabis law bypassing federal preemption issues is New York’s Marihuana Regulation & Taxation Act (MRTA).<sup>55</sup> In 2021, signed into law by former governor Andrew Cuomo, the MRTA legalized adult-use cannabis in New York State.<sup>56</sup> This piece of legislation “created a new Office of Cannabis Management (OCM) governed by a Cannabis Control Board to comprehensively regulate adult-use, medical, and hemp cannabis.”<sup>57</sup> This Act is not preempted<sup>58</sup> because it is regulating private individuals who choose to use cannabis;<sup>59</sup> the preemption doctrine would only apply if the Act positively conflicted with federal law.<sup>60</sup>

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<sup>53</sup> *Id.* (quoting *Hines v. Davidowitz*, 312 U.S. 52, 67 (1941) (examining the federal government’s superior authority over state laws that were in conflict with Congress’ scheme of regulation)).

<sup>54</sup> Salazar, *supra* note **Error! Bookmark not defined.**, at 328.

<sup>55</sup> *See, e.g.*, Marihuana Regulation & Taxation Act, 2021 N.Y. Laws 854A (legalizing marijuana for recreational use among adults and establishing a state Office of Cannabis Management).

<sup>56</sup> *See id.*; *New York’s Marijuana Regulation and Taxation Act (2021)*, MARIJUANA PROJECT POL’Y, [https://www.mpp.org/states/new-york/new-yorks-marijuana-regulation-and-taxation-act-\(2021\)](https://www.mpp.org/states/new-york/new-yorks-marijuana-regulation-and-taxation-act-(2021)) (stating governor Cuomo signed the law into effect)

<sup>57</sup> *Marihuana Regulation & Taxation Act (MRTA)*, N.Y. State Off. of Cannabis Mgmt., <https://cannabis.ny.gov/marihuana-regulation-and-taxation-act-mrta>.

<sup>58</sup> *See* 21 U.S.C. § 812(c)(c)(17) (2024) (classifying tetrahydrocannabinols as a Schedule 1 substance).

<sup>59</sup> *See* 21 U.S.C. § 812(b)(1) (2024) (classifying Schedule 1 substances as those with a high potential for abuse, no currently accepted medical use, and no accepted safety for use of the drug under medical supervision).

<sup>60</sup> *See supra* text accompanying notes 54–57.

This is further evidenced in the CSA. Under 21 U.S.C. § 903, Application of State Law, the CSA states,

[n]o provision of this subchapter shall be construed as indicating an intent on the part of the Congress to occupy the field in which that provision operates, including criminal penalties, to the exclusion of any State law on the same subject matter which would otherwise be within the authority of the State, unless there is a positive conflict between that provision of this subchapter and that State law so that the two cannot consistently stand together.<sup>61</sup>

While it seems unclear what Congress is stating directly, one noted inference is that § 903 “rejects any inference that Congress wanted to preempt the field of drug regulation . . . it makes federal law the exclusive law governing a particular subject.”<sup>62</sup> In other words, Congress does not want to assume responsibility for drug control.<sup>63</sup> Due to the ambiguity in Congress’s intent regarding § 903 and the conflicting nature of these state laws with the CSA, everything revolves around the federal government’s capacity to enforce federal drug laws.

The federal government is also bound by the anti-commandeering doctrine, which acknowledges the limit on congressional authority where legislative power is reserved for the States.<sup>64</sup> This doctrine enables states to pass

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<sup>61</sup> 21 U.S.C. § 903 (2024).

<sup>62</sup> Mikos, *Preemption*, *supra* note 51, at 12.

<sup>63</sup> *Id.*

<sup>64</sup> *See Murphy v. NCAA*, 138 S. Ct 1461, 1478 (2018) (holding that a provision of a federal law barring states from authorizing sports gambling violated the anti-commandeering doctrine by dictating the actions of a state legislature).

legislation legalizing psychedelic substances for certain uses.<sup>65</sup> Moreover, “commandeering compels state action,” which is prohibited.<sup>66</sup> Thus, under the anti-commandeering doctrine, states do not have to help federal law enforcement in their pursuit of arresting and prosecuting those that “break” federal law.<sup>67</sup>

#### *D. Federal Prosecution Resources & Response*

The Obama Administration’s position on state measures to legalize cannabis provided precedent for how the federal government might engage with states that legalize psychedelic drugs. The Obama Administration recognized the limited investigative and prosecutorial resources the federal government had when states began to enact legislation surrounding cannabis law.<sup>68</sup> In August 2013, Deputy Attorney General James Cole provided guidance regarding cannabis enforcement.<sup>69</sup> The Cole Memorandum urged United States attorneys not to prosecute individuals who used, possessed, cultivated, or distributed

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<sup>65</sup> *Psychedelic Legalization & Decriminalization Tracker*, PSYCHEDELIC ALPHA, <https://psychedelicalpha.com/data/psychedelic-laws> (last visited Mar. 30, 2024).

<sup>66</sup> Robert A. Mikos, *On the Limits of Supremacy: Medical Marijuana and the States’ Overlooked Power to Legalize Federal Crime*, 62 VAND. L. REV. 1421, 1446 (2019) [hereinafter Mikos, *Limits of Supremacy*].

<sup>67</sup> See Robert A. Mikos, *We Need a Cole Memorandum for Magic Mushrooms*, UNIV. ILL. L. REV. ONLINE 87, 89–90 (2021) [hereinafter Mikos, *Cole Memorandum*] (explaining how the anti-commandeering principle enabled states to refuse to assist federal regulators with enforcing laws criminalizing cannabis).

<sup>68</sup> See *id.* at 90 (explaining how federal authorities were unable to penalize states legalizing cannabis due to understaffing and the anti-commandeering doctrine).

<sup>69</sup> See generally Memorandum from Deputy Att’y Gen. James M. Cole to All United States Attorneys (August 29, 2013), [www.justice.gov/iso/opa/resources/3052013829132756857467.pdf](http://www.justice.gov/iso/opa/resources/3052013829132756857467.pdf) (instructing federal prosecutors not to prosecute cannabis users and suppliers that abided by state regulations tailored to federal enforcement priorities).

cannabis while in adherence with state regulations, as long as state laws aligned with federal enforcement priorities.<sup>70</sup> Cole recommended, instead, that offices work to prevent state-authorized cannabis activity from being used as a cover or pretext for the trafficking of other illegal drugs, and if found in violation, to enforce the CSA.<sup>71</sup>

The Biden Administration could adopt a similar position to the Obama Administration regarding psychedelic substances. Similar to the Obama Administration, the current administration should recognize that “the federal government plays only a limited role in the enforcement of criminal laws in the United States.”<sup>72</sup> Further, “[t]he federal government has neither the resources nor the political will to expand its prosecutorial and law enforcement resources to the degree necessary to take over sole enforcement of the nation’s drug laws.”<sup>73</sup> Due to the diminished capacity of the federal government to thwart these behaviors, the federal government would have to employ thousands of more federal agents, federal judges, as well as federal prisons to combat such “concern.”<sup>74</sup>

Thus, states may decide whether to enact laws legalizing psychedelic

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<sup>70</sup> *See id.* at 3.

<sup>71</sup> *See id.* at 1, 3.

<sup>72</sup> Sam Kamin, *Marijuana Law Reform in 2020 and Beyond: Where We Are and Where We’re Going*, 43 SEATTLE UNIV. L. REV. 883, 885 (2020).

<sup>73</sup> *Id.*

<sup>74</sup> Mikos, *Limits of Supremacy*, *supra* note 66, at 1464 (discussing how the CSA imposes harsh penalties but does not meaningfully diminish violations because agencies tasked with enforcement are underresourced).



substances based on priorities of the federal administration in power. If the administration in power seeks to advance the War on Drugs, federal directives might follow. In other words, federal resources could be dedicated to upholding and enforcing federal statutes and prosecuting those in direct violation, even if complying with state law.

An illustration of a shift in the political landscape occurred in 2016 with the election of President Trump. As Professor Sam Kamin noted, “[under the Trump administration, constituents saw the] continued expansion of marijuana law reform at both the state and federal levels.”<sup>75</sup> This stance was surprising to many cannabis activists, who presumed their opponents would vigorously attempt to repeal cannabis reform legislation.<sup>76</sup> As such, the Biden

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<sup>75</sup> Kamin, *supra* note 74, at 883.

<sup>76</sup> See Robert A. Mikos, *The Evolving Federal Response to State Marijuana Reforms*, 26 WIDENER L. REV. 1, 10–11 (2020) [hereinafter Mikos, *Evolving Federal Response*] (discussing how President Trump’s first Attorney General, Jeff Sessions, was opposed to marijuana legislation and rescinded the Cole Memorandum. However, enforcement practices themselves did not change because in 2014 Congress “attached riders to the DOJ’s annual budget, barring the agency from using any of its funding to prosecute individuals for possession, production, or distribution of marijuana that complies with state medical marijuana reforms”). The latest rider provides that:

None of the funds made available under this Act to the Department of Justice may be used, with respect to any of the States of Alabama, Alaska, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, Florida, Georgia, Hawaii, Illinois, Indiana, Iowa, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Utah, Vermont, Virginia, Washington, West Virginia, Wisconsin, and Wyoming, or with respect to the District of Columbia, Guam, or Puerto Rico, to prevent any of them from implementing their own laws that authorize the use, distribution, possession, or cultivation of medical marijuana. *Id.* at 11 n.58 (first citing Consolidated Appropriations Act, 2018, Pub. L. No. 115-141, § 538, 132 Stat. 348, 444–45 (Mar. 23, 2018); then citing *United States v. McIntosh*, 833 F.3d 1163 (9th Cir. 2016)).

Administration is positioned well to further the cannabis movement; psychedelic reform can ride on the proverbial coattails of the cannabis movement and follow a similar path where more states can enact legislation without much federal response.

Overall, states should be worried about federal preemption and federal prosecution, but as a matter of policy, the federal government will likely not engage in this issue.

#### *E. Future Outlook at the Federal Level*

Given the cannabis reform over the past twenty-five years, legal scholars ponder what types of responses by federal and state governments are most likely to happen. Similarly, as psychedelics continue to reshape the therapeutic landscape, these types of questions continually pass through the minds of state lawmakers and clinicians.<sup>77</sup> As noted earlier, congressional consensus is incrementally making progress.<sup>78</sup> Due to major support for the legalization of cannabis, Congress “is highly unlikely to devote the resources that would be needed to mount an effective campaign against legal marijuana, or even to lift the restrictions it has imposed on the use of existing enforcement resources.”<sup>79</sup> Congress could go further by enacting legislation to reschedule substances such

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<sup>77</sup> See Londono, *supra* note 16 (discussing the research of psychedelics).

<sup>78</sup> See Campbell, *supra* note 27 (Congress has allocated funding for psychedelic studies in the 2024 NDAA).

<sup>79</sup> See Mikos, *supra* note **Error! Bookmark not defined.**, at 15.

as cannabis and psilocybin off their Schedule I denomination or by amending relevant sections of the CSA.<sup>80</sup> However, these congressional actions seem remarkably grim.

Speaking more realistically, the likely outcome is through small steps of change at a gradual pace. For example, as seen in the cannabis industry, the Secure and Fair Enforcement (SAFE) Banking Act<sup>81</sup> “would bar federal financial regulators from penalizing banks that serve state-licensed marijuana businesses.”<sup>82</sup> This Act helps provide protection to institutions that serve state cannabis related businesses and further provides legitimacy to the cannabis industry.<sup>83</sup> Furthermore, the Act significantly streamlines the process for those businesses to access fundamental banking services, such as checking accounts and lines of credit.<sup>84</sup>

Given that psychedelic reform is in its nascent stage, the same forward-thinking regarding cannabis reform can be applied to psychedelics. Even though the current legal landscape does not call for state-licensed psychedelic businesses yet, the future may be promising if states incorporate

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<sup>80</sup> See Mason Marks, *Psychedelic Medicine for Mental Illness and Substance Use Disorders: Overcoming Social and Legal Obstacles*, 21 NYU J. LEGIS. & PUB. POL’Y 69, 115 (2018) (discussing the use of petitioning the DEA to change the federal scheduling of psychedelics).

<sup>81</sup> SAFE Banking Act of 2021, H.R. 1996, 117th Cong. (2021).

<sup>82</sup> Mikos, *Preemption*, *supra* note 51 **Error! Bookmark not defined.**, at 17.

<sup>83</sup> See *id.* at 3 (this bill broadly prevents a federal banking regulator from imposing penalties on a depository institution for offering banking services to a legitimate cannabis-related business).

<sup>84</sup> See *id.*

such businesses to become generators of revenue as a whole.

A different bill, the Veterans Medical Marijuana Safe Harbor Act,<sup>85</sup> was introduced by the 117th Congress in 2021.<sup>86</sup> According to the summary and basic premises,

the bill authorizes (1) a veteran to use, possess, or transport medical marijuana in accordance with applicable state or Native American tribal law; (2) a Department of Veterans Affairs (VA) physician to discuss with a veteran the use of medical marijuana as a treatment if the physician is in a state or on tribal land that authorizes such treatment; or (3) a VA physician to recommend, complete forms for, or register veterans for participation in a medical marijuana treatment program in accordance with applicable state or tribal law.<sup>87</sup>

If passed, this bill would pave the way for similar legislation regarding the use of psychedelic substances as medical treatment for similar populations.<sup>88</sup>

Given that the VA has clinical trials testing the effects of psychedelic drugs underway, the data obtained may indicate the promising effects of psychedelic use.<sup>89</sup> This could be the evidence needed to support similar statutory measures such as the Veterans Medical Marijuana Safe Harbor Act.<sup>90</sup> Psychedelic activists and clinicians can remain optimistic and view these bills as the appropriate steps forward in the psychedelic movement. As states continue to

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<sup>85</sup> Veterans Medical Marijuana Safe Harbor Act, H.R. 2588, 117th Cong. (2021).

<sup>86</sup> *Id.*

<sup>87</sup> H.R. 2588, 117th Congress (2021).

<sup>88</sup> *See id.* (summarizing proposed authorization of medical marijuana for veterans' health programs).

<sup>89</sup> *See supra* note 36 and accompanying text (discussing the VA funding for trials).

<sup>90</sup> H.R. 2588, 117th Cong. (2021).

refine and develop what their version of psychedelic reform entails, these examples highlight ways in which the federal government can support state-sponsored psychedelic legislation.

#### **F. *Interplay Between a Federal Agency and Current State Law***

##### *Example*

Since reform at the federal level is the least likely outcome, the current administration should address federal concerns through state measures.<sup>91</sup> This can be done by establishing a system whereby an executive agency, such as the Department of Justice, works with state officials and not against them.<sup>92</sup>

Colorado recently joined a host of states that, in some fashion, regulate and/or have decriminalized substances such as psilocybin.<sup>93</sup>

Under Colorado’s Proposition 122, now codified as the Decriminalization and Regulated Access Program for Certain

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<sup>91</sup> See Drug Enforcement Agency (DEA), *supra* note 6 (stating cannabis is still a Schedule I substance); see also *State Medical Cannabis Laws*, NAT’L CONF. OF STATE LEGS., <https://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx> (last visited April 8, 2024) (“As of April 24, 2023, 38 states, three territories and the District of Columbia allow the medical use of cannabis products.”).

<sup>92</sup> See Mikos, *Cole Memorandum*, *supra* note 67, at 92 (discussing how the federal government can foster a better relationship on state regulation of psychedelic substances).

<sup>93</sup> *Colorado Proposition 122, the Decriminalization, Regulated Distribution, and Therapy Program for Certain Hallucinogenic Plants and Fungi Initiative (2022)*, BALLOTPEDIA, [https://www.ballotpedia.org/Colorado\\_Proposition\\_122,\\_Decriminalization\\_and\\_Regulated\\_Access\\_Program\\_for\\_Certain\\_Psychedelic\\_Plants\\_and\\_Fungi\\_Initiative\\_\(2022\)](https://www.ballotpedia.org/Colorado_Proposition_122,_Decriminalization_and_Regulated_Access_Program_for_Certain_Psychedelic_Plants_and_Fungi_Initiative_(2022)) (stating the measure was passed by a margin over seven percent, with nearly 1.3 million voters in Colorado supporting this proposition & initiative).

Psychedelic Plants and Fungi Initiative,<sup>94</sup> Colorado decriminalized psilocybin and created a legal access program where people over the age of twenty-one can consume psilocybin in state-regulated settings.<sup>95</sup> Individuals twenty-one and older will be able to grow, possess, share, and use psychedelic mushrooms.<sup>96</sup>

Sale of psychedelic mushrooms and other plant-based psychedelic substances is currently not permitted for personal use under the Colorado legislation.<sup>97</sup> The measure requires the state to establish a regulated system for licensed facilities to offer supervised use of psychedelic mushrooms for individuals twenty-one and older, starting this year.<sup>98</sup> Starting in 2026, the state may choose to expand the type of substances that may be used at these facilities to include additional plant-based psychedelic substances.<sup>99</sup> Colorado will employ local governments to regulate operations and an appointed board will advise the Department of Regulatory Agencies in creating rules for this regulated access framework.<sup>100</sup>

Proposition 122 is a prime example of a highly regulated state program that considers federal concerns. These concerns are addressed by imposing certain

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<sup>94</sup> *Id.*

<sup>95</sup> *See id.*

<sup>96</sup> *See id.*

<sup>97</sup> *See id.*

<sup>98</sup> *See Prop. 122, Gen. Assemb. (Colo. 2022).*

<sup>99</sup> *See id.*

<sup>100</sup> *See id.*

age restrictions, requiring consumption only in state-regulated settings, establishing a regulated system for licensed facilities, and appointing a board to regulate this framework.<sup>101</sup> These inclusions address some of the federal government's concerns with respect to consumer safety and control.

Collaboration within the federal government, including with the Attorney General and the states, is essential to ensuring the Colorado legislation remains in effect. For example, if the DOJ begins to break up these state-regulated settings, Colorado could then allow individuals to use psilocybin at unregulated or unlicensed centers.<sup>102</sup> The aftermath of an unregulated state program seems to go against the federal government's interest in adhering to strict regulations.<sup>103</sup> This is a balancing act where multiple competing interests are at stake.<sup>104</sup> Clear guidance from the current administration on their position could prove useful and develop the type of relationship that the federal government and state governments can use going forward.<sup>105</sup>

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<sup>101</sup> *Id.*

<sup>102</sup> See Mikos, *Cole Memorandum*, *supra* note 67, at 91 (recommending the Biden Administration to issue a similar enforcement guidance, of no prosecution, for state-authorized psilocybin activities as it is already done with Marijuana).

<sup>103</sup> See *id.* at 92 (discussing how the Oregon Measure 109, Psilocybin Mushroom Services Program Initiative (2020) centers around a tightly regulated state program. It mirrors Colorado Proposition 122 in establishing a framework for administering psilocybin to individuals aged 21 and above).

<sup>104</sup> See *id.*

<sup>105</sup> President Biden and his administration seem fairly receptive to the idea of exploring with the use of researching the effects of psychedelic substances, but no real direction has been provided. See Press Release, U.S. Senator Schatz, Schatz & Booker Call for More Research On the Therapeutic Potential of Psychedelic Drugs (May 11, 2022) (on file with author) (explaining that U.S. Senators called on both the “National Institutes of Health (NIH) and the FDA to conduct more research into the potential therapeutic uses of psychedelics”).

## II. STATE LEGISLATION AIMED AT REFORMING PSYCHEDELIC SUBSTANCES

Historically, the federal government’s handling of contentious legislative initiatives has impeded the speed at which disputed issues can be resolved at the federal level. States recognize that the federal government lacks the ability to keep up with new trends, especially when it concerns items such as mind-altering substances. As noted earlier, the federal government, albeit slowly, is making some efforts in rethinking psychedelic substances using VA clinical trials.<sup>106</sup> Five trials of the drugs are being held in New York, California, and Oregon.<sup>107</sup> These are the first of their kind since the 1950s when scientists were experimenting differently with the use of psychedelic substances and their effects.<sup>108</sup> According to an Evidence Brief on Psychedelic Medications for Mental Health and Substance Use Disorders, the findings from ongoing clinical trials indicate that MDMA-assisted psychotherapy for PTSD could alleviate symptoms and potentially induce remission for certain individuals in the short term.<sup>109</sup> Furthermore, “[p]silocybin-assisted psychotherapy for depression also shows some promise.”<sup>110</sup>

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<sup>106</sup> See discussion *supra* Part I.

<sup>107</sup> See Londono, *supra* note 16.

<sup>108</sup> See *id.*

<sup>109</sup> See KATHERINE M. MACKAY ET AL., EVIDENCE BRIEF: PSYCHEDELIC MEDICATIONS FOR MENTAL HEALTH AND SUBSTANCE USE DISORDERS (2022).

<sup>110</sup> *Id.* at 2.



Even with this seemingly hopeful federal program, states are better equipped and better attuned to address constituents’ concerns as it relates to mental health treatment. Beginning with the push for cannabis reform with the passage of the Compassionate Use Act of 1996<sup>111</sup> in California, states have taken it upon themselves to ignite the psychedelics reform.<sup>112</sup> This is proven with more ballot initiatives asking voters throughout the United States to help push decriminalization measures and allow for the controlled use of psychedelics.<sup>113</sup> Legal scholars vary in their interpretations of the justifications, which can range from a broad support for decriminalization initiatives to acknowledging the medical benefits associated with these substances.<sup>114</sup>

#### A. *Varying State Approaches to Psychedelic Reform*

While states are identifying the need for psychedelic reform, they do differ in their approach to passing various legislation. For instance, the Oregon Psilocybin Services Act (“OPSA”)<sup>115</sup> and Colorado’s Decriminalization and Regulated Access Program for Certain Psychedelic Plants and Fungi Initiative

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<sup>111</sup> CAL. HEALTH & SAF. CODE § 11362.5.1 (West 2023).

<sup>112</sup> See generally Michael Vitiello, *Proposition 215: De Facto Legalization of Pot and the Shortcomings of Direct Democracy*, 31 U. MICH. J. L. REFORM 707 (1998) (discussing reform measures for medical marijuana).

<sup>113</sup> See generally Dustin Marlan, *Beyond Cannabis: Psychedelic Decriminalization and Social Justice*, 23 LEWIS & CLARK L. REV. 851 (2019) (discussing the measures taken to decriminalize of marijuana).

<sup>114</sup> *Id.* (Marlan considers several potential justifications for decriminalizing psychedelics: “(1) medical value; (2) religious freedom; (3) cognitive liberty; and (4) identity politics – i.e., analogy of a “psychedelic identity” to queer theory and the LGBTQ movement”).

<sup>115</sup> Or. Rev. Stat. Ann. § 475A (2023).

both created programs for the administration of psilocybin products.<sup>116</sup>

Currently, Oregon has provided a much more progressive effort than any other state in the United States. Under the OPSA, the Oregon Health Authority (“OHA”) is directed to license and regulate psilocybin products and the provision of psilocybin substances.<sup>117</sup> In Oregon, “psilocybin services refer to preparation, administration and integration sessions provided by a licensed facilitator.”<sup>118</sup> The OPSA ensures quality control by mandating that “the psilocybin products consumed must be cultivated or produced by a licensed psilocybin service center during an administration session.”<sup>119</sup> Those that are seeking such services are not referred to as patients, but as “clients.”<sup>120</sup> Clients that are receiving said services, must be at least twenty-one years old or older and will not be required to have a medical referral or a prescription.<sup>121</sup>

Under the OPSA, a client accesses psilocybin services in different increments. To start, the client first has a preparation session, “meet[ing] with a licensed facilitator for a preparation session.”<sup>122</sup> Next, the administration session occurs, whereby the client consumes the product at the service center and begins

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<sup>116</sup> See *id.*; Natural Medicine Health Act of 2022, Colo. Rev. Stat. § 12-170-102(h). |

<sup>117</sup> See Or. Rev. Stat. Ann. at § 475A.235(2)(b)(B).

<sup>118</sup> *Oregon Health Authority Public Health Division, OR. PSILOCYBIN SERVS.*, at 1 (2022), <https://sharedsystems.dhsoha.state.or.us/DHSForms/Served/le4226.pdf>.

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

<sup>120</sup> See *id.* (“People accessing psilocybin services are called ‘clients.’”).

<sup>121</sup> See *id.*

<sup>122</sup> *Id.* at 2.

their session with a licensed facilitator.<sup>123</sup> After partaking in the administration session, “the client can take part in an optional session [called the integration session] to follow up with a licensed facilitator.”<sup>124</sup> During this session, the client can learn about additional peer support and other resources.<sup>125</sup>

In order to provide these services, a “licensed facilitator must complete (1) a training program with curriculum approved by Oregon Psilocybin Services (OPS); (2) an examination administered by OPS, and (3) all other license requirements.”<sup>126</sup> Oregon takes the administration of psilocybin services very seriously, mandating strict adherence to certain regulatory requirements to maintain operability.<sup>127</sup> The psilocybin products themselves and how they are transported to a service center also must follow rigid guidelines.<sup>128</sup>

Psilocybin products are cultivated, produced, and/or processed by a licensed manufacturer, where they are tracked in a product tracking system.<sup>129</sup> The products are tested by a licensed testing laboratory.<sup>130</sup> The lab must also be accredited by the Oregon Environmental Laboratory Accreditation Program

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<sup>123</sup> *See id.*

<sup>124</sup> *Oregon Health Authority* at 2.

<sup>125</sup> *See id.*

<sup>126</sup> *Id.*

<sup>127</sup> *See id.*

<sup>128</sup> *Id.*

<sup>129</sup> *Id.*

<sup>130</sup> *Oregon Health Authority* at 2.

(“ORELAP”).<sup>131</sup> The test results are entered into the product tracking system.<sup>132</sup> The products are then sold or transferred from a licensed manufacturer to a licensed service center, which is again tracked in the product tracking system.<sup>133</sup>

Oregon’s efforts and methods can be seen as a blueprint for other states to follow. While these trials are still young, they are promising and the potential to have positive effects on patient care is high.<sup>134</sup> Additionally, the data can continue to help support the overall psychedelic movement throughout the United States.

Other cities and states have also pushed legislation in favor of decriminalizing psychedelics. For instance, in the District of Columbia, the Entheogenic Plant and Fungus Policy Act of 2020 (“Initiative 81”)<sup>135</sup> makes the investigation and arrest of adults for non-commercial possession, distribution, purchase, and cultivation of psychedelic and hallucinogenic plants among the lowest law enforcement priorities for the Metropolitan Police Department.<sup>136</sup>

Other states have taken a more prudent approach by creating task forces or research studies to gain a better understanding of psychedelics. For example,

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<sup>131</sup> *Id.*

<sup>132</sup> *Id.*

<sup>133</sup> *Id.*

<sup>134</sup> R.C. Van Court et al., *Diversity, Biology, and History of Psilocybin-Containing Fungi: Suggestions for Research and Technological Development*, *Fungal Biology* 126 at 314–16 (2022).

<sup>135</sup> D.C. CODE § 48-921.51–.53 (2021).

<sup>136</sup> *Id.* §§ 48-921.51(b), 48-921.52(b)

SB-519, a California psychedelic substances reform bill, would establish a working group under the<sup>137</sup> State Department of Public Health to convene a working group to research and make recommendations to the Legislature for regulations of psychedelic substances.<sup>138</sup> Similarly, in Utah, H.B. 167 established the Mental Illness Psychotherapy Drug Task Force,<sup>139</sup> tasked with conducting studies on drugs that could aid in the treatment of mental illness.<sup>140</sup>

Texas took a slightly different approach in introducing Texas House Bill 1802: Psychedelic Research for Veterans.<sup>141</sup> HB 1802 requires the Health and Human Services Commission, “with Baylor College of Medicine, and in partnership with a military veterans hospital or a medical center that provides medical care to veterans, to conduct a study of the efficacy of using alternative therapies” to treat post-traumatic stress.<sup>142</sup> Furthermore, the act required the Health and Human Services Commission, in collaboration with Baylor College of Medicine, to “perform a clinical trial on the therapeutic efficacy of using psilocybin in the treatment of treatment-resistant post-traumatic stress disorder in veterans.”<sup>143</sup> Lastly, the act requires quarterly progress reports of the study and a final written report of the results, and recommendations, by December

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<sup>137</sup> S.B. 519, 2022 Reg. Sess. (Cal. 2022) (as amended Aug. 15 2022, but not enacted).

<sup>138</sup> *Id.* § 2(a)

<sup>139</sup> H.B. 167, 2022 Leg., Gen. Sess. (Utah 2022)

<sup>140</sup> *Id.* § 2

<sup>141</sup> H.B. 1802, 87th Leg., Reg. Sess. (Tex. 2021).

<sup>142</sup> *Id.* §1(b)

<sup>143</sup> *Id.*

2024.<sup>144</sup>

This approach, in conjunction with the VA trials, demonstrates a particular focus on treating veterans.<sup>145</sup> Providing treatment to veterans may be one specific focus group to start with, paving the way for use by all individuals, including civilians, who want to treat any mental health issues they are experiencing.

Although states may vary in their approach to psychedelic substances legislation, the same underlying theme is present throughout – there is a growing understanding that psychedelics can have positive effects and can provide meaningful care to those in need.

### **III. MODEL LEGISLATION FOR PSYCHEDELIC REFORM**

While the increase in state-level legislation indicates a promising future for a more comprehensive and robust system that facilitates the use of psychedelic treatments, state legislature must bear in mind the uncertain response from federal authorities. To further psychedelic treatments without raising federal concerns, there are several safeguards that states can implement.

In states where regulated settings and facilities for the administration of psychedelics are already established, implementing a requirement for other psychedelics to be dispensed solely within these state-licensed facilities presents

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<sup>144</sup> *Id.* §1(d)(1)–(2)

<sup>145</sup> *See supra* note 36 (discussing the VA trials).

a strategic approach to minimizing potential risks associated with their use.<sup>146</sup>

Additional safeguards, such as state-mandated educational standards for psychedelic prescribers, could also be implemented.<sup>147</sup> Physicians, such as psychiatrists, have experience with altered states of consciousness, so they understand the effects psychedelics have on individuals and are in the best position to undergo additional training.<sup>148</sup> States should therefore pass laws requiring treatment providers to receive adequate training in treatment and safety procedures to prescribe psychedelics.<sup>149</sup>

States have various additional avenues through which they can enact regulations that establish a secure framework for patients to access treatment without triggering concerns from the federal government. For example, states can create a state registry where individual patients are tracked for their use of psychedelics.<sup>150</sup> The federal government would likely view this as an effective way for the states to know exactly which patients are receiving treatment.<sup>151</sup> This measure would function as a control mechanism, aligning with the

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<sup>146</sup> See Marks, *supra* note **Error! Bookmark not defined.**, at 136 (explaining how the practice of administering ketamine treatment in single doses, at a doctor's office to treat mental illness, reduces the risk of adverse reactions, diversion of drugs from legitimate channels, and the development of substance use disorders).

<sup>147</sup> *Id.*

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

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

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

<sup>151</sup> See generally Marks, *supra* note **Error! Bookmark not defined.** (explaining that applying similar practices for federally controlled substances would be more likely to minimize the risk of diversion and other concerns).

priorities outlined in the Cole Memo. However, this is a delicate balance because it raises privacy concerns<sup>152</sup> which could discourage doctors from prescribing treatments. It could also be a way for patients who are seeking treatment to be encouraged to obtain psychedelics on the black market.<sup>153</sup>

Furthermore, as psychedelics become more prevalent and mainstream, states may opt to restrict advertising for these substances until they are more widely accepted. Addressing substance use disorders could involve limiting advertisements for psychedelic medicines and regulating the use of psychedelics to specific patient demographics. Limiting advertising would be a tool to ensure that youth are not being exposed to these substances, which, if seen, likely would lead to illicit activity.<sup>154</sup> Moreover, such advertising would also be subject to regulation by the Food and Drug Administration (FDA).<sup>155</sup> Given that prescription drug advertisements fall under the purview of the FDA, such oversight would indicate the federal government's acknowledgment of the medicinal benefits of psychedelics and imply a reduced likelihood of federal intervention. Therefore, restricting advertising would not only mitigate youth exposure but also convey federal support for this form of treatment.

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<sup>152</sup> *Id.*

<sup>153</sup> *Id.*

<sup>154</sup> *Id.*

<sup>155</sup> *See* 21 U.S.C. § 352 ((giving the Food and Drug Administration the authority to regulate prescription drugs under Section 502(n) of the Food, Drug, and Cosmetic Act); *id.* § 353c (stating that the Secretary may require the submission of any television advertisement for a drug and may recommend or require changes to the advertisement depending on the nature of the statement).



Overall, implementing these safeguards will allow states to safely provide the right treatment for people with mental health issues.

#### *A. Proposed Regulatory Framework*

There are several contrasting ways in which legislation can be implemented at the various levels of government. At the federal level, as previously discussed, it could be done through breakthrough therapy designations, support from Congress, or administrative-level change. With federal legislation looking bleak for passing reform acts for psychedelic substances, the state and local governments are in a much stronger position to pass various reform measures.

In keeping with the current federal framework, states can pass legislation that will ensure a federal backlash does not occur. To do so, state legislatures need to develop a well-regulated system that addresses the mental health issues that people face, while providing a comprehensive and safe setting under strict conditions. A proposed model legislation could look as follows:

(1) State Attorney General's should issue a directive where prosecutors are directed to not target clinical settings or individual patients for partaking in the use of psychedelics.<sup>156</sup> This will ensure that decriminalization measures are

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<sup>156</sup> See Memorandum from N.J. Att'y Gen., Gurbir S. Grewal, to Dir., Div. of Crim. Just. & All Prosecutors, AG Directive 2021-1 (Feb. 22, 2021) (instructing state, county, and municipal prosecutors to dismiss pending charges as of February 22, 2021, for any marijuana offense that is no longer illegal under state law).

in place while recognizing the medical value.<sup>157</sup>

(2) State-regulated clinics or other types of settings need to be fully licensed.<sup>158</sup> Additionally, the clinicians or physicians that are administering these psychedelic medicines need to be board-certified.<sup>159</sup> Accreditation would allow these specialists to have the best training in the administration of psychedelics. Similar to continuing legal education (CLE) for attorneys, these physicians need to have yearly required training where they are educated on the law as it is drastically shifting, as well as continuing to study the medicines and their efficacy.

Implementing new training programs could prove highly beneficial in enhancing the quality of care provided at clinics. These programs could focus on advanced medical techniques, patient communication, and the latest developments in healthcare. Moreover, the inclusion of social workers in these clinics could significantly augment the support system for both doctors and patients.<sup>160</sup> Social workers could offer specialized counseling, assistance with

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<sup>157</sup> *Id.*

<sup>158</sup> *See, e.g., supra* notes 93–101 and accompanying text (detailing Colorado legislation that decriminalizes the possession of psilocybin and implements a licensing network for the therapeutic use of psychedelics for medical treatment of mental health issues); *supra* notes 115–133 (detailing the extensive licensing framework in Oregon for the manufacturing, distribution, and medical use of psychedelics for medical treatment).

<sup>159</sup> *See supra* note 158 (discussing the Colorado and Oregon licensing requirements).

<sup>160</sup> *See* Courtney Hutchison & Sara Bressi, *Social Work and Psychedelic-Assisted Therapies: Practice Considerations for Breakthrough Treatments*, 49 *CLINICAL SOCIAL WORK JOURNAL* 356, 362 (2021) (speaking to the value of training social workers to include them in the emerging field of psychedelic psychotherapy).

navigating the healthcare system, and emotional support, thereby contributing to a more holistic approach to patient care.<sup>161</sup>

(3) Funding needs to be earmarked for researchers to study the efficacy of these drugs in these clinical settings. Clinical trials would have to be through the FDA.<sup>162</sup> This research could be used to urge the federal government to rethink the scheduling of these substances.<sup>163</sup> Moreover, it could also be a means for other psychedelics such as ibogaine or DMT to become regulated.<sup>164</sup>

(4) The patients seeking these services must be over twenty-one years of age. Recognizing the value these psychedelic medicines bring to people who are on the brink of suicide or those who want to experiment, states need to be open to letting all individuals receive treatment.<sup>165</sup> This will help alleviate some of the concerns with people seeking psychedelics on the black market.

(5) Psychedelics will not be allowed to be sold at retail stores. In keeping with the priorities of the federal government, if a person is caught selling such psychedelics or is involved in giving substances to minors, they will pay a

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

<sup>162</sup> *See Marks, supra* note 80, at 137 (discussing how New York and Vermont were considering creating state-sponsored clinical trials in collaboration with the FDA. The proposed laws would allocate funds to study ibogaine therapy as a method to combat the opioid crisis in these states).

<sup>163</sup> *See supra* notes 5–8 (explaining that the DEA is responsible for drug schedule classification).

<sup>164</sup> *See supra* note 93 (citing Colorado Proposition 122 where in 2026, Colorado regulators could decide to create similar programs for DMT, ibogaine and mescaline).

<sup>165</sup> *See Marlan, supra* note 113, at 855 (highlighting how psychedelic medicines are being renewed to address the current mental health and opioid epidemics, but also how they are being found to “enhance the wellbeing of individuals without health problems”).

heavy fine and be subject to jail time.<sup>166</sup>

The proposed model legislation blends the federal government's desire for tight controls with state autonomy to implement their own safeguards that still allow for progressive psychedelic use. This seems to result in a healthy balance where patients are receiving an effective form of treatment without the federal government stepping in to shut it down. With this all-in mind, other factors need to be considered, as the above-mentioned items are the first steps of a regulatory framework.

#### IV. ADDITIONAL FACTORS TO BE CONSIDERED IN THE PSYCHEDELIC INDUSTRY

Other factors to be considered, especially in the aftermath of the cannabis boom, is the enthusiasm for commercializing and patenting psychedelics.<sup>167</sup> This raises concern that with more federal legislation, big pharmaceutical companies will swallow competition, potentially leaving patients paying exorbitant prices for treatment.<sup>168</sup> Seeking patient protection is a way to bar others from producing something similar, thus allowing for market control.<sup>169</sup> However, when something is naturally occurring, it is excluded subject matter

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<sup>166</sup> *Supra* notes 5–8 and accompanying text (explaining that the DEA is responsible for drug schedule classification).

<sup>167</sup> See generally Mason Marks & I. Glenn Cohen, *Patents on Psychedelics: The Next Legal Battlefield of Drug Development*, 135 HARV. L. REV. 212 (2022) (discussing the ethical, legal, and social implications of patenting these controversial substances).

<sup>168</sup> *Id.* at 216–17, 235.

<sup>169</sup> *Id.* at 216–17.

for patent eligibility.<sup>170</sup> Unfortunately, “patent applicants can overcome this hurdle by modifying the structure of psychedelic compounds, producing them through new methods, or creating novel formulations.”<sup>171</sup> After navigating these hurdles, the issuing of such patents will likely fall to only those that can afford the costs of research and development.<sup>172</sup> Taken together, if these large companies are the only ones obtaining meritless patents, over time they “will have an outsized influence over potential changes to the law, especially those that threaten their dominant positions.”<sup>173</sup>

As evidenced-based psychedelic treatments become more established, examiners at the Patent and Trademark Office should work to better understand the nature of psychedelic substances and compounds. Once that occurs, they can sift through these insignificant advancements that do not meet the patent eligibility requirements and reject any applications seeking patents on psychedelics.<sup>174</sup> Scholars and clinicians can hopefully continue to produce literature that provides insight into the psychedelic industry, educating those in

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<sup>170</sup> *See id.* at 218; *see also* 218 n.37 (citing *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948)) (stating that natural phenomena are “manifestations of laws of nature, free to all men and reserved exclusively to none”).

<sup>171</sup> *Marks & Cohen*, *supra* note 167, at 218.

<sup>172</sup> *See id.* (discussing how, in many cases, only large, well-capitalized firms can navigate the murky regulatory waters surrounding psychedelics research and development. Granting patent exclusivity enhances existing disparities, and the unique characteristics of psychedelics, together with the regulatory environment surrounding them, may increase the likelihood of issuing bad patents--patents granted on inventions that do not meet patentability requirements or that were patented in bad faith to block competition).

<sup>173</sup> *Id.* at 235.

<sup>174</sup> *See id.* at 218.

the position to better comprehend these naturally occurring substances and compounds.

An additional factor to consider is cost. Particularly, individuals who are of low socioeconomic are disparately disadvantaged because they cannot bear the costs of treatment. When considering the costs of treatment, one option will be to determine whether insurance companies will be supplementing the expense. If so, there needs to be an understanding of who qualifies for treatments, as well as the varying costs for different health plans. Another option, as seen in Oregon, once a service center is licensed, the licensee will determine the cost of their service.<sup>175</sup>

Other individuals, those with more financial resources, seek treatment outside the United States through private organizations.<sup>176</sup> These individuals are traveling all over, including Mexico and Jamaica, participating in very expensive treatment plans.<sup>177</sup> For example, a retreat in Mexico, for five days, can cost upwards of \$4,200, with a seven-day retreat costing \$6,000.<sup>178</sup> Another example includes U.S.-based organizations sending individuals overseas to participate in the treatment program.<sup>179</sup> A military veteran organization, Veterans Exploring Treatment Solutions (VETS), provides grants to Special

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<sup>175</sup> See Or. Rev. Stat. §§ 475A.305, 475A.450 (2023).

<sup>176</sup> See, e.g., *Book Your Retreat*, THE BUENA VIDA, <https://thebuenavida.net/application> (last visited Mar. 14, 2023). (offering retreats abroad).

<sup>177</sup> See e.g., *id*; SILO WELLNESS, *supra* note **Error! Bookmark not defined.**,

<sup>178</sup> BUENA VIDA, *supra* note 176.

<sup>179</sup> See *Fighting For Those Who Fought For Us*, VETERANS EXPLORING TREATMENT SOLS., <https://vetsolutions.org> (last visited Mar. 15, 2023).

Operations Forces (SOF) veterans.<sup>180</sup> These grants help the veteran travel outside the U.S. to receive psychedelic-assisted therapy treatment.<sup>181</sup>

While many of these trips seem to be wonderful vacation getaways, it calls for concern given that these retreats do not occur on U.S. soil. These different locations may provide “safe access” to psychedelic substances, but it is difficult to ascertain how well-regulated and well-controlled these retreats are. Emphasis needs to be placed on the fact that with little oversight and control, people seeking such treatment need to be very mindful of any potential negative consequences. With the state legislation framework in mind, at least users will know that their treatment is being closely monitored following strict adherence to rules and regulations.

Patents, commercialization, and costs are not the exhaustive list of items to be considered when drafting legislation, figuring out what works to regulate this rapidly evolving industry, and simultaneously providing treatment to people. The future models will have to take this all into account as they draft legislation.

## V. CONCLUSION

The “traditional approach” to treating patients with various mental health issues typically involves some version of talk therapy or providing a patient

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<sup>180</sup> *Id.*

<sup>181</sup> *See id.*

with copious medications.<sup>182</sup> However, an alternative treatment plan with the use of psychedelic substances or psychedelic medicines is a rejuvenated approach that is gaining momentum across the country.<sup>183</sup> Numerous states are recognizing that people are not getting the results they desire with these traditional approaches.<sup>184</sup> Thus, they are developing diverse forms of legislation that either create further studies into the use of psychedelics or are taking a more progressive position by allowing for psychedelic substances to be used under clinical supervision.<sup>185</sup> Even with these progressive reforms, the biggest concern is the federal response.<sup>186</sup>

The federal government could be the largest legal obstacle standing in the way of psychedelic substance use reform. Psilocybin, one of the most commonly used psychedelics, is still a Schedule I substance.<sup>187</sup> Under that designation and in the eyes of the federal government, psilocybin provides no medical benefits.<sup>188</sup> The same holds for cannabis, which is also a Schedule I

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<sup>182</sup> See *Mental Illness*, MAYO CLINIC, <https://www.mayoclinic.org/diseases-conditions/mental-illness/diagnosis-treatment/drc-20374974> (last visited Apr. 3, 2024).

<sup>183</sup> See *Tupper et al.*, *supra* note 10, at 1054 (discussing the reemergence of psychedelic substances in clinical research studies and their potential use in treating various mental health conditions such as PTSD, anxiety, depression, and addiction).

<sup>184</sup> See Marlan, *supra* note **Error! Bookmark not defined.**, at 854.

<sup>185</sup> See *supra* Part II. A (highlighting the different approaches states are taking to pass legislation related to psychedelic substances as well as states' efforts to decriminalize psychedelics or create task forces to study their potential benefits).

<sup>186</sup> See *supra* Part I. C (discussing the concept of federal preemption and the way it may apply to state laws regulating psychedelics and additionally, how the federal government's stance on psychedelic substances, particularly their classification as Schedule I drugs under the Controlled Substances Act, could be the largest legal obstacle to state-level psychedelic reform).

<sup>187</sup> See Drug Enforcement Agency (DEA), *supra* note 6.

<sup>188</sup> *Id.*



substance.<sup>189</sup> However, many states have legalized cannabis for recreational purposes in some capacity.<sup>190</sup> If anything is telling over the last decade of cannabis reform, then psychedelic substances have a glimmer of hope to follow in the same path.

Proponents of the psychedelic movement may argue that the federal government is better equipped in providing this type of treatment to individuals. Those in favor of implementation through a national landscape can easily argue that the federal government has the means and the resources that cast larger ways of minimizing health equity gaps that may exist between the various states. Moreover, the federal government has far greater regulatory authority, particularly in the healthcare industry. This could serve useful by allowing more access to healthcare services. Lastly, funding of such programs can have a significant impact on programs and initiatives, ensuring that there exists less health disparities.

However, due to the uncertainty of how the federal government will respond, states are in an adequate position to continuously push for reformative measures. States are better suited in providing this type of treatment because they are keener on the unique or special challenges associated with their populations.

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<sup>189</sup> *Id.*

<sup>190</sup> National Conference of State Legislatures (NCSL), Cannabis Overview, <https://www.ncsl.org/civil-and-criminal-justice/cannabis-overview> (last visited Apr. 17, 2024) (stating that twenty-four states have legalized small amounts of cannabis for adult recreational use).

Further, states have more flexibility to develop new approaches and find the most effective solution, cutting out blanket federal policies. Concurrently, the federal government is well suited in fostering a relationship with these states and working with them in their efforts. This can be done in several ways, either through the FDA or the U.S. Attorney General and the Department of Justice. Either way, the legal landscape going forward may be uncertain because of the federal government but the outlook of psychedelic use in some form by state legislative measures seems to be very promising.

# THE INCREASING GLOBALIZATION OF PHARMACEUTICAL CLINICAL TRIALS: BENEFITS, DRAWBACKS, AND CONCRETE SOLUTIONS

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<sup>1</sup> Alexa Chronister, Duke University School of Law, J.D. expected 2024; University of Delaware, B.A. 2020. Duke-Margolis Center for Health Policy Scholar. Thank you to Professor Arti Rai for her support and guidance through the writing process, the editors and staff of the *Health Law & Policy Brief* for their detailed review and feedback, and my family for their continued support of my academic and professional efforts.

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## INTRODUCTION

In 1996, Nigeria was experiencing a severe meningitis epidemic that resulted in nearly 12,000 fatalities.<sup>2</sup> The epidemic was combatted through the collaborative efforts of a variety of non-governmental organizations, including the International Committee of the Red Cross (ICRC), the World Health Organization (WHO), and a National Task Force created by the Federal Ministry of Health.<sup>3</sup> In Kano, Nigeria, Doctors Without Borders was treating children with chloramphenicol injections, an antibiotic endorsed by the WHO and already approved for American children.<sup>4</sup> At the same time, the United States (U.S.) pharmaceutical company, Pfizer, was working to bring a new antibiotic, “Trovan,” to market.<sup>5</sup>

Wall Street analysts predicted that Pfizer would reap \$1 billion in revenue each year if Trovan was approved for all of its potential uses, including for

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<sup>2</sup> Idris Mohammed, Abdussalem Nasidi, A. S. Alkali, M. A. Garbarti, E. K. Ajayi-Obe, Kudi A. Audu, Abdulmumini Usman & Suleiman Abdullah, *A Severe Epidemic of Meningococcal Meningitis in Nigeria, 1996*, TRANSACTIONS OF THE ROYAL SOC’Y OF TROPICAL MED. AND HYGIENE, 265, 265 (2000), <https://pubmed.ncbi.nlm.nih.gov/10974995>.

<sup>3</sup> *Id.*

<sup>4</sup> See Belinda Archibong & Francis Annan, *What Do Pfizer’s 1996 Drug Trials in Nigeria Teach Us About Vaccine Hesitancy?*, BROOKINGS (Dec. 3, 2021), <https://www.brookings.edu/blog/africa-in-focus/2021/12/03/what-do-pfizers-1996-drug-trials-in-nigeria-teach-us-about-vaccine-hesitancy> (noting that chloramphenicol is “a well-known antibiotic endorsed by the World Health Organization”); see also Joe Stephens, *Where Profits And Lives Hang In Balance*, WASH. POST (Dec. 17, 2000), [https://www.washingtonpost.com/archive/politics/2000/12/17/where-profits-and-lives-hang-in-balance/90b0c003-99ed-4fed-bb22-4944c1a98443/?itid=lk\\_inline\\_manual\\_29](https://www.washingtonpost.com/archive/politics/2000/12/17/where-profits-and-lives-hang-in-balance/90b0c003-99ed-4fed-bb22-4944c1a98443/?itid=lk_inline_manual_29) (explaining that Doctors Without Borders was using chloramphenicol to treat patients in Kano).

<sup>5</sup> Archibong & Annan, *supra* note 4.

treating meningitis.<sup>6</sup> However, preliminary testing of Trovan in adults revealed serious side effects, such as liver issues and cartilage abnormalities.<sup>7</sup> Pfizer could not find a sufficient number of U.S. patients for its trials<sup>8</sup> and saw the epidemic as an opportunity to test the drug in pediatric patients.<sup>9</sup> Trovan had not yet been tested in any pediatric patient.<sup>10</sup>

Pfizer conducted a trial at a hospital in Kano, where Doctors Without Borders was providing free treatment and chose a group of 200 children to participate.<sup>11</sup> The children were between three months and eighteen years old.<sup>12</sup> Half of them received Trovan and the other half received the standard treatment that Doctors Without Borders was providing.<sup>13</sup> Unfortunately, a month later, eleven of the children were dead and many who survived reported various disabilities, such as liver failure and paralysis.<sup>14</sup> Of those eleven, reports showed that five of the children were given Trovan and that the six who received the standard treatment were only given the full dosage on day one, receiving just one-

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<sup>6</sup> Stephens, *supra* note 4.

<sup>7</sup> Archibong & Annan, *supra* note 4.

<sup>8</sup> Stephens, *supra* note 4.

<sup>9</sup> Archibong & Annan, *supra* note 4.

<sup>10</sup> Belinda Archibong & Francis Annan, *We Are Not Guinea Pigs: The Effects Of Negative News On Vaccine Compliance*, BROOKINGS, 1, 4 (Dec. 2021) [https://www.brookings.edu/wp-content/uploads/2021/12/We-are-not-guinea-pigs\\_final.pdf](https://www.brookings.edu/wp-content/uploads/2021/12/We-are-not-guinea-pigs_final.pdf).

<sup>11</sup> Tamar Lewin, *Families Sue Pfizer On Test Of Antibiotic*, N.Y. TIMES (Aug. 30, 2001), <https://www.nytimes.com/2001/08/30/business/families-sue-pfizer-on-test-of-antibiotic.html>.

<sup>12</sup> Nicole Perlroth, *Pfizer's Nigerian Nightmare*, FORBES (Nov. 20, 2008) <https://www.forbes.com/forbes/2008/1208/066.html>.

<sup>13</sup> Stephens, *supra* note 4.

<sup>14</sup> Archibong & Annan, *supra* note 10, at 4.

third of the dose each day afterwards.<sup>15</sup> Pfizer contends that this is because the injections can be painful and an on-site doctor believed the lower-than-standard dose would be more than adequate.<sup>16</sup> However, this belief was not proven until years later when a study from Doctors Without Borders showed a lower dosage to be effective.<sup>17</sup> One of the children who died during the trial was a ten-year-old girl identified by her patient number, 0069.<sup>18</sup> She was given a dose of Trovan and a day later her health began declining with records noting that “one of her eyes froze in place.”<sup>19</sup> She died on her third day of treatment after receiving the same dose of Trovan each day, without additional intervention.<sup>20</sup>

The way in which the Trovan drug trials were facilitated would not have occurred in the U.S. First, Pfizer researchers prepared the study over just six weeks, as compared to the year or longer timeframe common in the U.S.<sup>21</sup> Second, American meningitis patients generally receive fast-acting intravenous medications to treat meningitis, but the Nigerian patients received an oral form of Trovan.<sup>22</sup> Critically, patient consent differed substantially. Many parents of trial participants claimed they were unaware that the Trovan trial was experimental

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<sup>15</sup> Perloth, *supra* note 12.

<sup>16</sup> *Id.*

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

<sup>18</sup> Stephens, *supra* note 4.

<sup>19</sup> *Id.*

<sup>20</sup> *Report Of The Investigation Committee On The Clinical Trial Of Trovan By Pfizer, Kano, 1996*, THE FED. MINISTRY OF HEALTH 1, 86 (2001), [https://www.circare.org/info/trovan\\_clinicaltrialreport.pdf](https://www.circare.org/info/trovan_clinicaltrialreport.pdf).

<sup>21</sup> Stephens, *supra* note 4.

<sup>22</sup> *Id.*

and that they believed their children were being treated with the standard medication.<sup>23</sup> Doctors, laboratory technicians, and others who helped combat the epidemic say that patients did not know they were participating in an experiment or that it was research.<sup>24</sup> If conducted in the U.S., standards would have required Pfizer to explain the nature of the experimental study, the risks, and alternative treatments to patients who then would have signed an approval.<sup>25</sup> While the researchers in Nigeria generated a consent form that a Nigerian committee approved, the families from rural villages were often illiterate.<sup>26</sup> Local nurses helped doctors speak to the families, but none of the nurses or the children's parents ever signed the forms.<sup>27</sup> Additionally, other planned trial procedures were deserted, including blood testing.<sup>28</sup> The patients were to undergo a blood test on arrival and then receive an additional test after five days.<sup>29</sup> Yet, according to an internal report from Pfizer, this practice "was generally abandoned 'due to the shortage of medical staff.'"<sup>30</sup>

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<sup>23</sup> Archibong & Annan, *supra* note 4.

<sup>24</sup> Stephens, *supra* note 4.

<sup>25</sup> *Id.*

<sup>26</sup> *Id.*

<sup>27</sup> *Id.*

<sup>28</sup> *Id.*

<sup>29</sup> *Id.*

<sup>30</sup> Stacey B. Lee, *Informed Consent: Enforcing Pharmaceutical Companies' Obligations Abroad*, 12 HEALTH & HUM. RTS. J., 15, 16 (2010), <https://cdn1.sph.harvard.edu/wp-content/uploads/sites/2469/2013/07/4-Lee.pdf> ("If a child was not responding well to Trovan [after the follow-up], protocol required switching the child's medication to ceftriaxone.").



In the end, the U.S. never approved marketing Trovan for children in the U.S. or in Nigeria.<sup>31</sup> A Food and Drug Administration (FDA) audit uncovered dozens of discrepancies in trial records, and Pfizer withdrew the drug's use for pediatric meningitis from its application.<sup>32</sup> The FDA advised doctors to use Trovan "only in rare cases and only in hospitals," after the agency received over 100 reports of patients suffering from liver damage while taking Trovan.<sup>33</sup> In Europe, regulators stopped sales of Trovan entirely.<sup>34</sup>

Pfizer's Trovan trials in Nigeria are not unique, and questionable foreign clinical trial practices are not confined to the 1990s. Decreased regulation and oversight of foreign clinical trials continue to allow lax standards that harm foreign populations. Foreign trials are technically required to be conducted under an Investigational New Device (IND).<sup>35</sup> INDs are requests from a sponsor of a clinical trial to receive FDA authorization in order to administer an investigational drug to humans.<sup>36</sup> Foreign trials conducted under INDs are required to comply with similar FDA regulations for trials conducted within the U.S., but if certain

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<sup>31</sup> Stephens, *supra* note 4.

<sup>32</sup> Perloth, *supra* note 12.

<sup>33</sup> Melody Petersen, *Unforeseen Side Effects Ruined One Blockbuster*, N.Y. TIMES (Aug. 27, 2000), <https://www.nytimes.com/2000/08/27/business/unforeseen-side-effects-ruined-one-blockbuster.html>.

<sup>34</sup> Stephens, *supra* note 4.

<sup>35</sup> Y. T. Yang, Brian Chen & Charles L. Bennett, *Offshore Pharmaceutical Trials: Evidence, Economics, and Ethics*, Mayo Clinic Proc: Innovations, Quality & Outcomes, 226, 227 (Sept. 2018), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6132216>.

<sup>36</sup> *Information For Sponsor-Investigators Submitting Investigational New Drug Applications (INDs)*, FDA, <https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/investigational-new-drug-applications-inds-cber-regulated-products>.

requirements are met, the FDA can consider data from foreign studies not conducted under an IND.<sup>37</sup> Unfortunately, the FDA is often unaware of studies that are not conducted under INDs because none of the data is required to be submitted to the FDA, unless and until a company seeks approval of the drug.<sup>38</sup> Thus, by the time these reports are submitted, a trial may have ended and harm may already have occurred.<sup>39</sup>

This issue is only amplified by the significant increase in the number of trials pharmaceutical companies are conducting overseas. Between approximately 1990–2010, foreign trials increased more than 2,000%, and in 2008, eighty percent of FDA-approved marketing applications contained data from foreign clinical trials.<sup>40</sup> Most of these trials are conducted in low- and middle-income-countries (LMICs),<sup>41</sup> primarily because they tend to have less regulation, lower overall costs, and a higher participant recruitment rate.<sup>42</sup> These foreign trials

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<sup>37</sup> Yang, *supra* note 35.

<sup>38</sup> *Id.*

<sup>39</sup> Stephens, *supra* note 4.

<sup>40</sup> See 'Explosive' Growth in Foreign Drug Testing Raises Ethical Questions, PBS (Aug. 23, 2011, 2:46 PM), <https://www.pbs.org/newshour/health/sending-us-drug-research-overseas> ("The Department of Health and Human Services reports more than a 2,000 percent increase in the number of foreign trials for U.S. drugs over the past two decades."); see also DPT. HEALTH & HUM. SERVS. OFF. INSPECTOR GEN., *Challenges to FDA's Ability to Monitor and Inspect Clinical Trials*, 1, 10 (June 2010) ("Eighty percent of approved marketing applications for drugs and biologics contained data from foreign clinical trials.").

<sup>41</sup> Ilja R. Pavone, *Legal Responses to Placebo-Controlled Trials in Developing Countries*, 27 GLOB. BIOETHICS, 76, 76 (May 2016), <https://doi.org/10.1080/11287462.2016.1192979>.

<sup>42</sup> See Yang, Chen & Bennet, *supra* note 37, at 226 (describing why trials are conducted outside the U.S.).

continue to pose pressing legal and ethical questions around the participation of vulnerable populations.

Poorly conducted foreign trials bring serious and broad-reaching consequences. There are not only critical ethical implications of conducting these trials on vulnerable populations in LMICs, but also a significant potential for global health to be harmed because of the distrust these trials can create. For example, in 2003, a few years after the Trovan trials ended, Muslim leaders led a boycott of polio vaccination campaigns.<sup>43</sup> Many boycott participants specifically cited the drug trials as a significant factor behind their involvement.<sup>44</sup> As a result of the boycott, polio prevalence increased by 30%, “setting back global polio eradication efforts by over a decade.”<sup>45</sup> Moreover, Muslim mothers significantly reduced vaccinations of their children born after 2000.<sup>46</sup>

The Trovan trials occurred decades ago, but they continue to significantly impact the health of Nigerians, as well as the rest of the world. The negative impacts of the Trovan trials and other medical experimentation have shaped

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<sup>43</sup> Archibong & Annan, *supra* note 10, at 4–5 (providing that Nigerian officials discovered news of the trials through a Washington Post exposé alleging Pfizer’s fault for the children’s deaths in the Trovan trials).

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

<sup>45</sup> *Id.* (stating that Nigeria became one of the last countries in the world to be declared polio-free in 2020).

<sup>46</sup> *Id.* at 7, 30 (noting that researchers examined the differences in mean vaccination outcomes for Muslim children born before and after the 2000 Washington Post exposé).

perspectives of Western medicine in Nigeria.<sup>47</sup> When COVID-19 hit, this deeply-rooted distrust significantly contributed to vaccine hesitancy and threatened to impede the global pandemic response.<sup>48</sup> One in five people in Lagos, Nigeria had contracted COVID-19 by October 2020, more cases than every African country combined.<sup>49</sup> Despite the Trovan trial's legacy of distrust in Nigeria, clinical trials continue to be conducted in other LMICs at lower standards and with significantly less regulation than trials in the U.S.<sup>50</sup>

This article will discuss the failure of current regulations to protect participants in foreign clinical trials and the risks these reduced standards pose for the health of foreign participants, as well as for global health more broadly. It will argue that the current requirements for foreign studies, especially for those not conducted under INDs, fail to protect trial participants abroad. Further, this article will argue that increased regulation is necessary, particularly in the wake of the FDA's recent push to diversify clinical trials.

The argument proceeds in four parts. Part I provides background on foreign clinical trials, including the increase in pharmaceutical trials conducted abroad, the benefits associated with these trials, as well as the significant concerns

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<sup>47</sup> Ibrahim Garba & Danielle Paquette, *In This Nigerian City, Pfizer Fears Loom Over the Vaccine Rollout*, WASH. POST (Mar. 20, 2021, 4:05 PM), <https://www.washingtonpost.com/world/2021/03/20/nigeria-pfizer-kano-coronavirus-trovan>.

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

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

<sup>50</sup> See Part II (outlining the less stringent regulatory landscape for foreign trials compared to U.S. trials).

they currently pose. Part II describes the current regulatory landscape and compares the laws for U.S. trials to trials conducted abroad. Part III discusses the inadequacy of current regulations and addresses arguments against changing current regulations. Finally, Part IV explains the FDA’s call to diversify clinical trials and sets out concrete recommendations for further regulation.

#### I. THE INCREASE IN PHARMACEUTICAL TRIALS CONDUCTED ABROAD – BENEFITS AND DRAWBACKS

Clinical trials have increasingly moved overseas in the past few decades. This trend began around the mid-1990s when trials started to be outsourced to foreign locations and trials in Western Europe and the U.S. began to decline.<sup>51</sup> Between approximately 1990–2010, foreign trials increased more than 2000%,<sup>52</sup> and in 2008, the Office of the Inspector General (OIG) reported that eighty percent of FDA approved marketing applications contained foreign trial data.<sup>53</sup> As of April 2, 2023, of the 447,322 studies registered on ClinicalTrials.gov, 237,177 (fifty-three percent) were non- U.S. only trials, compared to just 139,189 (31%) of trials that were U.S. only trials.<sup>54</sup> Conducting trials overseas offers advantages for pharmaceutical companies, as well as certain benefits for trial host countries and

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<sup>51</sup> Darby Hill, *Reining in the Commercialized Foreign Clinical Trial*, 36 J. LEG. MED., 367, 372 (2015), <https://doi.org/10.1080/01947648.2015.1137505>.

<sup>52</sup> ‘Explosive’ Growth in Foreign Drug Testing Raises Ethical Questions, *supra* note 40.

<sup>53</sup> See *Challenges to FDA’s Ability to Monitor and Inspect Clinical Trials*, *supra* note 40 and accompanying text.

<sup>54</sup> *Trends, Charts, and Maps*, ClinicalTrials.gov (2023), <https://clinicaltrials.gov/ct2/resources/trends>.

public health at large. However, there are also significant drawbacks. A key concern is the vulnerability of the participating populations, especially given that the most popular locations for trials are in LMICs such as China, India, Thailand, and Russia, as well as Latin American and Sub-Saharan African countries.<sup>55</sup>

*A. Motivations Behind Pharmaceutical Companies Conducting Clinical Trials Abroad*

Clinical trials are a very costly and time-consuming endeavor for pharmaceutical companies. While the exact cost and timeline of trials are debated, studies often report costs in the tens to hundreds of millions<sup>56</sup> and time from testing to marketing a drug is reported to be around seven-and-a-half years.<sup>57</sup> A significant factor driving both the cost and length of studies is participant recruitment challenges and subsequent dropout rates. Timelines for participant enrollment are not met in about eighty percent of trials, and every day a trial is

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<sup>55</sup> Pavone, *supra* note 41, at 79.

<sup>56</sup> See Thomas J Moore, James Heyward, Gerard Anderson, & G Caleb Alexander, *Variation in The Estimated Costs Of Pivotal Clinical Benefit Trials Supporting The Us Approval of New Therapeutic Agents, 2015–2017: A Crosssectional Study*, *BMJ OPEN*, 1, 2 (May 11, 2020), <http://dx.doi.org/10.1136/bmjopen-2020-038863> (finding that the estimated cost of trials for new therapeutics between 2015 and 2017 was between 20 and 102 million dollars); Y. Tony Yang, Brian Chen, & Charles L. Bennett, *supra* note 36, at 226 (“The average drug requires roughly \$2.6 billion to bring to market, more than half of which is spent on clinical trials.”); Thomas J. Moore, Hanzhe Zhang, & Gerard Anderson, *Estimated Costs of Pivotal Trials for Novel Therapeutic Agents Approved by the US Food and Drug Administration, 2015–2016*, 178 *JAMA INTERNAL MED.*, 1451, 1454 (Sept. 24, 2018), [10.1001/jamainternmed.2018.3931](https://doi.org/10.1001/jamainternmed.2018.3931) (stating that of the 138 trials conducted between 2015-2016, costs ranged from \$12.2 million–\$33.1 million).

<sup>57</sup> Aylin Sertkaya, Anna Birkenbach, Ayesha Berlind, & John Eyraud, *Examination Of Clinical Trial Costs and Barriers For Drug Development*, *ASPE* (July 24, 2014), 1-1, 4-3, <https://aspe.hhs.gov/reports/examination-clinical-trial-costs-barriers-drug-development>.

delayed can cost companies anywhere from \$600,000 to \$8 million each day.<sup>58</sup> Moreover, in between six and twenty-nine percent of trials, failure to recruit sufficient participants leads to the trial being terminated entirely.<sup>59</sup> Even when patients are recruited, high dropout rates—particularly in later stages of trials—pose significant barriers to success.<sup>60</sup> Overall, Americans’ participation in clinical trials remains low.<sup>61</sup> Moreover, significant racial and ethnic disparities exist amongst trial participants. It is even more challenging to recruit minority communities because of their distrust of the medical community due to the historical medical experimentation and abuses inflicted on these populations.<sup>62</sup>

Taking a clinical trial abroad provides companies with significant cost and time saving opportunities. First, researchers, physicians, nurses, and study coordinators overseas can be paid lower wages than those working in the U.S.<sup>63</sup>

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<sup>58</sup> Mette Brøgger-Mikkelsen, John Robert Zibert, Anders Daniel Andersen, Ulrik Lassen, Merete Haedersdal, Zarqa Ali, & Simon Francis Thomsen, *Changes In Key Recruitment Performance Metrics From 2008–2019 In Industry-Sponsored Phase III Clinical Trials Registered At Clinicaltrials.gov*, PLOS ONE 1, 2 (July 26, 2022), <https://doi.org/10.1371/journal.pone.0271819>.

<sup>59</sup> *Id.*

<sup>60</sup> See Walter Alexander, *The Uphill Path To Successful Clinical Trials*, 38 PHARMACY AND THERAPEUTICS, 225, 225 (Apr. 2013), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3684189> (explaining that phase 3 clinical trial dropout rates can sometimes be more than 30%).

<sup>61</sup> Shaohai Jiang & Y. Alicia Hong, *Clinical Trial Participation in America: The Roles Of Ehealth Engagement And Patient–Provider Communication*, 7 DIGIT. HEALTH, 1, 1 (Dec. 1, 2021), <https://doi.org/10.1177/20552076211067658>.

<sup>62</sup> Karen Allison, Deepkumar Patel & Ramandeep Kaur, *Assessing Multiple Factors Affecting Minority Participation In Clinical Trials: Development Of The Clinical Trials Participation Barriers Survey*, 14 CUREUS, 1,1 (Apr. 23, 2022), <https://pubmed.ncbi.nlm.nih.gov/35637812>.

<sup>63</sup> Pavone, *supra* note 40, at 77; see Rakesh Jalali, Angelica Nogueira-Rodrigues, Arunangshu Das, Bhawna Sirohi & Pankaj Kumar Panda, *Drug Development In Low- And Middle-Income Countries: Opportunity Or Exploitation?*, 42 AM. SOC’Y OF CLINICAL ONCOLOGY EDUC. BOOK, 3, 5 (June 3, 2022), [http://ascopubs.org/doi/full/10.1200/EDBK\\_10033](http://ascopubs.org/doi/full/10.1200/EDBK_10033) (arguing that much of the financial savings from taking clinical trials abroad is “attributable to the lower salaries” in LMICs).

Additionally, medical centers also often charge less than those in the U.S. For example, a “first-rate medical center in India charges one-tenth of the fee required by a second-tier American institution.”<sup>64</sup> Further, the general cost for patient procedures and testing are often lower.<sup>65</sup> Companies are also reducing costs by decreasing the time of trials. Enrollment deadlines are more easily met in these countries because they often have more willing participants, primarily due to issues of poverty and a lack of access to medical treatment.<sup>66</sup> Furthermore, decreased access to medical treatment generates a large pool of “treatment-naïve” patients — patients who have not received any other drug to treat their condition, and who usually present more advanced disease cases, compared to U.S. patients who present more risks for drug interactions.<sup>67</sup>

Additionally, these countries are often eager to host clinical trials. They sometimes actively work to attract medical research due to the financial, resource, and medical benefits a trial can bring.<sup>68</sup> In addition, many have “less stringent regulatory protections,” and oversight than the U.S.<sup>69</sup> This was the case in India, a

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<sup>64</sup> Yang, Chen & Bennett, *supra* note 37, at 226.

<sup>65</sup> See Frost & Sullivan, *Asia: Preferred Destination For Clinical Trials*, NOVOTECH, 1, 3 (Aug. 27, 2019), <https://novotech-cro.com/whitepapers/asia-preferred-destination-clinical-trials> (“Costs in Asia for procedures, diagnostic tests and visits are generally 30–40% lower than the US and European countries.”).

<sup>66</sup> Katrin Weigmann, *The Ethics Of Global Clinical Trials*, 16 EMBO REPORTS, 566, 566 (May 2015), <https://doi.org/10.15252/embr.201540398>.

<sup>67</sup> Frost & Sullivan, *supra* note 62, at 5.

<sup>68</sup> *Id.* at 11–12.

<sup>69</sup> See Bernardo Aguilera, David DeGrazia & Annette Rid, *Regulating International Clinical Research: An Ethical Framework for Policy-Makers*, 5 BMG GLOB. HEALTH, 1, 3 (May 2020),



previously popular location for foreign trials.<sup>70</sup> Foreign trials conducted in India consistently took advantage of the country's loose oversight and exploited loopholes for the minimal rules that did exist.<sup>71</sup> However, much of the sick population in India is poor, illiterate, and lacks access to quality healthcare.<sup>72</sup> A higher supply of willing participants than pharmaceutical companies demanded "resulted in inadequate protections for participants."<sup>73</sup> This high level of participant abuse resulted in 2013 litigation, where the Supreme Court of India paused the approval of new clinical trials until regulations were updated to protect participants.<sup>74</sup> The robust strengthening of trial regulations that followed made it more challenging, time-consuming, and costly to conduct trials in India.<sup>75</sup> This caused a drastic decrease in the number of foreign trials in the country.<sup>76</sup> More

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<https://gh.bmj.com/content/5/5/e002287> (discussing that increased cost can lead sponsors to move trials to countries with less regulation).

<sup>70</sup> Gerard Porter, *Regulating Clinical Trials In India: The Economics Of Ethics*, 18 DEVELOPING WORLD BIOETHICS, 365, 365 (July 9, 2017), <https://doi.org/10.1111/dewb.12156>.

<sup>71</sup> Samanth Subramanian, *Thousands of Indians Die in Unethical Clinical Trials*, THE NATIONAL (Sept. 17, 2018), <https://www.thenationalnews.com/world/asia/thousands-of-indians-die-in-unethical-clinical-trials-1.770992>.

<sup>72</sup> Mohandas K. Mallath & Tanuj Chawla, *Investigators' Viewpoint of Clinical Trials in India: Past, Present and Future*, 8 PERSP. IN CLINICAL RSCH. 31, 31 (2017), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5299802/pdf/PCR-8-31.pdf>.

<sup>73</sup> *Id.*

<sup>74</sup> *Id.* at 34.

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

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

recently, some of the strictest regulations have been relaxed and trials are once again increasing in the country.<sup>77</sup>

Overall, the benefits to pharmaceutical companies continue to push the relocation of clinical trials to LMICs. Moreover, these benefits are then likely transferred to patients in high-income countries who may receive drugs more quickly. Yet, price is likely to remain generally unaffected in high-income countries like the U.S. as companies often charge what the market can bear, independent of research and development costs.<sup>78</sup>

### *B. Benefits of Foreign Clinical Trials*

While there are many motivating factors for pharmaceutical companies to move clinical trials abroad, there are also more general benefits that these trials can bring to trial host countries and to global health overall. Clinical trials benefit host countries by strengthening their research capacity, thereby advancing health and development.<sup>79</sup> The infrastructure for clinical trials can help increase quality

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<sup>77</sup> See Moe Alsumidaie, *Indian Sites Share Challenges as Clinical Trials Grow*, APPLIED CLINICAL TRIALS (Nov. 14, 2022), <https://www.appliedclinicaltrials.com/view/indian-sites-share-challenges-as-clinical-trials-grow>.

<sup>78</sup> See Scott LaFee & Nicole Mlynaryk, *High R&D Isn't Necessarily Why Drugs Are So Expensive*, UC SAN DIEGO TODAY (Sept. 26, 2022), <https://today.ucsd.edu/story/high-rd-isnt-necessarily-why-drugs-are-so-expensive> (explaining that while “[p]harmaceutical companies claim they need to charge high drug prices to recover the costs of research and development . . . researchers found no link between the two”); see generally Nancy L. Yu, Zachary Helms & Peter B. Bach, *R&D Costs For Pharmaceutical Companies Do Not Explain Elevated US Drug Prices*, HEALTH AFFS.: FOREFRONT (Mar. 7, 2017), <https://www.healthaffairs.org/doi/10.1377/forefront.20170307.059036> (arguing that while pharmaceutical companies charge significantly higher prices in the U.S., high research and development costs are not responsible for this phenomenon).

<sup>79</sup> See Jalali et al., *supra* note **Error! Bookmark not defined.**

of care and improve patient outcomes overall, regardless of whether an individual patient participates in a trial.<sup>80</sup> This has been dubbed the “infrastructure effect.”<sup>81</sup> Moreover, by providing local doctors with exposure to advanced medical practices, the country’s medical research and domestic pharmaceutical industry may be strengthened.<sup>82</sup> Additionally, citizens of host countries stand to benefit from the opportunity to receive drugs from clinical trials. Many patients in LMICs have little or no access to drugs, and trials provide an important opportunity to receive treatment.<sup>83</sup>

Foreign clinical trials also stand to benefit global health more broadly. First, they may help improve our understanding of global diseases and foster global clinical innovation.<sup>84</sup> These trials may also help identify genetic differences that influence how diseases present and how patients respond to treatment.<sup>85</sup> In addition, LMICs provide access to treatment-naïve patients who allow trials to more accurately study the isolated effects of a particular trial drug.<sup>86</sup> Thus, while pharmaceutical companies stand to benefit from foreign trials,

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<sup>80</sup> *Id.*

<sup>81</sup> *Id.*

<sup>82</sup> See Porter, *supra* note **Error! Bookmark not defined.**

<sup>83</sup> See Yang, Chen & Bennett, *supra* note **Error! Bookmark not defined.**, at 226.

<sup>84</sup> Breanne M. Schuster, *For The Love of Drugs: Using Pharmaceutical Clinical Trials Abroad to Profit Off the Poor*, 13 SEATTLE J. FOR SOC. JUST. 1015, 1026 (2015), <https://digitalcommons.law.seattleu.edu/sjsj/vol13/iss3/16>.

<sup>85</sup> See *id.* (explaining that foreign trials can “help to shed valuable light on global diseases and ethnic differences that conducting research limited to the United States could not provide”).

<sup>86</sup> See Frost & Sullivan, *supra* note **Error! Bookmark not defined.**, at 10.

these trials also provide certain benefits to patients, host countries, and global health generally.

### *C. Drawbacks of Foreign Clinical Trials*

There are many potential benefits to conducting clinical trials abroad, but there are important considerations that may significantly lessen these perceived gains. First, while LMICs may be hot spots for clinical trials, participants from these countries may not benefit from the product they help produce. This is because most of the diseases that burden developing countries are not priorities for the pharmaceutical industry and thus little is invested into developing treatments for these conditions.<sup>87</sup> Also, patients are not guaranteed continuing treatment. Once the trial ends and treatment concludes, these lower income patients are left without access due to high drug costs, while patients in rich countries begin to reap the benefits of the trial.<sup>88</sup> This is evident by the fact that developing countries make up only a small portion of sales in the drug market.<sup>89</sup> Meanwhile, the U.S., Europe, and Japan comprise approximately 85% of the market.<sup>90</sup>

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<sup>87</sup> Pavone, *supra* note **Error! Bookmark not defined.**, at 77; see Weigmann, *supra* note **Error! Bookmark not defined.**, at 569 (explaining that tropical diseases remain neglected); see also Schuster, *supra* note 84 at 1034–35 (noting that while a lot of research is done in developing countries, “a petty percentage of research funding is devoted to drugs targeting . . . the primary ailments of those [developing] countries”).

<sup>88</sup> See Weigmann, *supra* note **Error! Bookmark not defined.**, at 569 (noting that the cost of the drugs produced by clinical trials makes them inaccessible to most people in LMICs and making them available to these patients could take years or decades).

<sup>89</sup> See Schuster, *supra* note 84, at 1034.

<sup>90</sup> *Id.*

Additionally, while LMICs may bring more willing trial participants and supply a larger amount of treatment-naïve patients, these increases in efficiency and effectiveness may not be entirely certain. Some worry that trial results from these populations may not be as applicable to American patients, especially if the participants have a genetic and cultural makeup that is very different from most Americans.<sup>91</sup> Genetic variations and cultural differences can result in a different profile of adverse events and may make certain drugs appear more effective.<sup>92</sup> Moreover, the benefits of treatment-naïve participants fall away when this more desperate population participates in multiple studies in order to increase their pay. When participants receive treatment from more than one trial at a time, it can negatively influence each individual trial by skewing the accuracy of trial data.<sup>93</sup> The risk of inaccurate data is especially high if researchers cannot account for this interference because they are unaware of the participants' involvement in multiple trials.<sup>94</sup>

Also, citizens in these countries are often more willing to participate as a result of higher poverty rates and minimal access to medical treatment.<sup>95</sup>

Companies are conducting trials at all phases overseas from phase I trials

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<sup>91</sup> Yang, Chen & Bennett, *supra* note **Error! Bookmark not defined.**

<sup>92</sup> *Id.*

<sup>93</sup> Open Channel, 'People Keep Falling Sick': How Poor Indians Are Recruited For Clinical Drug Trials, NBC NEWS (Mar. 2, 2012, 12:01 PM), <https://www.nbcnews.com/news/investigations/people-keep-falling-sick-how-poor-indians-are-recruited-clinical-flna293239>.

<sup>94</sup> *Id.*

<sup>95</sup> See Weigmann, *supra* note 66 and accompanying text.

typically involving healthy volunteers to phase III trials given to sick patients who are intended to receive the drug.<sup>96</sup> However, phase II, and more significantly, phase III trials are increasingly being moved abroad.<sup>97</sup> While phase I trials test a drug for the first time in a group of eighty or less participants, phase II and III trials increase that size to three-hundred and three-thousand participants, respectively.<sup>98</sup> Critically, phase II and III trials are where effectiveness is first determined, and where safety is confirmed before FDA approval.<sup>99</sup> The high cost of conducting phase III trials,<sup>100</sup> along with their higher dropout rates,<sup>101</sup> contribute to the popularity of hosting these trials in foreign countries. Yet, globally, almost 2 billion people lack any access to essential medicines,<sup>102</sup> which raises significant concerns regarding exploitation. While the opportunity to participate in a clinical trial helps address some of these countries' unmet medical

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<sup>96</sup> *Clinical Trial Phases Defined*, Cincinnati College of Medicine,

<https://med.uc.edu/depart/psychiatry/research/clinical-research/crm/trial-phases-1-2-3-defined>.

<sup>97</sup> Rakesh Jalali, Angelica Nogueira-Rodrigues, Arunangshu Das, Bhawna Sirohi & Pankaj Kumar Panda, *Drug Development in Low- and Middle-Income Countries: Opportunity or Exploitation?*, 42 *ASCO* 1, 4-5 (June 3, 2022), [https://ascopubs.org/doi/full/10.1200/EDBK\\_10033](https://ascopubs.org/doi/full/10.1200/EDBK_10033).

<sup>98</sup> *NIH Clinical Trials and You*, NIH, <https://www.nih.gov/health-information/nih-clinical-research-trials-you/basics>.

<sup>99</sup> *Id.*

<sup>100</sup> Aylin Sertkaya, Hui-Hsing Wong, Amber Jessup & Trinidad Beleche, *Key Cost Drivers of Pharmaceutical Clinical Trials in the United States*, 13 *CLINICAL TRIALS*, 117, 117 (Feb. 8, 2016), <https://doi.org/10.1177/1740774515625964> (finding that the average cost of a phase 3 trial ranged from 11.5 million to 52.9 million dollars, compared to a phase I trial which ranged from 1.4 million to 6.6 million dollars).

<sup>101</sup> Alexander, *supra* note 60.

<sup>102</sup> Sachiko Ozawa, Raja Shankar, Christine Leopold & Samuel Orubu, *Access to Medicines Through Health Systems in Low-and-Middle-Income Countries*, 34 *HEALTH POL'Y AND PLAN.*, iii1, iii1 (Dec. 2019), <https://doi.org/10.1093/heapol/czz119>.

needs, these needs are precisely what puts these groups at risk to be exploited.<sup>103</sup> Even if participants are not sick themselves, taking part in a trial might be the only way they can afford basic necessities to survive, such as food.<sup>104</sup> The money participants are paid is very little in American dollars, but is often considerably more than the traditional earnings in LMICs.<sup>105</sup>

In addition to concerns around more direct coercion, other considerations can also cause a lack of informed consent from trial participants. Critically, LMICs are disproportionately burdened with illiteracy. While most developed countries have a ninety-nine percent literacy rate, countries such as India have rates in the seventies and others such as South Sudan and Afghanistan have rates in the thirties.<sup>106</sup> Illiteracy can lead to patients thinking they are being treated for a disease, instead of understanding they are part of an experimental study.<sup>107</sup> Even if patients are literate, language barriers can create misunderstandings as a result

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<sup>103</sup> See Weigmann, *supra* note 66 and accompanying text.

<sup>104</sup> Schuster, *supra* note 84, at 1024.

<sup>105</sup> Open Channel, *supra* note 93.

<sup>106</sup> Katharina Buchholz, *This is How Much the Global Literacy Rate Grew Over 200 Years*, World Economic Forum (Sept. 12, 2022), <https://www.weforum.org/agenda/2022/09/reading-writing-global-literacy-rate-changed>.

<sup>107</sup> Schuster, *supra* note 81, at 1029. See e.g., Gabriela E. Minaya, Duilio J. Fuentes-Delgado, Antonio Ugalde & Núria Homedes, *A Missing Piece In Clinical Trial Inspections In Latin America: Interviews With Research Subjects In Peru*, 12 J. EMPIRICAL RSCH. ON HUM. RSCH. ETHICS, 232, 232 (July 21, 2017), <https://doi.org/10.1177/1556264617720756> (explaining that in a clinical trial held in Peru, most participants reported not understanding that they were signing up for an experimental study with new drugs that had not yet been approved).

of insufficient or incorrect translations.<sup>108</sup> Therefore, patients are often confused about their rights, including their fundamental right to withdraw from the trial.<sup>109</sup>

This potential exploitation of patients also extends to the countries themselves. In principle, countries hosting clinical trials can adopt regulations that protect citizens who participate. However, significant commercial and financial pressures may limit a country's ability to implement protective ethical regulations.<sup>110</sup> For example, after societal backlash led India to update its regulations for clinical trials, there was a major drop in trials conducted in India and research activities were shifted to other countries.<sup>111</sup> India's estimated loss was at least \$150–200 million in 2013.<sup>112</sup> Thus, both patients of LMICs and their governments can face significant pressures, that may rise to coercion, when choosing to participate in these fast-paced trials conducted under differing standards and regulations than those in the West.

Furthermore, when clinical trials do cause harm, companies rarely face sanctions and participants often lack adequate remedies. Under U.S. regulations, research institutions and pharmaceutical sponsors are not required to provide

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<sup>108</sup> Schuster, *supra* note 84, at 1029. See Suzanne Mistretta, *Amending Federal Regulations to Counteract Language Barriers in the Informed Consent Process*, 8 VOICES IN BIOETHICS, 1, 1 (Jan. 8, 2022), <https://doi.org/10.52214/vib.v8i.8815> (explaining that language barriers can interfere with informed consent).

<sup>109</sup> Schuster, *supra* note 84, at 1030.

<sup>110</sup> Porter, *supra* note 70, at 366.

<sup>111</sup> *Id.* at 371.

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



medical care or compensation for trial participants who are injured.<sup>113</sup> This is in stark contrast to most other developed nations that have adopted policies requiring those with research-related injuries to receive treatment or compensation.<sup>114</sup> India in particular has faced a significant number of deaths connected with clinical trials. For example, 2,209 people are reported to have died in clinical trials from 2011–2015.<sup>115</sup> However, inquiries into deaths are rare, especially because unlike in the U.S., countries may not have regulations in place to require an audit of deaths that occur during trials.<sup>116</sup> Moreover, families often do not receive compensation. Of the 443 deaths that occurred during clinical trials held in India during 2014 alone, just twelve were compensated.<sup>117</sup>

While trial participants have access to the tort system for a legal remedy, the system often falls short. The system is not equally navigable or accessible to these vulnerable populations because they may lack the social and financial support that are crucial to plaintiff success.<sup>118</sup> Additionally, the system typically only provides a remedy when negligence or intentional harm can be proved, yet harm can still be caused even when neither is present, particularly due to

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<sup>113</sup> Carolyn Riley Chapman, Sangita Sukumaran, Geremew Tarekegne Tsegaye, Yelena Shevchenko & Arthur L. Caplan, *The Quest for Compensation for Research-Related Injury in the United States: A New Proposal*, 47 J. L., MED., & ETHICS, 732, 733 (Dec. 2019), <https://pubmed.ncbi.nlm.nih.gov/31957586>.

<sup>114</sup> *Id.* at 736.

<sup>115</sup> Sanjeet Bagchi, *Thousands Die in Clinical Trials in India, but Compensation is Rarely Paid*, BMJ (Nov. 13, 2015), <https://doi.org/10.1136/bmj.h6149>.

<sup>116</sup> Open Channel, *supra* note 93.

<sup>117</sup> Bagchi, *supra* note 112.

<sup>118</sup> Chapman, Sukumaran, Tsegaye, et al., *supra* note 113.

decreased regulation.<sup>119</sup> Further barriers to the legal system also hinder participant recovery, including the challenge of finding legal counsel, the financial burden of legal fees, and the often lengthy timeline of litigation.<sup>120</sup>

## II. CURRENT REGULATORY LANDSCAPE

Before a clinical trial can begin in the U.S., companies must submit an Investigational New Device (IND) application to the FDA explaining that lab testing has already been completed and describing a plan for testing on human subjects.<sup>121</sup> However, foreign clinical trials do not require INDs.<sup>122</sup> Yet, FDA authority to oversee clinical trials only begins upon the submission of an IND.<sup>123</sup> This creates an enormous loophole where a trial can be conducted without FDA knowledge and a company can still eventually submit its data to support a drug application.<sup>124</sup>

### A. *Applicable Law*

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

<sup>120</sup> *Id.* at 733–34.

<sup>121</sup> C. Michael White, *The FDA's Lax Oversight of Research in Developing Countries can do Harm to Vulnerable Participants*, UCONN TODAY (Nov. 19, 2021), <https://today.uconn.edu/2021/11/the-fdas-lax-oversight-of-research-in-developing-countries-can-do-harm-to-vulnerable-participants>.

<sup>122</sup> André Ourso, *Can the FDA Improve Oversight of Foreign Clinical Trials: Closing the Information Gap and Moving Towards a Globalized Regulatory Scheme*, 21 ANN HEALTH L. (2012), 493, 499 (2012), <https://pubmed.ncbi.nlm.nih.gov/22606923>.

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

<sup>124</sup> C. Michael White, *Current System of Overseeing Drug Trials in Developing Countries by the FDA is Dangerous*, 54 ANNALS OF PHARMACOTHERAPY, 928, 928–29, <https://doi.org/10.1177/1060028020906484>.

Section 312 of Title 21 of the Code of Regulations sets out the laws concerning INDs for clinical trials.<sup>125</sup> INDs are requests from a sponsor of a clinical trial to receive FDA authorization in order to administer an investigational drug to humans.<sup>126</sup> Generally, human research studies must be conducted under an IND if certain conditions are met. These conditions include that 1) the research involves a drug, 2) the research is a clinical investigation, and 3) the clinical investigation is not otherwise exempt from IND requirements.<sup>127</sup> An IND application must include data from animal studies, manufacturing information, toxicity data, proposed protocols for trials, any data collected from prior research on humans, and information about the study's investigator.<sup>128</sup> After an IND is submitted, it is reviewed to determine if safety for human testing has been demonstrated, if the drug is able to be safely manufactured, and if the proposed trials have reasonable safeguards for participants.<sup>129</sup>

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<sup>125</sup> 21 CFR § 312.

<sup>126</sup> *Information For Sponsor-Investigators Submitting Investigational New Drug Applications (INDs)*, FDA, <https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/investigational-new-drug-applications-inds-cber-regulated-products>.

<sup>127</sup> *Investigational New Drug Applications (INDs) — Determining Whether Human Research Studies Can Be Conducted Without An IND*, FDA, 1, 2–3, <https://www.fda.gov/files/drugs/published/Investigational-New-Drug-Applications-%28INDs%29-Determining-Whether-Human-Research-Studies-Can-Be-Conducted-Without-an-IND.pdf>.

<sup>128</sup> *Investigational New Drug (IND)*, UNIV. AT BUFFALO, <https://www.buffalo.edu/research/research-services/clinical-and-behavioral-research/design-study/investigational-new-drug.html>.

<sup>129</sup> Ourso, *supra* note 122, at 498–500.

For foreign clinical trials specifically, the general acceptance of data is governed by § 312.120, while § 314.106(b) details the requirements for a drug application that uses exclusively foreign trial data.<sup>130</sup> Marketing applications can be submitted relying on data solely from foreign trials, even when the trial did not submit an IND.<sup>131</sup> These applications may be approved if three conditions are met: 1) the data provided is applicable to the population and medical practice of the U.S., 2) competent clinical investigators have performed the trials, and 3) the FDA validates the data through an inspection of the site or other appropriate means, but data can still be valid in the absence of an inspection.<sup>132</sup> Further, applicants planning to seek approval on foreign data alone are not required, but are encouraged, to meet with FDA officials prior to submission.<sup>133</sup>

However, recently, the FDA rejected Eli Lilly and Biologics' China's immunotherapy drug, despite positive clinical trial data from a trial in China.<sup>134</sup> The FDA cited the use of clinical trial data from China alone as a major factor behind rejecting the drug application.<sup>135</sup> Previous approvals based on more

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<sup>130</sup> 21 CFR § 314.106(b).

<sup>131</sup> *Challenges to FDA's Ability to Monitor and Inspect Clinical Trials*, *supra* note 40, at 6.

<sup>132</sup> 21 CFR § 314.106(b)(1)-(3).

<sup>133</sup> 21 CFR § 314.106(c).

<sup>134</sup> Dr. Charles Theuer, *The FDA Delivered A Big Win For Innovation Against Foreign "Me-Too" Drug Makers*, FORBES (Feb. 23, 2022),

<https://www.forbes.com/sites/forbesbooksauthors/2022/02/23/the-fda-delivered-a-big-win-for-innovation-against-foreign-me-too-drug-makers>.

<sup>135</sup> Jull Wechsler, *FDA Nixes Approvals Based Only On Foreign Data*, APPLIED CLINICAL TRIALS (Feb. 22, 2022), <https://www.appliedclinicaltrials.com/view/fda-nixes-approvals-based-only-on-foreign-data>.

limited foreign trial data were often for new drugs targeting serious diseases that lacked any currently effective treatments.<sup>136</sup> However, this immunotherapy drug was a “me too” drug. “Me too” drugs are those that contain the same therapeutic mechanism as an existing drug, and thus lack significant potential to improve the safety or efficacy of the existing drug.<sup>137</sup> Eli Lilly’s application was a test of the FDA’s view of both “me too” drugs whose clinical trials are conducted in a single foreign country, as well as of the recent trend in drug applications based specifically on Chinese data alone.<sup>138</sup> The denial clearly signaled the FDA’s reservations in both regards.<sup>139</sup> First, future drug applications may meet similar objections if they are only based on Chinese trial data because these trials often lack the diversity necessary to make the results applicable to the American population.<sup>140</sup> In addition, “me too” drugs that only use data from a single foreign study are also likely to face FDA objection.<sup>141</sup>

### *B. The IND Loophole*

Before 2008, under § 312.120, studies could be conducted abroad without an IND, provided that they adhered to either the 1989 Declaration of Helsinki principles or the regulations of the trial’s host country, whichever was stricter and

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<sup>136</sup> *Id.*

<sup>137</sup> Theuer, *supra* note 134.

<sup>138</sup> Wechsler, *supra* note 135.

<sup>139</sup> Ben Fidler, *FDA Rejects Lilly and Innovent Immunotherapy Sending Signal to Drugmakers*, BIOPHARMA DIVE (Mar. 24, 2022), <https://www.biopharmadive.com/news/eli-lilly-innovent-sintilimab-fda-rejection-china/620942>.

<sup>140</sup> *Id.*; Wechsler, *supra* note 135.

<sup>141</sup> Wechsler, *supra* note 133.

gave participants greater protection.<sup>142</sup> By not requiring foreign clinical trials to submit INDs before beginning research, a loophole is created for trials conducted overseas. This loophole allows pharmaceutical companies to begin trials without prior FDA review.<sup>143</sup> However, in 2008, the FDA noted that the number of new drug applications supported by foreign clinical trials was increasing and that this trend was likely to continue.<sup>144</sup> In response, it attempted to strengthen oversight of these foreign trials by amending § 312.120.<sup>145</sup> Importantly, despite the statute being amended, the loophole that existed before 2008 still persists.

The FDA articulated a variety of reasons for strengthening oversight through the amendment. First, the FDA was responding to the evolution in standards for the protection of human subjects. It explained that the revision aimed to ensure subject protection, while maintaining flexibility for trials to adapt to the differences in regulations between countries.<sup>146</sup> In addition, the agency used

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<sup>142</sup> Blake Wilson, *Clinical Studies Conducted Outside Of The United States And Their Role In The Food And Drug Administration's Drug Marketing Approval Process*, U. OA. J. INT'L L. 641, 652–57 (Aug. 6, 2013),

<https://scholarship.law.upenn.edu/cgi/viewcontent.cgi?article=1040&context=jil>.

<sup>143</sup> University at Buffalo, *supra* note 128.

<sup>144</sup> *Guidance For Industry And FDA Staff FDA Acceptance Of Foreign Clinical Studies Not Conducted Under An Ind Frequently Asked Questions*, FDA, 1, 2 (Mar. 2012), <https://www.fda.gov/files/about%20fda/published/FDA-Acceptance-of-Foreign-Clinical-Studies-Not-Conducted-Under-an-IND--Frequently-Asked-Questions.pdf>.

<sup>145</sup> 21 CFR § 312.120.

<sup>146</sup> Human Subject Protection; *Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application*, 73 FED. REG. 22,801 (Apr. 28, 2008) (to be codified at 21 CFR § 312.120).

the revision to provide additional specific guidance on how to ensure proper trial conduct and thus increase the validity of study data.<sup>147</sup>

In amending the statute, the FDA developed a new requirement that allowed studies to be conducted abroad without an IND as long as they were “conducted in accordance with good clinical practice (GCP), including review and approval by an independent ethics committee(IEC) and informed consent from subjects.”<sup>148</sup> First, GCP is defined by FDA regulations “as ‘a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials in a way that provides assurance that the data are credible and accurate and that the rights, safety, and well-being of trial subjects are protected.’”<sup>149</sup> Next, an IEC is defined at §312.3(b) as “a review panel that is responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in a clinical investigation, and is adequately constituted to provide assurance of that protection.”<sup>150</sup> The FDA allows for flexibility in meeting the IEC requirement, as local needs may cause IECs’ membership and organization to differ between countries.<sup>151</sup> Finally, informed consent is defined as “a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the

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<sup>147</sup> *Id.*

<sup>148</sup> FDA, *supra* note 127, at 1.

<sup>149</sup> *Id.* at 4.

<sup>150</sup> 21 CFR § 312.3(b).

<sup>151</sup> FDA, *supra* note 127, at 4.

trial that are relevant to the subject's decision to participate.”<sup>152</sup> This consent must be documented through written forms that are signed and dated by the participant, their parent, or their legally authorized representative.<sup>153</sup> Furthermore, the forms should be approved in writing by the IEC.<sup>154</sup>

Additionally, even if a foreign study does not meet the GCP standard, the FDA can grant a waiver. In order to receive a waiver, a waiver request must contain at least one of three pieces of information.<sup>155</sup> A request can 1) explain why compliance is impossible or unnecessary, 2) detail alternative means to satisfy the requirement, or 3) provide any other information to establish a reason for a waiver to be granted.<sup>156</sup> Further, a waiver can be granted if the FDA determines it would be in the interest of the public health to do so.<sup>157</sup> However, most foreign trials are conducted in accordance with GCP, and thus waiver requests are relatively rare.<sup>158</sup>

Despite the FDA’s aim to strengthen the integrity of foreign clinical trials through its 2008 amendment, it drew heavy criticism from those concerned that replacing the Declaration of Helsinki standards posed a threat to participant safety

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<sup>152</sup> *Id.*

<sup>153</sup> *Informed Consent FAQs*, HHS, <https://www.hhs.gov/ohrp/regulations-and-policy/guidance/faq/informed-consent/index.html>.

<sup>154</sup> FDA, *supra* note 127, at 4.

<sup>155</sup> 21 CFR § 312.120(c)(1).

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

<sup>157</sup> *Id.*

<sup>158</sup> *When Will Waivers Be Needed For Foreign Clinical Studies Not Conducted Under An IND?*, Proxima, <https://www.proximacro.com/faqs/when-will-waivers-be-needed-for-foreign-clinical-studies-not-conducted-under-an-ind>.



because they did not consider GCP an ethical standard.<sup>159</sup> The critics were right to be concerned about ethical standards in future clinical trials. The FDA is still attempting to clarify and provide guidance on the GCP standard and it released additional draft guidance on the standard as recently as 2023.<sup>160</sup> Moreover, researchers increasingly continue to go to developing countries to conduct clinical trials, and the FDA rarely prosecutes research violations.<sup>161</sup>

### III. INADEQUACY OF CURRENT REGULATIONS AND THE CASE FOR INCREASED OVERSIGHT

Although the FDA has updated its regulations and guidelines for foreign clinical trials since trials began moving overseas, current regulations do not adequately reflect the extent of this trend.<sup>162</sup> There is often a complete lack of oversight for foreign trials that do not submit INDs because the FDA may not be aware of these trials. Even for trials that submit INDs, oversight is often scarce and ineffective. In addition, current regulations do not result in a sufficient level of informed consent among trial participants. Finally, while there are valuable arguments made against increasing regulation, further regulation of foreign

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<sup>159</sup> Informed Consent FAQs, *supra* note 153.

<sup>160</sup> *E6(R3) GOOD CLINICAL PRACTICE (GCP)*, FDA (May 19, 2023), <https://www.fda.gov/media/169090/download>.

<sup>161</sup> Marisa Taylor, *FDA Launches Criminal Investigation Into Unauthorized Herpes Vaccine Research*, KFF (Apr. 12, 2018), <https://kffhealthnews.org/news/fda-launches-criminal-investigation-into-unauthorized-herpes-vaccine-research> [hereinafter *FDA Launches Criminal Investigation*].

<sup>162</sup> Hill, *supra* note 51.

clinical trials is vital, particularly in light of the FDA’s recent call to further diversify clinical trials.

A. *Lack of Oversight For Foreign Trials*

1. *The FDA may be unaware of trials without INDs*

When an IND is not submitted, and the FDA has not otherwise been consulted about a foreign trial, the agency lacks any knowledge of whether a clinical trial is taking place and where it is located.<sup>163</sup> It often takes years to complete all of the clinical trials necessary to successfully support drug applications,<sup>164</sup> which leaves the FDA in the dark until results are submitted.<sup>165</sup> Because the agency is unaware a trial is being conducted, if adverse events occur, companies can potentially recreate the study in another location without disclosing the failed study results.<sup>166</sup> Moreover, this allows companies to pick out trials that support their drug application, while failing to divulge studies that may

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<sup>163</sup> *Challenges to FDA’s Ability to Monitor and Inspect Clinical Trials*, *supra* note 40, at 11.

<sup>164</sup> *See Clinical Development Success Rates and Contributing Factors 2011 – 2020*, Biotechnology Innovation Organization, Pharma Intelligence, & QLS, 24 (Feb. 2021) (finding that from 2011–2020, the average length of a clinical trial was 2.3 years for phase I trials, 3.6 years for phase II trials, and 3.3 years for phase III trials); *see also* Chi Heem Wong & Kien Wei Siah, *Estimation of Clinical Trial Success Rates and Related Parameters*, *BIostatistics*, 273, 284 (Apr. 2019) (determining that median length for non-oncology trials ranges from 5.9–7.2 years and the median length for non-oncology trials is 13.1 years)

<sup>165</sup> *Id.* at 13, 17.

<sup>166</sup> White, *supra* note 124; *see also* C. Michael White & Lyla R. White, *Preventing A New Tuskegee: Food And Drug Administration Oversight Of Overseas Research Must Match That In The United States*, 62 *J. CLINICAL PHARMACOLOGY*, 434, 434 (Feb. 14, 2022), <https://accp1.onlinelibrary.wiley.com/doi/epdf/10.1002/jcph.1976> (explaining that if a pharmaceutical company’s study results are not to the company’s liking, the FDA would be unaware).

have revealed negative findings.<sup>167</sup> This not only poses serious concerns for the safety and efficacy of approved drugs, but could also allow adverse events and potentially troubling treatment of study participants to go undetected.

A recent example of a foreign trial escaping FDA oversight was the case of a university professor, who was not a licensed physician, yet conducted a clinical trial for a herpes vaccine.<sup>168</sup> Critically, the majority of the trial participants were Americans who were specifically flown to a foreign location to be vaccinated.<sup>169</sup> This was an egregious attempt to take advantage of relaxed international standards and evade FDA regulations.<sup>170</sup> Without an IND, the FDA was unaware of the trial and only launched a criminal investigation into the matter in 2018, two years after participants were injected overseas.<sup>171</sup> Moreover, while the FDA has begun to address the ethics of this study, the study was widely publicized with prominent investors financing the test and leaders giving public interviews regarding the trials.<sup>172</sup> For studies that are less publicized, the FDA may never hear about them and thus abuses may go unaddressed.

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<sup>167</sup> White, *supra* note 124.

<sup>168</sup> Taylor, *FDA Launches Criminal Investigation*, *supra* note **Error! Bookmark not defined.**

<sup>169</sup> Marisa Taylor, *Offshore Human Testing Of Herpes Vaccine Stokes Debate Over U.S. Safety Rules*, KFF Health News (Aug. 28, 2017), <https://kffhealthnews.org/news/offshore-rush-for-herpes-vaccine-roils-debate-over-u-s-safety-rules>.

<sup>170</sup> See Taylor, *FDA Launches Criminal Investigation*, *supra* note **Error! Bookmark not defined.** (stating that while the FDA has authority to criminally investigate, it rarely chooses to do so, instead “choosing to administratively sanction . . . researchers . . .”).

<sup>171</sup> See *id.* (stating that the researcher experimented on participants without FDA oversight).

<sup>172</sup> Alex Keown, *Big-Name Investor Peter Thiel Funds ‘Unethical’ Offshore Herpes Vaccine Trial*, BioSpace (Aug. 28, 2017), <https://www.biospace.com/article/big-name-investor-b-peter-thiel-b-funds-unethical-offshore-herpes-vaccine-trial>.

2. *For trials with INDs, oversight is often hindered by missing and nonstandard data and a lack of foreign site inspections*

Nonstandard or missing data can significantly complicate FDA oversight. Clinical trial reports may be missing site locations or subject enrollment, or otherwise exclude additional information.<sup>173</sup> When data is submitted, it may be in formats that the FDA is not able to analyze directly.<sup>174</sup> In addition, data may be presented inconsistently throughout a report making it challenging to locate information.<sup>175</sup> This not only can create an administrative burden and pose a risk to trial safety and efficacy, but it can also negatively impact the agency’s ability to meet timelines for reviewing drug applications.<sup>176</sup> In addition to submitted data, inspections of clinical trial sites are critical to oversight as they are used to ensure there are adequate protections for research participants, as well as verify the data’s quality and integrity.<sup>177</sup> However, funding for FDA inspections of foreign clinical trials “is woefully inadequate.”<sup>178</sup> In 2008, the FDA inspected less than 1% of foreign clinical trial sites.<sup>179</sup> There are many countries where the FDA does

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<sup>173</sup> *Challenges to FDA’s Ability to Monitor and Inspect Clinical Trials*, *supra* note **Error! Bookmark not defined.**, at 19.

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

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

<sup>176</sup> *Id.*

<sup>177</sup> *Id.* at 14.

<sup>178</sup> C. Michael White & Lyla R. White, *Preventing A New Tuskegee: Food And Drug Administration Oversight Of Overseas Research Must Match That In The United States*, 62 J. CLINICAL PHARMACOLOGY, 434, 434 (Feb. 14, 2022), <https://accp1.onlinelibrary.wiley.com/doi/epdf/10.1002/jcph.1976>.

<sup>179</sup> *Challenges to FDA’s Ability to Monitor and Inspect Clinical Trials*, *supra* note **Error! Bookmark not defined.** at 15.

not conduct any inspections, including countries with trials enrolling a large number of participants.<sup>180</sup> A significant contributor to the lack of foreign inspections is the significant logistical challenges officials often face. Inspectors frequently face tight timelines, struggle to obtain work visas, and can't access translators.<sup>181</sup> Additionally, the added cost of foreign inspections makes it more challenging for the agency to justify the necessity of these inspections.<sup>182</sup> Yet, even when logistical challenges are not complete barriers to inspection, officials may not inspect foreign trials until after they have already ended.<sup>183</sup> This is a result of the FDA not always having knowledge about ongoing foreign trials because these trials are often relieved of the obligation to submit an IND.<sup>184</sup>

*B. Current Regulations Lack Sufficient Informed Consent Requirements To Protect Participants*

Adequate informed consent is complex and challenging to obtain, and the U.S. has been heavily criticized for its failure to truly inform participants. Informed consent involves many elements, including explaining a patient's medical condition and existing treatment options, as well as the potential risks associated

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<sup>180</sup> See *id.* (noting that in 2008, Peru had the fourth largest trial enrollment, but the FDA did not inspect any of its trials).

<sup>181</sup> *Challenges to FDA's Ability to Monitor and Inspect Clinical Trials*, *supra* note **Error! Bookmark not defined.**, at 18.

<sup>182</sup> *Id.*

<sup>183</sup> *Challenges to FDA's Ability to Monitor and Inspect Clinical Trials*, *supra* note 40, at 15–17 (showing that FDA only inspects roughly 0.7% of foreign clinical trials sites, and that the lack of IND accounts for the lack of FDA oversight and accountability).

<sup>184</sup> Yang, Chen, & Bennett, *supra* note **Error! Bookmark not defined.**

with participating in a trial.<sup>185</sup> To comply with existing regulations, consent “must be voluntary, informed and with the individual providing consent having sufficient capacity to do so.”<sup>186</sup> Many clinical trial participants in Western countries, such as the U.S., lack an adequate understanding of the trial to support “meaningful”<sup>187</sup> informed consent.<sup>188</sup> This concern is only exacerbated during foreign trials, especially in LMICs that may present unique challenges complicating traditional practices.<sup>189</sup>

There are various barriers to achieving informed consent for U.S. clinical trial participants. First, consent documents are often very long, making it unlikely they are read completely and thus, participants are left without a material understanding of the trial.<sup>190</sup> For example, in a 2018 study, nearly half of trial

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<sup>185</sup> Tomasz Pietrzykowski & Katarzyna Smilowska, *The Reality Of Informed Consent: Empirical Studies On Patient Comprehension—Systematic Review*, TRIALS, 1, 1 (Jan. 14, 2021), <https://doi.org/10.1186/s13063-020-04969-w>.

<sup>186</sup> Katie Gillies, Alexander Duthie, Seonaidh Cotton & Marion K., Campbell, *Patient Reported Measures Of Informed Consent For Clinical Trials: A Systematic Review*, 13 PLOS, 1, 2 (June 27, 2018), <https://doi.org/10.1371/journal.pone.0199775>.

<sup>187</sup> See Rashmi Ashish Kadam, *Informed Consent Process: A Step Further Towards Making It Meaningful!*, PERSPECTIVES IN CLINICAL RSCH., 107, 107 (2017), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5543760/pdf/PCR-8-107.pdf> (referring to a higher level of informed consent as compared to the current standard which “is legally right but often inadequate in terms of simplicity and ease of understanding for the study participants”).

<sup>188</sup> See *id.* at 108 (mentioning studies on the “informed consent process in the western world [that] suggest that participants may not understand the study they are enrolled, neither their rights as participants despite having signed a consent form”).

<sup>189</sup> See *id.* at 107 (“Challenges related to informed consent may have larger dimensions in developing countries.”).

<sup>190</sup> Anne Wisgalla & Joerg Hasford, *Four Reasons Why Too Many Informed Consents to Clinical Research Are Invalid: A Critical Analysis Of Current Practices*, BMJ, 1, 1 (2022), <https://bmjopen.bmj.com/content/12/3/e050543>.

participants were unable to articulate even one risk of their trial.<sup>191</sup> Additionally, the documents often require a high literacy level, meaning that a high school or even college diploma may be necessary for sufficient comprehension of the complex information presented.<sup>192</sup> Simplifying informed consent documents to an eighth-grade reading level has been recommended, but most documents continue to be written at much higher levels.<sup>193</sup> This issue is significantly worse for those in LMICs where literacy rates fall behind the U.S.<sup>194</sup> In 2016, there were still 750 million adults who were illiterate across the globe.<sup>195</sup> Moreover, language barriers also play a role in patient understanding of consent documents, including language differences that initially appear minor, such as dialect differences.<sup>196</sup> Patient understanding can also be diminished by factors that can reduce a patient's capacity, including cognitive disability, mental disorders, disease severity, and age.<sup>197</sup>

Another major barrier is the frequent failure to achieve participants' full understanding of the differences between medical care and clinical trials. Clinical trials aim to collect knowledge on a particular scientific question and are

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<sup>191</sup> *Id.*

<sup>192</sup> *Id.* at 2.

<sup>193</sup> Kadam, *supra* note 189, at 108.

<sup>194</sup> See generally [SDG Global Goal 4: Quality Education, UN, \[https://unstats.un.org/UNSDWebsite/undatacommons/goals?v=dc/topic/sdg\\\_4\]\(https://unstats.un.org/UNSDWebsite/undatacommons/goals?v=dc/topic/sdg\_4\)](https://unstats.un.org/UNSDWebsite/undatacommons/goals?v=dc/topic/sdg_4) (explaining that lower income countries have lower literacy rates than countries in the West).

<sup>195</sup> *Id.*

<sup>196</sup> Wilson, *supra* note 142, at 666–67.

<sup>197</sup> Kadam, *supra* note 189, at 108.

primarily developed for the benefit of future patients.<sup>198</sup> This is very different from standard medical care that is more familiar to patients and focuses on benefiting a particular person.<sup>199</sup> Trial participants also often do not understand the availability of alternative treatments outside of their participation in the study.<sup>200</sup> These misunderstandings about the nature of a trial can significantly impair someone's ability to properly assess the potential risks with their participation.

Furthermore, physicians and patients themselves may overestimate the patient's understanding of trial information, impacting their ability to achieve informed consent. Patients may have the subjective impression that they are adequately informed about a study and doctors may underestimate the complexity of the information they provide to patients.<sup>201</sup> These potential misunderstandings may be heightened by cultural differences surrounding views on autonomy, paternalism in medicine, and collectivism. Patient autonomy in healthcare is critical to western countries, but is not as highly valued in other countries, particularly those that place community or divinity as values that supersede individual autonomy.<sup>202</sup> In countries including Ghana, Korea, China, India, Japan,

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<sup>198</sup> Wisgalla & Hasford, *supra* note 191, at 1–2.

<sup>199</sup> *Id.* at 2.

<sup>200</sup> *Id.*

<sup>201</sup> Pietrzykowski & Smilowska, *supra* note **Error! Bookmark not defined.**, at 2.

<sup>202</sup> Gregory A. Thompson, Jonathan Segura, Dianne Cruz, Cassie Arnita & Leeann H. Whiffen, *Cultural Differences in Patients' Preferences For Paternalism: Comparing Mexican And*



and Pakistan, paternalism in healthcare is actually preferred.<sup>203</sup> For example, a study in rural India showed that the majority of trial participants based their decision on whether to participate in clinical trials on their discussions with members of their community.<sup>204</sup> Further, the study found doctors and patients had a paternalistic relationship, “with patients having implicit trust in the medical system resulting in very limited participation in medical treatment decisions.”<sup>205</sup> In areas with poor access to health care and poverty, patient trust comes from physician respect and treatment assurance, compared to higher income countries where the primary factor in trust is physician competence.<sup>206</sup> Overall, these differences in values can influence patient and provider perception of patient understanding, interfering with a trial participant’s informed consent.

### *C. Arguments Against Increasing Regulation*

There are many arguments against increasing the regulation of foreign clinical trials that are important to consider and should inform any future regulation reform. First, if regulations are too stringent, the drug approval process could face significant delays, meaning new drugs will take longer to get to

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*American Patients’ Preferences For And Experiences With Physician Paternalism And Patient Autonomy*, 19 INT’L J. ENV’T RSCH. PUB. HEALTH, 1, 1–2 (2022), <https://doi.org/10.3390/ijerph191710663>.

<sup>203</sup> *Id.* at 2.

<sup>204</sup> Kadam, *supra* note 189 at 109.

<sup>205</sup> *Id.*

<sup>206</sup> Vijayaprasad Gopichandran & Satish Kumar Chetlapalli, *Trust In The Physician–Patient Relationship In Developing Healthcare Settings: A Quantitative Exploration*, 12 INDIAN J. MED. ETHICS 141, 146 (2015), <https://pubmed.ncbi.nlm.nih.gov/26228046>.

patients.<sup>207</sup> In addition to delays, complying with increased regulation can be incredibly costly, contributing to high drug prices.<sup>208</sup> This could potentially cost lives if the new drug is the only available treatment for a serious life-threatening condition.<sup>209</sup> On the other hand, fast-paced trials with little oversight and loose regulations are posing serious health concerns to participants in LMICs. Is it fair to lower standards, at the expense of the well-being of foreign participants, for pharmaceutical companies to bring their drugs to market cheaply and quickly for U.S. patients? The health and safety of trial participants aside, inadequate regulation can bring unsafe drugs to market, causing harm to American patients and those in other countries accessing these drugs.<sup>210</sup>

Additionally, some argue that the U.S. system is clearly imperfect, and thus it is not the best model to export to LMICs that lack the resources of the U.S.<sup>211</sup> Trial staff in developing countries often have more limited experience and may struggle to understand which requirements should be applied and when they should be applied.<sup>212</sup> This can increase the caution with which researchers approach trials, limiting research and contributing to trial complexity and

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<sup>207</sup> Weigmann, *supra* note 66, at 567.

<sup>208</sup> David J. Stewart, Gerald Batist, Hagop M. Kantarjian, John-Peter Bradford, Joan H. Schiller & Razelle Kurzrock, *The Urgent Need For Clinical Research Reform To Permit Faster, Less Expensive Access To New Therapies For Lethal Diseases*, 21 *CLINICAL CANCER RSCH.*, 4561, 4561 (2015), <https://doi.org/10.1158/1078-0432.CCR-14-3246>.

<sup>209</sup> Weigmann, *supra* note 66 at 567.

<sup>210</sup> *Id.*

<sup>211</sup> *Id.*

<sup>212</sup> Trudie Lang & Sisira Siribaddana, *Clinical Trials Have Gone Global: Is This A Good Thing?*, 9 *PLOS MED.*, 1, 4 (2012), <https://pubmed.ncbi.nlm.nih.gov/22719228>.

financial expenses.<sup>213</sup> Further, many of these countries set their own standards for clinical trials and forcing trial regulations to match those of the U.S. may be counter to the autonomy of these countries.<sup>214</sup> It may be unduly paternalistic to deny these patients the chance to access experimental treatments and to deny their countries the opportunity to benefit economically. However, participants are incredibly vulnerable and are at great risk for coercion. This would not be as large of a concern if the main priority of LMICs was the health and safety of trial participants, but as discussed, there is significant pressure on these countries to keep their standards low since increased regulation may drive trials to other countries instead.

Moreover, it is argued that market incentives may be sufficient to keep the industry in line with high ethical standards. Companies “have a strong financial interest in ensuring that trials are carried out in an ethically and scientifically rigorous fashion.”<sup>215</sup> However, these greater market incentives may also be competing against personal incentives. Chiefly, trial organizers may face conflicts of interests that can present personal financial incentives to neglect the wellbeing

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<sup>213</sup> *Id.*

<sup>214</sup> Schuster, *supra* note 84, at 1027.

<sup>215</sup> Kevin B. O’Reilly, *Outsourcing Clinical Trials: Is It Ethical To Take Drug Studies Abroad?*, AM. MED. NEWS (Sept. 7, 2009), <https://amednews.com/article/20090907/profession/309079969/4>.

of research participants in order to maximize personal profit.<sup>216</sup> Regardless of the merits of the market incentive argument, it is clear that these incentives have yet to be a strong enough force to maintain high ethical standards given the ongoing mistreatment of trial participants.

#### *D. Regulation Reform Is Vital*

The harm foreign clinical trials can cause for vulnerable populations has significant implications not only for the wellbeing of the participants, but for global health generally. In the U.S., previous harms inflicted on vulnerable populations have created profound distrust amongst certain minority groups.<sup>217</sup> As a result, their medication adherence is lower, and patients are less willing to implement physician advice and public health recommendations.<sup>218</sup> The extent of the impact of this distrust was seen during the COVID-19 pandemic where minority groups, such as African Americans, exhibited a disproportionate level of vaccine mistrust.<sup>219</sup> Many specifically cited the Tuskegee syphilis study from

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<sup>216</sup> Bobbi M. Bittker, *The Ethical Implications Of Clinical Trials In Low- And Middle-Income Countries*, 46 ABA HUM. RTS. MAGAZINE (June 14, 2021), [https://www.americanbar.org/groups/crsj/publications/human\\_rights\\_magazine\\_home/the-truth-about-science/the-ethical-implications-of-clinical-trials](https://www.americanbar.org/groups/crsj/publications/human_rights_magazine_home/the-truth-about-science/the-ethical-implications-of-clinical-trials).

<sup>217</sup> White & White, *supra* note 178.

<sup>218</sup> *Id.*

<sup>219</sup> Laura M. Bogart, Lu Dong, Priya Gandhi, Samantha Ryan, Terry L. Smith, David J. Klein, Luckie-Alexander Fuller, Bisola O. Ojikutu, James Aboagye & Brandon Harrison, *Black Americans Cite Low Vaccine Confidence, Mistrust, And Limited Access As Barriers To Covid-19 Vaccination*, RAND CORP., 1, 1 (2021), <https://doi.org/10.7249/RBA1110-1>.

1932 as the primary reason for their skepticism.<sup>220</sup> In that study, hundreds of African American participants were harmed and many died after they were given placebos, despite penicillin becoming the recommended treatment fifteen years into the research.<sup>221</sup>

The impact of adverse outcomes from foreign clinical trials may differ from the consequences we have seen domestically, but it is clear that skepticism and mistrust exist in foreign populations that have been previously harmed. Most recently, in Africa, the history of medical experimentation, threatened to undermine the fight against COVID-19.<sup>222</sup> This history not only includes Pfizer's 1996 Trovan trials, but other instances of mistreatment, such as trials in 1994 where placebo pills were given to pregnant mothers with HIV when a proven treatment was already available.<sup>223</sup> Public perception can be greatly shaped by these experiences that become saved in the collective memory of communities. The outcomes of Pfizer's Trovan trial were passed down from parents to children and from teachers to students.<sup>224</sup> Medical distrust can have serious consequences for the health of a region and the LMICs that hosted the trials are left to deal with

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<sup>220</sup> Debbie Elliott, In Tuskegee, *Painful History Shadows Efforts To Vaccinate African Americans*, NPR (Feb. 16, 2021), <https://www.npr.org/2021/02/16/967011614/in-tuskegee-painful-history-shadows-efforts-to-vaccinate-african-americans>.

<sup>221</sup> Elizabeth Nix, *Tuskegee Experiment: The Infamous Syphilis Study*, HISTORY (May 16, 2017), <https://www.history.com/news/the-infamous-40-year-tuskegee-study>.

<sup>222</sup> Ibrahim Garba & Danielle Paquette, *In This Nigerian City, Pfizer Fears Loom Over The Vaccine Rollout*, WASH. POST (Mar. 20, 2021), <https://www.washingtonpost.com/world/2021/03/20/nigeria-pfizer-kano-coronavirus-trovan>.

<sup>223</sup> *Id.*

<sup>224</sup> *Id.*

their populations' future skepticism. In Africa, COVID-19 vaccine safety messaging was amplified by public health officials in order to confront the distrust in their country that threatened progress during the pandemic.<sup>225</sup> Moreover, COVID-19 has demonstrated the impact of every country's health on the health of countries across the globe. Thus, the pandemic illustrated the ways in which the negative consequences from foreign trials not only impact trial host countries, but can also seriously impact the health of the rest of the world.

Furthermore, in light of the recent FDA push to diversify clinical trials, improving regulation of foreign trials is even more important. In April of 2022, the FDA expanded on previous guidance for the industry and issued draft guidance to increase diversity in clinical trials.<sup>226</sup> The agency cited the importance of clinical trial evidence in determining the safety and efficacy of drugs, as well as the underrepresentation of minorities.<sup>227</sup> This guidance was taken a step further in December of 2022, when Public Law 117-328 was passed requiring diversity action plans for clinical trials.<sup>228</sup>

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<sup>225</sup> *Id.*

<sup>226</sup> *Diversity Plans to Improve Enrollment of Participants From Underrepresented Racial and Ethnic Populations in Clinical Trials; Draft Guidance for Industry; Availability*, FDA (Apr. 13, 2022), <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/diversity-plans-improve-enrollment-participants-underrepresented-racial-and-ethnic-populations>.

<sup>227</sup> *Id.*

<sup>228</sup> Consolidated Appropriations Act, Pub. L. No. 117-328, § 3601, 136 Stat. 1042 (2023).

Arguably, taking clinical trials abroad can help address the diversity of the U.S. population.<sup>229</sup> However, as in the recent FDA rejection of Eli Lilly and Biologics' China's immunotherapy drug, clinical trial data from a single country or region may be limited in its applicability to the U.S. population.<sup>230</sup> Still, there is value in the diversity that can be provided by conducting research abroad. Yet, distrust of clinical research due to historical abuses is a barrier to participation for many minority groups.<sup>231</sup> Therefore, to reap the necessary benefits of clinical trial diversity, the regulation of foreign trials must be structured to adequately protect participants and preserve the applicability of data to the U.S. population.

#### IV. RECOMMENDATIONS FOR ADDITIONAL REGULATION IN THE WAKE OF THE FDA'S PUSH TO DIVERSIFY CLINICAL TRIALS

The FDA's push to diversify clinical trials highlights the importance of utilizing a diverse group of participants in drug research. Yet, for diversity to be realized from foreign trials, data will need to be applicable to the U.S. population. In many cases, this means data will need to be collected from multiple countries. Thus, trial participants must be significantly protected, not only for ethical reasons, but also to maintain the trust necessary for these countries to permit ongoing clinical research to be conducted. Participant safety can be improved

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<sup>229</sup> Ken Phelps, *Considerations In Using Foreign Trial Data In U.S. NDA Submissions*, CLINICAL LEADER (Aug. 3, 2012), <https://www.clinicalleader.com/doc/considerations-using-foreign-trial-data-u-s-nda-submissions-0001>.

<sup>230</sup> Wechsler, *supra* note 135.

<sup>231</sup> Garba & Paquette, *supra* note 222.

through increasing target inspections of foreign trial sites, enhancing FDA enforcement by more consistently applying penalties to violators of existing regulations, and by alerting the FDA to ongoing foreign trials by requiring INDs or similar documentation to be submitted. Additionally, enhancing the informed consent process is critical to increasing participant safety. Finally, improving access to remedies for those harmed in trials would help make participants whole and address the resulting distrust that often occurs after adverse trials.

*A. General Recommendations To Strengthen FDA Oversight*

The FDA does not seem to have adequate resources for oversight of clinical trials, even for those happening within the U.S.<sup>232</sup> Increasing funding and staffing for inspections could allow for inspections of sites after the FDA is alerted to a concern, an arguably bare minimum standard.<sup>233</sup> FDA regulated companies must pay user fees, which comprise forty-five percent of the FDA's budget.<sup>234</sup> Additional funding for FDA inspections could come from increasing these user fees.<sup>235</sup> If inspections could be more targeted and frequent, FDA oversight may significantly improve, particularly given the few foreign inspections that are currently conducted. Targeting sites for inspection would also be significantly enhanced if the FDA required clinical trial data to be submitted in

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<sup>232</sup> Maryanne Demasi, *FDA Oversight of Clinical Trials Is "Grossly Inadequate," Say Experts*, *BMJ*, 1, 2 (Nov. 16, 2022), <https://doi.org/10.1136/bmj.o2628>.

<sup>233</sup> *Id.*

<sup>234</sup> White & White, *supra* note 178.

<sup>235</sup> *Id.* at 436.



a standardized format.<sup>236</sup> Standardized data would also help the agency more accurately review evidence and determine when certain trial information may be missing.<sup>237</sup>

However, some argue that the FDA does have sufficient resources for effective oversight, and that efficiency issues are actually behind the lack of oversight.<sup>238</sup> Efficiency challenges may be contributing to weak FDA enforcement of current regulations. Agency enforcement has recently been found to often be “light-handed, slow-moving, and secretive.”<sup>239</sup> This suggests that improving the enforcement of existing regulations may make a significant difference and the addition of new regulations may not need to be as extensive. If companies who violate regulations face penalties on a more consistent basis, current regulations will likely be much more effective.

Additionally, companies conducting foreign trials should be required to submit an IND to maintain the welfare and safety of foreign participants.<sup>240</sup> While valid arguments against additional regulation exist, the existence of significance past abuse and the potential for future harm likely justify the need for the FDA to be aware of ongoing trials. If an IND requirement produces a serious chilling

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<sup>236</sup> *Challenges to FDA’s Ability to Monitor and Inspect Clinical Trials*, *supra* note 39, at iii.

<sup>237</sup> *Id.*

<sup>238</sup> Demasi, *supra* note 232.

<sup>239</sup> Charles Piller, *A Science Investigation Shows That FDA Oversight Of Clinical Trials Is Lax, Slow Moving, And Secretive—And That Enforcement Is Declining*, AM. ASS’N FOR THE ADVANCEMENT OF SCI. (Oct. 1, 2020), <https://www.science.org/content/article/fda-s-own-documents-reveal-agency-s-lax-slow-and-secretive-oversight-clinical-research>.

<sup>240</sup> Schuster, *supra* note 84, at 1060–61.

effect or considerably increases drug delays, a less stringent version of notifying the FDA of a future trial could be beneficial.

Lastly, additional research is needed on the status of foreign clinical trials. The last extensive government report on FDA oversight of clinical trials was from the Office of the Investigator General (OIG) in 2010.<sup>241</sup> Analysis of more recent data is necessary to understand where the FDA has improved its oversight and identify more targeted recommendations.

### *B. Improving Informed Consent*

There are a variety of informed consent requirements the FDA could consider to improve trial participants' comprehension and understanding. First, informed consent forms themselves could be simplified. Given the complexity of these documents, requiring basic language to be used and allocating sufficient time for participants to read the forms may decrease participant misunderstanding.<sup>242</sup> The forms should ideally not only be in a language the participant understands, but rather a language in which they have adequate proficiency to understand the complex ideas that are conveyed. In addition, presenting written information in a variety of alternative formats, such as images

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<sup>241</sup> *Challenges to FDA's Ability to Monitor and Inspect Clinical Trials*, *supra* note **Error! Bookmark not defined.**, at i.

<sup>242</sup> Kadam, *supra* note 189, at 108–110.

and infographics, may also aid in understanding.<sup>243</sup> Studies have shown that illustrations and different text styles can help those with impaired literacy skills improve their comprehension.<sup>244</sup>

Additionally, participant comprehension can be assessed to evaluate if a researcher's perception of a participant's understanding is accurate. This assessment can be done through conversations with participants and/or written evaluations that assess comprehension. For example, the "Teach Back Method" can be implemented while speaking with participants before they sign their informed consent form by asking participants to put the trial information they received into their own words.<sup>245</sup> Questionnaires can also be used to evaluate understanding by asking a variety of question types such as yes/no questions, short answer questions, and multiple choice questions.<sup>246</sup> The methods used should be designed around the needs of the population that the trial is recruiting and will likely be different as participant capacities change based on location. Moreover, assessing and improving participant comprehension does not have to end after the traditional informed consent process has concluded. Extended

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<sup>243</sup> Jaime Fons-Martinez, Cristina Ferrer-Albero & Javier Diez-Domingo, *Keys To Improving The Informed Consent Process In Research: Highlights Of The I-Consent Project*, 25 HEALTH EXPECT, 1183, 1184 (Aug. 2022), <https://pubmed.ncbi.nlm.nih.gov/35894807>.

<sup>244</sup> Kadam, *supra* note 189, at 110.

<sup>245</sup> *Id.*

<sup>246</sup> *Id.*

discussions can take place between participants and study coordinators, nurses, investigators, or other trial staff members.<sup>247</sup>

Ultimately, given the increased vulnerability of foreign trial participants, more of these practices may need to be implemented for foreign trials in order to improve participant understanding. On the other hand, less interventions may be necessary to achieve informed consent for domestic trials. Participant understanding is subjective. A difference in the method or frequency with which a trial uses informed consent tools does not necessarily indicate a difference in informed consent levels. Foreign participants will likely need increased intervention to achieve sufficient informed consent, as opposed to their domestic participant counterparts.

### *C. Increasing Remedies For Victims*

Finally, clinical trials are becoming increasingly globalized, yet there are no international standards regarding compensation for research-related injuries, and the U.S. does not have any national standard regarding these injuries.<sup>248</sup> Research-related injuries in LMICs are not insignificant. For example, documents presented to the Supreme Court in India in 2013 revealed that between 2005 and 2012 as many as 2,868 participants had died during trials, of which only 82 had

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<sup>247</sup> *Id.* at 108–10.

<sup>248</sup> George Rugare Chingarande & Keymanthri Moodley, *Disparate Compensation Policies For Research Related Injury In An Era Of Multinational Trials: A Case Study Of Brazil, Russia, India, China And South Africa*, BMC MED. ETHICS, 1, 2 (Feb. 17, 2018), <https://doi.org/10.1186/s12910-018-0244-y>.

been compensated.<sup>249</sup> As explained earlier, the U.S. tort system may fall short for many LMIC participants who may lack the financial and social support often critical for plaintiff success.<sup>250</sup> Providing participants an adequate remedy when they are harmed by clinical trials is important not only to make them whole, but also to combat the future medical distrust that often follows adverse trial effects.

Injured clinical trial participants could receive an adequate remedy by entitling all participants to receive compensation, as well as any required medical care, for any harm they experience as a result of a trial.<sup>251</sup> This could be financed through insurers that would have to cover medical care, or if participants are uninsured, companies themselves could be required to provide this care.<sup>252</sup> In order to combat the potentially significant financial burden this would place on companies, they could be required to obtain insurance to cover medical care for the uninsured, as well as compensation for other injuries or death.<sup>253</sup>

## CONCLUSION

Ultimately, clinical trial research has become increasingly globalized as pharmaceutical companies take trials abroad to reap the benefits of quicker, cheaper, less regulated research. However, current regulations fail to protect foreign clinical trial participants, which poses significant risks for the safety of

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<sup>249</sup> *Id.*

<sup>250</sup> Chapman, Sukumaran, Tsegaye, et al., *supra* note 113.

<sup>251</sup> *Id.* at 742–43.

<sup>252</sup> *Id.* at 742.

<sup>253</sup> *Id.* at 742–43.

participants, as well as for the health of U.S. patients and global health more broadly. Allowing foreign trials to be conducted without INDs often leaves the FDA in the dark. The FDA is not formally alerted to these foreign trials, unless after a trial ends researchers decide to use the collected trial data in a new drug application. Foreign trials should be required to submit INDs or other similar documentation in order to alert the U.S. to their initiation. This information will allow the FDA to better target an increased number of site inspections. Additionally, enforcement of current regulations should be improved through applying penalties to companies who violate the rules on a more consistent basis.

In the wake of the FDA's recent push to diversify clinical trials, improving regulation of foreign trials is even more significant. A variety of techniques can be used to increase informed consent including simplifying the language used in consent forms, providing trial information in a variety of formats, assessing comprehension on an ongoing basis, and continuing the consent conversation after the formal consent process has ended. However, when people are harmed, adequate remedies need to be available, particularly to help address the resulting distrust that often occurs after adverse trials. As the recent COVID-19 pandemic has demonstrated, the health of an individual country is not isolated, and while the importance of an individual country's health is important for ethical reasons, it is also critical to the health of the world.