

# Clinical Trial Data Reporting: Breaking Free of a Prisoner's Dilemma

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## ABSTRACT

Clinical trial results form the basis of the Food and Drug Administration's (FDA's) approval of medical products for public use. In 2007, Congress began requiring disclosure of clinical trial results to the registry ClinicalTrials.gov in hopes of establishing better oversight and accountability to the public. But even now, results for less than half of all trials are reported on time. Nearly a third are not reported at all. This Article examines how and why many clinical trial sponsors continue not to comply with statutory and regulatory trial results reporting mandates. The ensuing analysis contextualizes the status quo as a prisoner's dilemma: Due to lack of enforcement pressure and myriad incentives not to report clinical trial results, noncompliant trial sponsors may consider themselves to "win" when they do not disclose, but others do. As with any prisoner's dilemma, when parties seek to act in their best interest at the expense of others, everyone loses—including the very parties that thought they were coming out ahead. But unlike a normal prisoner's dilemma, losses in the context of clinical trial data reporting are not limited to the involved parties. Attritive behavior by noncompliant trial sponsors harms all stakeholders in the medical research enterprise by rendering inaccessible the significant research-related and public health benefits of collective compliance with trial data submission requirements.

## INTRODUCTION

A federal agency's decision-making can only be as robust as the data underlying the agency's decision, and when these decisions relate to public health, misinformation can result in significant consequences. The Food and Drug Administration (FDA), in carrying out its duty to vet the safety and effectiveness of medical products for use by the American public,<sup>1</sup> is no stranger to the need for thorough data when making decisions. Indeed, the agency requires the equivalent of a "literal truckload of paper" when determining whether to approve a prospective therapy for public use.<sup>2</sup> Much of

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<sup>1</sup> *What We Do*, U.S. FOOD & DRUG ADMIN. (Mar. 28, 2018), <https://www.fda.gov/about-fda/what-we-do> [<https://perma.cc/GN2M-U6LM>].

<sup>2</sup> *Health Law: How a New Drug is Approved, Part 2*, LAWSHELF EDUC. MEDIA, <https://lawshelf.com/shortvideoscontentview/health-law-how-is-a-new-drug-approved-part-2/> [<https://perma.cc/WT4Z-9QC9>].

this data comes from the results of clinical trials, which are studies conducted with a group of individuals to determine whether a medical product is likely to be safe and therapeutically effective in the general population.<sup>3</sup> FDA's ability to filter out unsafe and/or ineffective prospective therapies during its review is directly related to the quality—and quantity—of clinical trial information that the agency has at its disposal.

Given the difficulty of consistently vetting medical products' safety and effectiveness, government watchdogs and other investigators can help hold FDA accountable in carrying out its core mandate of "protecting the public health."<sup>4</sup> For example, in 2013, Professor Charles Seife used clinical trial data to identify six drugs FDA allowed to remain on the market "even though the clinical trials that were used to establish their safety and efficacy were found to be fraudulent."<sup>5</sup> The Project on Government Oversight similarly used clinical trial data to flag myriad safety-related concerns about the trials supporting FDA's approval of dabigatran (Pradaxa).<sup>6</sup> In 2014, the manufacturer of Pradaxa, Boehringer Ingelheim, spent \$650 million to settle thousands of Pradaxa-related injury lawsuits.<sup>7</sup> Government watchdogs, therefore, can often play an important role in protecting the public from potential harm.

But right now, watchdogs are hamstrung by a lack of accessible clinical trial data. While FDA does have access to the original data for investigational agents when they are submitted for approval, many trial sponsors are not making even *summary* clinical data accessible to the public.<sup>8</sup> Compounding this issue, for clinical trials completed between 2007 and 2017, the National Institutes of Health (NIH) does not require submission of results for trials used to secure FDA approval of a product that had not *previously* been approved for another use.<sup>9</sup> Absent robust clinical trial data reporting,

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(last visited Mar. 19, 2021) (noting that applications for new drug approvals are often "thousands of pages long" and that "this document was historically delivered to FDA as a literal truckload of paper copies," though the agency has since shifted to requiring electronic content submissions).

<sup>3</sup> *Conducting Clinical Trials*, U.S. FOOD & DRUG ADMIN. (Jun. 30, 2020), <https://www.fda.gov/drugs/development-approval-process-drugs/conducting-clinical-trials> [https://perma.cc/8MGW-2225] ("Clinical trials, also known as clinical studies, test potential treatments in human volunteers to see whether they should be approved for wider use in the general population.").

<sup>4</sup> *What we Do*, U.S. FOOD & DRUG ADMIN., *supra* note 1.

<sup>5</sup> *Seife v. U.S. Dep't Health & Human Servs.*, 440 F. Supp. 3d 254, 268 (S.D.N.Y. 2020) (citing the Declaration of Charles Seife); Charles Seife & Rob Garver, *FDA Let Drugs Approved on Fraudulent Research Stay on the Market*, PROPUBLICA.ORG (April 5, 2013), <https://www.propublica.org/article/fda-let-drugs-approved-on-fraudulent-research-stay-on-the-market> [https://perma.cc/XDD9-WXYJ].

<sup>6</sup> PROJECT ON GOV'T OVERSIGHT, DRUG PROBLEMS: DANGEROUS DECISION-MAKING AT THE FDA 12, 14, 21 (Oct. 15, 2015), (indicating concerns that the pre-approval trial was unblinded and intolerably sloppy with "readily identifiable errors," and that dabigatran had no known antidote if patients on the drug were to hemorrhage, which was a known potential adverse event related to drug use).

<sup>7</sup> *Id.* at 5. But note that this settlement only resolved lawsuits that were in federal court, which had been compiled into a multi-district litigation case; many more lawsuits for Pradaxa-related injuries continue at the state level. Tom Lamb, *Pradaxa Lawsuits And Settlements: Past, Present, And Future Aspects Are Explained In This 2017 Update Report*, DRUG INJURY WATCH (Mar. 21, 2017), <https://www.drug-injury.com/druginjurycom/2017/03/new-pradaxa-lawsuits-filed-state-courts-federal-mdl-settlements-legal-options-future-cases-update-report.html> [https://perma.cc/9CU2-SVB5] (indicating that after the settlement, "there began to be a number of new Pradaxa lawsuits being filed in various state courts around the country. And this was the start of what has been referred to as a 'round two' or the 'second wave' of Pradaxa drug injury litigation").

<sup>8</sup> *See infra* Section I.B.

<sup>9</sup> *See infra* Section I.A.

watchdog groups will be hard-pressed to find evidence of, for example, data mischaracterization and fraud that have condemned past trials, laying ripe ground for similar, avoidable public harm.

This Article examines *how* and *why* many trial sponsors continue not to comply with clinical trial data reporting requirements. In doing so, the Article contextualizes the status quo as a prisoner's dilemma: Due to lack of enforcement pressure and myriad incentives not to report clinical trial results,<sup>10</sup> noncompliant trial sponsors may consider themselves to "win" when *they* do not disclose, but *others* do. As with any prisoner's dilemma, when parties seek to act in their best interest at the expense of others, *everyone* loses—including those parties that thought they were coming out ahead. But unlike a normal prisoner's dilemma, losses in the context of trial data reporting are not limited to the involved parties. Attritive behavior by noncompliant trial sponsors renders inaccessible the significant benefits of collective compliance with trial data submission, resulting in harms that are borne by many stakeholders in the medical research enterprise.<sup>11</sup>

This Article analyzes these issues in four parts: Part I characterizes the statutory and regulatory bases of clinical trial data reporting requirements, the state of compliance with these enumerated requirements, and the justifiability of nonenforcement within the context of legislative delegation of discretionary authority. Part II delineates incentives (and lack of disincentives) for noncompliance with trial data reporting requirements. Part III explains why prudent stakeholders in the research enterprise have a responsibility to make clinical trial results publicly accessible. This Part also goes on to explain the many benefits—including for trial sponsors—brought about by collective disclosure of trial data. Part IV identifies paths forward for increasing compliance with results submission requirements. The paper then briefly concludes.

## I. HOW CLINICAL TRIAL DATA REPORTING WORKS—AND DOESN'T

In light of the drug industry's hesitance to share unfavorable drug data, as exemplified by incidents like that of paroxetine (Paxil) in 2006,<sup>12</sup> legislative concern grew that "negative [trial] results may or may not be released by sponsors."<sup>13</sup> To better understand the issue, Congress requested that the Office of Inspector General (OIG)

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<sup>10</sup> See *infra* Section II.A (describing, for example, trial sponsors' desire to protect trial data as proprietary information).

<sup>11</sup> See *infra* Section III.B (indicating a variety of benefits that result from collective trial data reporting but are not currently accessible due to the degree of noncompliance with trial results reporting requirements).

<sup>12</sup> Charles Piller, *Failure to Report: A STAT Investigation of Clinical Trials Reporting*, STAT (Dec. 13, 2015), <https://www.statnews.com/2015/12/13/clinical-trials-investigation/> [<https://perma.cc/S2F6-SV3E>] (stating that legislation addressing this issue was driven by congressional concern "that the pharma industry was hiding negative results to make treatments look better," including, for example, that drug manufacturers had hidden data showing Paxil, an antidepressant, might be causing increased suicidal ideation in teenagers).

<sup>13</sup> H.R. REP. NO. 110-225, at 12 (2007) (describing the clinical trial reporting issues underlying legislative intent to pass the Food and Drug Administration Amendments Act); see also Piller, *supra* note 12.

investigate FDA's oversight of clinical trials for drug approval.<sup>14</sup> In the early 2000s, the report showed, FDA exercised astonishingly little oversight over clinical trial procedures.<sup>15</sup> Despite FDA's robust examination of clinical trial protocols prior to trial commencement, the agency's ability to oversee trials already underway was lackluster due to lack of a sufficiently comprehensive clinical trial registry,<sup>16</sup> making it hard to keep track of trials for inspection.

In addition to empowering FDA to inspect clinical trial sites, prompt reporting of clinical trial data supports many different uses of that data by various stakeholders in the medical system. Perhaps most importantly, inadequate clinical trial data reporting compromises "safety and quality in medication use."<sup>17</sup> Gaps in knowledge that emerge due to inadequate trial reporting affect "clinical practice, patient self-management, and medication safety."<sup>18</sup> National clinical trial data banks—alongside an obligation to report data to these banks—are uniquely situated to fill this gap because clinical trials with *negative* results are seldom published by academic journals,<sup>19</sup> even though these same trials can uncover characteristics of a drug that meaningfully inform its safe and efficacious use.<sup>20</sup> In addition to promoting accurate medication use, clinical trial data reporting also enables efforts by academic researchers and watchdog groups to determine whether the clinical research enterprise is optimally functioning.<sup>21</sup> And there may also be some benefit to patient autonomy: Making clinical trial data, and requisite plain language summaries,<sup>22</sup> available to the public could bolster informed decision-making about its medical care.

Spurred on by concerns about drug safety and the need to make clinical trial information more readily available to the public,<sup>23</sup> Congress in 2007 enacted the Food and Drug Administration Amendments Act (FDAAA),<sup>24</sup> which enumerates—in Section 801—an "Expanded Clinical Trial Registry Bank" requiring registration of clinical trials prior to commencement, and, upon completion or termination,

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<sup>14</sup> OFFICE OF INSPECTOR GEN., DEP'T OF HEALTH & HUMAN SERVS., OEI-01-06-00160, THE FOOD AND DRUG ADMINISTRATION'S OVERSIGHT OF CLINICAL TRIALS, at i (Sept. 2007) ("The Office of Inspector General (OIG) received a congressional request to review FDA oversight of clinical trials after a series of news articles highlighted vulnerabilities.").

<sup>15</sup> *Id.* at ii (finding that, for example, FDA only inspected 1% of clinical trial sites from 2000–2005).

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

<sup>17</sup> INST. OF MED., PREVENTING MEDICATION ERRORS 271 (2006) (describing generally the impacts of failure to adequately disclose clinical data).

<sup>18</sup> *Id.* at 272.

<sup>19</sup> *Id.* ("[P]ositive study results are much more likely to be published than negative results.").

<sup>20</sup> *Id.* ("This publication bias yields an incomplete picture of the drug characteristics that must be known for more accurate medication use and error prevention, and can therefore have a *detrimental* effect on patients. This has clearly been a major issue with COX-2 inhibitors and NSAIDs.") (emphasis added).

<sup>21</sup> *See infra* Section II.B.

<sup>22</sup> 42 U.S.C. § 282(j)(2)(A)(ii)(I)(bb) (listing, as one of the basic content requirements for clinical trial registry information "a brief summary, intended for the laypublic").

<sup>23</sup> H.R. REP. NO. 110-225, at 12 (2007) (highlighting the FDAAA's goal of addressing "concerns raised by the [Institute of Medicine]'s report on drug safety in regard to the need for FDA to increase the availability of information to the public and to researchers for recruitment purposes and to communicate the risks and benefits of drugs"). The Institute of Medicine study cited here is the same report cited earlier, PREVENTING MEDICATION ERRORS. *See supra* note 17.

<sup>24</sup> Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823.

submission of clinical trial data by sponsors conducting “applicable clinical trials.”<sup>25</sup> NIH maintains this expanded clinical trial registry at the publicly accessible website [ClinicalTrials.gov](https://clinicaltrials.gov).<sup>26</sup> Although Congress codified, through the FDAAA, numerous clinical trial reporting requirements and delegates authority to the Department of Health and Human Services (HHS) to enforce compliance,<sup>27</sup> administrative agency oversight and enforcement remains lackluster even today. The following sections explore the interplay between Section 801’s requirements and related administrative regulations and characterize the dynamic variables underlying continuing noncompliance in clinical trial reporting.

### A. Statutory Mandates and Administrative Irreverence

Mandatory clinical trial registration and data submission (i.e., “reporting”) requirements apply to all “applicable clinical trial[s]” conducted in the United States unless statutorily excepted.<sup>28</sup> Clinical investigations of drugs,<sup>29</sup> biologics,<sup>30</sup> and devices<sup>31</sup> are considered “applicable clinical trial[s]” unless the investigation is intended to collect primarily preliminary safety or feasibility data.<sup>32</sup> Once an applicable clinical trial begins, usually marked by enrollment of the first patient, the “responsible party” (typically the trial sponsor<sup>33</sup>) must *register* the trial on [ClinicalTrials.gov](https://clinicaltrials.gov) within twenty-one days,<sup>34</sup> including “basic information” about the trial design (in a summary “intended for the lay public”), recruitment-related information, and contacts of the trial sponsor and responsible party.<sup>35</sup> Within one year after the earlier of the estimated date of completion or the actual completion or termination of the trial, the responsible party must also *submit* specific results and

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<sup>25</sup> Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 801, 121 Stat. 904–14.

<sup>26</sup> *ClinicalTrials.gov Background*, NAT’L INST. OF HEALTH (Jan. 2018), <https://clinicaltrials.gov/ct2/about-site/background> [<https://perma.cc/X7F5-T3H3>] (describing the development of the [ClinicalTrials.gov](https://clinicaltrials.gov) database after Congress passed § 801 of the FDAAA).

<sup>27</sup> Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 801, 121 Stat. 904–14.

<sup>28</sup> See 42 U.S.C. § 282(j)(1)(A)(i).

<sup>29</sup> § 282(j)(1)(A)(i), (vii) (including in the definition of “applicable clinical trial” an “applicable drug clinical trial,” where a “drug” broadly refers to both drugs, as defined in 21 U.S.C. § 321(g), and biological products, as defined in 42 U.S.C. § 262).

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

<sup>31</sup> § 282(j)(1)(A)(i), (vi) (including in the definition of “applicable clinical trial” an “applicable device clinical trial,” where a “device” refers to a device as defined in 21 U.S.C. § 321(h)).

<sup>32</sup> See § 282(j)(1)(A)(ii)–(iii). Here, the definition excepts clinical investigations of drugs or biological products that are in Phase I. § 282(j)(1)(A)(iii)(I). Phase I investigations are primarily meant to collect data on safety and only early evidence on efficacy if possible. 21 C.F.R. § 312.21 (2020). The definition similarly excepts device trials that only seek to “determine the feasibility of the device” or test “prototype devices” where the “primary outcome measure relates to feasibility and not to health outcomes.” § 282(j)(1)(A)(ii)(I).

<sup>33</sup> § 282(j)(1)(A)(ix).

<sup>34</sup> § 282(j)(2)(C)(ii). There is a minor exception for trials that were still ongoing on September 27, 2007; data for those trials were required to be reported one year later, by September 28, 2008. § 282(j)(1)(C)(iii).

<sup>35</sup> § 282(j)(2)(A)(ii).

summary data to ClinicalTrials.gov.<sup>36</sup> When creating these standards, Congress unambiguously indicated<sup>37</sup> its expectation that future clinical trial sponsors register and submit their data in a timely manner to ClinicalTrials.gov.

Within the mandated submission of trial data, the FDAAA distinguishes between “Basic” results<sup>38</sup> and “Expanded” results.<sup>39</sup> Basic results require four points of information: demographics and baseline characteristics of the study population; primary and secondary outcomes of the study (including tests of statistical significance); a “point of contact” to request scientific information about the trial; and a note indicating whether any agreements restrict the principal investigator’s ability to discuss or disclose the results of the trial after its completion.<sup>40</sup> Expanded results additionally require: a summary of the clinical trial and its results written in “non-technical, understandable language for patients”; a technical summary of the clinical trial and its results (so long as the summary and results are not “misleading or promotional”); the protocol in its entirety or inclusive of parts necessary to properly analyze trial results; and any other categories the Secretary of HHS sees fit to include.<sup>41</sup>

Basic and Expanded results submission requirements operate under different timelines and have within their purview different types of clinical trials. Applicable clinical trials<sup>42</sup> (ACTs) typically involve testing of either novel investigational agents (whether drugs, devices, or biologics) that FDA has not yet been approved for therapeutic use or agents that FDA has previously approved or licensed. When FDA approves the agent for the first time *following* completion of the clinical trial (i.e. a novel investigational agent), the FDAAA requires submission of Basic results to ClinicalTrials.gov within thirty days following approval or licensure.<sup>43</sup> When, on the other hand, the trial involves a previously approved drug, the FDAAA requires submission of Basic results within one year after the earlier of the estimated or actual completion date of the trial.<sup>44</sup> While the FDAAA similarly requires reporting of Expanded results for all ACTs involving previously approved products, it delegates authority to HHS to promulgate regulations governing the submission process of Expanded results to ClinicalTrials.gov.<sup>45</sup> Note that the FDAAA does *not* statutorily require responsible parties to report Basic results for trials involving novel

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<sup>36</sup> See § 282(j)(3)(B); *see also* § 282(j)(3)(E)(i).

<sup>37</sup> See H.R. REP. NO. 110-225, at 12 (2007) (“The Committee believes that information about trial results is important to providers and patients . . . . A uniform, centralized database and registry will help patients, providers, and researchers learn new information and make more informed healthcare decisions.”).

<sup>38</sup> § 282(j)(3)(C) (describing Basic results).

<sup>39</sup> § 282(j)(3)(D)(iii) (describing Expanded results).

<sup>40</sup> § 282(j)(3)(C)(i–iv).

<sup>41</sup> § 282(j)(3)(D)(iii)(I–IV).

<sup>42</sup> See *supra* notes 29–33 and accompanying text.

<sup>43</sup> § 282(j)(3)(E)(iv) (“With respect to an applicable clinical trial that is completed before the drug is initially approved . . . , the responsible party shall submit to the Director of NIH for inclusion in the registry and results data bank the clinical trial information . . . not later than 30 days after the drug or device is approved.”).

<sup>44</sup> § 282(j)(3)(C). *But see* § 282(j)(3)(E)(v) (caveating that when a drug manufacturer runs a clinical trial testing its own previously approved drug for a new use, Basic *and* Expanded results must be submitted to ClinicalTrials.gov within thirty days after, most typically, FDA approval of the new use of the product studied in the trial).

<sup>45</sup> See § 282(j)(3)(D)(i).

investigational agents that do *not* ultimately secure FDA approval. The FDAAA does, however, grant HHS discretionary authority to determine whether Expanded results for ACTs involving ultimately non-approved investigational agents should be submitted to ClinicalTrials.gov.<sup>46</sup>

Congress also initially established timelines for HHS to promulgate final regulations based on the FDAAA's delegation of rulemaking authority and required HHS to enforce compliance with trial registration and reporting mandates. Required reporting of Basic results went into effect on September 27, 2008, one year after the statute's enactment.<sup>47</sup> Congress allowed more time—three years—for HHS to promulgate final regulations addressing ACT reporting requirements for Expanded results.<sup>48</sup> Congress also required HHS to certify when responsible parties had met data submission deadlines, provide public notice of noncompliant responsible parties, and create facile mechanisms for the public to search for noncompliant entries.<sup>49</sup> Beyond this proverbial wall of shame, the FDAAA also requires that HHS try to enforce compliance by mandating certification of proper trial data submission as part of the progress report forms required of NIH grantees receiving federal funding.<sup>50</sup>

Though the FDAAA authorizes agency power to accomplish statutory directives, delegates rulemaking authority to the same effect, and establishes timelines for required administrative action, HHS—and more specifically NIH—have unjustifiably ignored the need to *promptly* promulgate regulation. Congress required, within three years (i.e., by 2010), promulgation of regulation to clarify requirements for reporting Expanded results and penalties for responsible parties conducting ACTs that fail to comply with regulation.<sup>51</sup> But NIH did not issue a notice of proposed rulemaking until 2014;<sup>52</sup> the agency did not issue its final rule (hereinafter, “Final Rule”) for Section 801 until 2016, seven years after the FDAAA's deadline for promulgation of regulation,<sup>53</sup> and the Final Rule did not actually go into effect until 2017.<sup>54</sup> The reason for this delay remains unclear, though by any reasonable measure, the holdup seems unwarranted.<sup>55</sup> Perennial concerns about administrative under-resourcing<sup>56</sup> could explain the delay to some degree, as might pushback by industry due to concerns about disclosure of private information that entities seek to protect as their intellectual

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<sup>46</sup> § 282(j)(3)(D)(ii)(II).

<sup>47</sup> See § 282(j)(2)(C) (describing reporting requirements for all ACTs that were “initiated after, or [were] ongoing on the date that is 90 days after, September 27, 2007”).

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

<sup>49</sup> § 282(j)(3)(E)(i)–(vi).

<sup>50</sup> § 282(j)(5)(A)(i)–(iv).

<sup>51</sup> § 282(j)(3)(D)(ii)(I).

<sup>52</sup> Clinical Trials Registration and Results Submission, 79 Fed. Reg. 69565 (proposed Nov. 21, 2014) (to be codified at 42 C.F.R. pt. 11).

<sup>53</sup> Clinical Trials Registration and Results Information Submission, 81 Fed. Reg. 64981 (proposed Sept. 21, 2016) (to be codified at 42 C.F.R. pt. 11).

<sup>54</sup> *Id.*

<sup>55</sup> See *infra* Section I.C.

<sup>56</sup> Aaron L. Nielson, *How Agencies Choose Whether to Enforce Laws: A Preliminary Investigation*, 93 NOTRE DAME L. REV. 1517, 1519–20 (2018) (“Agencies have finite resources; it is impossible for them to investigate and punish every potential violation of the law.”).

property.<sup>57</sup> Perusal of agency guidance documents, congressional reports and hearings, and the Final Rule itself uncovered no justification from NIH or FDA for the nearly decade-long delay between the FDAAA's enactment and NIH's promulgation of the Final Rule.

In addition to delay, even though the substance of the Final Rule is now in effect, parts of the Final Rule nevertheless contravene core statutory directives of the FDAAA that the regulation was meant to help accomplish. Perhaps the most salient of these: The Final Rule does not require responsible parties to submit Basic results for ACTs completed between September 27, 2007 (the date of enactment of the FDAAA) and January 18, 2017 (the date the Final Rule went into effect) if the trial studied a product that was approved by FDA *after* the trial's completion.<sup>58</sup> This arises due to a gap in the Final Rule's coverage of clinical trial data reporting requirements:

- The preamble to the Final Rule states that, for the purpose of determining whether to submit Basic results, a product is only considered approved, licensed, or cleared if the product was *already* approved prior to completion of the clinical trial.<sup>59</sup> If the product received approval after completion of the trial, the product is considered “to be a trial of an unapproved, unlicensed, or uncleared product.”<sup>60</sup> Applying these definitions:
- Responsible parties must submit Basic results for ACTs involving products that were approved *prior* to completion of the trial.<sup>61</sup> This requirement applies to trials ongoing as of September 27, 2007 and all other trials subsequently commenced.<sup>62</sup>
- Responsible parties must submit Basic results for ACTs involving products that were *not* approved prior to completion of

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<sup>57</sup> Till Bruckner, *Pharma and Medical Device Lobbies Stonewall on Transparency as Doctors and Patients Call for Fines on Companies Hiding Clinical Trial Results*, TRANSPARIMED (Dec. 7, 2018), <https://www.transparimed.org/single-post/2018/12/07/Pharma-and-medical-device-lobbies-stonewall-on-transparency-as-doctors-and-patients-call-for-fines-on-companies-hiding-clinical-trial-results> [<https://perma.cc/XWT5-DSTS>].

<sup>58</sup> See *Seife v. U.S. Dep't Health & Human. Servs.*, 440 F. Supp. 3d 254, 268 (S.D.N.Y. 2020) (finding that the Final Rule did not require clinical trial data results submission for ACTs involving products which would ultimately secure approval, but had not yet done so by trial completion, and where the trial was completed between the FDAAA's date of enactment and the date the Final Rule went into effect).

<sup>59</sup> Clinical Trial Registration and Results Information Submission, 81 Fed. Reg. 65,067 (Sept. 21, 2016) (codified at 11 C.F.R. § 42) (“Thus, if a drug product (including a biological product) or a device product is approved, licensed, or cleared for any use as of the primary completion date, we will consider that applicable clinical trial to be a trial of an approved, licensed, or cleared product.”).

<sup>60</sup> *Id.* (“Similarly, if a drug product (including a biological product) or a device product is unapproved, unlicensed, or uncleared for any use as of the primary completion date, regardless of whether it is later approved, licensed, or cleared, we will consider that applicable clinical trial to be a trial of an unapproved, unlicensed, or uncleared product.”).

<sup>61</sup> 42 C.F.R. § 11.42(a) (2019) (noting that “clinical trial results information must be submitted for any applicable clinical trial for which the studied product is approved, licensed, or cleared by FDA”).

<sup>62</sup> *Id.* (stating that these requirements apply to ACTs before and after January 18, 2017, the effective date of the Final Rule). The enactment date of the FDAAA (September 27, 2007) provides the cutoff date.



the trial.<sup>63</sup> This requirement applies to trials that were completed *on or after* January 18, 2017.<sup>64</sup>

- Under the Final Rule, therefore, Responsible parties do *not* have to submit Basic results for ACTs involving products that were *not* approved prior to completion of the trial if the trial was completed *after* September 27, 2007 but *before* January 18, 2017.

This section of the Final Rule directly contravenes the FDAAA’s requirement that responsible parties submit Basic results for ACTs testing investigational agents that were approved after trial completion.<sup>65</sup> The agency’s failure to enforce clinical trial data reporting required by the FDAAA creates a startling informational void—results submissions were not required for nearly a decade’s worth of ACTs that studied medical products that were ultimately approved by FDA and consumed by the American population. A recent ruling in the Southern District of New York, *Seife v. U.S. Department of Health and Human Services*, came to precisely the same conclusion.<sup>66</sup>

Even if HHS had appealed the decision in *Seife*, HHS almost certainly would not have received deference from the courts for its interpretation of the Final Rule in this context. Courts generally do defer to reasonable agency interpretations of their own regulations, so long as genuine ambiguity as to the call of the statutory text exists<sup>67</sup>—this deference is referred to as “*Auer* deference.”<sup>68</sup> But *Auer* deference is not without limit; when an agency’s interpretation of a regulation “parrots the statutory text,”<sup>69</sup> its interpretation is considered an extension of congressional intent that is due no special deference simply by virtue of intervening agency action.<sup>70</sup> Because the Final Rule adopts material text from the FDAAA—including the criteria for Basic results submission and the definitions of products serving as the bases of ACTs<sup>71</sup>—the Rule’s close resemblance to its authorizing statute would have precluded application of *Auer* deference. Nor would HHS have received deference under *Chevron, U.S.A., Inc. v. Nat. Res. Def. Council, Inc.*<sup>72</sup> Agency interpretations can only hope to pass the first

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<sup>63</sup> *Id.* § 11.42(b) (noting clinical trial results information must be submitted for trials “for which the studied product is not approved, licensed, or cleared by FDA”).

<sup>64</sup> *Id.* (stating that these requirements apply to ACTs “with a primary completion date on or after January 18, 2017”).

<sup>65</sup> 42 U.S.C. § 282(j)(3)(E)(iv) (“With respect to an applicable clinical trial that is completed before the drug is initially approved . . . the responsible party shall submit to the Director of NIH for inclusion in the registry and results data bank the clinical trial information . . .”).

<sup>66</sup> See *Seife v. U.S. Dep’t Health & Human Servs.*, 440 F. Supp. 3d 254, 278 (S.D.N.Y. 2020) (noting that “responsible parties knew since the FDAAA’s enactment in 2007 that the statute required them to submit Basic Results for each ACT of a product that is approved,” but that the Final Rule “included in its preamble an interpretation . . . that was contrary to the text of the FDAAA”).

<sup>67</sup> *Kisor v. Wilkie*, 139 S. Ct. 2400, 2415–17 (2019).

<sup>68</sup> *Auer v. Robbins*, 519 U.S. 452 (1997).

<sup>69</sup> *Kisor*, 139 S. Ct. at 2417 n.5 (internal citation omitted).

<sup>70</sup> *Gonzales v. Oregon*, 546 U.S. 243, 257 (2006).

<sup>71</sup> See *Seife*, 440 F. Supp. 3d at 265.

<sup>72</sup> *Chevron, U.S.A., Inc. v. Nat. Res. Def. Council, Inc.*, 467 U.S. 837, 842–43 (1984) (defining a two-step inquiry to determine when agencies receive deference for their interpretations of statute: First,

step of *Chevron* if Congress has not “unambiguously expressed” its intent.<sup>73</sup> The FDAAA’s enumerated requirement of Basic results submission for *all* ACTs used to secure FDA approval<sup>74</sup> could not be clearer, and the Final Rule’s explicit rejection of this requirement for certain trials cannot be reduced to merely interpretive difference. The agency’s interpretation of the Final Rule, therefore, would have been unlikely to receive deference on appeal.

Even with the ruling in *Seife*, the benefit will not immediately be evident. Processing data submissions for those missing ten years’ worth of clinical trials will likely be challenging. The timeline for compliance—or the quality of data that will emerge during the process—remains unclear. What *is* clear, however, is that the relevant provisions of the FDAAA unambiguously define statutory intent on this issue, and the Final Rule’s misinterpretation of the FDAAA’s reporting requirements here significantly hampers the ability of ClinicalTrials.gov to serve as an effective public repository of clinical trial information.

Other agency-related issues, moreover, pose barriers to effective leverage of ClinicalTrials.gov: NIH has yet to post a single public notice on ClinicalTrials.gov indicating that a responsible party was noncompliant in its clinical trial data reporting.<sup>75</sup> No place exists for the public to search for public notices of noncompliance (perhaps unsurprising given the former point).<sup>76</sup> Nor has NIH restricted or revoked access to federal funding as a result of trial data reporting noncompliance.<sup>77</sup> Though FDA indicated it would begin more aggressively enforcing reporting requirements, including penalizing noncompliant entities up to \$10,000 each day they delayed their submissions, the agency similarly has yet to levy a single fine.<sup>78</sup> All of these requirements—public notices of noncompliance on ClinicalTrials.gov,<sup>79</sup> a public-facing search engine for these notices,<sup>80</sup> and penalties for noncompliant entities<sup>81</sup>—were either required or authorized by the FDAAA.

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whether Congress has “directly spoken to the precise question at issue,” and second, “if the statute is silent or ambiguous with respect to the specific issue, the question for the court is whether the agency’s answer is based on a permissible construction of the statute”).

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

<sup>74</sup> 42 U.S.C. § 282(j)(3)(C).

<sup>75</sup> Charles Piller, *Transparency on Trial*, 367 *SCI.* 240, 241 (2020) (“NIH said at a 2016 briefing on the final rule that it would cut off grants to those who ignore the trial reporting requirements, as authorized in the 2007 law, but so far has not done so.”).

<sup>76</sup> Brenda Sandburg, *Court Rules More Trial Data Must be Posted on ClinicalTrials.gov*, XCONOMY (Mar. 4, 2020), <https://xconomy.com/national/2020/03/04/court-rules-more-trial-data-must-be-posted-on-clinicaltrials-gov/> [https://perma.cc/E2K9-X2H9].

<sup>77</sup> Lev Facher, *Federal Judge Rules Clinical Trial Sponsors Must Publish a Decade’s Worth of Missing Data*, STAT (Feb. 25, 2020), <https://www.statnews.com/2020/02/25/clinical-trial-sponsors-publish-missing-data/> [https://perma.cc/9G3H-HSEE] (noting that “the National Institutes of Health has never publicly named or withheld grant funding” as a result of failure to comply with trial data reporting requirements).

<sup>78</sup> 21 U.S.C. § 333(f)(3)(A) (2018); Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 801, 121 Stat. 920; Piller, *supra* note 75, at 241 (indicating that FDA does not plan to fine noncompliant entities until it issues “further ‘guidance’ on how it will exercise that power”).

<sup>79</sup> 42 U.S.C. § 282(j)(5)(E)(i).

<sup>80</sup> 42 U.S.C. § 282(j)(5)(E)(vi).

<sup>81</sup> 21 U.S.C. § 333(f)(3)(A) (2018) (stating that a civil monetary penalty applies to violations of the certification requirement codified in 42 U.S.C. § 282(j)(5)(B), as per § 331(jj)(1)).

Admittedly, the court in *Seife* held that NIH's inaction in this context is immune to judicial review.<sup>82</sup> Even though the FDAAA requires NIH to post notices of noncompliance, FDAAA also requires FDA to notify the noncompliant entity, which, due to the penalty being tied to the number of days of noncompliance, carries discretionary authority.<sup>83</sup> While NIH has a "nondiscretionary obligation to post public noncompliance notices" that does not require a discretionary determination, fulfilling that obligation does require FDA to have made a prior discretionary determination under its notice provision, immunizing both FDA and NIH action (or inaction) from judicial review.<sup>84</sup> But immunity to review does not erase the fact that NIH has failed to execute tasks that the legislature clearly intended under the auspices of the FDAAA's notice provisions—the agency's actions certainly seem *irreverent* of legislative intent, even if not violative.

Lack of administrative follow-up to the FDAAA—as exemplified by NIH's failure to post notices of noncompliance and the Final Rule's exemption of a decade's worth of ACTs from trial data reporting—has made enforcement more difficult, if not outright impossible in some cases.

### *B. Compliance with Reporting Requirements Remains Low*

Responsible parties continue to remain largely noncompliant not only with FDAAA's ACT data submission requirements but also with those of the Final Rule, perhaps because NIH and FDA's lack of enforcement action provides incentives for responsible parties to choose not to comply with clinical trial registration and reporting requirements. Indeed, responsible parties skirt Final Rule requirements in a number of ways. First, many responsible parties are outright noncompliant with regulation. A *Science* study looking at over 4,700 ACTs completed after 2017 (and therefore subject to the Final Rule) showed that most clinical trial sponsors delayed post-trial data submission, and a significant portion of them never submitted the data at all.<sup>85</sup> Second, responsible parties can potentially game data quality to delay registration or results submission, exhibiting effectively noncompliant behavior despite facially meeting regulation requirements. For example, even in cases where the trial sponsor submits the data on time, for example, quality control review by NIH before posting on ClinicalTrials.gov often finds a number of errors that make the data borderline unusable (including "showing data for more participants than were enrolled," or using "inconsistent units of measurement," both of which make it impossible to draw reasonable conclusions from the study).<sup>86</sup>

It is certainly possible that sponsors could simply be acting in good faith when encountering errors, and indeed, I would guess that many are good faith actors. The high rate of noncompliance, however, suggests that at least some subset of those errors may not be accidental and that those sponsors may be acting deliberately to delay results submission. These errors delay the process of posting the data but do not

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<sup>82</sup> *Seife v. U.S. Dep't Health & Human Servs.*, 440 F. Supp. 3d 254, 282 (S.D.N.Y. 2020) ("[J]udicial review also cannot be had of NIH's inaction under the NIH notice provision.")

<sup>83</sup> *Id.* at 280.

<sup>84</sup> *Id.* at 281–82.

<sup>85</sup> Piller, *supra* note 75, at 241 (finding that less than 45% of trials registered on ClinicalTrials.gov in the last two years submitted their data early or on time, and that results were *never* reported for more than 30% of trials registered on ClinicalTrials.gov during this time).

<sup>86</sup> Charles Piller, *Gaming the System*, 367 *Sci.* 243, 243 (2020).

invalidate the timeliness of submissions for 42 U.S.C. § 282 compliance purposes. In more egregious cases, the trial sponsor may simply choose to offer trial registration submissions of poor quality, which can delay public posting of the trial itself for months.<sup>87</sup> Indeed, the previous director of ClinicalTrials.gov, Deborah Zarin, recently indicated her belief that at least some companies leverage the quality control valve when registering clinical trials to “temporarily protect information [the companies] regard as proprietary.”<sup>88</sup>

Imagining how such a gaming situation might play out (or the type of thinking that might incentivize such behavior) is not difficult. Suppose, in January 2016, Company X is investigating a not-previously-approved product, Z, for therapeutic use in pancreatic cancer. The company also has preliminary research indicating that the product may be effective in colorectal and hepatic cancer as well, but another few years of preclinical investigation (through 2020) are required to determine whether Z is a good candidate for those additional therapeutic indications. Company X takes the following steps in seeking approval for Z’s use in pancreatic cancer: First, within twenty-one days of trial commencement (as FDAAA requires),<sup>89</sup> it submits registration information to NIH. But Company X presents unclear primary objectives for evaluation in the study,<sup>90</sup> resulting in rejection of their trial posting on ClinicalTrials.gov until Company X corrects these errors by a later date.<sup>91</sup>

In January 2019, after completing the trial and securing approval for Z’s use in pancreatic cancer, Company X submits the trial results as required within one year of approval. The results, however, are recorded in units of measurement inconsistent with the output researchers indicated they had been measuring (e.g., recording maximum blood plasma concentration using ‘seconds’ as the unit), prompting rejection and opportunity for correction by Company X. In April 2019, Company X resubmits the results; this time, NIH finds other indicia of incoherency in the trial results (failure to include clear time frames for data measurements, for example) and again rejects the submission. Company X again resubmits the results in November 2019, and after taking a few months to process the results, NIH finally uploads the results to ClinicalTrials.gov in February 2020. With the extra time, Company X has now finished its preclinical research on Z and knows Z is a good candidate for colorectal cancer; due to delays in registration and submission of trial results, Company X has a head start of more than a year over other entities that may be conducting similar research for these disease states. And Company X has created this advantage without violating a *single* regulation: Credit for registration of an ACT and submission of its

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<sup>87</sup> *Id.*

<sup>88</sup> *Id.* (indicating Ms. Zarin “has heard of companies that want to appear to comply with ClinicalTrials.gov’s legal mandate but deliberately file shoddy trial registrations—likely to be rejected and therefore delay public posting—to temporarily protect information they regard as proprietary”); *see also* Deborah Zarin, *The Culture of Trial Results Reporting at Academic Medical Centers*, 180 JAMA INTERNAL MED. 319, 319–20 (2020).

<sup>89</sup> 42 U.S.C. § 282(j)(2)(C)(ii).

<sup>90</sup> This is one of the required categories of information for the responsible party to submit to NIH so that the agency can register the trial on ClinicalTrials.gov. *See* 42 U.S.C. § 282(j)(2)(A)(ii).

<sup>91</sup> There is no given timeline in the Final Rule or the FDAAA for enforcing submission; this is presumably part of the delegated rulemaking authority under the FDA and NIH notice provisions of the FDAAA.

results are given upon handing the data to the appropriate agency. Company X has successfully gamed the Final Rule.

It may seem odd that any responsible party could engage in this kind of behavior when it must still submit credible clinical trial data to FDA in order to secure approval. But FDA and NIH might have different goals and purposes for this data. While FDA is primarily concerned with using clinical trial data to determine whether a product is safe and effective, NIH may be more concerned with the standardization of trial data for ease of input into its system and accessibility to the public, researchers, and other stakeholders. A trial could be very well-designed and indicate a statistically significant clinical benefit—sufficient to pass muster for FDA approval—but fail to present its summary findings in a way that lends to easy input and presentation in ClinicalTrials.gov.

Additionally, this dual channel for trial data—to FDA for drug approval and to NIH for ClinicalTrials.gov publication—creates other unique opportunities for gaming the system. Many entities simply do not register their trial at all on ClinicalTrials.gov even while seeking FDA approval of their product.<sup>92</sup> In 2014, for example, of the agency’s nineteen approvals of not-previously-approved products, ten (more than half) involved non-registered clinical trials, and one-third involved later-stage clinical trials that tested for efficacy.<sup>93</sup> Both the hypothetical involving Company X and this real-world example of the agency’s approvals in 2014 indicate the ripe ground for noncompliance when, as is the case now, no penalty is levied on responsible parties for flouting regulation.<sup>94</sup>

### C. *Is FDA Delay and Nonenforcement Otherwise Justified by Law?*

Agencies carry considerable authority to choose how—or whether—to enforce their regulations. When considering the impact of responsible parties’ ongoing noncompliance with the Final Rule, as well as NIH’s decision neither to publish noncompliance notices nor provide a search engine for the same on ClinicalTrials.gov, it is equally important to acknowledge the agency’s prerogative to delay or opt against enforcement—and to examine whether superseding justification for doing so may have existed. As is the case for many kinds of administrative discretion,<sup>95</sup> “discretionary

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<sup>92</sup> But note that the NIH ordinarily delays full posting of registration requirements for responsible parties seeking approval for a not-previously-approved medical product until after the product receives an approval decision. Limited information *is* posted, however, and the responsible party has the choice to disclose registration information prior to submitting the product for review. *See FDAAA 801 and the Final Rule*, CLINICALTRIALS.GOV (Aug. 2019), <https://clinicaltrials.gov/ct2/manage-recs/fdaaa#WhichTrialsMustBeRegistered> [<https://perma.cc/JKR4-NN3R>].

<sup>93</sup> Jennifer E. Miller, Marc Wilenzick, Nolan Ritcey, Joseph S. Ross & Michelle M. Mello, *Measuring Clinical Trial Transparency: An Empirical Analysis of Newly Approved Drug and Large Pharmaceutical Companies*, 7 *BMJ OPEN* 1, 4 (2017) (“Ten of 19 drugs (53%) had at least one undisclosed trial conducted in patients. Six drugs (32%) had at least one undisclosed phase II or III trial. At least 2864 patients participated in trials with undisclosed results.”).

<sup>94</sup> *See infra* Section II.A for more in-depth discussion of responsible parties’ incentives for noncompliance.

<sup>95</sup> *See, e.g.*, Aaron L. Nielson & Christopher J. Walker, *Strategic Immunity*, 66 *EMORY L.J.* 55, 57 (2016) (“The danger is that although discretion can be and, indeed, usually is used for the public’s benefit, it can also serve self-interested ends—for instance by allowing regulators to make their own lives easier.” (footnotes omitted)).

authority to determine when the law should and should not be enforced”<sup>96</sup> can be leveraged to yield good outcomes but is equally subject to potential for abuse.<sup>97</sup> Determining whether an agency’s enforcement discretion resides closer to either of those poles requires contextual evaluation of the agency’s action (or inaction) under applicable law.

With regard to clinical trial data reporting requirements, two major nonenforcement issues arise that have not already been discussed:<sup>98</sup> first, NIH’s delayed implementation of regulation clarifying Expanded results reporting requirements until six years after the statutorily mandated deadline;<sup>99</sup> and second, FDA’s choice not to enforce compliance with both statutory clinical trial reporting requirements (pre-2017) and those enumerated in the Final Rule (post-2017). Since the Supreme Court in *Heckler v. Chaney* held that “an agency’s decision not to prosecute or enforce . . . is a decision generally committed to an agency’s absolute discretion,” and therefore presumptively unreviewable,<sup>100</sup> FDA’s choice not to enforce—whatever the policy implications—is almost certainly justified by law.<sup>101</sup> The ensuing analysis therefore addresses whether NIH acted unreasonably in delaying its issuance of regulation for reporting Expanded results, leaving the substantive question of whether nonenforcement causes more harm than benefit to later sections discussing the public health impacts and policy implications of clinical trial data transparency.<sup>102</sup>

As a matter of due course, agencies frequently make determinations about when to promulgate regulation pursuant to or mandated by statutory provisions.<sup>103</sup> When an agency fails to meet a statutory timeline for a mandatory rulemaking provision, the courts typically evaluate the agency’s delay using a balancing test first established in *Telecommunications Research & Action Center v. FCC* (the “TRAC” test).<sup>104</sup> Courts applying this test look at several factors: whether Congress “provided a timetable or other indication” of the appropriate timeframe for agency action, whether delays implicate concerns of “human health and welfare,” competing agency priorities that could be undermined by expediting the delayed action, “the nature and extent of the interests prejudiced by delay,” and whether, in delaying action, the agency has treated

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<sup>96</sup> See Nielson, *supra* note 56, at 1520.

<sup>97</sup> See, e.g., Ruth Colker, *Administrative Prosecutorial Indiscretion*, 63 TUL. L. REV. 877, 880 (1989) (“As administrative agencies become more sensitive to political considerations, their exercise of discretion is more likely to be in response to these concerns, rather than to the facts and law of the specific cases.”).

<sup>98</sup> Other nonenforcement issues include FDA’s failure to enforce the statutory requirement that responsible parties submit Basic results for ACTs used to secure approval of novel products, as well as NIH’s choice not to label, or provide a public-facing search mechanism for finding, noncompliant parties. See *supra* notes 75–84 and accompanying text.

<sup>99</sup> 42 U.S.C. § 282(j)(3)(D)(i).

<sup>100</sup> *Heckler v. Chaney*, 470 U.S. 821, 831 (1985).

<sup>101</sup> DANIEL T. SHEDD, CONG. RESEARCH SERV., R43710, A PRIMER ON THE REVIEWABILITY OF AGENCY DELAY AND ENFORCEMENT DISCRETION 5 (2014) (noting that there are at least two major exceptions to the presumptive immunity of agency prosecution decisions: discriminatory enforcement actions that violate the Equal Protection clause, and nonenforcement actions that arise from agency exposition of its interpretation of a statute). Neither of these exceptions apply to FDA’s nonenforcement actions at issue here.

<sup>102</sup> See *infra* Section III.

<sup>103</sup> See SHEDD, *supra* note 101, at 3.

<sup>104</sup> *Telecomm. Research & Action Ctr. v. FCC*, 750 F.2d 70, 80 (D.C. Cir. 1984).

any party more favorably than others.<sup>105</sup> But when Congress includes *specific* deadlines for agency action, courts have treated the issue in one of two ways: most have held that an agency's failure to comply with those deadlines amounts to "failure to act" under the Administrative Procedure Act (APA)<sup>106</sup> in which "no balancing of factors is required or permitted,"<sup>107</sup> while some have held that courts retain discretion not to compel agency action even when the action is statutorily mandated under a specific timetable—these courts look to TRAC factors to determine whether mandamus is appropriate.<sup>108</sup>

The FDAAA enumerated a specific deadline (September 27, 2010) for issuing regulation on Expanded results submissions to ClinicalTrials.gov, and under either of these approaches taken by courts, NIH's delay constituted an unjustified "failure to act" under the APA. Under the first approach, the outcome is relatively straightforward: NIH delayed implementation despite a specific statutory deadline and, thus, improperly ignored the FDAAA's required timetable.<sup>109</sup> Courts have acknowledged that statutory deadlines for agency action may, at times, result in difficult tradeoff choices given the agency's need to conduct its own research (particularly for novel or complex areas) and follow due process before issuing regulation.<sup>110</sup> Competing priorities, however, categorically do not result in the kind of "irreparable injury" that courts have used at times to justify delay of agency implementation even under this less discretionary first standard.<sup>111</sup> And outside of such exceptional circumstances, these courts require swift agency action to correct delays. Indeed, in *Center for Food Safety v. Hamburg*, the court found actionable even FDA's less-than-one-year delay in issuing regulation subject to specific deadlines under the Food Safety and Modernization Act.<sup>112</sup> NIH's delay under the FDAAA, by contrast, was *nearly four years*.

Even under the second approach, analysis of TRAC factors also suggests NIH improperly delayed regulation of Expanded results submission as required by the FDAAA. Two factors weigh more heavily in this context: explicit statutory deadlines

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<sup>105</sup> *Id.* (internal citations omitted).

<sup>106</sup> See *Forest Guardians v. Babbitt*, 174 F.3d 1178, 1189–90 (10th Cir. 1999). See also *South Carolina v. United States*, 243 F. Supp. 3d 673, 687 (D.S.C. 2017); *Oxfam Am., Inc. v. SEC*, 126 F. Supp. 3d 168, 172–76 (D. Mass. 2015); *W. Watersheds Project v. Foss*, No. CV 04-168-MHW, 2006 WL 2868846, at \*3 (D. Idaho Oct. 5, 2006).

<sup>107</sup> *Biodiversity Legal Found. v. Badgley*, 309 F.3d 1166, 1174, 1177–78 & n.11 (9th Cir. 2002).

<sup>108</sup> *In re Barr Labs., Inc.*, 930 F.2d 72, 74–75 (D.C. Cir. 1991).

<sup>109</sup> See Michael D. Sant'Ambrogio, *Agency Delays: How a Principal-Agent Approach Can Inform Judicial and Executive Branch Review of Agency Foot-Dragging*, 79 GEO. WASH. L. REV. 1381, 1414 (2011) ("Courts will generally compel agency action that violates a clear statutory deadline.").

<sup>110</sup> This might include, for example, the need to post advanced notices of proposed rulemaking to receive public input before issuing final regulation if the rulemaking is a "rule" under § 553 of the APA. See *Ctr. for Food Safety v. Hamburg*, No. C 12-4529-PJH, 2013 WL 5718339, at \*2 (N.D. Cal. Oct. 21, 2013).

<sup>111</sup> *Id.* at \*2–3 (noting that meeting a statutorily mandated deadline does not constitute "irreparable injury" even if it interferes with other agency priorities, and that in the absence of such "irreparable injury" and convincing reason to believe the agency's position will be supported on appeal, any further delay is highly unlikely to be permitted).

<sup>112</sup> See *Ctr. for Food Safety v. Hamburg*, 954 F. Supp. 2d 965, 966–67, 971 (N.D. Cal. 2013).

and public health (as opposed to economic) impacts.<sup>113</sup> Delaying this regulation compromises general health and welfare and prejudices the interests of key stakeholders using ClinicalTrials.gov, namely watchdog groups and clinical researchers.<sup>114</sup> Not having access to Expanded results for clinical trials that have resulted in FDA approvals could make understanding the scope of previous research difficult for clinical researchers, which could result in duplicative effort. Lack of access would also impede ongoing efforts by watchdog groups and researchers to examine prior trials for safety or efficacy issues. This lack of understanding and examination pose potentially serious public health liabilities and suggest that the agency's choice to delay is more likely to cause harm than to offer any cognizable benefit.

Competing agency priorities are likely NIH's best justification under this standard, but courts have typically found this issue dispositive only when injunctive relief would result in little difference in agency policy.<sup>115</sup> Here, of course, delay resulted in considerable difference in policy; Expanded results were not required to be submitted until the agency issued regulation compelling such action. Finally, while an unreasonable delay *alone* is not dispositive,<sup>116</sup> violation of a specific statutory deadline weighs heavily against the agency.<sup>117</sup> Taken together, these factors indicate that NIH's delay in issuing regulation is not justified under the more discretionary TRAC factor test any more than it is under the nondiscretionary "specific deadline" standard. The agency's delay, therefore, was considerably closer to potential abuse of nonenforcement discretion than warranted exercise of executive authority to choose when to enforce.

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Despite unambiguous statutory mandates in the FDAAA enumerating a host of requirements related to clinical trial registration and data submission, FDA and NIH have fundamentally misinterpreted certain statutory requirements, unjustifiably delayed promulgation of statutorily mandated regulation, and opted not to enforce various statutory requirements and, later, those enumerated by each respective agency. While some of these actions are legally shielded, some were not—and some have run afoul of the law entirely.<sup>118</sup> Regardless of the legal defensibility of the agencies' nonenforcement actions and delay in issuance of regulation, the harms of these agency actions are manifest in the poor compliance rates with clinical trial data registration

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<sup>113</sup> SHEDD, *supra* note 101, at 10 ("First, statutory deadlines appear to be a significant factor in determining a case of unreasonable delay. When Congress signifies that it wants an agency to prioritize an action, the courts are more willing to enforce that priority. Second, courts appear to be more willing to compel an agency to act when the action involves public health or safety, compared to mere economic interests.").

<sup>114</sup> For a more in-depth analysis of stakeholder usage of ClinicalTrials.gov, see Section II.B.

<sup>115</sup> See, e.g., *In re Barr Labs., Inc.*, 930 F.2d 72, 75–76 (D.C. Cir. 1991) (finding that requiring agency action would result in inefficient reallocation of agency resources because the plaintiff's call for injunctive relief would do little more than putting them "at the head of the queue" of a process; it would not result in any change in policy).

<sup>116</sup> *In re Ctr. for Auto Safety*, 793 F.2d 1346, 1354 (D.C. Cir. 1986).

<sup>117</sup> SHEDD, *supra* note 101, at 10 ("[S]tatutory deadlines appear to be a significant factor in determining a case of unreasonable delay.").

<sup>118</sup> See *supra* notes 109–17 and accompanying text.



and submission requirements and the resultant harms on ongoing clinical research and medical practice.<sup>119</sup> Understanding the goals of government regulation in this context, and the reasons responsible parties have been hesitant to comply with FDAAA and Final Rule requirements, lays preliminary groundwork for addressing the issue.

## II. THE CHALLENGES OF DISCLOSURE-BASED REGULATION

As the cost of online disclosure decreases and public demand for transparency increases,<sup>120</sup> scholars have begun highlighting the government's efforts to "regulate by database."<sup>121</sup> In addition to merely promoting transparency, federal agencies increasingly publish publicly accessible databases in attempts to use disclosure to help regulate undesirable behavior.<sup>122</sup> In the past, the government had used disclosure relatively narrowly, "more to persuade than to inform" the public, with the hope of curtailing harmful behavior.<sup>123</sup> More recently, the government has sought to leverage transparency to shed light on unsavory practices and exert pressure on *disclosers*, rather than just the public, to change their underlying behavior.<sup>124</sup> Done optimally, disclosure-based regulation has the potential to correct market inefficiencies and improve consumer decision-making,<sup>125</sup> "preempt or at least deter undesired behavior,"<sup>126</sup> reduce "agency slack" due to underenforcement,<sup>127</sup> and increase government accountability through data transparency.<sup>128</sup> But expert opinion remains divided as to whether the government's disclosure-based regulation effectively alters the behavior of disclosers.<sup>129</sup>

Government efforts, moreover, often remain lackluster due to incomplete or inaccurate data collection in government databases—this is a perennial issue with disclosure-based regulation.<sup>130</sup> Regulation based on inaccurate or incomplete data poses serious concerns,<sup>131</sup> which can become magnified in the context of public

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<sup>119</sup> See *infra* Section III.B.

<sup>120</sup> Nathan Cortez, *Regulation by Database*, 89 U. COLO. L. REV. 1, 5 (2018).

<sup>121</sup> *Id.* at 4–5 ("We now rely on disclosure to regulate food nutrition, fuel economy, hospital quality, mortgages, securities, sex offenders, tire safety, toxic pollution, and workplace chemical exposure . . .").

<sup>122</sup> *Id.* at 5.

<sup>123</sup> Omri Ben-Shahar & Carl E. Schneider, *The Failure of Mandated Disclosure*, 159 U. PA. L. REV. 647, 744 (2011) (describing, as examples, the use of sanitation report cards or calorie count fact sheets to persuade consumers to make healthy choices about their food consumption).

<sup>124</sup> Cortez, *supra* note 120, at 5.

<sup>125</sup> *Id.* at 20–21.

<sup>126</sup> *Id.* at 23.

<sup>127</sup> Matthew C. Stephenson, *Public Regulation of Private Enforcement: The Case for Expanding the Role of Administrative Agencies*, 91 VA. L. REV. 93, 110 (2005).

<sup>128</sup> Cortez, *supra* note 120, at 27.

<sup>129</sup> See Richard Craswell, *Static Versus Dynamic Disclosures, and How Not to Judge Their Success or Failure*, 88 WASH. L. REV. 333, 339 (2013); Ryan Bubb, *TMI? Why the Optimal Architecture of Disclosure Remains TBD*, 113 MICH. L. REV. 1021 (2015). *But see* David C. Vladeck, *Information Access—Surveying the Current Legal Landscape of Federal Right-to-Know Laws*, 86 TEX. L. REV. 1787, 1792 (2008); Ben-Shahar & Carl E. Schneider, *supra* note 123, at 744.

<sup>130</sup> Cortez, *supra* note 120, at 30.

<sup>131</sup> Timur Kuran & Cass R. Sunstein, *Availability Cascades and Risk Regulation*, 51 STAN. L. REV. 683, 755–60 (1999).

health.<sup>132</sup> Responsible parties' noncompliance with clinical trial data registration and submission requirements under both the FDAAA and the Final Rule, therefore, raise similar concerns regarding use of flawed data to guide decision-making. Correcting this issue requires exploring the underlying rationales for discloser noncompliance.

### A. *Trial Sponsors Have Incentive Not to Comply*

Concerns over disclosure of proprietary information incentivize noncompliance with clinical trial data reporting requirements under the FDAAA and the Final Rule. Responsible parties almost always undertake clinical trials to investigate the potential utility of a drug, biological product, or device as a therapeutic intervention<sup>133</sup> with the end goal of securing FDA approval to market the therapy to consumers. Avoiding compliance with registration and reporting requirements delays the posting of proprietary information online, making it more difficult for a competitor to see the results or even topic of the research and safeguarding the responsible party's intellectual property.

While these incentives behind noncompliance might seem facially anti-competitive, protecting proprietary information is both a legitimate and routine business practice. Responsible parties (particularly industry) regularly seek to protect their intellectual property through patents or trade secrets.<sup>134</sup> These decisions require careful balancing: When choosing whether to patent their intellectual property, for example, responsible parties must weigh the cost of disclosure versus the benefit of a period of commercial exclusivity.<sup>135</sup> A responsible party that chooses to hold its property as a trade secret *forges* this guaranteed patent-exclusivity period in favor of potential for longer-lasting protection (i.e., so long as the trade secret can be kept confidential). These are difficult business decisions even in a vacuum; clinical trial data reporting obligations can complicate them further.

Responsible parties may be choosing not to comply with trial data reporting requirements because they see required disclosures as inextricable from certain trade secrets. Companies have long argued, for example, that data from failed clinical trials constitutes confidential commercial information because the data is used to develop

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<sup>132</sup> Failure to report issues with FDA-approved medical devices, despite mandatory reporting requirements, exemplifies underreporting that can result in public health issues due to lack of adequate—and accurate—safety information. See U.S. GOV'T ACCOUNTABILITY OFFICE, GAO/HEHS-97-21, MEDICAL DEVICE REPORTING: IMPROVEMENTS NEEDED IN FDA'S SYSTEM FOR MONITORING PROBLEMS WITH APPROVED DEVICES (1997).

<sup>133</sup> The overwhelming majority of clinical trials registered on ClinicalTrials.gov are interventional studies, which examine the therapeutic utility of drugs, biologics, medical devices, surgical procedures, behavioral therapy, and other treatments. See U.S. NAT'L LIB. MED., CLINICALTRIALS.GOV, TRENDS, CHARTS, AND MAPS (May 13, 2020), <https://clinicaltrials.gov/ct2/resources/trends#TypesOfRegisteredStudies>.

<sup>134</sup> INSTITUTE OF MEDICINE, SHARING CLINICAL TRIAL DATA: MAXIMIZING BENEFITS, MINIMIZING RISK 257–61 (2015) (noting patents and trade secrets as relevant intellectual property protection devices for responsible parties) [hereinafter SHARING CLINICAL TRIAL DATA].

<sup>135</sup> U.S. FOOD & DRUG ADMIN., FREQUENTLY ASKED QUESTIONS ON PATENTS AND EXCLUSIVITY (Feb. 05, 2020), [https://www.fda.gov/drugs/development-approval-process-drugs/frequently-asked-questions-patents-and-exclusivity#What\\_is\\_the\\_difference\\_between\\_patents\\_a](https://www.fda.gov/drugs/development-approval-process-drugs/frequently-asked-questions-patents-and-exclusivity#What_is_the_difference_between_patents_a) [https://perma.cc/QRA8-766S] (stating that a “new drug application (NDA) or abbreviated new drug application (ANDA) holder is eligible for exclusivity if statutory requirements are met”).

more effective follow-up therapies.<sup>136</sup> Though these concerns are generally attenuated when dealing with trials supporting approved drugs,<sup>137</sup> responsible parties could still be worried that disclosure of study design and endpoints could confer competitive advantage to other entities seeking to develop similar products—and that there is no effective way to disentangle research strategy from the parameters and data of the trial itself.

The more likely source of danger in this context, however, is disclosure of *non-summary* clinical information (as opposed to the *summary* clinical information required by Basic and Expanded results reporting), which is more likely to include notes on study design rationales or explanations of clinical development choices.<sup>138</sup> In fact, NIH and FDA addressed this concern explicitly when issuing the Final Rule, noting that results “in summary form”—as opposed to participant-level information—”can be disclosed without disclosing trade secret or other confidential commercial information.”<sup>139</sup>

Premature reveal of proprietary information could still potentially result in economic damage to responsible parties. Generic manufacturers, for example, could use the trial’s safety and effectiveness data to obtain faster approval for generic versions of the therapeutic, or competitors could use the same trial data—potentially including auxiliary research protocols hitherto protected as trade secrets<sup>140</sup>—to obtain faster approval for rival drugs of the same class. Indeed, FDA acknowledges the special protections due proprietary research information.<sup>141</sup> These particular concerns of course implicate a broader question about the economics of branded versus generic drugs, and the equities associated with intellectual property protection in this context.<sup>142</sup> But for present purposes, it is sufficient simply to say that as an exercise in

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<sup>136</sup> See, e.g., *Pub. Citizen Health Res. Group v. Food & Drug Admin.*, 185 F.3d 898 (D.C. 1999) (finding that the responsible party was not obligated to disclose results of failed trials even upon FOIA request because the party used data from those trials for ongoing research into successor therapies. The court did, however, determine that “conclusory and generalized” explanations for competitive harm were not sufficient to prevent disclosure of trial results).

<sup>137</sup> See SHARING CLINICAL TRIAL DATA, *supra* note 134, at 259 (noting that for “data associated with approved drugs . . . [,] the concern about data release leading competitors directly to successful alternative drugs may be diminished”).

<sup>138</sup> See *id.* (indicating that non-summary clinical information is likely to receive broad “confidential commercial information” designation because it could include information about “study results, clinical development decisions, rationales for study designs, and processes for running clinical trials”) (internal citations omitted).

<sup>139</sup> Clinical Trial Registration and Results Information Submission, 81 Fed. Reg. 64,996 (Sept. 21, 2016).

<sup>140</sup> Kristan Lansbery, *Protecting Trade Secrets in the Medical Product Approval Process*, FOOD & DRUG LAW INSTITUTE (Mar/Apr 2018), <https://www.fdpi.org/2018/04/update-protecting-trade-secrets-medical-product-approval-process/> [<https://perma.cc/R2WM-95CM>] (indicating a plethora of procedural items that constitute commercial trade secrets but would be required to be disclosed during clinical trial data reporting as part of the trial “design and results”).

<sup>141</sup> Aaron S. Kesselheim & Michelle M. Mello, *Confidentiality Laws and Secrecy in Medical Research: Improving Public Access to Data on Drug Safety*, 26 HEALTH AFF. 483, 485–86 (2007) (describing “the FDA’s understanding that research data are entitled to protection as proprietary information”).

<sup>142</sup> See generally Uche Ewelukwa, *Patent Wars in the Valley of the Shadow of Death: The Pharmaceutical Industry, Ethics, and Global Trade*, 59 U. MIAMI L. REV. 203 (2005) (exploring the relationship between pharmaceutical patent protection and public health and the effects in developing countries).

understanding the *responsible party's* perspective, delaying NIH's posting of proprietary clinical trial data does protect legitimate business interests. This incentive can apply to industry and academic medical centers alike; management of any clinical trial with prospective economic return is susceptible to the same pressures (at least in kind if not in degree) regardless of the institution involved.

Reporting clinical trial data also requires not insignificant effort from the responsible party without, from the responsible party's perspective, any *immediately* apparent gain. Perhaps paradoxically, in 2019 those institutions with the highest number of trials registered on ClinicalTrials.gov most often submitted clinical trial data in accordance with regulation despite—one might imagine—these institutions standing to save the most resources by not complying with submission requirements.<sup>143</sup> Compliance with regulation by industry members among these could be explained by *each* member's ongoing, or recently completed, scrutiny by FDA under the terms of Corporate Integrity Agreements put in place due to past bad-faith actions, some of which have provisions specifically highlighting commitments to data dissemination.<sup>144</sup> Another (more likely) explanation is that these institutions, both industry and non-industry, have more robust reporting systems in place because they routinely conduct many clinical trials. Having an efficient system in place can reduce the opportunity cost associated with investing resources for compliance with regulation, particularly when a company must do so for many clinical trials. By contrast, institutions that infrequently conduct clinical trials had *considerably* lower rates of compliance with regulation,<sup>145</sup> perhaps due to lack of standard procedures for data reporting, limited available resources to commit to reporting, or resource allocation decisions that did not make data submission a primary concern in the face of other priorities.

In addition to these affirmative reasons, trial sponsors also have little reason to comply because there is no penalty for not doing so. NIH does not publicly note, on the clinical trial page or elsewhere on ClinicalTrials.gov, that the trial sponsor failed to comply with registration or reporting requirements,<sup>146</sup> so there is no fear of public backlash. And since FDA has yet to impose any fines, monetary or otherwise, on noncompliant entities,<sup>147</sup> the agency similarly does not provide threat of punitive measures as incentive to comply. In the presence of a variety of compelling business reasons not to comply, and lack of consequences for failing to disclose clinical trial data, it is hardly surprising that trial sponsors exhibit such pervasive noncompliance.

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<sup>143</sup> Nicholas J. DeVito, Seb Bacon & Ben Goldacre, *Compliance with Legal Requirement to Report Clinical Trial Results on ClinicalTrials.Gov: A Cohort Study*, 395 LANCET 361, 365 (2020).

<sup>144</sup> Thomas Sullivan, *HHS OIG: Listing of Pharmaceutical and Device Corporate Integrity Agreements*, POLICYMED.COM (May 6, 2018), <https://www.policymed.com/2013/02/hhs-oig-listing-of-pharmaceutical-and-device-corporate-integrity-agreements.html> [<https://perma.cc/DC39-YLHL>]; see, e.g., DEP'T OF JUSTICE, CORPORATE INTEGRITY AGREEMENT BETWEEN THE OFFICE OF INSPECTOR GENERAL OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES AND GLAXOSMITHKLINE LLC 19–22 (July 2, 2012) (highlighting in GSK's corporate integrity agreement various commitments by the company to timely disseminate study data and report, when appropriate, the data to regulatory bodies).

<sup>145</sup> DeVito et al., *supra* note 143, at 361 (finding that institutions in the bottom quartile of number of trials registered on ClinicalTrials.gov had less than half the rate of compliance with data submission requirements as did institutions in the top quartile of registered trials).

<sup>146</sup> Piller, *supra* note 86, at 241.

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

Responsible parties' concerns about proprietary information disclosure, and its potentially detrimental effects on business interests, as well as resource allocation constraints on smaller responsible parties, must be taken seriously by any policy that aims to shift discloser behavior. Rather than solely pushing responsible parties to comply by fiat, agencies should also make efforts to increase disclosure of clinical trial data by considering how to offer carrots or sticks to positively engage relevant stakeholders and incentivize compliance by responsible parties. Several possible paths forward to incentivize compliance are discussed later in this Article.<sup>148</sup>

### *B. Clinical Trials and Big Data: The Chicken and Egg Problem*

With increasing availability of digitized information and better standardization of health data input in the last decade,<sup>149</sup> “big data”—large datasets that can be mined for patterns or trends often invisible to the human eye<sup>150</sup>—can offer meaningful contributions to medical research and practice. Big data analytics diverge from more traditional statistical tools by eschewing reliance on purely relational data (i.e., information expressed by predefined relationships) and instead accommodating mining of unstructured data (i.e., information that does not have predefined organization).<sup>151</sup> Advances in modern computing, particularly in machine learning, enable analysis of unstructured data to probe underlying patterns or trends.<sup>152</sup> Unstructured data often consists of a medley of quantitative and qualitative information,<sup>153</sup> making clinical trial data, which usually contain both metrics (e.g., blood pressure) and text (e.g., descriptions of the patient’s pain or adverse events<sup>154</sup>), good test cases for application of big data analytics.

Indeed, big data analysis of clinical trial results, including those stored on ClinicalTrials.gov, can help industry and academic medical researchers conduct more cost- and time-efficient research and development. While this topic is discussed at

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<sup>148</sup> See *infra* Section IV (discussing policy proposals to incentivize compliance with clinical trial data reporting requirements).

<sup>149</sup> Travis B. Murdoch & Allan S. Detsky, *The Inevitable Application of Big Data to Health Care*, 309 JAMA 1351, 1351 (2013) (describing the increase in digital data collection over the last decade as well as increasing use of tools, like EHRs, which repose a variety of quantitative and qualitative data in an easily accessible format).

<sup>150</sup> See *id.* (describing, for example, one application of big data analytics to mine unstructured electronic health record data helped develop an “automated identification” algorithm that outperformed traditional means of predicting postoperative complications).

<sup>151</sup> See *id.* (noting that big data analytics “are in contrast to traditional statistical methods (derived from the social and physical sciences), which are largely not useful for analysis of unstructured data such as text-based documents that do not fit into relational tables”).

<sup>152</sup> *Id.* (“Advances in analytic techniques in the computer sciences, especially in machine learning, have been a major catalyst for dealing with these large information sets.”). These advances particularly enable exploration of health care information, which is overwhelmingly in the form of unstructured data. Elizabeth O’Dowd, *Unstructured Healthcare Data Needs Advanced Machine Learning Tools*, HITINFRASTRUCTURE.COM (July 2, 2018), <https://hitinfrastructure.com/news/unstructured-healthcare-data-needs-advanced-machine-learning-tools> [<https://perma.cc/MV4L-2JLT>] (noting that “[a]bout 80% of healthcare data is unstructured”).

<sup>153</sup> Christine Taylor, *Structured vs. Unstructured Data*, DATAMATION.COM (Mar. 28, 2018), <https://www.datamation.com/big-data/structured-vs-unstructured-data.html> [<https://perma.cc/HNT6-EEUJ>].

<sup>154</sup> 21 C.F.R. § 312.32 (2019) (defining an adverse event as “any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related”).

length later in this Article,<sup>155</sup> a brief example of big data integration into therapeutic research may be helpful here to illustrate the potential for benefit. Suppose Company X is developing a therapy for a multifactorial disorder, which has several genetic and/or environmental determinants,<sup>156</sup> and wants to use a predictive biomarker, which is a molecular proxy for an individual's likelihood to respond to therapy,<sup>157</sup> to identify good candidates for trial recruitment. To narrow down the field of optimal candidates, Company X could peruse the endpoints or clinical measurements taken for participants in prior trials studying this disorder. From this targeted list, the company could then look at public health record repositories containing genomic and metabolite profiles of patients with the disorder to determine which biomarker candidates would be feasible for use in a broad pool of trial participants.<sup>158</sup> But for this to work—and work well—the pool of available clinical trial results must be robust.

Benefits of big data to researchers, before any other downstream considerations, require a dataset of sufficient size and accuracy. Pooled clinical trial data for a particular condition approximates, in theory, the larger patient population suffering from that condition. But without a sufficiently robust volume of information, the pooled data cannot comprehensively reproduce the disease dynamics within that population (or, for that matter, the range of response to a well-studied therapy). If a researcher uses an underpowered database for big data analysis, such as Company X's predictive biomarker search, doing so may result in inaccurate conclusions that would not provide useful information to responsible parties and could run the risk of causing delays in the research process. This potential for inaccuracy is all the more salient because many medical products are the subject of continued study beyond the trial originally used to secure approval for therapeutic use. Prospective failure to report clinical trials, then, could affect validity of prior big data analyses *even if* the data pool at the time of analysis was robust. Unless responsible parties commit to ongoing, timely compliance with trial data reporting requirements, they will be hard-pressed to reap the rewards of big data analysis during their research and development of medical products.

These factors contribute to the prisoner's dilemma that perversely incentivizes noncompliance. A responsible party wins if *all* responsible parties report trial results because that would create a sufficiently large set of data for the responsible party to leverage its own analytics-aided research. But the responsible party loses if it is the *only* one reporting trial data because it will have expended more time and resources on submission than its rivals, and shared data that could confer competitive advantage,

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<sup>155</sup> See *infra* Section III.B.ii.

<sup>156</sup> NAT'L LIB. MED., *What are Complex or Multifactorial Disorders* (accessed June 9, 2020), <https://ghr.nlm.nih.gov/primer/mutationsanddisorders/complexdisorders> [https://perma.cc/B6PK-RQN4] (defining multifactorial disorders as those that “do not have a single genetic cause—they are likely associated with the effects of multiple genes (polygenic) in combination with lifestyle and environmental factors”).

<sup>157</sup> Robert M. Califf, *Biomarker Definitions and their Applications*, 243 EXPERIMENTAL BIOLOGY & MED. 213, 216 (2018) (“When the level of a biomarker changes in response to exposure to a medical product or an environmental agent, it can be called a *pharmacodynamic/response biomarker*.”).

<sup>158</sup> Some private software companies, like NextBio, are already creating and operating platforms that allow for these types of big data analyses. See Suzanne Elvidge, *Digging for Big Data Gold: Data Mining as a Route to Drug Development Success*, CLINICAL LEADER, <https://www.clinicalleader.com/doc/digging-for-big-data-gold-data-mining-as-a-route-to-drug-development-success-0001> [https://perma.cc/NS7M-4Z9D].

without receiving any reciprocal benefit. That the sole discloser loses is especially true in the context of trial protocols and statistical analysis plans (SAPs), which can be of considerable use to others researching the same or similar disease states—since protocols and SAPs describe in detail the conduct of trial procedures and analysis of trial data—but could confer a competitive disadvantage to the discloser if their rivals are not similarly disclosing.

If the pool of clinical trial results and protocol and SAP information available at ClinicalTrials.gov is not useful for big data analytics until it reaches a critical mass, responsible parties may think there is no incentive to go through the trouble *now* when there is *no* short-term payoff for their efforts (or even a guarantee of long-term payoff since that depends on cooperation by all responsible parties), but there *is* risk of cognizable and immediate business harm if they submit their trial results or confidential protocols while others do not. This way of thinking, however, renders inaccessible the research benefits made available when parties collectively disclose.

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Regulation by disclosure is already challenging, but it is doubly so when nonenforcement coincides with affirmative reasons not to disclose. The validity of these reasons aside, responsible parties seem principally concerned that timely and complete disclosure of clinical trial data results in competitive disadvantage. This concern may be borne out by any number of seemingly reasonable rationales, such as reluctance to disclose proprietary information—often the results of years of effort—that the responsible party fears may enable competitors or generics to bring rival products to market. In most cases of nondisclosure, though, the choice not to disclose can likely be understood as the result of a prisoner’s dilemma: Responsible parties think they stand to gain the most when *they* do not disclose but *others* do. Nonenforcement further encourages this kind of behavior because non-disclosing responsible parties do not need to consider the risk of agency-levied penalties when acting this way. But it is important that we find a way to incentivize compliance with trial data reporting requirements: As in a real prisoner’s dilemma, all stakeholders stand to benefit *considerably* more from cooperation, which in this case would provide a robust and up-to-date pool of trial data available through ClinicalTrials.gov.

### III. ROBUST CLINICAL TRIAL DATA REPORTING: DUES AND BENEFITS

Despite the many incentives—and lack of disincentives—for noncompliance, many responsible parties do nevertheless report their trial results.<sup>159</sup> These include entities that prolifically conduct clinical trials<sup>160</sup> and might, in theory, stand to gain the *most* by not complying with regulation. While ongoing scrutiny of certain responsible parties under Corporate Integrity Agreements<sup>161</sup> may explain compliance to some degree, it certainly cannot explain it entirely. This behavior may be better understood

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<sup>159</sup> DeVito et al., *supra* note 143, at 365.

<sup>160</sup> See FDA’s TRIALS TRACKER (accessed June 10, 2020), <http://fdaa.trialstracker.net/?status%5B%5D=reported> [https://perma.cc/6SS2-C2NB] (indicating that responsible parties have submitted results for nearly 70% of ACTs (4,668/6,717) conducted since implementation of the Final Rule, of which 64% (3,006/4,668) were submitted on time).

<sup>161</sup> Sullivan, *supra* note 144.

in light of the various responsibilities and benefits that prudent stakeholders in the research enterprise should recognize when conducting clinical trials. These responsibilities and benefits also underscore why noncompliant responsible parties should strongly reconsider their choice not to register their trials or submit trial results to ClinicalTrials.gov—and why FDA and NIH should consider addressing noncompliance through enforcement action.

*A. Stakeholders Have a Responsibility to Report Clinical Trial Data*

Clinical trials result from collaborative efforts between the responsible party, funding entities, and trial participants, among others. And as with any collaborative venture, clinical trials can only be successful when those involved (“involved entities”) shoulder their respective obligations. In doing so, each involved entity naturally takes on the responsibility to perform its part. Though few legal *duties* bind involved entities beyond performative obligations, these entities ought to appreciate the various ethical and legal *responsibilities* to each other that emerge from their interactions during the course of the clinical trial. These responsibilities adhere not only due to involved entities’ interactions with each other but also because involved entities are members of the research and healthcare enterprise at large, and as prudent stakeholders therein, they should conduct clinical research in ways that are sustainable, accountable, and impactful.

*i. Respect for Clinical Trial Participants*

Medical research relies on the willingness of clinical trial participants to weather the unknown in exchange for incremental advances in therapeutic knowledge. As Francis Collins, the current director of NIH, noted in 2014, “[m]edical advances would not be possible without participants in clinical trials.”<sup>162</sup> Director Collins was not speaking in the abstract—he delivered these comments to contextualize NIH’s release of proposed regulations to expand clinical trial data reporting pursuant to FDAAA requirements.<sup>163</sup> In light of the contributions of clinical trial participants, Director Collins emphasized that “[w]e owe it to every trial participant . . . to support the maximal use of this knowledge for the greatest benefit to human health.”<sup>164</sup> Doing so is necessary, though not sufficient, to fulfill the ethical responsibility that arises from individuals’ voluntary exposure to potential experimentation-related harms.<sup>165</sup>

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<sup>162</sup> *HHS and NIH Take Steps to Enhance Transparency of Clinical Trial Results*, NAT’L INST. HEALTH (Nov. 19, 2014), <https://www.nih.gov/news-events/news-releases/hhs-nih-take-steps-enhance-transparency-clinical-trial-results> [<https://perma.cc/KN4F-WEAM>].

<sup>163</sup> *Id.* (indicating the NIH had, on the day of publication, proposed policy to make clinical trial data reporting to the NIH more transparent, and against that backdrop, delivering comments from Director Collins).

<sup>164</sup> *Id.*; the NIH as an institution has similarly noted the ethical obligation to make clinical trial results publicly accessible. *See also* Clinical Trial Registration and Results Information Submission, 81 Fed. Reg. 65,067 (Sept. 21, 2016) (stating that a public record of clinical trial results “also fulfills an obligation to trial participants that is established between them and the research team. Individuals participate in clinical trials with the understanding that the research will contribute to the expansion of knowledge pertaining to human health”).

<sup>165</sup> Monique L. Anderson, Karen Chiswell, Eric D. Peterson, Asba Tasneem, James Topping & Robert M. Califf, *Compliance with Results Reporting at ClinicalTrials.gov*, 372 NEW ENG. J. MED. 1031, 1032



And indeed, clinical trial participants—even if voluntarily—sometimes expose themselves to considerable harm. This situation was seen to devastating effect in 2006, when all participants in an early-phase trial of TGN1412, an immunostimulatory antibody, experienced multiorgan failure that resulted in immediate hospitalization<sup>166</sup> and debilitating ongoing trauma more than a decade later.<sup>167</sup> Though an extreme example, the TGN1412 trial underscores the serious harms that can come from failure to disclose trial data in a timely manner. A therapy similar to TGN1412 had been tested more than ten years earlier with comparable results,<sup>168</sup> but because the earlier trial was never registered (nor its results reported),<sup>169</sup> participants in the TGN1412 trial experienced potentially avoidable and indisputably irrevocable harm. Though FDA does require reporting of serious adverse events in early-stage (i.e., Phase I) trials,<sup>170</sup> like that of TGN1412, these notices do not enter a public-facing data registry (as is the case for submitted trial results) that other researchers can reference when conducting their own research.<sup>171</sup> Neither the FDAAA nor the Final Rule presently requires submission of Phase I trial results.<sup>172</sup>

Though most trials do not result in grave physical injury, every trial participant exposes him- or herself to risk of physical and psychological harm as well as minor, more common, harms. The number of adverse events, or harms related to use of a medical product, that emerge during a clinical trial sometimes exceeds the number of trial participants.<sup>173</sup> These harms can run the gamut from heart attacks to depression

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(2015) (“The human experimentation that is conducted in clinical trials creates ethical obligations to make research findings publicly available.”).

<sup>166</sup> Ganesh Suntharalingam, Meghan R. Perry, Stephen F. Ward, Stephen J. Brett, Andrew Castello-Cortes, Michael D. Brunner & Nicki Panoskaltis, *Cytokine Storm in a Phase I Trial of the Anti-CD28 Monoclonal Antibody TGN1412*, 355 NEW ENG. J. MED. 1018, 1018 (2006).

<sup>167</sup> See Kathryn Knight, *The Lifelong Shadow Hanging Over the Elephant Man Drug Trial Victims After the Human Guinea Pigs Were Left Horribly Disfigured and Fighting for Their Lives*, DAILYMAIL.COM (Feb. 21, 2017), <https://www.dailymail.co.uk/news/article-4236132/Lifelong-shadow-hanging-Elephant-Man-drug-trial-men.html> [<https://perma.cc/B4HG-KMGU>] (describing trial participants’ experiences dealing with amputation of extremities, various surgeries, impeded locomotion, and compromised immune systems).

<sup>168</sup> Thomas Wicks, *Clinical Trial Transparency: The Stepping Stones to Disclosure*, CLINICAL LEADER (June 1, 2015), <https://www.clinicalleader.com/doc/clinical-trial-transparency-the-stepping-stones-to-disclosure-0002> [<https://perma.cc/CG32-3Y6J>] (describing, in the context of the TGN1412 trial, the “controversy [that] emerged because a similar study had been done in 1994 with similar outcomes”).

<sup>169</sup> *Id.* (noting that information on this previous trial was not available on any “public registry” that the TGN1412 researchers could have accessed prior to commencement of their, later, trial).

<sup>170</sup> 21 C.F.R. § 314.50(d)(5)(vi)(a) (2019) (requiring that responsible parties submit information regarding “demonstrated . . . adverse effects” for any trials supporting a new drug application).

<sup>171</sup> The agency does maintain the FDA Adverse Event Reporting System (FAERS), which makes *post-approval* adverse event reports submitted to FDA publicly accessible, but it does not report pre-approval (i.e., clinical trial) adverse events. *Questions and Answers on FDA’s Adverse Event Reporting System (FAERS)*, U.S. FOOD & DRUG ADMIN. (June 4, 2018), <https://www.fda.gov/drugs/surveillance/questions-and-answers-fdas-adverse-event-reporting-system-faers> [<https://perma.cc/CM7B-RZA9>].

<sup>172</sup> *FDAAA 801 and the Final Rule*, CLINICALTRIALS.GOV (August 2019), <https://clinicaltrials.gov/ct2/manage-recs/fdaaa#WhichTrialsMustHaveResults> [<https://perma.cc/G5N5-PUHN>] (including among exclusions to results submissions requirements “Phase I trials” of drugs or biological and analogous “feasibility” studies for devices).

<sup>173</sup> Rachel Phillips, Lorna Hazell, Odile Sauzet & Victoria Cornelius, *Analysis and Reporting of Adverse Events in Randomised Controlled Trials: A Review*, BMJ OPEN, Mar. 1, 2019, at 1 (“Often large

to loss of mobility. And not all of these harms are bounded by the period of exposure: Some harms (such as chronic pain) may outlast the trial, while others may not arise until much later (such as increased risk of cancer or other disease as a result of trial participation). Not all harms are medical, moreover, as participants also commonly deal with “discomfort, inconvenience, and loss of work time.”<sup>174</sup> Though participants acknowledge these risks when providing informed consent prior to trial commencement,<sup>175</sup> doing so does not discount the litany of health hazards, physical and psychological injuries, and other harms that trial participants shoulder.

By voluntarily assuming risks and experiencing harm (and doing so without expectation of personal benefit<sup>176</sup>), some scholars argue that trial participants enter a social contract that “imposes an ethical obligation that the results lead to the greatest possible benefit to society.”<sup>177</sup> Researchers violate the social contract, moreover, when the “trial fails to provide useful information”<sup>178</sup>—or no information at all, as is the case when responsible parties fail to submit their data. Merely providing trial results to participants is similarly insufficient because that does not provide the research community the opportunity to translate those results into generalizable principles that advance science. Indeed, when clinical trial results are “not reported publicly or accessibly,” researchers do not satisfy the assurances—under this theory of an ethical “social contract”—made to participants that “their involvement will contribute to knowledge.”<sup>179</sup> Although this is a relatively novel approach to clinical trial ethics, in recent years, large research entities have echoed these same concerns: The International Committee of Medical Journal Editors, for example, recently affirmed its support of “an ethical obligation to responsibly share data generated by interventional clinical trials because participants have put themselves at risk.”<sup>180</sup>

Responsible parties have a responsibility to trial participants, therefore, to uphold their end of this social contract by promptly and accurately submitting the results of their clinical trials, which can then be used by the larger medical research community to maximize their utility. Reporting results to ClinicalTrials.gov is important for all trials, but doubly so for failed clinical trials, in which the vast majority of participants

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numbers of AEs are reported during a study, sometimes exceeding the number of patients in the clinical trial.”).

<sup>174</sup> Howard Bauchner, Robert M. Golub & Phil B. Fontanarosa, *Data Sharing: An Ethical and Scientific Imperative*, 315 JAMA 1237, 1238 (2016).

<sup>175</sup> *Informed Consent for Clinical Trials*, U.S. FOOD & DRUG ADMIN. (Jan. 2018), <https://www.fda.gov/patients/clinical-trials-what-patients-need-know/informed-consent-clinical-trials> [<https://perma.cc/E62K-TXBG>].

<sup>176</sup> At least some patients in most trials are given placebo treatments that do not contain the investigational therapy. These patients, from the outset, forsake any personal benefits of participation in the clinical trial.

<sup>177</sup> See Bauchner et al., *supra* note 174, at 1238.

<sup>178</sup> *Id.*

<sup>179</sup> Kay Dickersin & Iain Chalmers, *Recognizing, Investigating and Dealing with Incomplete and Biased Reporting of Clinical Research: From Francis Bacon to the WHO*, 104 J. ROYAL SOC. MED. 532, 532 (2011).

<sup>180</sup> Darren B. Taichman, Joyce Backus, Christopher Baethge, Howard Bauchner, Peter W. de Leeuw, Jeffrey M. Drazen, John Fletcher, Frank A. Frizelle, Trish Groves, Abraham Haileamlak, Astrid James, Christine Laine, Larry Peiperl, Anja Pinborg, Peush Sahni & Sinan Wu, *Sharing Clinical Trial Data—A Proposal from the International Committee of Medical Journal Editors*, 374 NEW ENG. J. MED. 384, 384 (2016).

receive no personal benefit for participation despite shouldering the same risks as participants in other, successful trials. Reporting clinical trial results to ClinicalTrials.gov acknowledges the sacrifices of these participants and recognizes that “it is owed to them that this sacrifice should be given the greatest possible chance of having an impact.”<sup>181</sup>

### ii. Government Transparency

The American taxpayer also makes sacrifices (though less voluntarily<sup>182</sup> and less directly corporeal) that put onus on the government to ensure clinical trial results are publicly accessible. Many clinical trials are supported, at least in part, by NIH research grants or other sources of federal funding.<sup>183</sup> This is especially true of research done by academic research centers and, of course, NIH institutes<sup>184</sup> and is increasingly so even for private corporations, which often collaborate with academic research centers to do clinical research.<sup>185</sup> Unfortunately, entities that often receive the most NIH research funding also comprise some of the most routinely noncompliant entities.<sup>186</sup>

When the government makes use of public funds, furnished by taxpayers, it has a responsibility to ensure that the money is used efficiently towards the public good. This responsibility applies doubly so for “significant national investments” that regularly absorb billions of federally funded dollars, such as clinical trial research.<sup>187</sup> Many comments on NIH’s policy for Dissemination of NIH-Funded Clinical Trial Information reflected precisely this point, indicating that making trial results publicly accessible is “particularly appropriate because NIH-funded clinical trials are supported by public funding, and recipients of those funds have a special obligation to ensure that the nation’s investment is maximized.”<sup>188</sup> And this investment can only be *maximized* when all stakeholders have access to (and are therefore able to make use

<sup>181</sup> Iain Brassington, *The Ethics of Reporting All the Results of Clinical Trials*, 121 BRITISH MED. BULL. 19, 22 (2017) (internal citation omitted).

<sup>182</sup> Benjamin Tucker’s griping, more than a hundred years ago, captures the feeling of many a taxpayer today: “To force a man to pay for the violation of his own liberty is indeed an addition of insult to injury.” Geoffrey James, *130 Inspirational Quotes About Taxes* (Apr. 13, 2015), <https://www.inc.com/geoffrey-james/130-inspirational-quotes-about-taxes.html> [<https://perma.cc/RH3V-RNHX>].

<sup>183</sup> *Clinical Trial-Specific Funding Opportunities*, NAT’L INST. HEALTH (Dec. 21, 2018), <https://grants.nih.gov/policy/clinical-trials/specific-funding-opportunities.htm> [<https://perma.cc/FUJ4-JPVZ>].

<sup>184</sup> Kevin E. Noonan, *Top 50 NIH-Funded Research Institutions FY2019*, PATENT DOCS (June 6, 2019), <https://www.patentdocs.org/2019/06/top-50-nih-funded-research-institutions-fy2019.html> [<https://perma.cc/PZ22-B76D>].

<sup>185</sup> Bonnie W. Ramsey, Gerald T. Nepom & Sagar Lonial, *Academic, Foundation, and Industry Collaboration in Finding New Therapies*, 376 NEW ENG. J. MED. 1762, 1764 (2017) (describing models of academic and industry partnerships in a variety of disease states, such as cystic fibrosis and multiple myeloma).

<sup>186</sup> Piller, *supra* note 86, at 240–41.

<sup>187</sup> NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information, 81 Fed. Reg. 65,125 (Sept. 21, 2016); *see also* NAT’L INST. HEALTH, NIH REACHES ANOTHER MILESTONE TOWARD CLINICAL TRIAL STEWARDSHIP REFORMS (May 2, 2017), <https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-reaches-another-milestone-toward-clinical-trial-stewardship-reforms> [<https://perma.cc/5Z4U-HNUQ>] (stating that the NIH is the “largest public funder of clinical trials in the United States” and spends about \$3 billion per year funding clinical trial research).

<sup>188</sup> NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information, 81 Fed. Reg. 64,923 (Sept. 21, 2016).

of) the trial data.<sup>189</sup> In fact, NIH itself acknowledged this obligation to make trial data publicly accessible in both the policy itself and its answers to commenters who had argued against its implementation.<sup>190</sup> The agency specifically noted that providing “more complete information” about clinical trials can help to “conserve resources” and prevent “suboptimal return” on financial investment by reducing costs, including by “minimizing redundant trials.”<sup>191</sup> Doing so “optimize[s] the public investment in research.”<sup>192</sup>

Despite highlighting the importance of clinical trial data reporting, however, NIH has not taken the steps necessary to realize the public registry that its 2016 policy envisioned. The agency has not issued public notices on ClinicalTrials.gov trial entries when a responsible party is noncompliant, and correspondingly, the agency also has not made a public-facing, searchable index of noncompliant entities.<sup>193</sup> Nor is there evidence available that NIH withheld future funding or terminated current grant money as a result of trial registration or data submission noncompliance<sup>194</sup> despite indicating it would do so in the Final Rule.<sup>195</sup> It is possible, however, that NIH could have taken action in the intervening time that will be apparent as recent funding decisions become publicly available. To the extent it has not done so, though, to uphold the responsibility NIH has to members of the American public—who fund its research grants—the agency needs to take appropriate steps (including, but not limited to, enforcement action) to promote compliance with its clinical trial registration and results submissions guidelines.

### *iii. Public Health Imperative*

FDA oversees the approval process for therapeutic use of drugs, biologics, and devices, with the goal of ensuring approved medical products are effective for their indicated use and safe for consumption by the intended population. The agency relies on access to clinical trial results to make accurate comparative safety and efficacy evaluations, and the robustness of the agency’s decision calculus relies on the comprehensiveness of the dataset to which the agency is comparing the investigational agent under review. Admittedly, the agency does have access to more trial results than are available through ClinicalTrials.gov; even if responsible parties do not report their trial results to ClinicalTrials.gov, they do have to report the results to FDA as part of

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<sup>189</sup> See *supra* notes 176–81 and accompanying text.

<sup>190</sup> *E.g.*, NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information, 81 Fed. Reg. 64,925 (Sept. 21, 2016) (“[A] fundamental premise of all NIH-funded research is that the results of such work must be disseminated in order to contribute to the general body of scientific knowledge and, ultimately, to the public health. The NIH awardees have always been expected to make the results of their activities available to the research community and to the public . . .”).

<sup>191</sup> *Id.* at 65,125.

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

<sup>193</sup> See *supra* notes 75–77 and accompanying text.

<sup>194</sup> Facher, *supra* note 77 (noting that “the National Institutes of Health has never publicly named or withheld grant funding” as a result of failure to comply with trial data reporting requirements).

<sup>195</sup> 42 C.F.R. § 11.66(c) (2019) (“If it is not verified that the required registration and results clinical trial information for each applicable clinical trial for which a grantee is the responsible party has been submitted, any remaining funding for a grant or funding for a future grant to such grantee will not be released.”).

the medical product approval process.<sup>196</sup> But when responsible parties delay or fail to make available the results of *subsequent* trials (like follow-up safety trials for approved medical products) or *related* trials (like trials for other medical products with similar mechanisms of action), the agency may nevertheless be forced to make approval decisions on the basis of an inaccurate dataset. I would therefore advocate for more robust enforcement of deadlines for trial data reporting to ensure FDA has all relevant information before making decisions.

Even if the agency has access to all relevant trial data when making an approval decision, moreover, responsible parties' delay or failure to post results to ClinicalTrials.gov can still jeopardize public health. As we have seen from time to time throughout FDA's history, the agency is not infallible, and the public sometimes experiences harm when the agency fails to properly evaluate an investigational agent before approval or does not promptly recall a medical product after new knowledge of safety risks.<sup>197</sup> The risk of these harms warrants stronger enforcement of clinical trial registration and reporting requirements so that watchdog groups can timely assess agency action. Publicly accessible, and promptly reported, clinical trial results can empower government watchdog groups to proactively identify missteps and raise flags before extensive harms occur to public health.

Publicly accessible clinical trial results can also uniquely help prevent "duplication of unsafe and unsuccessful trials" and reduce the risk for volunteers participating in clinical trials.<sup>198</sup> Clinical trials for investigational agents that do not support approval, licensure, or clearance (i.e., failed trials) can serve as important benchmarks for future research. As noted by commenters on NIH's policy on trial data dissemination, giving responsible parties access to the results of failed trials reduces the chances that they will similarly design or conduct trials that are "potentially ineffective or harmful," since "similar interventions have been shown to be harmful or ineffective in previous, unpublished clinical trials."<sup>199</sup> Avoiding duplication of trials that are ineffective or unsafe protects volunteers from potential harm due to trial participation.

More generally, reporting failed clinical trial data also allows for more accurate meta-analyses, including reviews on effective and safe clinical trial practices. These reviews can influence study design for future clinical trials, such as choosing the endpoints that best approximate clinical efficacy in a specific context or validating that safety assessments accurately measure risks associated with drug use. In providing a more robust dataset for these analyses, therefore, failed clinical trial data can also help to ensure less health risk to volunteers in future, unrelated studies as well as to the general medical-product-using public. These benefits are all the more poignant

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<sup>196</sup> 21 C.F.R. § 314.50(d)(5) (2019) (requiring clinical trial results when filing a New Drug Application).

<sup>197</sup> See, e.g., Eric J. Topol, *Failing the Public Health—Rofecoxib, Merck, and the FDA*, 351 NEW ENG. J. MED. 1707, 1707 (2004) (describing the results of Merck's VIGOR trial, FDA committee analyses, and follow-up meta-data studies that all suggested, as early as 2000, that rofecoxib use increased risk of adverse cardiovascular events); A myocardial infarction is the medical term for a heart attack. HARVARD HEALTH PUBLISHING, *Heart Attack (Myocardial Infarction)*, HARVARD MED. SCH. (Feb. 2019), [https://www.health.harvard.edu/a\\_to\\_z/heart-attack-myocardial-infarction-a-to-z](https://www.health.harvard.edu/a_to_z/heart-attack-myocardial-infarction-a-to-z) [<https://perma.cc/C6JW-NPFG>].

<sup>198</sup> NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information, 81 Fed. Reg. 64,923 (Sept. 21, 2016).

<sup>199</sup> Clinical Trials Registration and Results Information Submission, 81 Fed. Reg. 64,993 (Sept. 21, 2016).

because most of the time, researchers do not publish the results of failed clinical trials in academic journals.<sup>200</sup> Thinking that prestigious publications are unlikely to be interested, many researchers do not even bother *trying* to submit the results of failed trials.<sup>201</sup> Public registries like ClinicalTrials.gov, then, are often the only viable repositories for data from failed trials, underscoring the importance of compliance with—and agency enforcement of—Final Rule trial data reporting requirements.

Private companies, which constitute a sizeable portion of responsible parties, admittedly do not have a *duty* to protect public health, but a variety of business reasons nevertheless incentivize corporate investment in improving public health. For one, as of last year, the pharmaceutical industry is the most poorly regarded of the major industries in the U.S., an issue likely exacerbated by some major drug companies' recent implication in the opioid crisis.<sup>202</sup> Even with vaccine development during COVID-19 taking the limelight, public opinion regarding the pharmaceutical industry has only marginally improved.<sup>203</sup> As chief executives have become more responsive to public pressure regarding corporate social responsibility,<sup>204</sup> commitments to improved transparency (such as making trial results publicly accessible on ClinicalTrials.gov) may help restore public trust. And public trust is important beyond mere optics. When the public does not trust industry, finding volunteers for clinical trials, securing funding from prospective investors, and building goodwill with regulatory agencies can become significantly more difficult<sup>205</sup>—all of which may adversely affect the company's bottom line. Even if industry may not consider itself a steward of public health, therefore, business reasons to act in the interest of public health nevertheless abound.

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<sup>200</sup> Thomas J. Hwang, Daniel Carpenter, Julie C. Lauffenburger, Bo Wang, Jessica M. Franklin & Aaron S. Kesselheim, *Failure of Investigational Drugs in Late-Stage Clinical Development and Publication of Trial Results*, 176 JAMA INTERNAL MED., 1826, 1829 (2016) (finding publication of only 40% of clinical trial results that failed to secure FDA approval of the studied investigational agent).

<sup>201</sup> Ivan Oransky & Adam Marcus, *Many Clinical Trials' Findings Never Get Published. Here's Why That's Bad*, STAT (Aug. 19, 2016), <https://www.statnews.com/2016/08/19/clinical-trials-unpublished-studies/> [<https://perma.cc/79A5-Y6VS>] (“The ‘file drawer problem’—‘Oh, those results aren’t interesting enough for a prestigious journal that can help our careers’—is a real one.”).

<sup>202</sup> Justin McCarthy, *Big Pharma Sinks to the Bottom of U.S. Industry Rankings*, GALLUP (Sept. 3, 2019), <https://news.gallup.com/poll/266060/big-pharma-sinks-bottom-industry-rankings.aspx?> [<https://perma.cc/L3L7-8P4Y>] (describing the “lawsuits, protests, and public shaming” that have accompanied the opioid epidemic and forecasting that the “industry’s rating likely will not recover until its role in the opioid epidemic is addressed . . .”).

<sup>203</sup> Beth S. Bulik, *Is COVID-19 Really Improving Pharma’s Reputation? Takeda Survey Says Not Too Much*, FIERCEPHARMA.COM (Dec. 17, 2020), <https://www.fiercepharma.com/marketing/takeda-u-k-survey-finds-only-minor-pharma-reputation-gains-during-pandemic> [<https://perma.cc/ER9A-NQFH>].

<sup>204</sup> Andrew Dunn, *Public Trust in Drugmakers Is at an All-Time Low. Can Biopharma Recover?*, BIOPHARMA DIVE (Sept. 11, 2019), <https://www.biopharmadive.com/news/pharma-industry-public-trust-gallup-business-roundtable/561986/> [<https://perma.cc/J8EM-XSBU>] (noting the increased pressure that CEOs face to “play a more active role in society” and providing several examples of private leadership speaking out on social issues).

<sup>205</sup> Jennifer Miller, *How Full Disclosure of Clinical Trial Data Will Benefit the Pharmaceutical Industry*, PHARMACEUTICAL J. (June 15, 2016), <https://www.pharmaceutical-journal.com/opinion/comment/how-full-disclosure-of-clinical-trial-data-will-benefit-the-pharmaceutical-industry/20201274.article?> [<https://perma.cc/UKB6-97WZ>].

### *B. All Stakeholders Benefit from Robust Clinical Trial Data Reporting*

Collective compliance with clinical trial results reporting (“collective data reporting”) produces a robust dataset in ClinicalTrials.gov that all stakeholders in the medical research enterprise can apply to their own work. But the ability to leverage this data relies on the dataset’s completeness; poor compliance with trial results reporting in the status quo undermines analyses that seek to use trial data available through ClinicalTrials.gov. This causes a spectrum of ongoing harms that can be broadly divided into three types: harm by inaccessibility, harm by distortion, and harm by denial.

Poor trial results reporting makes certain trial data *inaccessible*, which can cause harm by, for example, making it impossible for government watchdogs to access results for trials that they may seek to investigate. Poor trial results reporting also *distorts* trends that medical researchers may seek to find (such as the risk of cardiovascular adverse events in a particular class of drugs) by masking data points that could materially impact the conclusions of meta-analyses. And some stakeholders may withhold action altogether because investment only makes sense with a dataset of requisite completeness. This could include, for example, resource-intensive approaches like machine learning-guided analysis of trial data, which may not make sense to pursue if the researcher knows beforehand that the dataset to be processed is not sufficiently robust. Poor trial results reporting in this context, therefore, *denies* these stakeholders the opportunity to leverage clinical trial data. Compliance with trial results reporting obviates these different types of harms and allows the various stakeholders in the research enterprise to fully take advantage of trial data in ClinicalTrials.gov.

#### *i. Evidence-Based Clinical Decision-Making*

Collective data reporting benefits physicians by improving evidence-based clinical decision-making in a number of ways: decreasing evidentiary distortion in systematic reviews that form the basis of clinical practice guidelines, making trial results available for use by physicians facing perplexing individual cases, scientifically informing off-label use of medical products, and empowering artificial intelligence-based clinical decision support.

Since its rise in the early 1990s, the evidence-based medicine (EBM) paradigm, which advocates using “current best evidence in making decisions about the care of individual patients,”<sup>206</sup> has contributed to increasing empiricism in clinical decision-making. Two of the most enduring contributions among these, scholars posit, are the “development of more sophisticated hierarchies of evidence” and the related “development of the methodology for generating trustworthy recommendations” for clinical action in a particular case.<sup>207</sup> Given the sheer volume of health information and medical research available today, clinicians stratify different types of evidence to distinguish between generalizable evidence, which can support clinical decision-

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<sup>206</sup> David L. Sackett, William M. C. Rosenberg, J. A. Muir Gray, R. Brian Haynes & W. Scott Richardson, *Evidence Based Medicine: What It Is and What It Isn't*, 312 *BMJ* 71, 71 (1996).

<sup>207</sup> Benjamin Djulbegovic & Gordon H. Guyatt, *Progress in Evidence-based Medicine, A Quarter Century On*, 390 *LANCET* 415, 415 (2017).

making in a variety of contexts, and particularized evidence, which may be helpful only in closely analogous cases.<sup>208</sup>

Along this divide, generalizable evidence (usually in the form of systematic reviews) informs development of clinical practice guidelines, which “assist practitioner and patient decisions about appropriate health care for specific clinical circumstances.”<sup>209</sup> Because clinical encounters can exhibit significant case-to-case variability, these guidelines must anticipate a spectrum of possibilities. Systematic reviews provide a meta-analysis of relevant literature on a particular topic, assessing the “quality of existing studies” and providing a “high-quality summary” of the issue.<sup>210</sup> Because systematic reviews summarize and scrutinize many sources of data, they reside higher up on the EBM totem pole than individual clinical trials.<sup>211</sup> And due to their generalizability, systematic reviews are regularly incorporated into clinical practice guidelines.<sup>212</sup> In fact, for nearly a decade now, the Institute of Medicine has *required* that recommendations be “informed by a systematic review of evidence” in order to be considered clinical practice guidelines.<sup>213</sup>

Collective data reporting helps avoid distorted findings in meta-analyses and meaningfully shapes clinical decision-making due to clinical practice guidelines’ reliance on systematic reviews. Though findings from systematic reviews are typically more robust than conclusions drawn from single studies, reviews are not without their own pitfalls. Notwithstanding the potential for methodological issues, even a well-executed systematic review can fail to accurately characterize an issue if it surveys an incomplete dataset. This drawback is especially salient in the context of clinical research because academic journals often underreport results from failed clinical trials, which provide valuable depth to systematic reviews. If responsible parties do not upload their trial data to ClinicalTrials.gov, therefore, they risk distorting the results of systematic reviews that touch on clinical issues presented in their trial, and in doing so, they also risk distorting clinical practice guidelines that rely on the findings from those systematic reviews. Clinical practice guidelines based on distorted systematic reviews may not always be materially different,<sup>214</sup> but when they are, harm to the patient is more likely.

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<sup>208</sup> See OXFORD CENTRE FOR EVIDENCE-BASED MEDICINE, *Explanation of the 2011 OCEBM Levels of Evidence* (2011), <http://www.cebm.net/2011/06/explanation-2011-ocbm-levels-evidence/> [<https://perma.cc/LKD8-5D6P>].

<sup>209</sup> INSTITUTE OF MEDICINE, *CLINICAL PRACTICE GUIDELINES: DIRECTIONS FOR A NEW PROGRAM* 38 (Marilyn J. Field & Kathleen N. Lohr eds., 1990).

<sup>210</sup> Mike Clarke & Iain Chalmers, *Reflections on the History of Systematic Reviews*, 23 *BMJ EVIDENCE-BASED MED.* 121, 121 (2018) (describing the characteristics of systematic reviews).

<sup>211</sup> OXFORD CENTRE FOR EVIDENCE-BASED MEDICINE, *2011 Levels of Evidence* (2011), <https://www.cebm.net/wp-content/uploads/2014/06/CEBM-Levels-of-Evidence-2.1.pdf> [<https://perma.cc/UXR3-G44S>] (indicating that systematic reviews are nearly invariably the first source (i.e., Level 1) clinicians should go to when practicing EBM, and that, along those lines, “a systematic review is generally better than an individual study”).

<sup>212</sup> Paul G. Shekelle, *Clinical Practice Guidelines: What’s Next?*, 320 *JAMA* 757, 757 (2018) (describing the continued and consistent role systematic reviews have played in forming clinical practice guidelines).

<sup>213</sup> INSTITUTE OF MEDICINE, *CLINICAL PRACTICE GUIDELINES WE CAN TRUST* 4 (2011).

<sup>214</sup> Marie Baudard, Amélie Yavchitz, Philippe Ravaud, Elodie Perrodeau & Isabelle Boutron, *Impact of Searching Clinical Trial Registries in Systematic Reviews of Pharmaceutical Treatments: Methodological Systematic Review and Reanalysis of Meta-Analyses*, 356 *BMJ* 1, 6 (2017) (noting that incorporation of unpublished trial data into systematic reviews changed the treatment effect estimates but



Admittedly, physician compliance with clinical practice guidelines has been lackluster over the last two decades,<sup>215</sup> as has physician use of systematic reviews to inform patient treatment;<sup>216</sup> but recent trends, and benefits of collective data reporting, might actually make both easier to use. The sheer number of clinical practice guidelines, many of which are duplicative or contradictory, can disincentivize physicians from applying them to patients at all.<sup>217</sup> Since the Institute of Medicine required that all guidelines be based on systematic reviews,<sup>218</sup> the number of clinical practice guidelines has nearly halved in the last few years, leaving physicians with a more manageable set of recommendations.<sup>219</sup> And though different groups may interpret the same data in contradictory ways, that possibility becomes less likely the more robust the dataset becomes—as would be the case if responsible parties were to collectively report their trial results. Finally, a physician may hesitate to use a systematic review because reviews often address narrow clinical topics that may not always anticipate a particular patient’s medical issue.<sup>220</sup> Collective trial data reporting may help address this issue specifically: For common physician questions, such as a patient presenting a puzzling array of co-morbidities, relevant information may be easier to find through ClinicalTrials.gov, which may link to a pertinent publication.

When a physician encounters a situation where clinical practice guidelines may not apply and no pertinent systematic review is available, collective data reporting still supports EBM by making available more clinical trial results, which physicians may look to next.<sup>221</sup> Even without a more systematic analysis, clinical trials can shape how physicians practice medicine<sup>222</sup> and may serve as helpful bases of evidence when making decisions about individual patients. Some scholars have found, however, that

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not the statistical significance or qualitative assessment of treatment effectiveness. The authors do, however, indicate “searching clinical trial registries remains *an essential recommendation* for the conduct of systematic reviews and should be enforced” (emphasis added).

<sup>215</sup> See Elizabeth A. McGlynn, Steven M. Asch, John Adams, Joan Keesey, Jennifer Hicks, Alison DeCristofaro & Eve A. Kerr, *The Quality of Health Care Delivered to Adults in the United States*, 348 NEW ENG. J. MED. 2635, 2641 (2003) (reporting that patients received recommended care about 55% of the time).

<sup>216</sup> Andreas Laupacis & Sharon Straus, *Systematic Reviews: Time to Address Clinical and Policy Relevance as Well as Methodological Rigor*, 147 ANNALS INTERNAL MED. 274, 274 (2007) (“Despite advances in the conduct and reporting of systematic reviews, current evidence suggests that they are used less frequently by clinicians and policymakers than one might think.”).

<sup>217</sup> See Shekelle, *supra* note 212, at 757–58 (noting the near-doubling of clinical practice guidelines in the 2000s, that many guidelines cover the same topics but are written by different organizations, and that any “substantial differences” in major recommendations make it less likely that physicians will adhere to them in clinical practice).

<sup>218</sup> INSTITUTE OF MEDICINE, *supra* note 213, at 4.

<sup>219</sup> *Id.* at 757 (pointing to a decrease from 2,619 guidelines in 2014 to 1,440 in 2018).

<sup>220</sup> Laupacis & Straus, *supra* note 216, at 273.

<sup>221</sup> See *Explanation of the 2011 OCEBM Levels of Evidence*, OXFORD CENTRE FOR EVIDENCE-BASED MEDICINE, <http://www.cebm.net/2011/06/explanation-2011-ocbm-levels-evidence/> [<https://perma.cc/MF4C-A9M3>] (last visited Mar. 11, 2021).

<sup>222</sup> See, e.g., J.P. Mohr, J.L.P. Thompson, R.M. Lazar, B. Levin, R.L. Sacco, K.L. Furie, J.P. Kistler, G.W. Albers, L.C. Pettigrew, H.P. Adams, Jr., C.M. Jackson & P. Pullicino, *A Comparison of Warfarin and Aspirin for the Prevention of Recurrent Ischemic Stroke*, 345 NEW ENG. J. MED. 1444, 1447–48 (2001) (finding that warfarin did not outperform aspirin in reducing risk of recurrent ischemic stroke and, in view of other risks of warfarin and the higher risks of anticoagulants generally, requiring “close monitoring” when using warfarin as compared to non-steroidal anti-inflammatory drugs like aspirin).

physicians undervalue clinical trial research coming from industry sponsors,<sup>223</sup> which suggests diminished benefits of collective trial data reporting. The same researchers, however, noted that physicians did not *categorically* reject industry-sponsored trials; physicians distinguished between trials of varying methodological rigor regardless of the funding source.<sup>224</sup> Many of the most noncompliant responsible parties, moreover, are academic institutions and governmental agencies<sup>225</sup> for which physicians do not have the same impetus to downgrade credibility as they do for industry. Making more trial results readily available through collective data reporting can, therefore, help provide physicians a stronger foundation for EBM decision-making.

Doctors also routinely prescribe medical products off-label without “adequate supporting data” to guide their decisions;<sup>226</sup> collective data reporting can help minimize potential risk to the public by better informing safe and effective off-label use. Physicians typically use drugs off-label when, in their medical judgment, the drug may be well-suited for the patient given her particular circumstances and physiology (or, for example, when all approved treatments for the patient’s condition have failed).<sup>227</sup> Physicians prescribe off-label relatively often: Studies have shown that off-label use accounts for nearly one-fifth of all prescriptions, but in the vast majority of those cases, the off-label use has “little to no scientific support.”<sup>228</sup> Admittedly, even robust collective data reporting cannot correct underlying behavioral issues (like prescribing off-label without checking trial results or academic literature). But making trial results more readily available—particularly for failed trials that may shed light on expected efficacy of off-label use and inform safety and risk analysis—can help those physicians that *are* committed to EBM make more informed clinical decisions.

Collective data reporting also empowers integration of artificial intelligence-facilitated clinical decision support programs. Because much of the healthcare data that underlies physician decision-making is unstructured, artificial intelligence (AI) platforms (like IBM’s Watson Health) are increasingly used to sift through biomedical research literature and other sources of clinical trial data, like ClinicalTrials.gov, to support physician decision-making.<sup>229</sup> Even the best AI programs, however, can only

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<sup>223</sup> Aaron S. Kesselheim, Christopher T. Robertson, Jessica A. Myers, Susannah L. Rose, Victoria Gillet, Kathryn M. Ross, Robert J. Glynn, Steven Joffe & Jerry Avorn, *A Randomized Study of How Physicians Interpret Research Funding Disclosures*, 367 *NEW ENG. J. MED.* 1119, 1124 (2012) (finding that physicians “downgraded the credibility of industry-funded trials”).

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

<sup>225</sup> Piller, *supra* note 75, at 240–41.

<sup>226</sup> Off-label prescribing is “the prescription of a medication in a manner different from that approved by the FDA.” Randall S. Stafford, *Regulating Off-Label Drug Use—Rethinking the Role of the FDA*, 358 *NEW ENG. J. MED.* 1427, 1427 (2008). It is both “legal and common” but is “often done in the absence of adequate supporting data.” *Id.*

<sup>227</sup> *Id.* at 1427.

<sup>228</sup> David C. Radley, Stan N. Finkelstein & Randall S. Stafford, *Off-Label Prescribing Among Office-Based Physicians*, 166 *ARCHIVES INTERNAL MED.* 1021, 1023, 1025 (2006) (finding that “about 21% of all estimated uses for commonly prescribed medications were off-label,” that 73% of off-label uses “lacked evidence of clinical efficacy,” and that 73% of off-label uses were not supported by “strong scientific evidence”).

<sup>229</sup> See Brenda Segaria & Jennifer Mele, IBM WATSON HEALTH, AI IN HEALTHCARE 15 (2018), [https://hfmanj.org/images/downloads/March\\_26\\_2019/hfma\\_ibm\\_wh\\_3.26.pdf](https://hfmanj.org/images/downloads/March_26_2019/hfma_ibm_wh_3.26.pdf) [<https://perma.cc/3Z7S-U9YB>] (describing features of Watson Health’s portfolio of AI-powered tools, which analyze a variety of

generate insights as robust as the dataset from which it generates its heuristics allows. And, like humans, AI programs cannot tell if their findings are being distorted due to insufficient or inaccessible data that could otherwise meaningfully weigh on the research question the AI is probing. As health systems continue to adopt AI support to parse through clinical research data, physicians may grow more reliant on AI perusal of relevant research literature and trial results, particularly as the exponential increase in both types of information makes keeping abreast of current developments infeasible. As that reliance grows, collective data reporting will become increasingly essential to ensure that AI-based clinical decision support is poised to do optimal good—and perhaps more importantly—to do no harm.

### *ii. Informed Future Research Efforts*

Collective data reporting and registration can also improve responsible parties' future clinical research efforts by facilitating recruitment of trial participants, decreasing the likelihood of duplicative research, and improving clinical trial target selection and study design.

Difficulty in recruiting participants dooms many clinical trials before they even have the chance to test whether a prospective therapy works. Recruitment often imposes significant economic and time burdens on researchers to the extent that some scholars identify recruitment issues as the “number one barrier to clinical research.”<sup>230</sup> Trial sponsors are beginning to turn to AI to resolve the recruitment problem. Modern-day AI platforms can use sophisticated natural language processing<sup>231</sup> to examine the type of textual, unstructured data that often informs whether a patient might be a good candidate for a clinical trial. Examples of unstructured data include doctors' notes and other text entries in electronic health records as well as inclusion and exclusion criteria<sup>232</sup> listed on ClinicalTrials.gov. When sponsors timely register their trials on ClinicalTrials.gov, physicians can then use these platforms to help patients find trials in which they might be eligible to participate. Public-facing AI platforms like DQuest offer analogous services by translating inclusion and exclusion criteria listed for a trial on ClinicalTrials.gov into lay-language questions that an individual can use to determine her eligibility for participation.<sup>233</sup> But any AI platform used to facilitate recruitment can only identify trials that have been registered on ClinicalTrials.gov—these tools are most effective when responsible parties promptly register their trials.

Collective data reporting can take this technology one step further: While processing registration data may help determine whether a patient is eligible for a trial,

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unstructured data to “help[] doctors and patients make better-informed, evidence-based treatment decisions”).

<sup>230</sup> Marcus Woo, *Trial by Artificial Intelligence*, 573 NATURE S100, S100–01 (2019).

<sup>231</sup> Michael J. Garbade, *A Simple Introduction to Natural Language Processing*, BECOMINGHUMAN.AI (Oct. 15, 2018), <https://becominghuman.ai/a-simple-introduction-to-natural-language-processing-ea66a1747b32> [<https://perma.cc/B5HQ-E9AY>] (describing natural language processing as “a branch of artificial intelligence” that aims to “read, decipher, understand, and make sense of the human languages in a manner that is valuable”).

<sup>232</sup> U.S. FOOD & DRUG ADMIN., EVALUATING INCLUSION AND EXCLUSION CRITERIA IN CLINICAL TRIALS 1–2 (Apr. 16, 2018), <https://www.fda.gov/media/134754/download> [<https://perma.cc/PR8V-F4VK>] (defining *inclusion criteria* as the “characteristics required for study entry, such as stage of disease” and defining *exclusion criteria* as the “characteristics that disqualify patients from participation,” including among these “comorbidities or concomitant treatment”).

<sup>233</sup> Woo, *supra* note 230, at S101.

future AI programs might be able to use past trial results to predict whether a patient is likely to benefit from a trial. These predictions could be particularly helpful when a patient may be eligible for multiple ongoing trials for their condition. Analysis of a robust dataset of prior trials, for example, might shed light on patient characteristics that may favor or disfavor certain types of drugs over others, which could inform a patient's decision to enroll in a particular trial. As influential scholars and entities (including the Institute of Medicine) increasingly support sharing of individual-participant data from trials,<sup>234</sup> and as ClinicalTrials.gov continues to build functionality based on public comments similarly in support of facilitating participant-level data sharing,<sup>235</sup> these analyses can become even more tailored to a prospective participant's physiology. With evolving statistical optimization techniques, researchers can distinguish the characteristics of subpopulations in clinical trials that respond exceptionally well to prospective therapies—even when the trial failed to produce a statistically significant therapeutic benchmark on the whole.<sup>236</sup> With sufficient collective data reporting input, AI platforms leveraging these statistical optimization techniques can use these subpopulation analyses to help gauge whether a patient may not only be eligible but also whether, given her particular characteristics, she may be likely to benefit from participation in the trial.

In addition to simplifying the recruitment process for trials, collective data reporting also reduces the chance of researchers conducting a duplicative trial. The more promptly a responsible party submits their trial results to ClinicalTrials.gov, the more likely it is that other researchers will see the trial results and avoid duplicating a trial that has already been conducted. Avoiding duplicative work is especially critical given the overlap of common drug targets—the twenty thousand-odd medical products that FDA had approved as of 2011 only interacted with 2% of human proteins.<sup>237</sup> The limited number of druggable targets greatly increases the chance of duplicative work when researchers cannot find up-to-date records of trial results on ClinicalTrials.gov. Given the years-long timeframe of drug discovery, some duplicative work is of course still likely, but collective data reporting can certainly decrease the likelihood of its occurrence.

Failed clinical trials are infrequently reported in journals but are valuable commodities to clinical researchers seeking to conduct a successful trial. Collective data reporting—and particularly inclusion of failed trials—provides an undistorted

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<sup>234</sup> Jeffrey M. Drazen, *Sharing Individual Patient Data from Clinical Trials*, 372 *NEW ENG. J. MED.* 201, 201–02 (2015) (summarizing the IOM report's findings as in favor of individual-level data sharing, even after having weighed privacy issues and other concerns, given the “guiding principle . . . that participants put themselves at risk to participate in clinical trials”).

<sup>235</sup> See NAT'L LIB. MED., SUMMARY OF RESPONSES TO REQUEST FOR INFORMATION (RFI): CLINICALTRIALS.GOV MODERNIZATION 3 (Apr. 28, 2020) (noting feedback from many data users requesting that ClinicalTrials.gov include functionalities to support detailed technical trial comparisons, such as being able to search for trials with similar patient characteristics, disease subtypes, etc.).

<sup>236</sup> Dimitris Bertsimas, Nikita Korolko & Alexander M. Weinstein, *Identifying Exceptional Responders in Randomized Trials: An Optimization Approach*, 1 *INFORMS J. OPTIMIZATION* 187, 196–98 (2019) (describing several case studies in which application of optimization techniques to individual-level data identified specific participant subpopulations, characterized by an array of clinical indicia and vital measurements, that responded well to the tested treatment).

<sup>237</sup> Beth Kwon, *Chemical Biologist Targets 'Undruggable' Proteins Linked to Cancer in Quest for New Cures*, *MEDICALXPRESS.COM* (May 16, 2011), <https://medicalxpress.com/news/2011-05-chemical-biologist-undruggable-proteins-linked.html> [<https://perma.cc/PZ2Z-WKD6>].

evidentiary base for researchers to perform idiosyncratic analyses to determine appropriate study design or target selection. Suppose, for example, a team of researchers wants to research whether a gastrointestinal anti-inflammatory drug is also effective as a chemotherapeutic agent in pancreatic cancer. And two years prior, a different research group completed a trial that found the drug was ineffective in treating hepatic cancer. If that group had promptly reported its trial on hepatic cancer, the current research group would have had a wealth of information to guide its own trial: effective and ineffective study endpoints, relevant inclusion and exclusion criteria, effective doses, and differences in metabolism or pharmacokinetics that could affect drug delivery to the pancreas versus the gastrointestinal tract. And of course, any systematic reviews of study design or target selection for a particular condition equally benefit from an undistorted pool of results. Collective data reporting enables many different kinds of iterative developments in medical research that improve future clinical trials.

*iii. Precise Oversight by Government Watchdogs*

The value of collective data reporting in the context of government watchdogs is apparent from real-world examples provided earlier in the paper,<sup>238</sup> which illustrate harm due to inaccessible trial results. Collective data reporting, though, is helpful not only to the government watchdogs themselves, but also to the regulatory agency and applicable entities underwriting the scrutinized action. When government watchdogs operate using incomplete or inaccurate data, they run the risk of both false negatives (failing to identify legitimate risks to the public) and false positives (inaccurately flagging harmless items as risks to the public). Collective trial data reporting enables watchdogs to precisely and accurately distinguish between risks and non-risks, which ensures the interests of all relevant stakeholders are protected: Medical product-manufacturers do not receive unwarranted and undue scrutiny but are held accountable for cases of malintent or negligence; FDA is not harangued but does receive scrutiny for unjustifiable decision-making; and calibrated watchdog efforts may (hopefully) make corrective action to safeguard the public health more likely.

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Responsible parties' noncompliance with trial results reporting requirements is inappropriate in light of their ethical responsibility to maximize the benefit of trial data generated by participants' assumption of risk. Noncompliance is also inefficient because disclosure of results would make future research less wasteful and more impactful. FDA's and NIH's failure to enforce results submission is similarly inappropriate not only in the context of the ethical responsibility to trial participants, but also because those federal agencies have broader charges to ensure prudent use of government funds and promote the welfare of the American public. Failure to enforce is inefficient, too, because it denies a panoply of benefits to stakeholders in the medical research enterprise, including important contributions to evidence-based clinical decision-making. Even having made the case that collective data reporting yields benefits and has strong ethical justification, though, it is naïve to expect that discloser behavior will shift organically. The next appropriate question, then, is how to

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<sup>238</sup> See *supra* notes 5–17 and accompanying text.

positively engage responsible parties to incentivize their compliance with results reporting.

#### IV. ACHIEVING BETTER COMPLIANCE

To be successful, measures to improve compliance need to address the various systemic and idiosyncratic reasons why responsible parties fail to promptly report clinical trial results. These span a wide spectrum of issues: industry seeing intellectual property disclosures as a zero-sum game; academic researchers hesitating to report failed trial results due to lack of citability; entities (especially smaller ones) not wanting, or being able, to shoulder the administrative cost of results reporting; and front-end inefficiencies that complicate results submission, to name a few. Due to the breadth of these issues, successful compliance-promoting measures need to anticipate the interests of all involved stakeholders.<sup>239</sup> And ideally, these measures should include a mix of positive and negative incentives for parties to comply with regulation.<sup>240</sup>

The issue of negative incentives is relatively more straightforward: NIH and FDA should more actively sanction responsible parties that fail to comply with results submission requirements under the Final Rule and the FDAAA. NIH and FDA have not issued any of a number of available enforcement actions—civil monetary penalties, public notices of noncompliance, or (as far as we know) restrictions on federal research grantees, for example—even though many responsible parties repeatedly fail to report trial results on time, or at all. Perhaps because responsible parties have little reason to fear negative consequences for their noncompliance, they continue not to comply with regulation despite the systemic harms that result from this behavior. Applying sanctions helps deconstruct this prisoner’s dilemma by imposing costs for noncompliance that responsible parties must then weigh when choosing whether to submit results, which can help deter future wrongdoing.

Of course, rigid application of punitive measures may not be ideal either, as optimal enforcement often requires calibrating agency sanctions to avoid overenforcement harms.<sup>241</sup> But in the context of trial results submission, the lack of any current enforcement actions by FDA or NIH obviates the immediate need to worry about the risk of excessive sanctions. Certain characteristics of this regulatory scheme, in fact, make addressing underenforcement issues easier than otherwise might be the case. Independent funding sources, for example, can help depoliticize enforcement actions and make the agency less susceptible to pressure from legislative authorities that

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<sup>239</sup> See David L. Markell & Robert L. Glicksman, *A Holistic Look at Agency Enforcement*, 93 N.C. L. REV. 1, 7 (2014) (noting that those “seeking to design effective regulation should consider the multiplicity of actors” and make efforts to understand the “capacity of each actor to affect compliance”).

<sup>240</sup> See *id.* at 22 (“Strategies that embody a mix of rewards and sanctions have the potential to contribute to achieving desired compliance levels.”); see also Victor E. Schwartz & Phil Goldberg, *Carrots and Sticks: Placing Rewards as Well as Punishment in Regulatory and Tort Law*, 51 HARV. J. LEG. 315, 363 (2014) (arguing, in the context of compliance programs that mixing statutorily provided “sticks” with targeted “carrots” is the “best way to institutionalize and incentivize the right corporate behaviors”).

<sup>241</sup> Rachel E. Barkow, *Overseeing Agency Enforcement*, 84 GEO. WASH. L. REV. 1129, 1143–49 (2016) (discussing issues that arise when agencies over-enforce regulation).

control its budgetary allocation.<sup>242</sup> In this case, FDA could independently fund its own enforcement efforts using revenues generated from fines imposed for noncompliance with trial results. In the last three years alone, FDA could have collected billions of dollars<sup>243</sup>—that is in the realm of the operating budget of the agency.<sup>244</sup>

In addition to using sanctions, FDA and NIH should positively incentivize responsible parties' compliance with trial results reporting requirements. Although industry trial sponsors are often concerned about the cost of intellectual property disclosure, the agencies already address this issue through a variety of measures, including delayed registration requirements and allowances for temporary nondisclosure of failed preliminary trials used in follow-up studies.<sup>245</sup> The agencies could do more, however, to make submission, which some have cited as an issue in the past, easier for responsible parties.<sup>246</sup> In fact, NIH recently solicited feedback on precisely this issue, and a plethora of suggested improvements emerged: “additional standardization of data elements,” “making it easier to submit information on nontraditional studies that does not easily fit the current required data elements,” “streamlining the data entry process” by allowing automatic filling of related fields or upload of Excel files or those from other “electronic data-capture systems,” better access to one-on-one support for data submission issues, and integration of data reporting requirements between local Institutional Review Boards, NIH, and ClinicalTrials.gov.<sup>247</sup>

FDA and NIH (and, when applicable, the responsible parties' larger parent organizations) should also consider providing more support for smaller responsible parties to navigate the results submission process. The agencies could, for example, provide guidance on model compliance personnel systems that smaller entities could integrate into their organizational charts to support trial results submission. Similarly, especially for academic centers that have larger university administrations, other entities should consider housing personnel (such as “senior transparency officer[s]”) that are “versed in trial conduct and reporting” and can help “investigators overcome barriers that prevent them from timely reporting of trial results.”<sup>248</sup> Universities should also consider a responsible party's history of compliance when making tenure or

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<sup>242</sup> Rachel E. Barkow, *Insulating Agencies: Avoiding Capture Through Institutional Design*, 89 TEX. L. REV. 15, 22–23 (2010) (providing the example of legislators threatening budget cuts if the SEC were to engage in overaggressive enforcement).

<sup>243</sup> FDAAA TRIALS TRACKER, *Who's Sharing Their Clinical Trial Results?* (June 19, 2020), <http://fdaaa.trialstracker.net/> [<https://perma.cc/4ZA9-M36R>] (showing that as of June 19, 2020, FDA could have imposed fines of \$10,369,595,494 for noncompliance with the Final Rule and FDAAA's trial results reporting requirements).

<sup>244</sup> *Fact Sheet: FDA at a Glance*, U.S. FOOD & DRUG ADMIN. (Nov. 18, 2020), <https://www.fda.gov/about-fda/fda-basics/fact-sheet-fda-glance> [<https://perma.cc/BT77-YUE2>] (indicating FDA's budget for 2020 was \$5.9 billion).

<sup>245</sup> See *supra* Section II.A.

<sup>246</sup> See Clinical Trial Registration and Results Information Submission, 81 Fed. Reg. 64,991 (Sept. 21, 2016) (noting comments suggesting that ClinicalTrials.gov should provide “easier submission mechanisms”).

<sup>247</sup> NAT'L LIB. MED., SUMMARY OF RESPONSES TO REQUEST FOR INFORMATION (RFI): CLINICALTRIALS.GOV MODERNIZATION 5 (Apr. 28, 2020).

<sup>248</sup> Michael O'Riordan, *Most Clinical Trial Sponsors Fail to Report Data as Mandated by FDA*, TCTMD (Jan. 21, 2020), <https://www.tctmd.com/news/most-clinical-trial-sponsors-fail-report-data-mandated-fda> [<https://perma.cc/A3TN-HT2Z>].

promotion decisions, which would provide a positive reason for investigators to take time and report trial results,<sup>249</sup> especially those of failed trials that are not likely to be published. Making ClinicalTrials.gov entries citable, and providing relevant citation credit, could similarly incentivize academic investigators to comply.

If FDA and NIH positively incentivize and remove barriers to compliance with trial results reporting requirements, they also bear more legitimacy when imposing sanctions, which makes legislative or other political pressure less likely to be effective. Perhaps more importantly, if the agencies take time to highlight this issue as an important one, that may push the larger medical research community to do so as well. And even if not, the threat of economic or reputational harms—alongside removal of barriers that could be used as justifications to the public or to courts for noncompliance—should be sufficient to begin raising prompt trial results submissions and opening the door to the benefits of collective data reporting.

## CONCLUSION

The aim of this Article is to draw needed attention to the poor state of compliance with the FDAAA and Final Rule's clinical trial results submission requirements, the benefits that come from collective clinical trial reporting, and the harms that occur in its absence. In characterizing how and why noncompliance rates have steadfastly remained high even after statutory and regulatory mandates, the goal is to shed light on readily available positive and negative incentives that, if instituted, can promptly begin to correct this problem. As technology evolves, the conjoined efforts of health-oriented federal agencies and the medical research enterprise are poised to generate lasting benefits for Americans. But this is only possible when responsible parties make their trial results publicly accessible, which at present will require that FDA and NIH take necessary steps to incentivize results submission—including, when needed, enforcement of the law.

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<sup>249</sup> *Id.* ("If completeness of reporting was a criterion in individual academic evaluations, this could have a considerable signaling effect within the local research community.") (internal citation omitted).