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## Article

# Crowdsourcing Clinical Trials

Jonathan J. Darrow<sup>†</sup>

[T]he FDA has released too many drugs for sale only to have to take them off the market later as new information concerning side effects develops. Under this procedure it is the American people who unknowingly serve as guinea pigs for experiments by the drug companies.

—U.S. Senator Estes Kefauver et al. (1962)<sup>1</sup>

### INTRODUCTION

Pharmaceutical approval today suffers from a serious ethical flaw: newly FDA-approved drugs are *de facto* “tested” on an unknowing general public in the months and years immediately following drug approval,<sup>2</sup> without either the informed consent of the consuming public or an understanding by the public of the risks that remain.<sup>3</sup> This post-approval human “testing” occurs due to the inherent inability of even the largest clinical trials to detect rare adverse events,<sup>4</sup> as became famously evi-

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1. S. REP. NO. 87-1744, at 43 (1962), *reprinted in* 1962 U.S.C.C.A.N. 2884, 2907.

2. See Jesse A. Berlin et al., *Adverse Event Detection in Drug Development: Recommendations and Obligations Beyond Phase 3*, 98 AM. J. PUB. HEALTH 1366, 1367 (2008) (“Drugs are therefore, *as a rule*, made available for public use before rare but potentially serious [adverse] reactions have been identified and their probability quantified.”).

3. See discussion *infra* Part II.C.

4. Berlin et al., *supra* note 2, at 1367 (“[P]remarketing studies of new

dent following the high profile withdrawal of Vioxx<sup>®</sup> (rofecoxib), a pain medicine launched in 1999<sup>5</sup> that is estimated to have caused the death of more than 26,400 people before it was removed from the market in 2004.<sup>6</sup> In addition, although new drug development costs continue to rise rapidly, a disconcerting number of new drugs are no more effective than older, cheaper drugs,<sup>7</sup> and in many cases nearly indistinguishable in efficacy from placebo.<sup>8</sup> These two phenomena are not unrelated: clinical trial costs are rising in part *because* so many drugs are minimally effective in producing the desired results, owing to the inverse relationship between the degree of efficacy and the number of subjects needed to establish that efficacy with the requisite level of certainty.<sup>9</sup> As with safety, the consuming pub-

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pharmaceuticals cannot reliably detect rare, but potentially important, adverse events.”).

5. Snigdha Prakash & Vikki Valentine, *Timeline: The Rise and Fall of Vioxx*, NPR (Nov. 10, 2007, 2:40 PM), <http://www.npr.org/templates/story/story.php?storyId=5470430>.

6. See *infra* note 132; *Merck Announces Voluntary Worldwide Withdrawal of VIOXX(R)*, PRNEWswire (Sept. 30, 2004), <http://www.prnewswire.co.uk/news-releases/merck-announces-voluntary-worldwide-withdrawal-of-vioxxr-156068395.html>.

7. See MARCIA ANGELL, THE TRUTH ABOUT THE DRUG COMPANIES: HOW THEY DECEIVE US AND WHAT TO DO ABOUT IT 76 (2004) (“In fact . . . drugs can be approved that are actually *worse* than drugs already on the market.”); *L’année 2011 du Médicament: Un Sursaut en France en Faveur des Patients après Mediator, dans un Contexte de Surplace Général* [New Drugs and Indications in 2011: France Is Better Focused on Patients’ Interests After the Mediator Scandal, But Stagnation Elsewhere], 32 LA REVUE PRESCRIRE 134, 135 (2012) (Fr.), translated in 21 PRESCRIRE INT’L 106, 107 (2012) (evaluating 998 new drugs between 2002 and 2011 and concluding that only two were true breakthroughs).

8. See, e.g., Irving Kirsch et al., *The Emperor’s New Drugs: An Analysis of Antidepressant Medication Data Submitted to the U.S. Food and Drug Administration*, PREVENTION & TREATMENT, July 15, 2002, at 10, available at <http://alphachoice.com/repository/assets/pdf/EmperorsNewDrugs.pdf> (concluding that the difference in efficacy between various antidepressant drugs and placebos was “relatively small . . . and its clinical significance . . . dubious”).

9. See generally Allan Donner, *Approaches to Sample Size Estimation in the Design of Clinical Trials—A Review*, 3 STAT. MED. 199 (1984) (presenting the various methods used to calculate sample sizes for clinical trials and reviewing their application in practice); P.M. Fayers & D. Machin, *Sample Size: How Many Patients Are Necessary?*, 72 BRIT. J. CANCER 1 (1995) (discussing the need to calculate sample sizes in clinical trials and the problems that arise in their calculation which often lead to inadequate class sizes and misleading results); Stephen L. George & M.M. Desu, *Planning the Size and Duration of a Clinical Trial Studying the Time to Some Critical Event*, 27 J. CHRONIC DISEASES 15 (1974) (discussing the methods used to derive the required number of patients and necessary duration of clinical trials by looking at the time to

lic and even physicians often fail to appropriately distinguish between truly effective drugs and those of minimal value.<sup>10</sup> This Article explores the possibility of crowdsourcing the post-approval phase of clinical trials as a means of supplementing existing clinical trial practice in order to address safety concerns, clarify efficacy levels, and gather post-approval adverse event data in a manner more ethical than the current practice.

### I. THE PROBLEM: CURRENT DRUG APPROVAL PRACTICE AND THE REQUIREMENT OF CONSENT

New drugs generally cannot be approved in the United States without undergoing lengthy and expensive clinical trials,<sup>11</sup> which by law involve clinical testing on human subjects.<sup>12</sup> Although the institution of informed consent requirements helps to reduce the concern that might otherwise be directed against such testing,<sup>13</sup> consent is an imperfect solution to the evaluation of new drugs. Even in an ideal world where subjects have full understanding of all aspects and implications of a trial, informed consent is not a complete solution, in part because human testing exposes subjects to risk notwithstanding their consent and full information. More importantly for present purposes, the informed consent that protects pre-approval study subjects is not applicable to drugs administered during post-approval clinical care.<sup>14</sup> This Part explores the fundamental paradox associated with clinical testing of new drugs, the ethical issue that follows approval of those drugs, and the inadequacy of informed consent in mitigating this ethical failing.

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some critical event); John M. Lachin, *Introduction to Sample Size Determination and Power Analysis for Clinical Trials*, 2 CONTROLLED CLINICAL TRIALS 93 (1981) (discussing the importance of calculating a sample size in a clinical trial and the general methods for deriving a sample size and power analysis).

10. See, e.g., Barbara J. Evans, *Seven Pillars of a New Evidentiary Paradigm: The Food, Drug, and Cosmetic Act Enters the Genomic Era*, 85 NOTRE DAME L. REV. 419, 498 (2010) (“[E]fficacy failure is estimated to occur with 30–60% of the prescriptions written in the United States.”). The problem of minimal or nonexistent efficacy is not limited to drugs, however. It has been noted that “about 50 percent of common medical practices, which are routinely reimbursed by CMS and other payers, may be of no benefit to patients.” Rachel A. Lindor, *Advancing Evidence-Based Medicine by Expanding Coverage with Evidence Development*, 52 JURIMETRICS J. 209, 210 (2012).

11. See Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151, 153–54 (2003).

12. 21 U.S.C. § 355(d) (2012).

13. See *infra* notes 53–55 and accompanying text.

14. See *infra* notes 53–61 and accompanying text.

## A. THE PARADOX OF HUMAN TESTING

The fundamental paradox of clinical trials lies in the fact that their purpose is to screen out drugs whose risk-benefit ratio is unacceptable, in order to avoid exposing people to worthless or harmful drugs.<sup>15</sup> Yet because computer modeling, *in vitro* testing, and animal experimentation are not fully predictive of a drug's behavior in a human, the only way to ultimately determine the risk-benefit ratio of a drug is to administer it to humans and see what happens<sup>16</sup>—the very scenario that clinical testing is supposed to prevent.

This paradox has been partially addressed in two principal ways: (1) phased testing; and (2) informed consent. Under the phased approach, testing begins with a pre-clinical laboratory phase that may involve *in vitro* testing, computer modeling, and animal testing, the results of which must provide a basis for the drug sponsor to conclude that the drug is “reasonably safe” for human testing to begin.<sup>17</sup> Human testing, more commonly known by the somewhat euphemistic designation of “clinical trials,” is itself divided into phases, generally progressing from twenty to eighty people in Phase 1, to several hundred in Phase 2, to several thousand in Phase 3,<sup>18</sup> with continuous and periodic evaluation to determine whether further progression is warranted.<sup>19</sup> Generally following Phase 3 trials, the FDA will evaluate the drug candidate's dossier and either approve or reject the drug.<sup>20</sup> This progressive, phased design reduces as much as possible the number of people exposed to a new drug at each phase.

In addition to phased testing, clinical trial participants must also give their informed consent prior to participation in a

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15. See 21 U.S.C. § 355(d) (requiring the FDA to refuse to approve a new drug if, on the basis of “adequate and well-controlled investigations,” the drug is not both safe and effective).

16. The Declaration of Helsinki, for example, recognizes that “[m]edical progress is based on research that ultimately must include studies involving human subjects.” World Medical Association [WMA], *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*, at ¶ 5 (Oct. 2008).

17. See 21 C.F.R. § 312.23(a)(8) (2013) (covering “[p]armacology and toxicology information”).

18. See *id.* § 312.21 (covering “[p]hases of an investigation”).

19. See *id.* § 312.32(b)–(c) (covering periodic review and reporting to FDA); *id.* § 312.33 (covering “[a]nnual reports”).

20. 21 U.S.C. § 355(b)(1) (2012) (requiring that a new drug application contain “full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use”).

study.<sup>21</sup> Such consent helps to ensure that participants are adequately informed of the uncertainty regarding the risks and benefits of the product that is being tested and are voluntarily allowing themselves to be subjected to those risks.<sup>22</sup>

Unfortunately, the protections of informed consent largely cease to apply once government approval is granted.<sup>23</sup> At that very same moment, the careful expansion of the number of subjects exposed to an experimental drug under phased testing turns to a sudden explosion in patient consumption following approval.<sup>24</sup> This confluence of dramatically increased usage and reduced protections sets the stage for a serious—but oddly under-appreciated—ethical conundrum.

#### B. THE ETHICAL ELEPHANT IN THE ROOM

Even after the government approves a drug and releases it to the public, all of the drug's characteristics will not yet be known. As a Senior Medical Officer of the European Medicines Agency (the European analogue to the FDA) has pointed out, the particular moment of a drug's approval is somewhat arbitrary, occurring in the middle of a gradual increase in regulators' understanding of the drug at a point where information is considered to be sufficient, but certainly not complete.<sup>25</sup> There is nothing magical that occurs the day a drug is approved; the drug is no safer the morning following approval than it was the night before, when sales were prohibited.<sup>26</sup> Although it is true that under current law drugs must be deemed safe and effective prior to being placed on the market,<sup>27</sup> the phrase "safe and effective" represents not a mathematical or scientific certainty,

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21. 45 C.F.R. § 46.116 (2013).

22. *See id.*

23. *See infra* notes 56–61 and accompanying text.

24. *See* sources cited *infra* notes 32–33.

25. *See* Hans-Georg Eichler, Senior Med. Officer, European Medicines Agency, Presentation at Brigham & Women's Hospital, Division of Pharmacoepidemiology and Pharmacoeconomics: Adaptive Licensing for New Drugs: Implications for Comparative Effectiveness Research (Sept. 12, 2012) [hereinafter Eichler, Presentation on Adaptive Licensing for New Drugs]; *see also* Hans-Georg Eichler et al., *Balancing Early Market Access to New Drugs with the Need for Benefit/Risk Data: A Mounting Dilemma*, 7 NATURE REVIEWS DRUG DISCOVERY 818, 822 (2008) (providing a graphical illustration of the gradually increasing "knowledge surface" over time and its relationship to drug approval thresholds).

26. Eichler, Presentation on Adaptive Licensing for New Drugs, *supra* note 25.

27. 21 U.S.C. § 355(b) (2012).

but a legal assessment. The unstated but obvious reality is that this legal assessment is sometimes later proven to be wrong. That significant uncertainty remains even following FDA-approval is evident from the fact that new drugs are sometimes withdrawn, often within a few years of approval, following a series of severe adverse events or deaths.<sup>28</sup> The FDA acknowledges, as it must, that clinical trials do not provide complete information with respect to risk.<sup>29</sup> Because risks remain and data continues to be collected, new drugs are undergoing de facto “human testing” after receiving the FDA’s seal of approval.

The occurrence of de facto testing is reason for concern, but the practice might be justified on the basis that there is simply no other alternative. At some point a drug must be either released to the public or rejected. Although requiring larger clinical trials might appear to be an obvious solution, rare adverse events are difficult or impossible to discern in even the largest clinical trials.<sup>30</sup> Vioxx, for example, had undergone a relatively large Phase 3 trial involving 8076 subjects, but the trial was

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28. See Thomas N. Tiedt, *The Drug Safety System Conundrum*, 62 FOOD & DRUG L.J. 547, 548 (2007) (“High-profile market withdrawals of high-revenue prescription drugs spurred by the notoriety of life threatening drug reactions identified after FDA approval and broad patient use have cost the pharmaceutical industry billions of dollars in lost annual revenues (e.g., Vioxx, Bextra, Baycol, Rezulin, Lotonex, Propulsid, Seldane, Pondimin, Redux.”); James L. Zelenay, Jr., *The Prescription Drug User Fee Act: Is a Faster Food and Drug Administration Always a Better Food and Drug Administration?*, 60 FOOD & DRUG L.J. 261, 308 n.412 (2005). Scholars have indicated that shortened or last-minute decisions by the FDA are more likely to result in a harmful drug being approved. Daniel Carpenter et al., *Drug-Review Deadlines and Safety Problems*, 358 NEW ENG. J. MED. 1354, 1354 (2008); see also Clark Nardinelli et al., *Drug Review Deadlines and Safety Problems*, 359 NEW ENG. J. MED. 95, 96 (2008) (containing author’s reply by Daniel Carpenter); Mary K. Olson, *The Risk We Bear: The Effects of Review Speed and Industry User Fees on New Drug Safety*, 27 J. HEALTH ECON. 175, 175 (2008) (“[F]aster reviews are associated with increased counts of serious adverse drug reactions.”).

29. Stephen A. Goldman et al., *Clinical Therapeutics and the Recognition of Drug-Induced Disease*, MEDWATCH (FDA), June 1995, at 1, available at <http://www.fda.gov/downloads/Safety/MedWatch/UCM168515.pdf> (“[I]n most cases [clinical trials] are neither large enough nor long enough to provide all information on a drug’s safety.”).

30. See J.A. Lewis, *Post-Marketing Surveillance: How Many Patients?*, 2 TRENDS IN PHARMACOLOGICAL SCI. 93, 93 tbl.I (1981) (presenting the number of patients required to detect rare adverse events). Similarly, differences in efficacy may not be clear even with relatively large trials. See Salim Yusuf et al., *Why Do We Need Some Large, Simple Randomized Trials?*, 3 STAT. MED. 409, 412 (1984) (“It is not sufficiently widely appreciated just how large clinical trials really need to be, in order to detect such moderate differences [in therapeutic benefit] reliably.”).

nevertheless “not powerful enough to reliably detect rare adverse events with a prevalence of 1%–2% compared with placebo.”<sup>31</sup> Once pre-approval clinical trials are completed and the drug is released on the market, however, the number of people using it will generally increase dramatically,<sup>32</sup> in some cases by a factor of 1000 or more.<sup>33</sup> This explosion in consumption can reveal rare, but serious adverse events such as death.<sup>34</sup>

The ethical elephant in the room is that the general public is largely unaware of the risks that remain with newly approved drugs,<sup>35</sup> and does not sufficiently appreciate the extent to which understanding of a drug continues to evolve following approval. To state the ethical problem more concisely, under the current system patients are being used as de facto test subjects following drug approval without their knowledge or informed consent.<sup>36</sup> When adverse events do occur, the unfortunate victims or their loved ones understandably feel betrayed.<sup>37</sup>

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31. Mark Greener, *Drug Safety on Trial*, 6 EMBO REP. 202, 203 (2005).

32. See FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: GOOD PHARMACOVIGILANCE PRACTICES AND PHARMACOEPIDEMIOLOGIC ASSESSMENT 3 (2005), available at <http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126834.pdf>.

33. In the case of Vioxx, approximately twenty million people worldwide took the drug in a span of five years. Alex Berenson, *For Merck, the Vioxx Paper Trail Won't Go Away*, N.Y. TIMES, Aug. 21, 2005, at A1.

34. See sources cited *supra* note 28.

35. See *Are Prescription Drugs Safe? Not Necessarily*, CONSUMER-REPORTS, Nov. 2009, <http://www.consumerreports.org/cro/2012/05/are-prescription-drugs-safe-not-necessarily/index.htm> (“The Food and Drug Administration approved them, your doctor prescribes them, and you see them advertised on TV—so your medications must be safe, right?”); Trisha Torrey, *Is it Possible Newly FDA Approved Drugs and Medical Devices Aren't Safe?*, ABOUT.COM, <http://patients.about.com/od/drugsandsafety/f/Is-It-Possible-Newly-FDA-Approved-Drugs-And-Medical-Devices-Are-Not-Safe.htm> (last updated June 20, 2013) (feeling the need to answer the question posed in the article title); see also Paul Slovic et al., *Risk Perception of Prescription Drugs: Results of a National Survey*, 41 DRUG INFO. J. 81, 98 (2007) (concluding generally that “[p]rescription medicines were perceived to be high in benefit and low in risk”); sources cited *infra* notes 37, 39, 263, 269.

36. The type of consent needed in an ordinary treatment (as opposed to research) setting is referred to as “consent to treatment” and is addressed *infra* Part II.D.

37. See, e.g., Patrick McDonnell, *Chapter 9: Drug Safety and Pharmacovigilance*, in MODERN PHARMACEUTICAL INDUSTRY: A PRIMER 189 (Thomas M. Jacobsen & Albert I. Wertheimer eds., 2010) (“[T]he FDA has let the American people down, and, sadly, betrayed a public trust.” (quoting an FDA safety official following the Vioxx withdrawal)); *ADHD Drug Linked to 500 Percent Increased Risk of Sudden Death in Children*, HEALTH WATCH (Dec. 2010), <http://www.manataka.org/page2355.html> (“[Parents] believe the FDA wouldn't approve a drug so dangerous that it could kill their child with-



They assumed, reasonably, that the FDA-approved drug was safe and effective. “[S]afe . . . and . . . effective” is, after all, central to the legal standard for drug approval.<sup>38</sup> Disclaimers in the labeling, when they exist, may affect liability but do not substantially diminish the sense of betrayal since labels are almost never understood or even read by patients,<sup>39</sup> let alone by family members.<sup>40</sup> A means of effectively communicating the remaining risk is needed.

This ethical problem is not new. In the Senate Report to the 1962 Drug Amendments, Senators Kefauver, Carroll, and others complained that “the FDA has released too many drugs for sale only to have to take them off the market later as new information concerning side effects develops. Under this procedure *it is the American people who unknowingly serve as guinea pigs* for experiments by the drug companies.”<sup>41</sup> The Senators’ criticism was directed at the pre-1962 approval process under which a new drug application would automatically become effective, thereby allowing the drug sponsor to market the drug

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out warning. And they believe the drug companies would never sell products that harm people.”); *cf.* CHUCK WHITLOCK, MEDISCAMS: DANGEROUS MEDICAL PRACTICES AND HEALTH CARE FRAUDS—AND HOW TO PREVENT THEM FROM HARMING YOU AND YOUR FAMILY 224 (St. Martin’s Griffin 2003) (“We’d all like to think . . . that the FDA wouldn’t allow unsafe products to be sold in the U.S. at all . . . .”); Eric Zicklin, *I.V. League*, SPY, Mar. 1994, at 18, 18 (“The FDA wouldn’t let them give us anything *too* dangerous.” (internal quotation marks omitted)); *Democratic Members Urge FDA to Act on Tanning Salon Dangers*, FOX 31 DENVER (Feb. 17, 2012, 10:19 AM ), <http://littleton.kdvr.com/news/health/110499-democratic-members-urge-fda-act-tanning-salon-dangers> (“[T]he FDA wouldn’t approve tanning salons if it weren’t safe.” (internal quotation marks omitted)).

38. 21 U.S.C. § 355(b)(1) (2012).

39. See D.C. Berry et al., *Provision of Information About Drug Side-Effects to Patients*, 359 LANCET 853, 853–54 (2002); Saul Shiffman et al., *Consumer Understanding of Prescription Drug Information: An Illustration Using Anti-depressant Medication*, 45 ANNALS PHARMACOTHERAPY 452, 456 (2011) (finding that key warnings and directions “were not understood by a substantial majority of the respondents”); Almut G. Winterstein et al., *Evaluation of Consumer Medication Information Dispensed in Retail Pharmacies*, 170 ARCHIVES INTERNAL MED. 1317, 1319–20 (2010) (noting that 6% of 365 pharmacies surveyed provided no written information, none provided the official package insert, and of those that provided written information there were “[l]arge disparities in quality and length”); Andrew Moore & Henry McQuay, *Do Patients Understand Side-Effect Risks?*, PULSE, Nov. 29, 2004, at 42, 42.

40. See H. Shonna Yin et al., *Health Literacy Assessment of Labeling of Pediatric Nonprescription Medications: Examination of Characteristics that May Impair Parent Understanding*, 12 ACAD. PEDIATRICS 288, 294 (2012).

41. S. REP. NO. 1744 (1962), reprinted in 1962 U.S.C.A.N. 2884, 2907 (emphasis added).

to the public, sixty days after the application was submitted.<sup>42</sup> The solution, according to Kefauver and his colleagues, was to give the FDA more time to review a drug by eliminating the automatic approval provision.<sup>43</sup> The resulting 1962 law, still in effect today, gives the FDA 180 days to either approve a drug or give notice to the applicant of the opportunity for a hearing.<sup>44</sup> This well-intentioned solution, however, does not fully resolve the problem. No matter how much time the FDA has to consider a new drug application, it simply will not have sufficient data with respect to rare adverse events—data that can only be generated by the dramatic increase in usage that will generally occur following approval.<sup>45</sup>

Once drugs are released on the market, it often becomes apparent fairly quickly which are less safe than previously believed. A task force report to the FDA commissioner notes that “[i]n most cases, withdrawals occur during the first or second year following approval,” though “there have been cases where drugs were withdrawn 3, 4, and up to 5 years after approval.”<sup>46</sup> In fact, the long tail of drug withdrawals appears to be longer than these statements might suggest. Qureshi et al. recently identified 740 drugs approved by the FDA between 1980 and 2009, and determined that thirty of them had been withdrawn for safety reasons.<sup>47</sup> Although these researchers were primarily

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42. *Id.* at 2905.

43. *Id.* at 2907.

44. Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780, 784 (1962) (codified as amended at 21 U.S.C. § 355(c)(1) (2012)).

45. TASK FORCE ON RISK MGMT., FOOD & DRUG ADMIN., MANAGING THE RISKS FROM MEDICAL PRODUCT USE: CREATING A RISK MANAGEMENT FRAMEWORK 28–29 (1999), available at <http://www.fda.gov/downloads/Safety/SafetyofSpecificProducts/UCM180520.pdf>. Another possibility is to slow down the U.S. approval process such that drugs are first released in foreign markets, thereby intentionally recreating the drug lag of decades past. In addition to the obvious ethical problem in doing so, such a “solution” would merely shift the burden elsewhere rather than reduce it. See Zelenay, *supra* note 28, at 262, 327–28 (noting the potential adverse effect of the Prescription Drug User Fee Act (PDUFA), which has speeded drug review times, on the U.S. public’s health).

46. TASK FORCE ON RISK MGMT., *supra* note 45, at 34.

47. Zaina P. Qureshi et al., *Market Withdrawal of New Molecular Entities Approved in the United States from 1980 to 2009*, 20 PHARMACOEPIDEMIOLOGY & DRUG SAFETY 772, 775 tbl.3 (2011); see also Amalia M. Issa et al., *Drug Withdrawals in the United States: A Systematic Review of the Evidence and Analysis of Trends*, 2 CURRENT DRUG SAFETY 177, 179 tbl.1 (2007) (providing approval and withdrawal dates for twenty drugs withdrawn between 1993 and 2006 that are mostly but not entirely consistent with those provided by

concerned with the reasons for withdrawal and not the timing, the approval and withdrawal dates they identified for these thirty drugs can be used to determine the duration each drug was on the market. The following chart was accordingly constructed to illustrate how soon after approval these drugs were withdrawn.

FIGURE 1: New Molecular Entity Withdrawals by Years Since Approval, 1980–2009

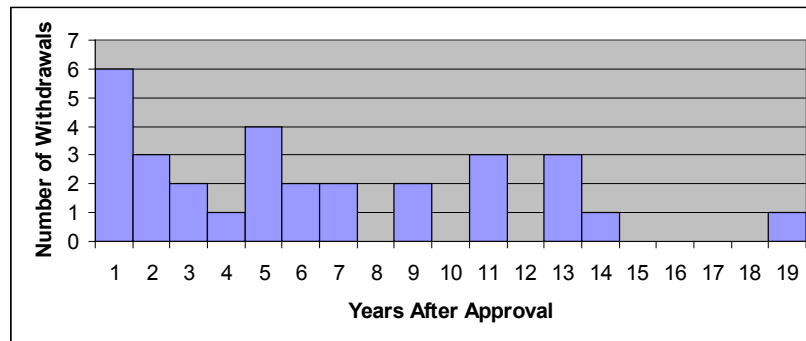


Figure 1 shows that one in five drugs (20%) was withdrawn for safety reasons within the first year following approval, and slightly more than half (53%) were withdrawn within five years of approval. These figures support the conventional notion that newly approved drugs are more likely to be withdrawn for safety reasons, if at all, within the first several years following approval.<sup>48</sup> Nevertheless, the long tail of the withdrawal curve also indicates that even somewhat older drugs may still be subject to withdrawal for safety reasons. Crowdsourcing, as described *infra*, can help address the risks flowing from both of these phenomena by increasing awareness of risks during the early years and by improving data capture so that dangerous drugs can be identified and removed from the market more quickly.

Qureshi et al., with the differences possibly reflecting differing methodology and sources consulted).

48. Qureshi et al. report that about 75% of discontinued drugs were withdrawn for what appear to be financial or commercial reasons, rather than safety. Qureshi et al., *supra* note 47, at 776.

## C. INFORMED CONSENT

It may be unavoidable to test a drug on the public following appropriately thorough clinical trials. Knowledge of a drug is, after all, never absolutely complete.<sup>49</sup> It is irresponsible, however, to collect post approval data in the ad hoc manner currently in place, in which it is well known that most serious adverse events go unreported, not to mention less serious ones.<sup>50</sup> More importantly, the impossibility of absolute and comprehensive knowledge is not an excuse for conducting this post-approval human testing without obtaining the public's informed consent.<sup>51</sup> It is entirely within the realm of feasibility to ensure that the public more clearly understands the risks involved in consuming drugs and particularly the uncertainties that inevitably accompany the most recently-approved drugs.<sup>52</sup>

Both national and international law prohibit testing on human subjects unless those subjects voluntarily consent after being informed of the likely risks and benefits of the research. The Nuremberg Code of 1947, which was drafted following egregious ethical violations that occurred at the hands of certain Nazi physicians, declares that “[t]he voluntary consent of the human subject is absolutely essential.”<sup>53</sup> Two decades later, the World Medical Association adopted the Declaration of Helsinki, which (as amended) provides that “[p]articipation by . . . subjects in medical research must be voluntary” and that “each potential subject must be adequately informed of . . . the anticipated benefits and potential risks of the study.”<sup>54</sup> In the United

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49. See *id.* at 776–77 (discussing the importance of continuous testing throughout the product's life cycle).

50. See *infra* Part II.C.3 (discussing methods of obtaining adverse effects post-approval).

51. See JILL A. FISHER, *MEDICAL RESEARCH FOR HIRE: THE POLITICAL ECONOMY OF THE PHARMACEUTICAL INDUSTRY* 25 (2009) (describing ethical norms for medical testing).

52. See Bruce E. Onofrey, *From Molecule to Medicine Cabinet: A Drug's Long Journey from Development to Approval*, *REV. OPTOMETRY*, June 15, 2013, at 30 (describing a black box warning).

53. 2 TRIALS OF WAR CRIMINALS BEFORE THE NUERNBERG MILITARY TRIBUNALS UNDER CONTROL COUNCIL LAW NO. 10, at 181 (U.S. Gov't Printing Office 1949). The principles now known as the Nuremberg Code were first included in the judicial decision of the so-called “Doctor's Trial,” and are available at <http://ori.dhhs.gov/education/products/RCRintro/c03/b1c3.html> (last visited Nov. 25, 2013).

54. WMA, *supra* note 16, ¶¶ 22, 24; see also International Covenant on Civil and Political Rights art. 7, Mar. 23, 1976, 999 U.N.T.S. 172 (“[N]o one shall be subjected without his free consent to medical or scientific experimentation.”); COUNCIL FOR INT'L ORGS. OF MED. SCI., INTERNATIONAL ETHICAL

States, a portion of the Code of Federal Regulations known as the “Common Rule” prohibits human testing “unless the investigator has obtained the legally effective informed consent of the subject.”<sup>55</sup> These laws and international instruments create baseline norms that help to protect people from being unknowingly or unwillingly exposed to the risks that accompany experimental medical treatments.

Under current law and practice, however, the “human testing” (which term is rarely used) that follows FDA approval has traditionally escaped the confining strictures of human subject research on the apparent basis that the drug has been formally tested as much as is practicable, and that the discovery of adverse events via legally-required monitoring does not constitute human subject research at all.<sup>56</sup> Therefore, the informed consent principles of the Nuremberg Code, Declaration of Helsinki, and Common Rule are not applied.<sup>57</sup> From the perspective of the pharmaceutical company, this distinction is sensible. Following FDA approval, attention turns from clinical trials to producing and selling.<sup>58</sup> With the exception of Phase 4 studies, the post-approval period has no clinical trial sites, principal investigators, clinical research associates (monitors), or clinical report forms.<sup>59</sup> Adverse event reports are almost an afterthought. From the perspective of the prescribing practitioner, as well, considering the administration of newly approved drugs to be “research” makes little sense. The primary purpose

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GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS, at guideline 4 (3d ed. 2002), available at <http://www.fhi360.org/resource/international-ethical-guidelines-biomedical-research-involving-human-subjects> (“Individual Informed Consent”).

55. 45 C.F.R. § 46.116 (2012); see also 21 C.F.R. § 50.20 (2013) (containing the analogous FDA provision regarding informed consent of human subjects). The Common Rule derives its name from the fact that it applies broadly across federal agencies. See 45 C.F.R. § 46.101; FISHER, *supra* note 51, at 28.

56. See generally Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, 44 Fed. Reg. 23,193 (Apr. 18, 1979) (finding it “important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research,” but also acknowledging that “[t]he distinction between research and practice is blurred partly because both often occur together”).

57. See *id.* (noting the difficulty in distinguishing between practice and research).

58. See 21 C.F.R. § 312.84 (2013) (discussing marketing applications).

59. Phase 4 studies are post-approval studies requested by the FDA that seek to provide additional information about a drug’s risks, benefits, and optimal use. See *id.* § 312.85.

of post-approval administration of new drugs is treatment, not data gathering.<sup>60</sup> Patients are not “enrolled” in a clinical trial, nor are they randomized such that some receive only placebo.<sup>61</sup>

From the patient perspective, however, these differences are illusory. The relevant concern to the patient is the level of risk that remains in the pill that they are taking, balanced against the likely benefit.<sup>62</sup> It matters little whether the risk is undertaken and data is collected under the label of a “clinical trial” or under the “normal care” of a physician.<sup>63</sup> Both involve the administration of a substance by a healthcare provider to a patient where uncertain risks and benefits remain.<sup>64</sup> The absence of an enrollment protocol or informed consent procedure merely obscures the fact that there is still uncertainty with respect to the substance in question.<sup>65</sup> The difference of placebo control is also not as great as it first appears, in part because some clinical trials do not use placebo controls.<sup>66</sup> Even where placebo controls are used, many patients do not adequately appreciate that the primary purpose of the clinical trial is not to treat them or that they may receive no treatment at all.<sup>67</sup> As with drugs undergoing pre-approval clinical testing, post-approval “testing” involves incomplete information, risks to the patient, and the collection of data based on patient outcomes that will be collected, considered, and used to benefit future patients.<sup>68</sup>

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60. See *id.* § 312.84 (approving drugs when need for treatment outweighs potential risks).

61. Shockingly, a recent study found that “[a]bout half of the [surveyed physicians] reported prescribing placebo treatments . . . on a regular basis.” Jon C. Tilburt et al., *Prescribing “Placebo Treatments”: Results of National Survey of US Internists and Rheumatologists*, 337 *BRITISH MED. J.* a1938, \*3 (2008), available at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2572204/pdf/bmj.a1938.pdf>. The ethics of such prescribing practices are addressed elsewhere. See, e.g., Howard Brody, *The Lie that Heals: The Ethics of Giving Placebos*, 97 *ANNALS INTERNAL MED.* 112 (1982); Sissela Bok, *The Ethics of Giving Placebos*, 231 *SCI. AM.*, Nov. 1974, at 17, 17–18.

62. See 21 C.F.R. § 312.84.

63. See Onofrey, *supra* note 52, at 26, 30.

64. *Id.*

65. Cf. Qureshi et al., *supra* note 47, at 776 (finding twenty-five percent of studied drugs were discontinued for safety reasons after FDA approval).

66. See 21 C.F.R. § 314.126(b)(2)(iii)–(iv).

67. See Jill A. Fisher, *Procedural Misconceptions and Informed Consent: Insights from Empirical Research on the Clinical Trials Industry*, 16 *KENNEDY INST. ETHICS J.* 251, 256–57 (2006).

68. See *infra* Part II.C.

## D. CONSENT TO TREATMENT

Although the informed consent guidelines may not apply to post-approval administration of new drugs, this does not mean that patients are entirely without protection. Under an array of legal theories, patients cannot be treated until they provide adequate informed consent, known as “consent to treatment.”<sup>69</sup> Patients injured as a result of newly approved medications can bring suits against the physician based upon theories of negligence, assault and battery, and misrepresentation, among others.<sup>70</sup>

The potential theories of liability, however, are governed by a patchwork of state statutory and common laws, and actions based upon them are not especially common.<sup>71</sup> In general, however, the elements needed to establish a case of failure to obtain consent to treatment are: “(1) the existence of a material risk unknown to the patient; (2) the failure of the defendant to disclose the risk; (3) the probable refusal of the patient to undergo the proposed treatment, had the risk been disclosed; and (4) resulting injury to the patient.”<sup>72</sup> The relatively few cases involving pharmaceuticals that have emerged have often, though not always, found one of these elements to be lacking. For example, in *Carmichael v. Reitz*, a patient sued her doctor on the basis of lack of informed consent after an endometriosis drug prescribed by the doctor caused pulmonary embolisms.<sup>73</sup> The California appeals court found the third element lacking, noting that there was “no substantial evidence” that the patient would have refused treatment if a full explanation of risks had

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69. See generally FAY A. ROZOVSKY, CONSENT TO TREATMENT: A PRACTICAL GUIDE (4th ed. 2012) (describing the basic rules of consent to treatment).

70. See *id.* § 1.01[D].

71. See *Valles v. Albert Einstein Med. Ctr.*, 758 A.2d 1238, 1245 (Pa. Super. Ct. 2000) (“[A]ppellate courts have declined to extend the doctrine [of informed consent] to include the administration of drugs . . . .”); Gerald F. Tietz, *Informed Consent in the Prescription Drug Context: The Special Case*, 61 WASH. L. REV. 367, 367 (1986) (“Medical patients rarely bring suit against prescribing physicians on an informed consent theory in the context of prescription drug therapy.”); see also Albert Averbach, *Physician’s Liability for Prescription Drugs*, 43 ST. JOHN’S L. REV. 535, 554 (1969) (“It is a rare occurrence that a physician will be found liable for the administration of a drug which seemed reasonable in the light of foresight, although disastrous in terms of hindsight.”).

72. Lauren Krohn, *Cause of Action Against Physician for Negligence in Prescribing Drugs or Medicines*, in 9 CAUSES OF ACTION 1, 17 (Wesley H. Winborne et al. eds., 1986).

73. *Carmichael v. Reitz*, 17 Cal. App. 3d 958, 966 (Cal. Ct. App. 1971).

been given.<sup>74</sup> In another case, the Supreme Judicial Court of Massachusetts overturned a jury's \$1 million award for failure to obtain informed consent for treatment with prednisone, holding that there was insufficient evidence to show "that the physician knew or reasonably should have known that the probability [the] particular risk [in question] would materialize was other than negligible."<sup>75</sup>

Other cases suggest that plaintiffs who are not adequately informed of prescription drug risks may sometimes have a viable cause of action. For example, in *Cottam v. CVS Pharmacy*, a plaintiff was awarded \$357,000 after a pharmacist negligently failed to warn him of risks accompanying the drug trazodone.<sup>76</sup> Similarly, an alleged failure to obtain a patient's informed consent to treatment with prednisone was found to create a genuine issue of material fact in light of disagreement over what information was actually disclosed.<sup>77</sup> Although these cases resulted in an outcome favorable to the plaintiff, they involve the failure to communicate *known* risks, and do not speak to a failure to communicate the uncertainty and generalized risks that remain when newly approved prescription drugs are released on the market.<sup>78</sup>

Despite a small number of plaintiff-favorable cases, the general attitude of the courts toward informed consent in the context of prescription drugs has been one of deference to the medical profession.<sup>79</sup> Past judicial treatment of informed consent has been described as creating "excessive paternalism" and granting doctors "effective immunity" from liability.<sup>80</sup> The

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74. *Id.* at 968–69. While a lack of causation may justify the denial of liability, it does not resolve the ethical shortcoming created when a failure to transmit risk information prevents the patient from facing those risks voluntarily and on a fully informed basis. See Krohn, *supra* note 72, at 19 (discussing that it is easier to bring a claim under a theory of lack of informed consent than negligence).

75. *Precourt v. Frederick*, 481 N.E.2d 1144, 1149–50 (Mass. 1985).

76. *Cottam v. CVS Pharmacy*, 764 N.E.2d 814, 817–18, 823 (Mass. 2002). The claims against the physicians were settled prior to trial. *Id.* at 817.

77. *Mercado-Velilla v. Asociacion Hosp. del Maestro*, 902 F. Supp. 2d 217, 227 (D.P.R. 2012).

78. See *Hernandez v. United States*, 665 F. Supp. 2d 1064, 1076 (N.D. Cal. 2009) ("Physicians have a duty to inform their patients of the *known* risks . . . associated with proposed treatments." (emphasis added)); *Dunn v. Yager*, 58 So. 3d 1171, 1200 (Miss. 2011) ("[T]he physician must disclose only *material known risks*." (internal quotation marks omitted)).

79. See, e.g., *Precourt*, 481 N.E.2d at 1149–50.

80. Lars Noah, *Informed Consent and the Elusive Dichotomy Between Standard and Experimental Therapy*, 28 AM. J.L. & MED. 361, 367 (2002).



Illinois Supreme Court's view with respect to drug risk disclosures is representative: "The doctor, functioning as a learned intermediary between the prescription drug manufacturer and the patient, decides which available drug best fits the patient's needs and chooses which facts from the various warnings should be conveyed to the patient, and *the extent of disclosure is a matter of medical judgment.*"<sup>81</sup> This wide latitude provided to doctors by courts has been aptly criticized by one commentator as "[e]xtreme deference to the medical profession."<sup>82</sup> Another pointed out the natural consequence of this deference: "Many physicians choose not to disclose all the risks involved with the use of a medication, or any treatment, reasoning that a patient's knowledge of such information is not needed for a patient's informed consent."<sup>83</sup> If physicians do not consider risk information important enough to disclose to a patient, efficacy information is even less likely to be disclosed.

Given the rarity of suits based upon lack of informed consent and the absence of rigorous policing by courts of informed consent to treatment, it is no surprise that actual disclosures to patients are minimal.<sup>84</sup> When it comes to prescription drugs, "treatment consent" is a lofty concept that rapidly descends to lip service in practice. In his book *The Silent World of Doctor and Patient*, Jay Katz notes:

The history of the physician-patient relationship from ancient times to the present bears testimony to physicians' caring dedication to their patients' physical welfare. The same history, by its account of the silence that has pervaded this relationship, also bears testimony to physicians' inattention to their patients' right and need to make their own decisions. Little appreciation of disclosure and consent can be discerned in this history . . . .<sup>85</sup>

The FDA has also expressed concern with the absence of robust consent procedures for drugs, noting in particular the oddity that "simple surgical procedures, often posing less severe risks to the patient [than medications], routinely require detailed patient consent," while the administration of medications involves minimal consent procedures and "little or no" in-

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81. Kirk v. Michael Reese Hosp. & Med. Ctr., 513 N.E.2d 387, 393 (1987) (emphasis added).

82. Tietz, *supra* note 71, at 395.

83. Elizabeth C. Melby, *The Psychological Manipulation of the Consumer-Patient Population Through Direct-to-Consumer Prescription Drug Advertising*, 5 SCHOLAR 325, 332 (2003).

84. See Tietz, *supra* note 71, at 367.

85. JAY KATZ, *THE SILENT WORLD OF DOCTOR AND PATIENT* 28 (1984).

formation exchange.<sup>86</sup> Steven Joffe and Robert Truog of Harvard Medical School add that a “more deliberate and thorough consent process” may be in order where the risks of treatment must be balanced against the risks of non-treatment.<sup>87</sup> In the vaccine context, one commentator notes that the law may lead physicians to not involve patients in the decision making process.<sup>88</sup>

The absence of robust information exchange in the doctor-patient relationship is fueled by the hierarchical relationship between doctors and patients and the associated expectation that the doctor’s role is to decide, while the patient’s role is to trust.<sup>89</sup> To borrow the title of a popular book, when it comes to substantive discussions of the possible risks and benefits of impending treatments, physicians today are “Strangers at the Bedside.”<sup>90</sup>

#### E. INFORMED CONSENT IS NOT THE ONLY PROBLEM: EFFICACY AND COST ISSUES

Continued safety risks are not the only concern when new drugs are released on the market. Many new drugs also suffer from a lack of substantial efficacy.<sup>91</sup> This is not to say that new drugs are completely ineffective, though occasionally that may later be revealed to be the case.<sup>92</sup> More often, however, a drug either is simply not very effective in treating its stated indications, or it is not any more effective (and possibly less effective)

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86. FDA Prescription Drug Product Labeling; Medication Guide Requirements, 60 Fed. Reg. 44,182–83 (Aug. 24, 1995).

87. Steven Joffe & Robert D. Truog, *Consent to Medical Care: The Importance of Fiduciary Context*, in *THE ETHICS OF CONSENT: THEORY AND PRACTICE* 369 (Franklin G. Miller & Alan Wertheimer eds., 2010).

88. Daniel A. Cantor, Comment, *Striking a Balance Between Product Availability and Product Safety: Lessons from the Vaccine Act*, 44 AM. U. L. REV. 1853, 1868–69 (1995).

89. See Janet L. Dolgin, *Debating Conflicts: Medicine, Commerce, and Contrasting Ethical Orders*, 35 HOFSTRA L. REV. 705, 711–12 (2006).

90. DAVID J. ROTHMAN, *STRANGERS AT THE BEDSIDE: A HISTORY OF HOW LAW AND BIOETHICS TRANSFORMED MEDICAL DECISION MAKING* 1–2 (1991).

91. See Jonathan J. Darrow, *Pharmaceutical Efficacy: History and Regulation* (unpublished S.J.D. dissertation, Harvard Law School) (on file with author).

92. See, e.g., *FDA Commissioner Removes Breast Cancer Indication from Avastin Label*, U.S. FOOD & DRUG ADMIN. (Nov. 18, 2011), <http://www.fda.gov/NewsEvents/Newsroom/ucm279485.htm> (announcing the agency’s revocation of breast cancer indication for Avastin due to its failure “to provide a benefit, in terms of delay in the growth of tumors, that would justify its serious and potentially life-threatening risks”).

than existing treatments.<sup>93</sup> The absence of substantial efficacy for newly FDA-approved drugs is entirely legal under United States law, which requires only that the *evidence* of efficacy be substantial.<sup>94</sup> This is known as the “substantial evidence” standard, and usually requires that drug sponsors submit at least two “adequate and well-controlled investigations.”<sup>95</sup> However, there is no requirement that the efficacy itself be substantial.<sup>96</sup> So long as two adequate and well-controlled studies demonstrate statistically significant improvement over placebo, a drug can be approved whether it provides 99% relief, 50% relief, or 1% relief.<sup>97</sup>

Moreover, there is no requirement that the level of efficacy be clearly communicated to either consumers or physicians.<sup>98</sup> As a consequence, studies have shown that consumers overestimate drug efficacy by 1000% (one thousand percent) or more.<sup>99</sup> Physicians, trusted by patients to be experts who know more than they do about the drugs that they take, nevertheless prescribe billions of dollars of these underwhelmingly potent drugs per year.<sup>100</sup>

Worse still, the vapid drug efficacy standard contributes both directly and substantially to the high cost of the new drugs that are produced. This relationship between drug cost and drug efficacy can be explained mathematically, in relatively simple terms: The smaller the difference in efficacy between a new drug and a placebo, the larger the data set needed to es-

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93. See, e.g., Irving Kirsch & Guy Sapirstein, *Listening to Prozac but Hearing Placebo: A Meta-Analysis of Antidepressant Medication*, 1 PREVENTION & TREATMENT Article 2a (1998) (estimating that seventy-five percent of the response to active antidepressant medication can be attributed to the placebo effect); John Carey, *Vytorin: A Setback for Merck and Schering*, BLOOMBERG BUSINESSWEEK (July 22, 2008), <http://www.businessweek.com/stories/2008-07-22/vytorin-a-setback-for-merck-and-scheringbusinessweek-business-news-stock-market-and-financial-advice> (“The trial showed no benefit at all to the drug combination, compared with a statin alone.”).

94. 21 U.S.C. § 355(d) (2012).

95. *Id.*; Warner-Lambert Co. v. Heckler, 787 F.2d 147, 151 (3d Cir. 1986) (“Because the Act uses the plural ‘investigations,’ the FDA requires drug manufacturers to submit at least two ‘adequate and well-controlled’ studies showing the effectiveness of the drug.”).

96. See 21 U.S.C. § 355.

97. See *id.*

98. See *id.*

99. See, e.g., Lisa M. Schwartz et al., *Using a Drug Facts Box to Communicate Drug Benefits and Harms*, 150 ANNALS INTERNAL MED. 516, 524 (2009).

100. See DARROW, *supra* note 91.

establish that efficacy with the requisite  $p=.05$  level of certainty.<sup>101</sup> A larger data set means larger or longer clinical trials,<sup>102</sup> and clinical trials contribute the largest component of the cost of new drugs, approximately 50% by most estimates.<sup>103</sup> This inverse relationship between cost and efficacy level creates a situation where the least effective drugs will require the largest and most expensive trials.<sup>104</sup> These clinical trials' costs, as a component of "research and development costs," are often used to justify the high consumer prices of the drugs that result.<sup>105</sup>

## II. CROWDSOURCING AS A SOLUTION TO THE ETHICAL PROBLEM, AND OTHER BENEFITS

There are a number of possible solutions to the safety and efficacy challenges that remain following FDA approval of new drugs. For example, the FDA could require even larger Phase 3 studies as a means to detect rare adverse events. To guard against minimally efficacious drugs, Congress might enact minimum standards for efficacy itself, supplementing current standards that address only the amount and quality of evidence

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101. See LAWRENCE M. FRIEDMAN ET AL., *FUNDAMENTALS OF CLINICAL TRIALS* 148 (4th ed. 2010) ("[T]he smaller the difference in intervention effect . . . the larger the study must be.").

102. See Donner, *supra* note 9, at 199.

103. KEWAL K. JAIN, *THE HANDBOOK OF BIOMARKERS* 107 (2010) ("[C]linical trials . . . account for approximately 60% of the total drug development costs."); Samiran Nundy et al., *A New Colonialism?—Conducting Clinical Trials in India*, 352 *NEW ENG. J. MED.* 1633, 1634 (2005) ("[D]rug trials . . . can run to 40 percent of the cost of drug development."); Peter Lansbury, *An Innovative Drug Industry? Well, No*, *WASH. POST*, Nov. 16, 2003, at B2 ("Phase 3 trials account for roughly 50 percent of the total cost of bringing a drug to market.").

104. Other scholars have noted similarly perverse behavior in the pharmaceuticals sector, such as the "inverse benefit law," which holds that "the ratio of benefits to harms among patients taking new drugs tends to vary inversely with how extensively the drugs are marketed." Howard Brody & Donald W. Light, *The Inverse Benefit Law: How Drug Marketing Undermines Patient Safety and Public Health*, 101 *AM. J. PUB. HEALTH* 399, 399 (2011).

105. See, e.g., Carmelo Giaccotto et al., *Drug Prices and Research and Development Investment Behavior in the Pharmaceutical Industry*, 43 *J.L. & ECON.* 195, 195–96, 212 (2005) ("[D]rug prices are expected to influence R & D spending directly . . . . [O]ur multiple-regression findings support this expected direct effect."); PUB. CITIZEN, *RX R&D MYTHS: THE CASE AGAINST THE DRUG INDUSTRY'S R&D "SCARE CARD"* 1 (2001), available at <http://www.citizen.org/documents/ACFDC.PDF> ("The central claim of PhRMA's campaign is ominous: if anything is done to restrain high U.S. prescription drug prices, then research and development (R & D) to find new drugs for life-threatening diseases will suffer.").

of that efficacy.<sup>106</sup> However, any objective standard with respect to efficacy beyond statistical significance would necessarily be somewhat arbitrary, and even the largest Phase 3 studies will not be able to detect extremely rare adverse events that only become apparent when the entire relevant consumer population is given access to the drug in question.<sup>107</sup> That is, of course, unless one is willing to turn the entire relevant consumer population into a “Phase 4 study.” The current proposal involves using a crowdsourcing model to do just that.

#### A. WHAT IS CROWDSOURCING?

In order to evaluate the feasibility of crowdsourcing as a means of collecting relevant post-approval drug data, it is helpful to understand what “crowdsourcing” is. The term itself was coined in a 2006 *Wired* magazine article as a variation on “outsourcing,” but where businesses look not to an outside company to perform a task but to some nebulous “crowd” of people.<sup>108</sup> Since then, its meaning has evolved to describe a number of different, but related phenomena that utilize the power of a distributed group of people to achieve a given result.<sup>109</sup> For example, crowdsourcing might involve the contribution of dispersed individuals working asynchronously to build and refine a unified product, as with open source software like Linux and Apache.<sup>110</sup> Alternately, it could involve offering a prize to the public at large for the first or best solution to a specific prob-

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106. See 21 U.S.C. § 355(d) (2012).

107. See Berlin et al., *supra* note 2, at 1366; Margaret Gilhooley, *Commercial Speech, Drugs, Promotion and a Tailored Advertisement Moratorium*, 21 HEALTH MATRIX 97, 97 (2011).

108. Jeff Howe, *The Rise of Crowdsourcing*, WIRED, June 2006, at 177.

109. See, e.g., Julie D. Polovina, *Mutant Biologics: The 2010 Health-Reform Legislation's Potential Impact on Reducing Biologic Research and Development Costs*, 100 GEO. L.J. 2291, 2310 (2012) (“[C]rowdsourcing’ is defined as companies ‘outsourcing’ tasks historically done by employees to the general public to take advantage of a free and large labor pool.”); Sarah Cove, *What Does Crowdsourcing Really Mean?*, WIRED, July 12, 2007, <http://www.wired.com/techbiz/media/news/2007/07/crowdsourcing?currentPage=all> (describing crowdsourcing as a “kind of industrial age, corporatist framing of a cultural phenomenon”); Jeff Howe, *Crowdsourcing: A Definition*, CROWDSOURCING, <http://www.crowdsourcing.com> (last visited Nov. 25, 2013) (“Crowdsourcing is the act of taking a job traditionally performed by a designated agent (usually an employee) and outsourcing it to an undefined, generally large group of people in the form of an open call.”).

110. See Richard F. Heller et al., *Capacity-building for Public Health: <http://peoples-uni.org>*, 85 BULL. WORLD HEALTH ORG. 930, 931 (2007), available at <http://www.who.int/bulletin/volumes/85/12/07-044388.pdf>.

lem, as when the British government in 1714 established a prize for whomever could solve the very practical problem of determining longitude at sea,<sup>111</sup> or when Netflix more recently offered a prize to whomever could improve its film recommendation system.<sup>112</sup>

In fact, the past several years have witnessed the success of a surprisingly broad array of crowdsourcing models. In Fort Myers, Florida, a local news service used the contributions of individuals to unmoderated discussion boards to help investigate local sewer and water rate hikes that were widely perceived to be unjust.<sup>113</sup> In another case, a business called iStockphoto revolutionized the stock photo market by crowdsourcing digital images from more than 20,000 contributors, undercutting the existing market in price by as much as 99%.<sup>114</sup> Distributed computing such as SETI@home aggregates the excess capacity of millions of idle computers to perform useful functions.<sup>115</sup> Individualized technical challenges have been partially crowdsourced, such as the performance of computer help-desk functions at a state university.<sup>116</sup> The majority of iPhone applications are developed not by Apple, the maker of the iPhone, but by unrelated developers who work independently to create many of the hundreds of thousands of applications that are then aggregated by Apple and made available for sale through its App Store.<sup>117</sup>

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111. See *Following the Crowd*, ECONOMIST, TECH. Q., Sept. 4, 2008, <http://www.economist.com/node/11999251>.

112. See Steve Lohr, *The Crowd Is Wise (When It's Focused)*, N.Y. TIMES, July 19, 2009, at BU4.

113. Steve Fox, *Looking to Crowdfund? Better Have a Dog in the Race*, NEWASSIGNMENT.NET (Nov. 9, 2006, 11:04 AM), [http://web-archive-net.com/page/1580579/2013-03-10/http://newassignment.net/blog/steve\\_fox/nov2006/09\\_a\\_gannett\\_silo\\_i](http://web-archive-net.com/page/1580579/2013-03-10/http://newassignment.net/blog/steve_fox/nov2006/09_a_gannett_silo_i).

114. Howe, *supra* note 108, at 178.

115. *Id.*

116. Jeffrey R. Young, *Colleges Try "Crowdsourcing" Help Desks to Save Money*, CHRON. HIGHER EDUC., Nov. 6, 2009, at A1.

117. See Ann Bartow, *A Portrait of the Internet as a Young Man*, 108 MICH. L. REV. 1079, 1101 (2010) ("[T]ens of thousands of applications have subsequently been independently developed for the iPhone . . ."); Chris Foresman, *iOS App Success Is a "Lottery": 60% (or More) of Developers Don't Break Even*, ARS TECHNICA (May 4, 2012, 12:15 PM), <http://arstechnica.com/apple/2012/05/ios-app-success-is-a-lottery-and-60-of-developers-dont-break-even> (noting that Apple facilitates the process of application development and distribution by granting would-be developers access to Apple's developer program for \$99 per year).

## B. CROWDSOURCING OF CLINICAL TRIALS: THE MODEL IN BRIEF

Crowdsourcing as a solution to the ethical and other problems described in Part II is relatively straightforward, involving the Internet-based collection of data during the post-approval period. There would be no need to alter the FDA approval process until the point of approval. During the pre-approval period, pharmaceutical companies would continue to proceed through the preclinical period and phased clinical trial period as under current practice. When safety and efficacy information reaches a suitable threshold, however, the FDA would grant only a conditional approval, which would remain conditional until sufficient information was collected via the crowdsourcing platform.

Patients would be made aware of the conditional nature of the approval through, for example, the use of a symbol indicating that the drug is newly approved. This symbol, possibly along with other signals and warnings, would help to ensure that patients understand the uncertainty that accompanies new drugs. Critically, patients would also be encouraged to participate in an online data gathering platform that would allow them to enter feedback about the drug, essentially inviting the entire patient population to contribute to an uncontrolled Phase 4 study. This online crowdsourcing platform would not only gather data and in return provide useful aggregated data to the patient, but also would itself serve as an unmistakable signal to patients that safety and efficacy information about the drug was still being gathered. These elements of conditional approval and post-approval crowdsourcing are examined in greater detail below.

### 1. Conditional Approval and Product Marking

By appropriate statutory amendment, the FDA could be granted the power to “conditionally approve” drugs following Phase 3 testing. Patients taking the drug during a certain period following this conditional approval could be explicitly informed of the conditional nature of the approval and the uncertainty that remains. Uncertainty could be communicated in various ways, such as requiring patients to sign a consent form, or placing special markings or “pink caps” (or some other color) on the prescription bottles or other packaging during this period. A system by which colored caps or other symbols are used to warn patients and healthcare providers of the risks of new drugs has already proved its feasibility in the United Kingdom,

where an inverted black triangle has long been used to denote the risks associated with newly approved drugs.<sup>118</sup> Unfortunately, the British black triangle system has in the past not been well understood even within that country's medical profession and therefore has not been particularly effective.<sup>119</sup> One team of researchers, for example, reported that "few doctors in the United Kingdom know the meaning of the 'black triangle' system," and found that underreporting of adverse events with respect to black triangle drugs remained a problem.<sup>120</sup> Another noted that doctors in England had prescribed Vioxx to 42,000 patients, despite the appearance of the black triangle on that product.<sup>121</sup>

Nevertheless, these shortcomings likely reflect the system's implementation rather than its potential, and in 2007 an expert committee under contract from the Department of Health and Human Services recommended that the U.S. import a system similar to the U.K. model to the United States.<sup>122</sup> In its report, the committee "recommend[ed] that Congress amend the FD&C Act to require that product labels carry a special symbol such as the black triangle used in the United Kingdom or an equivalent symbol for new drugs, new combinations of active substances, and new systems of delivery of existing drugs."<sup>123</sup> Later the same year, Congress responded by instructing the FDA to submit to Congress a report on how best to communicate to the public the risks and benefits of new drugs, including possible consideration of the use of a unique new drug symbol on labeling and in advertising.<sup>124</sup>

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118. See Richard M. Martin et al., *Underreporting of Suspected Adverse Drug Reactions to Newly Marketed ("Black Triangle") Drugs in General Practice: Observational Study*, 317 BRIT. MED. J. 119, 119 (1998); *Black Triangle Scheme—New Medicines and Vaccines Subject to EU-wide Additional Monitoring*, MEDS. & HEALTHCARE PRODS. REG. AGENCY, <http://www.mhra.gov.uk/Safetyinformation/Howwemonitorthesafetyofproducts/Medicines/BlackTriangleproducts/index.htm#11> (last modified Nov. 18, 2013) (explaining the black triangle scheme as a "system to identify medicines that are being monitored particularly closely by regulatory authorities").

119. See Martin et al., *supra* note 118.

120. *Id.*

121. Paul A. Dieppe et al., *Lessons from the Withdrawal of Rofecoxib*, 329 BRIT. MED. J. 867, 868 (2004).

122. INST. OF MED. OF THE NAT'L ACADS., *THE FUTURE OF DRUG SAFETY: PROMOTING AND PROTECTING THE HEALTH OF THE PUBLIC* 171 (Alina Baciu et al. eds., 2007).

123. *Id.*

124. Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 904, 121 Stat. 823 (2007) (codified as amended in scattered sections



Unfortunately, the resulting 2009 report rejected the use of a special symbol and instead favored listing the initial year of approval in the Highlights section of the healthcare professional labeling.<sup>125</sup> Although listing the approval year provides greater information than a symbol—physicians and consumers can easily calculate the time a drug has been on the market—its significance is unlikely to be appreciated by patients. Even if patients read the Highlights section of the physician labeling and see the year of approval, they are unlikely to understand that it is a flag of possible increased risk. In 2013, the European Commission came to a different conclusion, adopting a regulation that expands the use of the inverted black triangle throughout the European Union.<sup>126</sup> Future research might measure consumer and physician comprehension of risk under these two contrasting systems.

Labeling is not the only place where a special symbol can increase awareness of risk. Advertisements for new drugs could also be required to include whatever symbol is chosen as a warning indicator for new drugs, and to disclose to viewers the meaning of this symbol. The advertisements might also be re-

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of 21 U.S.C.); H.R. REP. NO. 110-937, at 80–82 (2009) (noting the Institute of Medicine’s findings that the FDA and pharmaceutical industry do not make safety concerns transparent to the public in a timely, effective manner). The FDA had earlier considered and rejected the black triangle system. *See Discussion Drafts Concerning Prescription Drug User Fee Act Reauthorization, Medical Device User Fee and Modernization Act Reauthorization, Drug Safety, and Certain Pediatric Pharmaceutical and Device Legislation: Hearing Before the Subcomm. on Health of the H. Comm. on Energy and Commerce*, 110th Cong. 87 (2009) (statement of Caroline Loew, Senior Vice President, PhRMA) (“FDA considered a similar requirement in December 2000—a black triangle on new drugs for three years following approval—and, following a five-year public stakeholder process, abandoned the idea on the ground that the triangle would not be ‘universally understood, could be confusing to the prescriber (even with a concerted educational effort) and therefore may not serve its intended purposes.’” (quoting 71 Fed. Reg. 3922, 3936–37 (Jan. 24, 2006) (as codified in 21 C.F.R. pts. 201, 314, 601))).

125. FOOD & DRUG ADMIN., REPORT TO CONGRESS: FDA AMENDMENTS ACT OF 2007 SECTION 904: COMMUNICATING TO THE PUBLIC ON THE RISKS AND BENEFITS OF NEW DRUGS 15–16 (2009), available at <http://www.fda.gov/downloads/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticAct/FDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/FDAAImplementationChart/UCM267478.pdf>.

126. Commission Implementing Regulation 198/2013, 2013 O.J. (L 65) 17, 17–18 (EU); see also Commission Regulation 1027/2012, 2012 O.J. (L 316) 38, 39 (EU) (requiring a “black symbol” for drugs that are subject to additional monitoring); Commission Regulation 1235/2010, 2010 O.J. (L 348) 1, 8 (EU) (same).

quired to disclose “the date the drug was approved and that the existing information may not have identified or allowed for full assessment of all serious risks of using the drug,” to borrow language from a proposed 2007 bill that did not pass.<sup>127</sup> Alternately or additionally, doctors could be encouraged via the promulgation of guidelines to simply inform patients at the time of prescribing: “This is a new drug that has been conditionally approved by the FDA in [year], and there is always some uncertainty and risk right after a drug is placed on the market.” If oral warnings and special symbols are judged insufficient, patients might be required to sign a brief consent form acknowledging awareness of the date the drug was approved and the fact that unknown risks may remain despite conditional approval.

Nowhere is the need for better disclosure more evident than in the case of Vioxx. If patients had been informed that Vioxx was no more effective than ibuprofen or Advil (naproxen)—and convincing, independent meta-studies have shown that it is not<sup>128</sup>—and that as a new drug it carried some unknown and unknowable risk,<sup>129</sup> many of the tens of millions of patients who took the drug during the five years it was on the market (1999–2004)<sup>130</sup> may well have opted for the older, time-tested medications. However, they were not so informed,<sup>131</sup> and as a result it is estimated that at least 26,400 people died in the

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127. Enhancing Drug Safety and Innovation Act, H.R. 1561, 110th Cong., § 101(o)(4)(G)(i)(I) (2007). First Amendment concerns, especially over certain “moratorium” provisions that would have allowed the FDA to prohibit advertising entirely for up to three years after drug approval, eventually contributed to the bill’s defeat. See Mark I. Schwartz, *To Ban or Not to Ban—That Is the Question: The Constitutionality of a Moratorium on Consumer Drug Advertising*, 63 FOOD & DRUG L.J. 1, 3 (2008).

128. ROGER CHOU ET AL., OR. EVIDENCE-BASED PRACTICE CTR., COMPARATIVE EFFECTIVENESS AND SAFETY OF ANALGESICS FOR OSTEOARTHRITIS 3–4 (2006), available at <http://effectivehealthcare.ahrq.gov/repFiles/AnalgesicsFinal.pdf>.

129. See Berlin et al., *supra* note 2, at 1366–67.

130. Berenson, *supra* note 33, at A25.

131. *FDA, Merck, and Vioxx: Putting Patient Safety First?: Hearing Before the S. Comm. on Fin.*, 108th Cong. 14 (2004), at 13 (statement of David J. Graham, Associate Director for Science, Office of Drug Safety, Food and Drug Administration) (noting that Vioxx’s labeling initially said nothing about heart attack risks and when the information was added, it was not included in the label’s warning section).

United States,<sup>132</sup> without having the option to either accept or decline the new medication based on informed consent.

## 2. Crowdsourcing

Following a conditional approval by the FDA, a drug would be released on the market, but consumers would be directly involved in contributing safety and efficacy data during the period of conditional approval. In a word, the final phase of study would be “crowdsourced.” Crowdsourcing has the potential not only to reveal adverse events more quickly but also to raise awareness of the risks that remain. By involving consumers directly in the study process, they will necessarily be placed on notice that the drug is still under study, resolving the problem that exists today where drugs are de facto tested on members of the public without their understanding or consent. In addition, by designing the online crowdsourcing platform in a transparent manner that aggregates patient feedback and presents it in a user-friendly manner, consumers could more easily become aware of actual drug risks and benefits. Rather than imposing a specific but arbitrary level of safety or efficacy that must be achieved in order to secure approval, the current standard of statistical significance could be retained with consumers instead protected through improved disclosure and awareness of each product’s risk-benefit profile.

There are a number of additional benefits to crowdsourcing the final phase of clinical trials. By involving consumers directly, wherever they happen to reside, the volume of data and the geographic and demographic scope of the data would expand dramatically, potentially revealing risks or benefits to certain subpopulations. The utilization of web-based software to manage the crowdsourcing process could allow for a certain amount of automation of data manipulation and analysis. By allowing patients to enter their own data, errors that can result from the lengthy, telephone-game chain of information transmission—oral transmission from patient to physician, dictation by physician, transcription by transcriptionist, transmission to research center, forwarding to statistician, etc.—may be reduced.<sup>133</sup> Fi-

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132. *Id.* at 14. Dr. Graham estimated that between 88,000 to 139,000 “excess” heart attacks were caused by Vioxx, with 30% to 40% of these resulting in death. *Id.* Conservatively multiplying the lower numbers in each of these ranges produces  $88,000 * 30\% = 26,400$ . Significantly, these figures only represent United States deaths, but Vioxx was sold throughout the world. See Berenson, *supra* note 33, at A25.

133. See U.S. GOV’T ACCOUNTABILITY OFFICE, GAO-10-68, DRUG SAFETY:

nally, by reducing the need for a physician or other prescriber in the data collection aspect of the process, which may earn for their site between \$1600 to \$20,000 per patient enrolled in a traditional clinical trial,<sup>134</sup> there is a the potential for substantial and much needed cost reduction.

Despite the potential benefits, the implementation of a crowdsourcing model faces substantial challenges. Crowdsourcing might be difficult or impossible to randomize, control, and blind, characteristics that constitute the current gold standard for assessing a drug's qualities. Any data that is collected may be of poor quality due to a deficiency in professional oversight or involvement. Consumers may simply lack access to an Internet connection. Legal obstacles, such as the lack of clear authorization for the FDA to establish such a system,<sup>135</sup> may also be problematic. Practical opposition may come from consumers, who may be concerned about privacy or unwilling to undertake the risks, or from industry, which may fear losing control of an important component of the clinical trial process. It might be argued that existing models of conditional approval or post-approval monitoring are already sufficient.

In short, if crowdsourcing clinical trials is to be viable, it must not only overcome these and other challenges, but also offer greater value than existing protocols. The remainder of this Article further develops the possible contours of a crowdsourcing model both by comparing and contrasting it with existing post-market programs and by exploring and responding to foreseeable arguments against its implementation.

### C. CROWDSOURCING COMPARED WITH EXISTING MODELS

The many health related organizations moving into the crowdsourcing space, including the clinical trial space,<sup>136</sup> reflect

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FDA HAS BEGUN EFFORTS TO ENHANCE POSTMARKET SAFETY, BUT ADDITIONAL ACTIONS ARE NEEDED, at 25 (Nov. 2009), available at <http://www.gao.gov/assets/300/298135.pdf> (“[A]utomatic processing will cut down on errors related to data entry . . . .”); *infra* Part III.A (responding to challenges over the data quality and methodological reliability of crowdsourcing as a model for Phase 4 testing).

134. See Jill A. Fisher, *Practicing Research Ethics: Private-Sector Physicians & Pharmaceutical Clinical Trials*, 66 SOC. SCI. & MED. 2495, 2503 (2008).

135. See *infra* Part III.B.1 (addressing the possibility that crowdsourcing might not meet 21 U.S.C. § 355(d)'s requirement of “adequate and well-controlled investigations”).

136. See M. Swan, *Crowdsourced Health Research Studies: An Important Emerging Complement to Clinical Trials in the Public Health Research Ecosys-*

optimism that a distributed clinical trial model with increased patient input is possible. At the same time, the FDA has long been requesting the assistance of others as part of its programs to monitor drugs once released on the market.<sup>137</sup> This monitoring of pharmaceutical once in the marketplace, or “pharmacovigilance,”<sup>138</sup> takes the form both of required reporting and voluntary submission of adverse event reports. In addition, a number of programs or policies allow early access to drugs with the expectation that additional information will be gathered later. It is worth briefly reviewing these programs to explore how crowdsourcing as described herein may be able to improve upon the status quo.

### 1. Risk Evaluation and Mitigation Strategies (REMS)

The Food and Drug Administration Amendments Act of 2007 authorized the FDA to require drug sponsors to submit Risk Evaluation and Mitigation Strategies (REMS).<sup>139</sup> REMS may be required for either drugs whose approvals are pending, as a condition of approval, or for already-approved drugs.<sup>140</sup> The statutory purpose of REMS is to “ensure that the benefits of the

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tem, 14 J. MED. INTERNET RES., Mar. 2012, at e46, <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3376509/>.

137. See, e.g., FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: GOOD PHARMACOVIGILANCE PRACTICES AND PHARMACOEPIDEMIOLOGIC ASSESSMENT 4 (Mar. 2005), available at <http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126834.pdf> (“FDA recommends that sponsors make a reasonable attempt to obtain complete information for case assessment during initial contacts and subsequent follow-up . . .”).

138. See *id.* at 1.

139. Food and Drug Administration Amendments Act of 2007 (FDAAA), Pub. L. No. 110-85, § 901(b), 121 Stat. 823, 926 (2007). The decision to require drug sponsors to submit and implement a REMS is made jointly by the Office of New Drugs and the Office of Surveillance and Epidemiology, whose offices are housed within the FDA’s Center for Drug Evaluation and Research (CDER). See FOOD & DRUG ADMIN., MEMORANDUM OF AGREEMENT BETWEEN THE OFFICE OF NEW DRUGS AND THE OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY IN THE CENTER FOR DRUG EVALUATION AND RESEARCH 2 (2009), available at <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM111520.pdf>. The Office of Surveillance and Epidemiology in turn houses the Office of Pharmacovigilance I and II and the Office of Epidemiology I and II. *Office of Surveillance and Epidemiology (OSE)—Divisions*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm169536.htm> (last updated Aug. 21, 2013). For CDER’s organizational structure see *CDER Offices and Divisions*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm075128.htm> (last updated Nov. 22, 2013).

140. See 21 U.S.C. § 355-1(a)(1) (2012).

drug outweigh the risks of the drug,” and generally involve the submission of assessments to the FDA at eighteen months, three years, and seven years.<sup>141</sup> In addition to these reports, REMS may also involve three other types of elements: (1) a Medication Guide, which is a document given to consumers that contains warning information for drugs that pose potentially serious risks;<sup>142</sup> (2) a communication plan, that may include “Dear Doctor” letters or the dissemination of information via professional societies;<sup>143</sup> and (3) “elements to assure safe use” (ETASU), a catch-all category that might include, for example, such safeguards as limiting access to a drug to those patients who enroll in a registry.<sup>144</sup> The registry may include data on clinical outcomes and safety, among other things.<sup>145</sup> Although specific REMS goals are proposed by the drug sponsor and will be different in each case, an example goal suggested in the FDA’s draft guidance is “[p]atients taking W drug should be aware of the serious risks relative to the potential benefits.”<sup>146</sup>

REMS falls far short of the model of patient crowdsourcing proposed herein because, among other things, it leaves primary responsibility for data collection in the hands of drug sponsors.<sup>147</sup> In addition, its complicated processes and lack of standardization<sup>148</sup> have led to criticisms that it is burdensome to both patients and healthcare system as a whole.<sup>149</sup> In one case, for example, the imposition of REMS resulted in a 39% drop in consumption.<sup>150</sup> Because sales rebounded to expected levels af-

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141. *Id.* § 355-1(a)(1), (d).

142. *Id.* § 355-1(e)(2).

143. *Id.* § 355-1(e)(3).

144. *Id.* § 355-1(f)(1), (3)(F).

145. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: FORMAT AND CONTENT OF PROPOSED RISK EVALUATION AND MITIGATION STRATEGIES (REMS) 14 (2009), available at <http://www.fda.gov/downloads/Drugs/Guidances/UCM184128.pdf>.

146. *Id.* at 9.

147. See 21 U.S.C. § 355-1(a)(1) (stating that the drug sponsor is responsible for submitting proposed REMS).

148. See Scot Walker, *Maximizing REMS Potential*, DRUG TOPICS, Sept. 2012, at 24, 24.

149. See Susan C. Nicholson et al., *Risk Evaluation and Mitigation Strategies (REMS): Educating the Prescriber*, 35 DRUG SAFETY 91, 102 (2012) (“REMS for the opioid class of drugs with potentially burdensome requirements for the healthcare system has been under discussion . . . since March 2009.”).

150. Kate Traynor, *REMS Review Explores Programs’ Burdens*, 69 AM. J. HEALTH-SYS. PHARMACY 92, 94 (2012).

ter 10 months,<sup>151</sup> this drop likely reflected the system's burdens rather than thoughtful and deliberate patient avoidance resulting from a newfound appreciation of product risks. These burdens of REMS almost certainly will translate into increased costs for the industry, with likely impact on the drug costs faced by consumers.<sup>152</sup> Moreover, at one point almost half of all REMS plans included only a medication guide.<sup>153</sup> Simply handing another lengthy document to patients, without more, is unlikely to have as great a degree of impact as would involving patients directly in data collection.<sup>154</sup>

Despite its challenges, REMS establishes the feasibility of a number of elements that may be desirable in a crowdsourcing model. The example goal of increased patient awareness of the risks of "W drug"<sup>155</sup> is a nod in the direction of informed consent, although it is stated merely as an aspiration rather than a requirement for treatment. REMS also confirms the feasibility of conditioning the distribution of new drugs on the agreement to collect and report information related to clinical outcomes.<sup>156</sup> Although REMS places this burden on the drug sponsor, the statutory language appears flexible enough to place the obligation to report, at least indirectly, on the patients themselves. REMS allows drug sponsors to monitor and evaluate implementation "by health care providers, pharmacists, and other parties in the healthcare system who are responsible for implementing [elements to assure safe use];"<sup>157</sup> the inclusion of the phrase "and other parties" suggests that the statute may allow at least part of the obligation to report to be placed on patients themselves. Finally, REMS provides for the possibility that the reporting of assessments beyond year three be eliminated if the FDA determines that serious risks have

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151. *Id.*

152. See Nicholson et al., *supra* note 149, at 102.

153. See Dima Qato & G. Caleb Alexander, *Improving the Food and Drug Administration's Mandate to Ensure Postmarketing Drug Safety*, 306 J. AM. MED. ASS'N 1595, 1595 (2011).

154. See *id.* ("The ability of Medication Guides alone to substantially improve the safe use of drugs remains doubtful and unproven, at best.")

155. FOOD & DRUG ADMIN., *supra* note 145, at 9.

156. See Andrew Wilson & Christopher-Paul Milne, *FDA's Risk Evaluation and Mitigation Strategies (REMS): Effective and Efficient Safety Tools or Process Poltergeist?*, 66 FOOD & DRUG L.J. 569, 574 (2011) ("[P]armacists have often had to maintain multiple sets of records that exist separately from their normal systems, creating considerable redundancy and complexity.")

157. 21 U.S.C. § 355-1(f)(4) (2012) (emphasis added).

been adequately identified and managed.<sup>158</sup> This provision suggests that, in the proposed crowdsourcing model, a three-year period following a conditional approval may be a reasonable default period after which the approval could become a regular approval unless contrary action is taken by the FDA.

## 2. Conditional Approval, Accelerated Approval, and Phase 4 Studies

A number of other FDA-administered programs allow for relatively faster approval in conjunction with some form of post-approval data gathering. Under the FDA's accelerated approval regulations, the FDA may grant approval based on a so-called "surrogate endpoint," such as tumor shrinkage, that is believed to correlate with a clinical endpoint, such as increased survival for cancer patients.<sup>159</sup> As a condition to the grant of accelerated approval, the drug sponsor is required to complete Phase 4 studies to verify clinical benefit.<sup>160</sup> FDA oversight of Phase 4 studies has been lax, however, according to the U.S. Office of the Inspector General.<sup>161</sup> In addition, Phase 4 testing generally involves only a tiny fraction of the post-approval market, if such testing is conducted at all.<sup>162</sup> In contrast, crowdsourcing would seek to capture a much larger percentage, perhaps approaching 100%, of this market. Like accelerated approval, crowdsourcing might allow for somewhat earlier (conditional) approval of a drug, balanced by better disclosure to patients and improved post-approval data capture.

The FDA also administers a conditional approval program for animal drugs under which a drug may be marketed before complete efficacy data is available so long as two conditions are met. First, there must be a reasonable likelihood that the drug is effective.<sup>163</sup> Second, the drug must have been proven safe in

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158. *Id.* § 355(d)(4)(C).

159. 21 C.F.R. § 314.510 (2013) (referring to drugs); *id.* § 601.41 (referring to biologics); *see also id.* § 312.85 (describing "Phase 4 Studies").

160. *Id.* § 314.510; *id.* § 601.41.

161. OFFICE OF INSPECTOR GEN., OEI-01-04-00390, FDA'S MONITORING OF POSTMARKETING STUDY COMMITMENTS, at iii, 17 (2006); *see also* U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-06-402, DRUG SAFETY: IMPROVEMENT NEEDED IN FDA'S POSTMARKET DECISION-MAKING AND OVERSIGHT PROCESS, at 5 (2006) ("FDA lacks a clear and effective process for making decisions about, and providing management oversight of, postmarket drug safety issues.").

162. *See* OFFICE OF INSPECTOR GEN., *supra* note 161, at 17.

163. 21 U.S.C. § 360ccc(a)(2)(B).



accordance with the usual full FDA approval standard.<sup>164</sup> The label of any new animal drug that has been only conditionally approved must bear a statement that the drug has been “conditionally approved by FDA pending a full demonstration of effectiveness under application number [\_\_\_\_\_].”<sup>165</sup> A crowdsourcing model might borrow this notice requirement from the conditional approval statute. Drugs that have been only conditionally approved could bear a statement analogous to the one just quoted, either instead of or in addition to a clear marking, such as a pink cap or symbol as suggested above.<sup>166</sup>

The conditional approval statute also provides for the possibility that the one-year conditional approval may be extended for up to four additional years, for a total of five years.<sup>167</sup> Crowdsourcing following a conditional approval would simply serve to clarify efficacy levels while also gathering adverse event data in a more ethical and comprehensive manner. Like the animal drug statute, the conditional approval system implemented in connection with a post-approval crowdsourcing system could involve the ability to extend the conditional approval period following a default term of three years (or some other duration deemed appropriate by the FDA based on statistical considerations). After three years, the conditional approval would automatically become a regular approval unless the FDA acts to prevent this.

In addition to REMS and the accelerated and conditional approval programs, the FDA also administers a post-market surveillance program called MedWatch, which approaches a true crowdsourcing model in that it accepts input from a distributed group of patients, doctors, and others relating to the adverse effects of approved drugs.

### 3. FDA MedWatch Program

MedWatch crowdsources post-approval safety information of drugs, biologics, medical devices, dietary supplements, infant formula, and cosmetics.<sup>168</sup> The program allows both consumers

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164. See *id.* § 360ccc(a)(2)(A); see also Laura Avery, *Conditional Approval for Animal Drugs: What Does This Mean for Veterinarians?*, FDA VETERINARIAN NEWSL. (FDA, Washington D.C.), Apr. 28, 2011, available at <http://www.fda.gov/AnimalVeterinary/NewsEvents/FDAVeterinarianNewsletter/ucm252075.htm>.

165. 21 U.S.C. § 360ccc(f)(1)(A).

166. See *supra* Part II.B.1.

167. 21 U.S.C. § 360ccc(d).

168. *How Consumers Can Report an Adverse Event or Serious Problem to*

and healthcare professionals to submit “serious adverse events” or “therapeutic inequivalence/failure[s]” that are suspected of being associated with an FDA approved-product.<sup>169</sup> According to MedWatch Medical Director Norman Marks, the program is needed because “[s]ometimes there are risks that only come to light after a medical product gets on the market and is used in a larger number of patients, for a longer period of time, and in patients whose health characteristics are different from those of the patients studied before approval.”<sup>170</sup>

While the program seeks to address post-approval safety concerns and utilizes the crowdsourcing of information as a means to do so, there are substantial differences between MedWatch and the current proposal. First, although consumers under the MedWatch program may file reports directly with the FDA, they are encouraged to take the FDA’s reporting form (FDA form 3500) to their doctors who “can provide clinical information based on [the consumer’s] medical record that can help FDA evaluate [the consumer’s] report.”<sup>171</sup> Because the reporting system is voluntary (sometimes referred to as “passive”<sup>172</sup>), it has been widely acknowledged that most relevant adverse events likely go unreported.<sup>173</sup> Similarly, because the

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FDA, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053074.htm> (last updated June 5, 2013) [hereinafter *Reporting by Consumers*].

169. *Reporting Serious Problems to FDA*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm> (last updated Aug. 23, 2013). Manufacturers are also required to report adverse events of which they are aware. *See id.* The Federal Adverse Event Reporting System (FAERS) combines these mandatory reports with the voluntary reports submitted by patients and physicians via MedWatch. *See FDA Adverse Event Reporting System (FAERS)*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm> (last updated Sept. 10, 2012); *see also* Syed Rizwanuddin Ahmad, *Adverse Drug Event Monitoring at the Food and Drug Administration*, 18 J. GEN. INTERNAL MED. 57, 57 (2003) (“AERS receives adverse events information from 2 principal sources: mandatory reports from pharmaceutical companies . . . and adverse event reports that physicians, pharmacists, nurses, dentists, and consumers submit directly to the FDA’s MedWatch program.”).

170. *FDA 101: How to Use the Consumer Complaint System and MedWatch*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm049087.htm> (last updated Sept. 3, 2013).

171. *Reporting by Consumers*, *supra* note 168.

172. *See* Eichler et al., *supra* note 25, at 823.

173. *See* Bartlett v. Mut. Pharm. Co., 760 F. Supp. 2d 220, 234 (D.N.H. 2011) (“According to FDA estimates, more than 90 percent of adverse events go unreported.”).

system involves ad hoc, non-obligatory reporting<sup>174</sup> on a standardized form that applies to everything from drugs to cosmetics, large amounts of valuable efficacy or other data is often not collected.<sup>175</sup> In 2010, patients and physicians directly submitted 28,950 spontaneous reports,<sup>176</sup> with many lacking critical information.<sup>177</sup> Most importantly, however, the program does little or nothing to warn consumers at the time of prescription that a given drug is new or that new drugs continue to carry risk, failing completely to address the ethical issue of lack of informed consent.

In contrast, the proposed crowdsourcing system would proactively make contact with patients around the time of prescription by obtaining each patient's consent and encouraging (or possibly, requiring<sup>178</sup>) that patient to participate in the associated crowdsourcing project. Rather than use a standardized form, Internet-based questions could be tailored to the particular drug and condition in question. For example, patients taking cholesterol-lowering drugs might be given the option to check off boxes corresponding to side effects such as muscle pain, stomach pain, diarrhea, or headache. If the patient answers in the affirmative, the software might prompt for additional information, such as the number of hours that elapsed between drug administration and the adverse effect. Questions could be created based upon commonly experienced adverse events of existing drugs within the same class. Although the

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174. Drug sponsors, in contrast to patients and healthcare providers, are required to report adverse events of which they are aware. 21 C.F.R. § 310.305 (2013) (applying to marketed prescription drugs without new drug applications); *id.* § 312.32(c)(1)(i-iv) (referring to clinical trials); *id.* § 314.80 (referring to new drug applications); *id.* § 314.98 (applying to abbreviated new drug applications); *id.* § 600.80 (referring to biological products).

175. See *MedWatch Online Voluntary Reporting Form*, U.S. FOOD & DRUG ADMIN., <https://www.accessdata/fda.gov/scripts/medwatch> (last visited Nov. 25, 2013).

176. *Reports Received and Reports Entered into FAERS by Year*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070434.htm> (last updated June 11, 2013).

177. *Review of the FDA/CDER Pharmacovigilance Program*, FDA SCI. BD. SUBCOMM. (May 20, 2011), <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/ScienceBoardtotheFoodandDrugAdministration/UCM255639.pdf>; see Ahmad, *supra* note 169, at 57 ("One of the limitations of spontaneous reports is that, in general, they are poorly documented . . .").

178. Mandatory patient registries created under REMS, for example, demonstrate the feasibility of a participation requirement. See *supra* note 144 and accompanying text.

questions would vary depending on the drug, there could be coordination among different medications in the same class or in related classes in order to maximize comparability of the data. A free-form box might allow patients to enter other adverse events possibly related to the medicine that were not included in the prepared list. If a particular new or unusual side effect is reported in a sufficient number of responses, system administrators might add that side effect to the existing list. The system would therefore be standardized, while retaining flexibility. Patients would of course remain free to consult with their doctors, and doctors would be free to continue to report adverse events, but primary responsibility for data submission would remain with the patient.<sup>179</sup> Importantly, patients should be provided the ability to learn more about the drug they are taking or other treatments, as an incentive to visit and contribute to the site. This information could include aggregated and anonymized safety and efficacy data derived from the responses of others.

A final program administered by the FDA, known as Sentinel, aggregates vast quantities of dispersed patient data, but does so indirectly by examining existing health records contained in the databases of entities such as insurance companies and hospitals.

#### 4. Sentinel

The Food and Drug Administration Amendments Act of 2007 (FDAAA) recognized, in the words of one scholar, that “drawing more information from the physician-patient experience into the regulatory process with enhanced FDA market presence will shore up the reliability of prescription drugs.”<sup>180</sup> To this end, Congress directed the FDA to collaborate with public, academic, and private entities to “develop validated methods for the establishment of a post-market risk identification and analysis system to link and analyze safety data from mul-

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179. Placing primary responsibility on patients would reverse the practice of the current system, under which FDA encourages patients to report indirectly via their physicians, rather than complete the online form themselves. See *Reporting by Consumers*, *supra* note 168. Although patients can nevertheless self-report, the online form is currently not tailored to any particular drug. *Id.*

180. See Michael J. Malinowski, *Doctors, Patients, and Pills—A System Popping Under Too Much Physician Discretion? A Law-Policy Prescription to Make Drug Approval More Meaningful in the Delivery of Healthcare*, 33 CARDOZO L. REV. 1085, 1121 (2012).

tiple sources, with the goals of including, in aggregate . . . at least 100,000,000 patients by July 1, 2012.”<sup>181</sup> Once these methods are established, the FDA is further directed by the FDAAA to establish procedures for post-market risk surveillance that involves data mining of electronic health data (such as Medicare data or private health insurance claims data).<sup>182</sup> Embracing this statutory command, the FDA launched its Sentinel Initiative in 2008<sup>183</sup> and reported achieving the milestone of 100 million patients in June 2012.<sup>184</sup>

The Sentinel Initiative is a major milestone in post-market monitoring because it allows active surveillance of safety rather than relying on the passive reporting that characterizes other programs such as MedWatch.<sup>185</sup> It is also notable for its commitment to leverage a distributed network of data and place results in the public domain.<sup>186</sup>

Nevertheless, the Sentinel Initiative has a number of drawbacks that might be addressed by the proposed crowdsourcing system. First, the Sentinel Initiative is primarily aimed at risk identification and analysis, and does not directly address efficacy research.<sup>187</sup> Second, the Government Accountability Office has reported that the FDA’s funds for purchasing data have been chronically inadequate, despite increases.<sup>188</sup> Third, and most importantly, Sentinel is layered and

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181. 21 U.S.C. § 355(k)(3)(B) (2012).

182. *Id.* § 355(k)(3)(C).

183. FOOD & DRUG ADMIN., THE SENTINEL INITIATIVE: ACCESS TO ELECTRONIC HEALTHCARE DATA FOR MORE THAN 25 MILLION LIVES 2 (2010), *available at* <http://www.fda.gov/downloads/Safety/FDAsSentinelInitiative/UCM233360.pdf> [hereinafter THE SENTINEL INITIATIVE]; FDA’s *Sentinel Initiative: Transforming How We Monitor the Safety of FDA-Regulated Products*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Safety/FDAsSentinelInitiative/ucm2007250.htm> (last updated Nov. 22, 2013).

184. Melissa Robb, *FDA’s Mini-Sentinel Exceeds 100 Million Lives (and Counting)*, FDA VOICE (June 29, 2012), <http://blogs.fda.gov/fdavoices/index.php/2012/06/fdas-mini-sentinel-exceeds-100-million-lives-and-counting-a-major-milestone-in-developing-a-nationwide-rapid-response-electronic-medical-product-safety-surveillance-program>.

185. See *supra* note 172 and accompanying text.

186. See *About Mini-Sentinel: Background*, MINI-SENTINEL, [http://www.mini-sentinel.org/about\\_us](http://www.mini-sentinel.org/about_us) (last visited Nov. 25, 2013).

187. See Bethany Fox, *Closing the Information Gap: Informing Better Medical Decisionmaking Through the Use of Post-Market Safety and Comparative Effectiveness Information*, 67 FOOD & DRUG L.J. 83, 91–92 (2012). But see Evans, *supra* note 10, at 497–98 (arguing that through a “sleight of definition” the FDAAA does allow efficacy research).

188. See U.S. GOV’T ACCOUNTABILITY OFFICE, *supra* note 133, at 11, 28–30.

cumbersome.<sup>189</sup> The FDA's acknowledgement that the Sentinel is a "complex endeavor"<sup>190</sup> puts it mildly. Five years after the FDAAA, the FDA is still conducting a pilot program called Mini-Sentinel whose scope and complexity belie its name.<sup>191</sup> Rather than allowing individuals to contribute directly to a database that could be mined for data, Mini-Sentinel begins with the formulation of questions by the FDA that are transmitted to a Coordinating Center, which in turn submits these questions to more than twenty collaborating institutions including insurance companies and hospitals.<sup>192</sup> These collaborating institutions then mine their own databases, transmit the summarized results to the Coordinating Center, which in turn aggregates the responses and transmits them to the FDA.<sup>193</sup> The process requires each collaborating partner to transform its data into standardized format.<sup>194</sup> It has so far cost at least \$125 million.<sup>195</sup>

Crowdsourcing has a number of advantages over the Sentinel system. The primary motivating factor behind this complex, layered approach seems to be a concern for patient privacy, although a desire to leverage existing data and involve established institutions are probably also factors. In the proposed crowdsourcing system, by contrast, privacy concerns in most cases would be largely avoided by encouraging patients to contribute information of their own volition. For those situations where data collection is especially critical (such as with certain drugs currently subject to REMS), patient reporting could be required and privacy safeguarded in a manner analo-

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189. See JUDITH A. RACOOSIN ET AL., *FDA's Sentinel Initiative: Active Surveillance to Identify Safety Signals*, in PHARMACOEPIDEMIOLOGY 544–47 (Brian L. Strom et al. eds., 5th ed. 2012); Richard Platt et al., *The U.S. Food and Drug Administration's Mini-Sentinel Program: Status and Direction*, 21(S1) PHARMACOEPIDEMIOLOGY & DRUG SAFETY 1, 3–5 (2012) (describing the complex structure of the Mini-Sentinel Distributed Data System).

190. THE SENTINEL INITIATIVE, *supra* note 183, at 2.

191. See *About Mini-Sentinel: Background*, *supra* note 186.

192. THE SENTINEL INITIATIVE, *supra* note 183, at 5.

193. *Id.* at 4–5; see also Patient Protection and Affordable Care Act, Pub. L. No. 111-148, § 6301(b), 124 Stat. 119, 740 (2010) (codified at 42 U.S.C. § 299b-37(f) (2006)) (mandating "the development and use of clinical registries and health outcomes research data networks, in order to develop and maintain a comprehensive, interoperable data network to collect, link, and analyze data on outcomes and effectiveness from multiple sources, including electronic health records").

194. THE SENTINEL INITIATIVE, *supra* note 183, at 6.

195. See Food and Drug Administration Amendments Act of 2007 (FDAAA), Pub. L. No. 110-85, § 905(d), 121 Stat. 823 (2007).

gous to that provided under the current system. Data quality could also be improved. Unlike Sentinel, which relies on preexisting data created for other purposes that often lacks key information on relevant health factors,<sup>196</sup> a crowdsourcing platform could prompt users to enter the information that is relevant to the task. Voluntary contribution of data would also lead to cost savings, since there would be no need to purchase data, although costs for platform development, awareness campaigns, and data analysis would still be necessary. There would also be no need to undertake the challenging task of integrating data distributed across disparate providers, such as where a patient receives a diagnosis at one health center, reports an adverse event at a second, and receives follow-up treatment at a third, possibly each in different states or countries. Whereas the Sentinel system requires transfer of information from patient to doctor to database to Coordinating Center to FDA,<sup>197</sup> crowdsourcing would vastly simplify the process by accepting direct entry of data by patients into an online platform where anonymized data would be aggregated and analyzed directly by the FDA, interested third parties, or even patients themselves.

#### D. SYNTHESIS

The above discussion suggests that crowdsourcing clinical trials is not only feasible, but may be able to improve upon various aspects of current practice. The feasibility of crowdsourcing is reflected in the fact that some form of crowdsourcing is already present in existing FDA policies and programs, including REMS, accelerated approval, MedWatch, and Sentinel. Consumers are already able to report clinical outcomes directly to the FDA, even if in practice this happens only in a sporadic manner. Conditional or other forms of early approval followed by post-approval data gathering already find precedent in the law.

The proposed system, however, would seek to improve upon the status quo in a number of ways. First, under the proposed system, most if not all patients would be invited to offer feedback at the time of prescription about the medicines they

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196. Asher Mullard, *Unleashing the Mini-Sentinel*, 11 NATURE REVIEWS DRUG DISCOVERY 255, 256 (2012) (pointing at the lack of potentially useful information related to patient weight or pulmonary function).

197. See Susan Forrow et al., *The Organizational Structure and Governing Principles of the Food and Drug Administration's Mini-Sentinel Pilot Program*, 21(S1) PHARMACOEPIDEMIOLOGY & DRUG SAFETY 12, 13 (2012).

are about to consume. Such proactive, routine, and early communication with patients would help to ensure against the occurrence of human testing without consent, resolving the ethical flaw that exists today. Second, the model would seek to transform MedWatch's drab and tedious online form into an exciting, user-friendly portal of information, where patients could input not only adverse events, but also perceived benefits and even comparative impressions of the medicine vis-à-vis other drug or non-drug treatments. Third, although the altruistic desire to contribute information in order to help others would remain a motivation, patients under the proposed model would be incentivized to contribute primarily by the self-interested desire to visit a website where they can learn more about the drug they are taking. Dramatically expanding the functionality of the current system so that patients (or prospective patients) could easily review both the individual and aggregated feedback of others would therefore be a key element of the proposed model. In short, the crowdsourcing model would improve the status quo by turning a world of passive and disconnected patients into a community of people who are united by a common desire to learn about a medicine and share their experiences in using it.

For some drugs, particularly those used to treat minor conditions, only a fraction of patients are likely to thoroughly embrace and participate in any voluntary crowdsourcing platform. Yet even a small percentage could contribute a volume of data vastly greater than that produced under current programs, both because the entire population of patients would be potentially able to contribute and because participation would not be limited by proximity to a clinical trial site. Geographic inclusiveness, in particular, would be expanded immensely in light of the ubiquity of mobile phones around the world. The promise of "big data" for solving healthcare problems is only now beginning to be appreciated and explored.<sup>198</sup>

A fourth improvement over the status quo stems from the fact that the Internet is ideally suited for the automation of data aggregation and analysis. In contrast to current clinical trial practice, therefore, the proposed crowdsourcing model would

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198. See, e.g., Meghan F. Coakley et al., *Unlocking the Power of Big Data at the National Institutes of Health*, 1 *BIG DATA* 183 (2013); Simon I. Hay et al., *Big Data Opportunities for Global Infectious Disease Surveillance*, *PLOS MEDICINE*, Apr. 2, 2013, <http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001413>.



avoid the need to translate patient input, via healthcare-worker intermediaries, from an analog paper environment to a digital one. This would help to reduce the likelihood of data entry errors and speed discovery of adverse events.<sup>199</sup>

Fifth and finally, there is an advantage to crowdsourcing that both the government and public should find particularly attractive: cost. REMS places substantial and possibly onerous burdens on drug companies.<sup>200</sup> Government monitoring, particularly Sentinel, requires a complex, layered infrastructure. These burdens are relatively new, having been implemented by FDAAA only in 2007.<sup>201</sup> As their costs become clearer, pressure to substitute more efficient, less expensive means of collecting and disseminating relevant information will increase. A patient-driven, Internet-based crowdsourcing platform can shift part of the burden from the FDA, industry, and physicians, for whom data collection is an obligatory task, to patients who have a self-interested desire to both learn and share information.

### III. ADDRESSING CHALLENGES

Despite the potential advantages, there are numerous challenges and concerns that will have to be addressed as part of a clinical trial crowdsourcing system. These include concerns over data quality, a lack of ability or willingness of laypersons to participate, the absence of randomization, blinding and control, opposition from industry, the need to assure adequate privacy, and a range of potential legal hurdles. These challenges will be addressed in turn.

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199. See, e.g., U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 133 (acknowledging that "automatic processing will cut down on errors related to data entry and should allow for more timely availability of reports"); cf. *infra* Part III.A.1 (addressing the concern that laypersons cannot contribute reliable data).

200. See, e.g., Anthera Pharm., Inc., Quarterly Report (Form 10-Q), at 29 (Mar. 31, 2012), available at <http://markets.on.nytimes.com/research/stocks/fundamentals/drawFiling.asp?docKey=137-000110465912033177-0IOCR2NFG RD5ROBH157C2CDJON&docFormat=HTM&formType=10-Q> (warning investors that REMS "may make it more difficult or burdensome . . . to obtain approval" and that "any approvals . . . may be . . . subject to onerous post-approval requirements").

201. Food and Drug Administration Amendments Act of 2007 (FDAAA), Pub. L. No. 110-85, §§ 901 (REMS), 905a (Sentinel), 121 Stat. 823 (2007).

### A. DATA QUALITY AND METHODOLOGICAL CONCERNS

The most significant concerns about crowdsourcing clinical trials relate to potential data quality problems, of which there are many. Laypersons may be insufficiently educated, insufficiently motivated, or simply lack the capacity to contribute to a clinical trial database. Even if sufficient participation and ability is assumed, crowdsourcing would not necessarily be randomized, controlled, or blinded, and would therefore lack appropriate scientific control.

#### 1. Laypersons Cannot Contribute Reliable Data

Laypersons may be perceived as lacking the appropriate education, experience, or motivation to reliably obtain or enter clinical data.<sup>202</sup> Most laypersons will not have medical training or experience in administering clinical trials. In some cases, equipment will be needed to obtain trial data that patients simply will not have. Few patients, for example, have sphygmomanometers at home with which to measure blood pressure, and even if the device were provided its use would require some training and would in any event pose practical problems for self-administration (the use of a traditional sphygmomanometer is easier with two hands). In other cases, the evaluation may ultimately address characteristics that require complex judgments, such as the extent to which a patient is depressed or has reduced cognitive ability (e.g., Alzheimer's). It might also be feared that the absence of tight controls or oversight with respect to data entry could allow drug sponsors, competitors, or other malicious actors to input fraudulent data that make drugs appear either better or worse than they really are.

Although these are genuine challenges, they are not insurmountable. In some cases specialized equipment may not be needed, such as when evaluating the efficacy of analgesic medicines (painkillers) or decongestants. In other cases, simple equipment that most consumers can use either with or without physician instruction will be adequate, such as the use of a

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202. The assumption that lay consumers lack the ability to appropriately interact with or address health-related issues without sufficient supervision is not limited to clinical trials. Prescription drugs and corrective eyewear, for example, cannot lawfully be obtained without the permission of an authorized prescriber. The assumption of consumer ignorance and lack of self-control, etc., may be the proper subject of reexamination in light of the wealth of information that is now available to consumers via the Internet, but is beyond the scope of this Article.

home thermometer in the evaluation of the efficacy of an anti-pyretic (fever-reducer). More complex questions of efficacy can be broken down into a series of simpler questions (e.g., level of depression or attention deficit). If the patient is unable to contribute data (advanced Alzheimer's Disease or pediatric conditions, for example), parent, adult child, or other caregiver may be able to do so. Parents in particular may be especially attentive, motivated, and comprehensive in reporting adverse events and improvements in their child's condition and may have the ability to monitor and report on a more frequent basis than could a physician. In some cases where it is impractical to self-evaluate with precision, such as measuring the effectiveness of sleeping pills in terms of minutes-until-sleep, patients can nevertheless record their subjective post-hoc impressions, such as whether they think it took them more or less time to fall asleep after taking the medication, how restfully they slept, and whether they awoke during the night. Side-effects, as opposed to efficacy, will often be even easier to recognize and report. For example, the side effects reported in the labeling for Ditropan (oxybutynin, an incontinence drug), include headache, blurred vision, constipation, nausea, and dizziness.<sup>203</sup>

In many cases it may be straightforward for patients or their caregivers to self-report with respect to both efficacy and adverse events. Sometimes, however, self-reporting may simply not be possible, such as where measurements require lab work or cannot be performed outside of a healthcare facility. In these cases, patients could be given online access to their health records.<sup>204</sup> It is common sense that patients should have easy access to their own health records (with reasonable exceptions, as under current law<sup>205</sup>), and with the move toward electronic health records the feasibility of accessing such data online in-

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203. FOOD & DRUG ADMIN., REFERENCE ID 3105471, DITROPAN, at 9 tbl.3 (2012), available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/017577s038lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/017577s038lbl.pdf).

204. Patients already have a general right of access, with some sensible exceptions, to their health records. 45 C.F.R. § 164.524 (2012). However, the healthcare entity remains in control. Individuals must request access, and may have to wait up to sixty days for a response. *Id.* § 164.524(b)(2)(ii). That response may be a denial, in which case the patient has a right to appeal to an administrator within the healthcare entity, *id.* § 164.524(a)(3), but the right of review does not apply in all cases. *Id.* § 164.524(a)(2). "Access" may be satisfied by allowing inspection rather than copying. *Id.* § 164.524(c)(1). Finally, the healthcare provider may charge a fee. *Id.* § 164.524(c)(4). In short, access under the current regime is in most cases possible, but difficult.

205. *Id.* § 164.524.

creases. Electronic health records could even be leveraged to automatically transfer certain relevant data, reducing both the effort needed and the likelihood of errors.

More generally, the assumption that data collected in the presence of a healthcare worker will be of higher quality than if input directly by patients may simply be wrong. From the perspective of physician-investigators, the administration of clinical trials is a for-profit enterprise,<sup>206</sup> and there may therefore be varying levels of commitment to ensuring data accuracy. Turnover among trial “monitors” is high,<sup>207</sup> creating learning-curve quality concerns. Pharmaceutical companies, who have an interest in sufficient numbers of trial participants completing the study protocol, may be eager to “grant ‘exceptions’ when patient-subjects have failed to follow the study protocol perfectly or mistakes are made.”<sup>208</sup> There is evidence to indicate that a substantial minority (37%) of investigators fail to adequately supervise their trials, which has earned this derelict elite the appellation “phantom investigators.”<sup>209</sup> In some cases, fortunately a small minority, clinical trial staff have even committed outright misconduct such as the fabrication or falsification of data.<sup>210</sup> In the case of post-approval adverse event reporting,<sup>211</sup> doctors may be “reluctant to take the time to fill out lengthy drug safety reports.”<sup>212</sup> According to one commentator:

Some have estimated that under 1 percent of [post-approval] adverse events are reported by doctors. Indeed, the FDA has so little confidence in safety information coming from physicians’ offices that they have a full-time staff whose job it is to read medical journals for letters about drug reactions, figuring that doctors are actually more likely to write to a journal than to the FDA.<sup>213</sup>

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206. See FISHER, *supra* note 51, at 39 (noting the increase of private clinical trials and compensation for physicians).

207. *Id.* at 117.

208. *Id.* at 123.

209. Valerie Gamache, *Chasing Away Phantom Investigators*, 8 CENTERWATCH 1, 1 (2001).

210. Barbara K. Redman et al., *Research Misconduct Among Clinical Trial Staff*, 12 SCI. & ENG’G ETHICS 481, 482 (2006) (noting 235 cases of alleged misconduct during an eight-year period).

211. See *supra* Part II.C.3.

212. DAVID GRATZER, *THE CURE: HOW CAPITALISM CAN SAVE AMERICAN HEALTHCARE* 158 (2006).

213. *Id.* The 1% figure is derived from a 1984 study of data from a one-year period in 1970. See H. Denman Scott et al., *Rhode Island Physicians’ Recognition and Reporting of Adverse Drug Reactions*, 70 R.I. MED. J. 311, 316 (1987) (citing Allen C. Rossi & Deanne E. Knapp, *Discovery of New Adverse Drug Reactions: A Review of the Food and Drug Administration’s Spontaneous Report-*

When adverse event reports are filled out, they are often woefully incomplete. One recent study, for example, found that more than a third of adverse event reports failed to record the age of the patient and that nearly half reported “other” as the outcome.<sup>214</sup>

Subjects who participate in clinical trials may also be more likely to contribute poorer data than might initially be presumed. Like physician-investigators, some clinical trial participants are motivated by the generous sums of money that are doled out to induce participation, potentially creating quality concerns.<sup>215</sup> In some cases, notably in Phase 1 trials, participants generally are not even suffering from the disease in question. People are also subject to the social desire to express appreciation for the efforts of their caregivers, and may politely inflate reports of improvement. At the same time, compliance in taking pills, recording journal entries, and showing up for appointments is reported to be a chronic problem<sup>216</sup> and can make data analysis challenging.<sup>217</sup> In addition, because subjects have the right to drop out of trials at any time for any reason,<sup>218</sup>

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*ing System*, 252 J. AM. MED. ASS'N 1030 (1984). Another study reported the much higher figure of 5%, but this is still a very small minority. Audrey Smith Rogers et al., *Physician Knowledge, Attitudes, and Behavior Related to Reporting Adverse Drug Events*, 148 ARCHIVES OF INTERNAL MED. 1598, 1598, 1600 (1988). This study also reported that “nearly half of physician respondents stated they were unaware that the FDA maintained a reporting system [at all].” *Id.* at 1599. Although awareness and reporting may have increased, the consensus view over the decades has been that only a small minority of adverse events are reported. See Adil E. Shamoo, *Adverse Event Reporting—The Tip of an Iceberg*, 8 ACCOUNTABILITY IN RES. 197, 197 (2001).

214. Sheila Weiss-Smith et al., *The FDA Drug Safety Surveillance Program: Adverse Event Reporting Trends*, 171 ARCHIVES OF INTERNAL MED. 591, 591 (2011).

215. Cf. Richard Titmuss, *The Gift of Blood*, 35 SOC'Y 88, 93 (1998) (“Over the past decade many studies . . . have incriminated the paid [blood] donor . . . as the major source of infection.”).

216. See, e.g., Graham Dunn & Els Goetghebeur, *Analysing Compliance in Clinical Trials*, 14 STAT. METHODS IN MED. RES. 325, 325 (2005) (“Clinical trials and noncompliance form two sides of one coin . . .”).

217. See Susan Armijo-Olivo et al., *Intent to Treat Analysis, Compliance, Drop-Outs and How to Deal with Missing Data in Clinical Research: A Review*, 14 PHYSICAL THERAPY REVIEWS 36, 45 (2009) (“[I]t has been shown through recent simulation studies that [the ‘per protocol’] and [‘as treated’ approaches] provide inappropriate results when dealing with missing data.”); Jane C. Lindsey & Nuala M. McGrath, *Interpreting Treatment Differences When Patients Drop Out of a Clinical Trial*, 12 AIDS PATIENT CARE & STDs 275, 276 (1998) (noting that the correlation between compliance and treatment effect “can make interpretation of treatment differences problematic”).

218. See 45 C.F.R. § 46.116(a)(8) (2012) (“[T]he subject may discontinue

data may be incomplete, which can similarly frustrate analysis.<sup>219</sup>

In contrast, patients participating in crowdsourcing will have a different and perhaps better-aligned mix of motivations. Most importantly, they will have a personal interest in the outcome of the “study” since, by virtue of their participation, they will normally be suffering from the disease in question. The sense of personal investment, described by one commentator as “hav[ing] a dog in the race,” has repeatedly been cited in explanation of the success of various crowdsourcing models.<sup>220</sup> Patient contributions are also likely to be vastly greater in volume, since anyone with an Internet-enabled cell phone anywhere in the world could potentially contribute. According to Pedro Domingos, a professor of computer science and engineering at the University of Washington who specializes in data mining, “a dumb algorithm with lots and lots of data beats a clever one with modest amounts of it,” at least “as a rule of thumb.”<sup>221</sup>

In the end, data quality problems will arise in any enterprise that involves data.<sup>222</sup> There is no question that a proposed crowdsourcing system that includes greater patient involvement must be prepared to address the data quality issues that will inevitably arise.

## 2. Laypersons May Be Unwilling or Unable to Participate

Some patients will be unwilling to contribute to the crowdsourcing of information for conditionally approved drugs.

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participation at any time without penalty or loss of benefits . . .”).

219. See A. Heyting et al., *Statistical Handling of Drop-Outs in Longitudinal Clinical Trials*, 11 STAT. MED. 2043, 2043 (1992) (“In longitudinal clinical trials, difficulties often arise due to patients *dropping out* of the trial . . .”). In particular, the reasons for drop-out can complicate analysis, and include both recovery and lack of improvement, among others. *Id.* at 2044.

220. Fox, *supra* note 113.

221. Pedro Domingos, *A Few Useful Things to Know About Machine Learning*, 55 COMM. ACM 78, 85 (2012); see also Alon Halevy et al., *The Unreasonable Effectiveness of Data*, IEEE INTELLIGENT SYS., Mar.–Apr. 2009, at 8, 9 (“For many tasks, once we have a billion or so examples, we essentially have a closed set that represents (or at least approximates) what we need, without generative rules.”).

222. See, e.g., David Wagner, *Google Flu Trends Wildly Overestimated This Year’s Flu Outbreak*, ATL. WIRE (Feb. 13, 2013), <http://www.theatlanticwire.com/technology/2013/02/google-flu-trends-wildly-overestimated-years-flu-outbreak/62113> (noting Google Flu Trends suggested a 10% nationwide infection rate, while the more accurate number from the Centers for Disease Control was 6%).

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To the extent that patients are unwilling to participate because they do not want to undertake the risks associated with new drugs, such unwillingness would itself vindicate the need for informed consent.

In other cases, however, there may be a lack of willingness or ability to participate that is not related to risk. Some patients may be less able to participate due to illiteracy, the absence of an Internet-enabled cell phone or computer, or simply the lack of time or interest to become involved. In these cases, it becomes important to distinguish between the ethical function and the information-gathering function of the proposed crowdsourcing model. All patients who desire to consume a newly approved drug must, for ethical reasons, consent to the risks. Labeling a drug as “conditionally approved” and encouraging the patient to contribute adverse event and other outcome data via an online crowdsourcing platform is almost certain to command the attention of the patient. Combined with an online consent form, the ethical function can therefore be fulfilled relatively quickly and easily.<sup>223</sup> In contrast, the data gathering function would require a greater level of involvement that could, depending on the drug, last for months or even years. Embedding the consent form within the crowdsourcing platform could facilitate participation, but it is to be expected that only a portion of consumers during the conditional approval period will fully contribute.

Nevertheless, there is reason for optimism. As noted above, patients have a vested interest in the safety and effectiveness of the drugs they take. An appropriately-designed crowdsourcing platform would allow patients to view aggregate (and appropriately anonymized) data contributed by others, satisfying the inherent desire for treatment-related information that suffering individuals naturally exhibit. At the same time, the platform would allow individuals to contribute their own data. While juxtaposing the presentation of data with the contribution of data might seem complicated from the perspective of existing clinical trial practice, this is what already occurs on established crowdsourcing platforms such as the rating systems of eBay or Amazon.com, where users can both view data entered by others and contribute their own ratings. Those rating

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223. For illiterate individuals or those who lack access to the Internet, such online consent might be facilitated at a doctor’s office or pharmacy computer where risks could be explained orally and a digital signature, in the form of an “X” if necessary, could be entered.

systems may not be perfect, but the success of those companies and others attest to the fact that even an imperfect system can be immeasurably useful.<sup>224</sup>

In addition, patients may be motivated to contribute to post-approval crowdsourcing by pride in authorship and the satisfaction of contributing to a public good, rather than by money. Such motivations seem to underlie the vast contributions to other crowdsourced public goods, such as Wikipedia.<sup>225</sup> It may also be possible to create opportunities for what has been termed “microattribution,”<sup>226</sup> where crowdsourcing participants are given credit—using a pseudonym or “handle,” if they like—for the data that they enter. Free-form comments entered by contributors about efficacy or safety might be labeled this way, for example. The not-for-profit nature of the crowdsourcing sponsor can also be important, since contributors may be more hesitant to contribute to a “public good” without compensation if the product of those efforts will be leveraged to fill a corporation’s coffers.<sup>227</sup> For this reason, the post-approval phase of drug evaluation should probably be administered either by a government affiliated non-profit or the government itself. MedWatch and other post-approval surveillance programs are already administered this way.<sup>228</sup>

It may also be possible to incentivize participation more directly. For example, insurance reimbursement could be augmented, or insurance premiums reduced, for those patients who enter complete data. The possibility of using insurance premium incentives to encourage insureds to take certain actions has long been reflected in automobile insurance industry practice, where premium discounts are made available for insureds who

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224. See James R. Wolf & Waleed A. Muhanna, *Feedback Mechanisms, Judgment Bias, and Trust Formation in Online Auctions*, 42 DECISION SCI. 43, 47 (2011) (summarizing research related to electronic feedback systems and concluding that “online reputation systems can be effective in reducing perceived transaction-specific risk due to information asymmetry”).

225. See generally Andrea Forte & Amy Bruckman, *Why Do People Write for Wikipedia? Incentives to Contribute to Open-Content Publishing*, PROC. GROUP, at 4 (2005), <http://jellis.org/work/group2005/papers/forteBruckmanIncentivesGroup.pdf> (“[C]ontributors often claim ownership of articles on their own user pages by creating lists of the articles for which they believe they ought to receive credit.”).

226. See *Crowdsourcing Human Mutations*, 43 NATURE GENETICS 279, 279 (2011).

227. *Following the Crowd*, *supra* note 111.

228. See *supra* Part II.C.



complete approved driver safety courses, for example.<sup>229</sup> The motivation for insurance companies to offer incentives is that the desired consumer action will, on average and in the long term, reduce the dollar value of claims that must be paid out. Coverage could even be made conditional on the contribution of data, a model that is already utilized by Medicare's "coverage with evidence development" (CED) program under which an "item or service is covered only when provided within a setting in which there is a pre-specified process for gathering additional data."<sup>230</sup> Existing programs such as these suggest the practicality of directly incentivizing individuals to participate in crowdsourcing.

### 3. Crowdsourcing Is Neither Randomized, Controlled, Nor Blinded

An obvious concern to the crowdsourcing of what essentially amounts to clinical trial data is that it may not produce useful information. Unlike clinical trials, crowdsourced information would be neither randomized, controlled, nor double-blinded. This is a significant reason for pause. However, concerns over the absence of these "gold standard" characteristics in post-approval data collection are substantially mitigated by the fact that, by the time crowdsourcing begins, the drug will have already undergone clinical trial Phases 1, 2, and 3. Under the current system, these trials generally (but not always) are randomized, controlled, and double-blinded. The primary purpose of crowdsourced information is therefore to supplement gold-standard testing, not replace it. In addition, the volume of crowdsourced data may be orders of magnitude larger than clinical trial data, potentially allowing detection of efficacy or risk characteristics that had gone undetected during clinical trials, such as effects on subpopulations or rare adverse events. The FDA would not rely solely on this information to approve additional indications, but it could influence the decision of

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229. See, e.g., *Auto Discounts Available in New York*, STATE FARM, [http://www.statefarm.com/insurance/auto\\_insurance/discounts/new-york.asp](http://www.statefarm.com/insurance/auto_insurance/discounts/new-york.asp) (last visited Nov. 25, 2013) (describing both a driver training discount and an accident prevention course discount).

230. CTRS. FOR MEDICARE & MEDICAID SERVS., GUIDANCE FOR THE PUBLIC, INDUSTRY, AND CMS STAFF: NATIONAL COVERAGE DETERMINATIONS WITH DATA COLLECTION AS A CONDITION OF COVERAGE: COVERAGE WITH EVIDENCE DEVELOPMENT, at III(5) (2006), available at <https://www.cms.gov/Medicare/Coverage/determinationprocess/downloads/ced.pdf>. The authority for the CED policy is based on 42 U.S.C. § 1395y(a)(1)(E) (2006).

drug sponsors to undertake particular Phase 4 trials, or of the FDA to require certain trials, and it could also affect subsequent trial design.

#### 4. Health Information Is Too Technical and Complex to Be Crowdsourced

Although health challenges might appear to be too technical or complex to be effectively crowdsourced, a number of existing and historic examples suggest that this is not the case.<sup>231</sup> Among these is the remarkable practice of health information crowdsourcing described by Herodotus who, as an historian writing in the fifth century B.C., has provided what must be one of the earliest recorded instances of crowdsourcing of any type:

[W]hen a man is ill they lay him in the public square, and the passers-by come up to him, and if they have ever had this disease themselves, or have known any one who has suffered from it, they give him advice, recommending him to do whatever they found good in their own case . . . .<sup>232</sup>

In the modern era, a project co-led by the World Bank and the Global Alliance for Vaccines and Immunizations utilized prize-based crowdsourcing to incentivize the development of a pneumococcal vaccine that was successfully rolled out in 2011.<sup>233</sup> Google-backed startup 23andMe.com is gathering massive amounts of genetic data directly from the public and inviting customers to contribute information that can clarify the role of genetics in disease.

While the crowdsourcing of treatment options and the development of a new pneumonia vaccine serotype provide evidence that crowdsourcing may have some place in the broader healthcare sphere, these examples do not speak directly to the feasibility of using crowdsourcing to evaluate the safety and efficacy of a given new treatment, i.e., to the crowdsourcing of clinical trials. However, a number of new organizations or platforms have begun to move into this space, providing early in-

231. See generally USING WEB 2.0 FOR HEALTH INFORMATION (Paula Younger & Peter Morgan eds., 2011) (compiling more than a dozen short articles exploring the use of blogs, wikis, RSS feeds, and other Web 2.0 technologies to, for example, support research (Chapter 5), identify health content for the developing world (Chapter 6), and support patient needs (Chapter 7)).

232. See VII TRANSACTIONS OF THE NEW YORK STATE MEDICAL ASSOCIATION 355 (E.D. Ferguson ed., 1890) (quoting Herodotus).

233. See Jonathan J. Darrow, *Essential Medicines: Why International Price Discrimination May Increasingly Be the Wrong Solution to a Global Drug Problem*, 39 J.L. MED. & ETHICS 291, 294 (2011).

sight into how clinical trial crowdsourcing might work. DIYgenomics, founded in 2010, bills itself as a “non-profit research organization founded . . . to realize personalized medicine through crowdsourced health studies and apps.”<sup>234</sup> CureTogether, an organization founded in 2008 that discarded the earlier name “Patient-Driven Research” as too long, is currently partnering with universities to conduct health-related studies using online methods for gathering data.<sup>235</sup> One of these, co-sponsored with Emory University, is seeking to determine whether online crowdsourcing of dermatological survey information can outperform clinic-based collection of such data.<sup>236</sup> A means to conduct crowdsourced clinical trials online has been provided by another company called Genomera, whose web-based platform allows third-party researchers to conduct clinical studies “at Internet scale.”<sup>237</sup> Researchers can create a study, enroll participants, automate protocol tasks and data collection, communicate with participants, and analyze results.<sup>238</sup>

With all of the new health information generated by the crowd, venues are needed to aggregate, organize, and distribute it. Treato seeks to synthesize the billions of online health-related discussions into usable information, including efficacy comparisons of similar medications.<sup>239</sup> The Journal of Participatory Medicine has emerged as a forum for the publication of research related to crowdsourced health research, among other topics.<sup>240</sup>

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234. *About DIYgenomics*, DIYGENOMICS, <http://www.diygenomics.org/about.php> (last visited Nov. 25, 2013).

235. *About CureTogether*, CURETOGETHER, <http://curetogether.com/blog/about> (last visited Nov. 25, 2013); *Ongoing Studies*, CURETOGETHER, <http://curetogether.com/blog/ongoing-studies> (last visited Nov. 25, 2013).

236. *Welcome to the Emory University School of Medicine Dermatology Study at CureTogether*, CURETOGETHER, <http://curetogether.com/emorydermstudy> (last visited Nov. 25, 2013).

237. *We're Crowd-Sourcing Health Discovery by Helping Anyone Create Group Health Studies*, GENOMERA, <http://genomera.com> (last visited Nov. 25, 2013).

238. *Clinical Studies at Internet Scale*, GENOMERA, <https://docs.google.com/spreadsheets/viewform?formkey=dEJNbm5ucERfVW91NjV5eDQ4cVJ6eWc6MQ#gid=0> (last visited Nov. 25, 2013).

239. *See What Millions of Patients Are Saying*, TREATO, <http://treato.com> (last visited Nov. 25, 2013).

240. J. PARTICIPATORY MED., <http://www.jopm.org> (last visited Nov. 25, 2013); see, e.g., Melanie Swan et al., *Citizen Science Genomics as a Model for Crowdsourced Preventive Medicine Research*, J. PARTICIPATORY MED., Dec. 23, 2010, <http://www.jopm.org/evidence/research/2010/12/23/citizen-science>

## B. LEGAL, ETHICAL, AND POLITICAL CHALLENGES

Despite the nascent forms of healthcare crowdsourcing just described, there remain a number of legal, ethical, and political challenges to the creation of generally applicable government-backed crowdsourcing model herein proposed. These concerns relate to statutory clinical trial standards, privacy, uncertainty communication, and opposition from various stakeholders.

## 1. Crowdsourcing Does Not Meet the Statutory Requirements of “Adequate and Well-Controlled” Studies

The scientific concern that crowdsourcing is not randomized, controlled, or blinded has an analogous legal concern, namely, that crowdsourcing cannot meet the standards for “adequate and well-controlled” studies that are at the core of the drug approval process.<sup>241</sup> Federal law currently provides that an application for a new drug cannot be approved unless the FDA finds that there is “*substantial evidence* that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof.”<sup>242</sup> “Substantial evidence” is in turn defined as “evidence consisting of *adequate and well-controlled investigations*, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved.”<sup>243</sup> The adequate and well-controlled investigations described in the statute refer to what are more commonly known as “clinical trials,” and are described in FDA regulations as generally involving randomization, blinding, and some form of control,<sup>244</sup> the familiar characteristics of the gold standard.<sup>245</sup>

Neither the regulations nor the statute, however, bar the utilization of crowdsourcing, not least because they apply only to refusing to approve an application for a new drug, while crowdsourcing would take place after (conditional) approval. Even were this not the case, the regulations are flexible on each element of the gold standard, indicating that randomization

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-genomics-as-a-model-for-crowdsourced-preventive-medicine-research.

241. 21 U.S.C. § 355(d) (2012).

242. *Id.* (emphasis added).

243. *Id.* (emphasis added).

244. 21 C.F.R. § 314.126(b)(2)(5) (2013).

245. Ted J. Kaptchuk, *The Double-Blind, Randomized, Placebo-Controlled Trial: Gold Standard or Golden Calf?*, 54 J. CLINICAL EPIDEMIOLOGY 541, 541 (2000).

and blinding are only “usually” required, that controls other than placebo control are acceptable in some cases, and that even “uncontrolled studies . . . will be considered on their merits.”<sup>246</sup> In any event they allow the Director of the FDA’s Center for Drug Evaluation and Research (CDER) to “waive in whole or in part any of the criteria” for an adequate and well-controlled investigation, including randomization, control, and blinding.<sup>247</sup>

Because crowdsourcing takes place after a conditional approval, but could help to clarify both efficacy and safety, it straddles the line between pre-approval clinical investigations and post-approval monitoring. As is evident from the discussion of the FDA post-approval monitoring programs above, the FDA has relatively broad discretion in deciding how best to monitor the market. Its existing methods range from spontaneous reports from patients or physicians (MedWatch), to Phase 4 clinical trials, to REMS (a program that itself exhibits considerable flexibility), to active data mining of databases maintained by partner organizations via a specially created Coordinating Center (Sentinel). The diversity of data gathering methods suggests that there is room to consider a crowdsourcing method that has the potential to combine the simplicity of patient-self reporting with the scope of Sentinel, while having the potential additional advantages transparency, real-time data, reduction in transcription errors, broad public participation, and low cost. At a minimum, the crowdsourcing model could alert the FDA to potential issues that could then be explored with more robust methods. This canary-in-the-coal-mine approach is already reflected in the MedWatch system as discussed above.<sup>248</sup>

## 2. Crowdsourcing Will Present Unacceptable Risks to Patient Privacy

The reporting, storage, and analysis of personal health information raises legitimate privacy concerns that must be considered in the creation and implementation of any health-related crowdsourcing system. In order to design a system that

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246. 21 C.F.R. § 314.126(e); *see also id.* § 314.126(b)(2)(i) (explaining that placebo-controlled studies “usually include[] randomization and blinding of patients or investigators, or both” (emphasis added)); *id.* § 314.126(b)(2)(iii), (iv) (allowing for “no treatment concurrent control” and “active treatment concurrent control,” instead of placebo control); *id.* § 314.126(b)(2)(v) (providing for the use of historical controls in “special circumstances”).

247. *Id.* § 314.126(c).

248. *See supra* Part II.C.3.

adequately protects patient privacy, it is important to focus on those aspects of privacy that matter most to the people whose privacy is at stake. Privacy concerns do not arise from the simple fact that information relates to health, but from a concern that sensitive and personal health information that an individual wishes to remain private might be used needlessly, wrongfully, or without authorization for a purpose of which the individual would not approve. Privacy rules exist primarily to protect the reasonable expectations of the individuals involved, and to prevent adverse action or outcomes of the wrongful use of that information.

One should therefore not assume that any system that aggregates the health information of individuals into a useful form that is publicly disclosed is inherently unworkable due to privacy concerns. In fact, existing laws and policies already aggregate health information of individuals and disclose it publicly. Clinical trial results aggregate what is in some cases very personal health information from hundreds or thousands of individuals, and make it available to the public as part of the patient package inserts that accompany prescriptions in paper form and which are also available online. For example, one patient package insert notes that of 199 people who took Ditropan (oxybutynin chloride), 15.1% experienced constipation.<sup>249</sup> Similarly, the FDA Adverse Event Reporting System (FAERS), which includes adverse event report forms submitted by individual patients, makes available to the public not only aggregated statistical information from these reports,<sup>250</sup> but also “raw data consisting of individual case safety reports extracted from the FAERS database.”<sup>251</sup> The FAERS website also makes clear that individual case safety reports can be obtained under the Freedom of Information Act.<sup>252</sup>

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249. FOOD & DRUG ADMIN., REFERENCE ID 3105471, DITROPAN, 9 tbl.3 (2012), available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/017577s038lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/017577s038lbl.pdf).

250. FDA Adverse Event Reporting System (FAERS) Statistics, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070093.htm> (last updated June 11, 2013).

251. FDA Adverse Event Reporting System (FAERS) (formerly AERS), U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm> (last updated Sept. 10, 2013).

252. *Id.*

The key to establishing a crowdsourcing system that adequately protects privacy is to combine informed contribution of data with mechanisms to ensure that information is not individually identifiable. Unlike the FAERS database, where public access to case reports requires technical knowledge of relational databases, the proposed crowdsourcing model would allow users to easily view aggregated data with respect to a particular pharmaceutical product. By viewing the aggregated data of others, consumers will have a good idea of how their information will be used even before signing the click-through privacy agreement and entering their own data. Anonymity could be assured by making available for public display only information that is not personally identifiable, to the extent that personally identifiable information must be entered at all.<sup>253</sup> Current regulations already require similar anonymizing with respect to the reporting of adverse drug events.<sup>254</sup>

Health-related privacy concerns have been addressed at length by the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA) which, along with its associated regulations, provides helpful guidance that could be used in the creation of a crowdsourcing system to ensure adequate protection of patient privacy.<sup>255</sup> The regulations allow certain uses of protected health information if consent<sup>256</sup> or authorization is obtained.<sup>257</sup> Additional flexibilities are contemplated with respect to the disclosure of protected (i.e., individually identifiable<sup>258</sup>) health information to public health authorities or others in connection with post-marketing surveillance or

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253. Names, social security numbers, and other personally identifiable information might need to be entered, for example, to ensure against fraudulent entries by pharmaceutical companies or their competitors who seek to boost (or detract from) the performance outcomes measured by the crowdsourcing platform. Even if the entry of such information is necessary, however, it could be segregated from the information that is displayed or publicly made available.

254. *See, e.g.*, 21 C.F.R. § 314.80(h) (2013) (“An applicant should not include in [adverse event] reports under this section the names and addresses of individual patients; instead, the applicant should assign a unique code number to each report, preferably not more than eight characters in length.”).

255. Health Insurance Portability and Accountability Act of 1996 (HIPAA), Pub. L. 104-191, 110 Stat. 1936.

256. 45 C.F.R. § 164.506(b) (2012).

257. *Id.* § 164.508; *see also* § 164.510 (allowing for use or disclosure of protected health information “provided that the individual is informed in advance of the use or disclosure and has the opportunity to agree to or prohibit or restrict the use or disclosure”).

258. *Id.* § 160.103.

tracking of FDA-regulated products.<sup>259</sup> The regulations also provide for liberal use of “de-identified information” and acknowledge the possibility that individually identifiable information could be de-identified yet be designed to be re-identifiable, if medically necessary for example, by the use of a code.<sup>260</sup> The de-identification provisions are particularly helpful for suggesting information that should not be made available to the public: names, address or zip code (the first three digits of zip codes can be used so long as the resulting geographic area contains more than 20,000 people), telephone numbers, email addresses, social security numbers, Internet Protocol address numbers, and any other data that presents more than a “very small” risk “that the information could be used, alone or in combination with other reasonably available information . . . to identify an individual.”<sup>261</sup> The detailed regulations of HIPAA would thus provide a useful starting point in addressing privacy concerns. Nevertheless, additional challenges must also be addressed, including difficulties in communicating uncertainty and opposition from various groups.

### 3. Uncertainty Cannot Be Adequately Communicated

An additional concern is that, outside the highly regulated structure of traditional clinical trials, participants in a crowdsourcing system could not adequately comprehend the risks that remain. This failure of understanding could take either of two forms. First, participants may not adequately appreciate that a drug that has been released to the public as “conditionally approved” by the FDA could nevertheless carry substantial risks including the risk of death. Yet this concern is no different than what exists under the status quo, and is the very problem that conditional approval combined with crowdsourcing is designed to solve. As discussed above, the establishment of “conditional approval,” oral risk disclosures by a prescriber, and written or visual disclosures on the product itself, combined with the act of visiting and contributing to an Internet-based crowdsourcing platform can only increase patient’s recognition of risk as compared to the current system.

The second failure, however, is that all of the additional disclosures, visual cues, and other warning signals might overshoot their goal, inducing patients to overestimate the risks

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259. *Id.* § 164.512.

260. *Id.* § 164.502(d)(2).

261. 45 C.F.R. § 164.514(b)(1)(i).



that remain. As a result, patients who could potentially benefit from treatments might forgo them out of fear. This is not just a theoretical problem: this is the very problem that has frustrated vaccination campaigns and associated disease eradication efforts for centuries, namely, that perceived risks are wildly out of proportion to actual risks.<sup>262</sup> Although providing numerical risk information to patients is an obvious solution, even this can be problematic. Studies in the European Union have shown that when patients are presented with drug risk information in either percentage or verbal terms, they tend to overestimate risk.<sup>263</sup> In any event, crowdsourcing is designed to develop risk information that does not yet exist, so that same information could not possibly be made available to consumers prior to their participation in the crowdsourcing platform.

Nevertheless, there are several reasons that concerns of risk overestimation are a manageable in the case of crowdsourcing. First, unlike vaccination campaigns, which often involve inducing individuals who are not ill to take a medicine that solves no existing discomfort, crowdsourcing would occur in most cases only after an individual voluntarily presents at the doctor's office with a problem significant enough to motivate the visit. Second, the user-friendly presentation of aggregated data that is part of the crowdsourcing system would itself help to educate patients about the potential risks and benefits. Improved understanding of a drug's risk/benefit profile is, after all, the major objective of crowdsourcing. Summary results from pre-approval clinical trials could also be made accessible in a user-friendly format as part of the crowdsourcing

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262. See Martin Kaufman, *The American Anti-Vaccinationists and Their Arguments*, 41 BULL. HIST. MED. 463, 471 (1967) (noting the professed belief that vaccination caused "scrofula, cancer, and innumerable other ills" and "spread smallpox on an epidemic scale" (quoting Edward Jenner)); Robert M. Wolf & Lisa K. Sharp, *Anti-Vaccinationists Past and Present*, 325 BRIT. MED. J. 430, 431 (2002) (noting the long history of objection to vaccination, based in part on parents' beliefs that vaccination was not efficacious or safe). Similarly, the belief that vaccination causes autism, based on a 1998 Lancet article, was subsequently debunked, renounced by most of its co-authors, and the article retracted by the publisher. See Claudia Wallis, *Debunked*, TIME, Feb. 15, 2010, at 18.

263. See P. Knapp et al., *Perceived Risk of Medicine Side Effects in Users of a Patient Information Website: A Study of the Use of Verbal Descriptors, Percentages, and Natural Frequencies*, 14 BRIT. J. HEALTH PSYCHOL. 579, 580 (2009) (citing studies); see also Moore & McQuay, *supra* note 39, at 42 (reporting study results showing that patients find it challenging to understand risk levels when presented in words, e.g. "very common," and even more difficult to understand risk levels when presented in numbers).

platform. Third, unlike vaccines, the effectiveness of most new drugs does not approach anywhere near 100%, and so a failure to consume these medicines has an arguably far smaller negative impact on health. Moreover, even in those unfortunate cases where the failure to take a medicine does substantially impair the health the individual, it generally would not threaten the health of hundreds or thousands of other individuals, as could the failure to be vaccinated.

Moreover, an overestimation of risks is less likely to occur if appropriate, clearly presented information is made available to patients. For example, consent forms might summarize in table format the tiny percentages of serious adverse events occurring in recently approved drugs, or even in familiar over-the-counter drugs such as aspirin, in order to provide a baseline of risk. The European Union (EU) studies cited above addressed an EU guideline that recommended presenting risk information by the use of five qualitative descriptions: very rare, rare, uncommon, common, very common. Given that these words are entirely devoid of precision, the study findings that patients were unable to divine their percentage equivalents is hardly surprising, if not particularly expected. In one study, patients quite reasonably estimated, on average, that “very common” meant an incidence of approximately 65%, but under the European Union guidelines this label could have indicated a frequency of only around 10%.<sup>264</sup> Doctors were similarly unable to understand the EU guidelines, estimating that “common” meant around 25%, while the guidelines translated this as meaning as little as 1%.<sup>265</sup> While these studies suggest that communication of risk information may require some forethought, they should not be read to suggest that efforts at communicating risk are futile.

One might also look to history for reassurance that the sky will not fall if additional cautionary disclosures are made. According to one commentator, “[w]hen informed consent as an official doctrine was first mandated by federal regulation in the early 1980s, many researchers in the scientific community worried that detailing the potential risks of participation would frighten away prospective human subjects.”<sup>266</sup> Despite theorized concerns, the number of clinical trials more than doubled be-

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264. Berry et al., *supra* note 39, at 853–54.

265. Knapp et al., *supra* note 263, at 581.

266. FISHER, *supra* note 51, at 169.

tween 1988 and 1998,<sup>267</sup> and by late 2013 there were over 138,000 clinical trials registered at ClinicalTrials.gov.<sup>268</sup>

Despite these figures, it is reasonable to expect some decrease in consumption as a result of better risk disclosure. A small decrease in the number of patients willing to try a new medicine, however, is desirable to the extent that patients who have the greatest risk aversion should be free to decline treatment on the basis of accurate and complete information. Declining conditionally approved treatment is particularly appropriate for drugs for which there are equally effective and time-tested substitutes, as was the case with Vioxx.

#### 4. Opposition from Industry and Physicians

The presence of conditional approval, special symbols and other warnings may deter some patients from accepting a medication, and some doctors from prescribing it, a result that engender opposition from sponsoring pharmaceutical companies. Industry opposition can be expected to be all the more intense because reduced sales immediately following approval have the greatest effect on the lifetime revenues of a drug. Revenues during the initial years are worth more not only because of the time value of money and the discounting of future revenue, but also because early sales can build brand loyalty and increase patient (and doctor) switching costs.

It is not only pharmaceutical companies that are likely to resist change. Physicians may be concerned that, in some cases, declining treatment may not be in the best interests of patients, or that patients may irrationally overvalue the magnitude of risk and simultaneously undervalue the benefit of the drug. More cynically, physicians might worry that providing patients with additional information about a drug can adversely affect the doctor-patient relationship, upsetting the power dynamic between physicians and their patients and leading doctors to experience an erosion of the value of their medical advice.

For a number of reasons, these hypothesized concerns of pharmaceutical companies and physicians are insufficient to justify preservation of the status quo. From a policy perspec-

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267. David L. Sackett & John Hoey, *Why Randomized Controlled Trials Fail but Needn't: A New Series Is Launched*, 162 CANADIAN MED. ASS'N J. 1301, 1301 (2000).

268. *Trends, Charts, Maps*, CLINICALTRIALS.GOV, <http://www.clinicaltrials.gov/ct2/resources/trends#RegisteredStudiesOverTime> (last visited Nov. 25, 2013).

tive, any hypothesized fear that additional risk disclosure would lead patients to irrationally overvalue risk and undervalue benefit ignores the evidence that patient bias currently tends heavily in the other direction.<sup>269</sup> To the contrary, then, additional disclosure would help to right current patient misperceptions of risk and value. Nor is there any basis in law for denying patients ready access to relevant and truthful risk information. As the Supreme Court has stated:

[The government does not have] an interest in preventing the dissemination of truthful commercial information in order to prevent members of the public from making bad decisions with the information. . . . “There is, of course, an alternative to this highly paternalistic approach [of preventing the dissemination of truthful information]. That alternative is to assume that this information is not in itself harmful, that people will perceive their own best interests if only they are well enough informed, and that the best means to that end is to open the channels of communication rather than to close them . . . .”<sup>270</sup>

Although the Supreme Court was speaking in the First Amendment context, it is similarly paternalistic and wrong in the present context to withhold accurate information from patients in order to prevent them from making bad decisions. In addition, providing patients with accurate information is efficient in an economic sense: the patient, not the doctor, knows the patient’s own level of risk aversion or risk preference. By providing the patient with more information on which to base a decision, those patients who are more risk averse will self-select to decline the medication. Doctors cannot know the level of risk aversion of their patients better than the patients themselves do.<sup>271</sup>

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269. See, e.g., Joel J. Davis, *Riskier than We Think? The Relationship between Risk Statement Completeness and Perceptions of Direct to Consumer Advertised Prescription Drugs*, 5 J. HEALTH COMM.: INT’L PERSP. 349, 365 (2000) (noting an “FDA/Prevention Magazine finding that a majority of consumers believe that DTC advertising makes the advertised drugs appear harmless”); Schwartz et al., *supra* note 99, at 524 (explaining that patients tend to overestimate efficacy by a factor of ten or more); cf. Peter H. Schwartz & Eric M. Meslin, *The Ethics of Information: Absolute Risk Reduction and Patient Understanding of Screening*, 23 J. GEN. INTERN. MED. 867, 867 (2008) (“[R]esearch shows that individuals overestimate the benefits and underestimate the possible risks of [medical] screening.”).

270. *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 374–75 (2002) (quoting *Va. State Bd. of Pharm. v. Va. Citizens Consumer Council*, 425 U.S. 748, 770 (1976)).

271. Adopting the more expansive “patient-centered” duty to inform—which requires the disclosure of provider-specific information, such as a particular physician’s familiarity with a surgical tool—does not resolve this concern because although it addresses the doctor’s particular circumstances it

More generally, the great irony of crowdsourcing is that its potential to offer substantial improvement over existing methods may constitute the very reason that it is opposed. A number of high-profile examples illustrate the reluctance of businesses or institutions to welcome crowdsourcing even when there is dramatic potential for greater efficiency. Napster's vastly more efficient (if illegal) means of music distribution by a suddenly-enabled public led to desperate attempts by the music industry to shut down file-sharing; legal online distribution was only reluctantly embraced by the industry years after the potential had become obvious.<sup>272</sup> Despite the meteoric rise of Wikipedia's crowdsourcing model, which has rendered virtually forgotten the traditional icons of encyclopedic information such as *World Book* and *Collier's*, the world's most renowned English-language encyclopedia—the Encyclopedia Britannica—did not begin to consider a new, more participatory approach until 2008.<sup>273</sup> Apple Computer's refusal to crowdsource third-party applications when it introduced the Macintosh personal computer in 1984, at a time when IBM was open to such collaboration, led to a squeeze in Apple's market share from which it has still not recovered.<sup>274</sup> Apple did not make the same mistake with its iPhone, which is open to third-party developers.<sup>275</sup>

These examples should not be read to suggest that crowdsourcing will always produce better results than closed, tightly-controlled systems, but they do reflect a tendency toward skepticism and reluctance when it comes to embracing

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does not speak to the particular patient's level of risk-aversion. See Wlosinski v. Cohn, 713 N.W.2d 16, 24–25 (Mich. Ct. App. 2005). See generally Robert Gatter, *Informed Consent Law and the Forgotten Duty of Physician Inquiry*, 31 LOY. U. CHI. L.J. 557 (2000) (arguing that informed consent law should take into account the treatment goals of individual patients, but does not).

272. See generally Erin Anderson et al., *Strategic Channel Design*, 38 SLOAN MGMT. REV. 59, 59 (1997) (“Changes in distribution channels come slowly, partly because the inherent complexity of the many links that connect value-adding functions in a channel obscures the need for change. Distribution channels are also dauntingly rigid and stable because of powerful, persistent inertia.”).

273. See NANCY E. WILLARD, *CYBER SAVVY: EMBRACING DIGITAL SAFETY AND CIVILITY* 74 (2012). Britannica ceased publishing its print edition in 2010. Tom McCarthy, *Encyclopedia Britannica Halts Print Publication After 244 Years*, GUARDIAN (UK), Mar. 13, 2012, <http://www.guardian.co.uk/books/2012/mar/13/encyclopedia-britannica-halts-print-publication>.

274. See JAN RUNE HOLMEVIK, *INTER/VENTION: FREE PLAY IN THE AGE OF ELECTRACY* 43–44 (2012).

275. *Steve Jobs Confirms Native iPhone SDK by February*, APPLE INSIDER (Oct. 17, 2007, 11:00 AM), <http://appleinsider.com/article/?id=3317>.

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collaboration in a way that may disrupt existing models. This reticence may be more pronounced the greater the perceived risk of loss of control, the more significant the required shift in industry culture or structure, and the larger the potential loss of profits. All of these factors are present with the crowdsourcing of clinical trials, and opposition is therefore likely to come from many sides. Even if crowdsourcing is limited to post-approval studies, it may chip away at a potentially significant source of income for physicians and contract research organizations (CROs), and reveal a lessened need for participant recruiters, site administrators, and monitors. Conditional approval and online participation in drug evaluation will produce greater awareness of risks, and may lead to reduced sales to the disappointment of drug companies. Doctors, pharmaceutical companies, and the FDA, who currently exercise near-oligopoly power over a drug's perceived utility and risks, may fear a loss of collective control as the public comes to have a greater role in the data generation and decision-making process. This shift in the center of gravity from government regulators, multinational companies, and a learned medical elite to ordinary citizens will threaten engrained cultural norms that such health matters are beyond the capacity of an untrained public. In short, crowdsourcing post-approval clinical trials would constitute the regulatory equivalent of a disruptive technology.<sup>276</sup>

That change will upset expectations of entrenched interests is not, of course, a justification for rejecting a new approach. Instead, crowdsourcing should stand or fall based on the extent to which it can more effectively and efficiently serve the purposes of clinical trials. As argued above, crowdsourcing has the potential to provide better notice to patients about risks, closing a troublesome loophole in existing informed consent requirements. The cost savings of disintermediating CROs, physicians, and other players may be significant. It is true that uncertainty remains as to the quality of data that would be produced from a crowdsourcing system. Yet, as argued above, there is reason to believe that data could be as good or better than under the current financially-motivated system. It should be recalled that similar concerns were expressed with the quality of volunteer-contributed Wikipedia ar-

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276. See Joseph L. Bower & Clayton M. Christensen, *Disruptive Technologies: Catching the Wave*, 73 HARV. BUS. REV. 43, 43–45 (1995).

ticles, but ultimately rejected.<sup>277</sup> Moreover, as data quality problems are identified, as they inevitably will be, an Internet-based system can be centrally modified to address them.<sup>278</sup>

### CONCLUSION

Transitioning from the limited crowdsourcing that already occurs today to a more comprehensive process that involves the input of large numbers of widely dispersed patients is the next natural—and perhaps inevitable—step. Under current clinical trial practice, patients are already exposed to risks and misunderstood benefits once new drugs are approved by the FDA. The proposed system merely attempts to capture the data that is already being generated post-approval, but that in most cases is never recorded, analyzed, or made available for the benefit of others. More importantly, crowdsourcing clinical trials merits serious consideration because of the ethical problem that it addresses. It helps ensure informed consent because the act of self-reporting efficacy and side effect information will itself serve as a clear indication that the drug is still under study. In so doing, it gives patients a greater role in their own health care. At the same time, it helps to generate a valuable public good: accurate and timely information about the safety and efficacy of new drugs. Yet there is one more compelling reason to crowdsource clinical trials, namely, that it is now far easier and less expensive to collect massive amounts of data directly from patients. Although the Internet has been developing rapidly since at least the mid-1990s, only in the last few years have patients around the world had the ability to input benefits and side effects directly into their computers, phones, or other electronic devices.

The extent to which crowdsourcing will supplant existing clinical trial practice and the exact form that it will take remain to be seen. What is perhaps more certain is that as drug development costs continue to climb into the stratosphere and the need to rein in healthcare spending takes on increased urgency, something will have to change. The instant proposal is a

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277. See Jim Giles, *Internet Encyclopedias Go Head to Head*, 438 NATURE 900, 900 (2005) (noting that numerous errors were found in both Wikipedia and Britannica, but that “the difference in accuracy was not particularly great”).

278. See generally Yan (Lindsay) Sun & Yuhong Liu, *Security of Online Reputation Systems: The Evolution of Attacks and Defenses*, 29 IEEE SIGNAL PROCESSING MAG. 87 (2012) (describing both attack strategies and defense mechanisms).

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relatively modest one that involves crowdsourcing of only the post-approval phase of drug evaluation, but it is easy to imagine a more expanded version. Because existing clinical trial practice already involves human testing, the real question is not whether the public should be used as test subjects but how to most effectively minimize risk, ensure informed consent, and collect useful data. That a networked infrastructure and distributed patient input will play a greater role in this process is almost certain. Indeed, as we have seen it is already occurring both within and outside of the FDA. Given the historically glacial pace of change at the FDA and the relative infancy of both the Internet and of its use in crowdsourcing, it is likely that substantial beneficial