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**Clinical Trial 2.0: Can Health 2.0 Transform the FDA Drug
Approval Process?**

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Abstract

Historically, patient activism has played a great part in shaping the drug approval process. Today, aided by developing web technologies, patients are once again seeking increased involvement in their medical care. Their desire to be involved is manifesting in the development of patient-run clinical trials, where patients, with the aid of online health-oriented social networks, are testing the safety and effectiveness of new drugs. While these trials are not currently recognized as valid, scientifically rigorous endeavors and are not accepted by the FDA as evidence of the safety and effectiveness of new drugs, small changes in trial structure can make these patient initiatives a meaningful part of the drug development process. This paper examines the structure and challenges of patient-run clinical trials in the context of the drug development and approval process and suggests an point-of-care design alternative as a way to address the concerns aroused by such patient-led studies. Ultimately, the paper concludes that the enormous social value of such studies should not be ignored, and that the medical, scientific, and regulatory communities should work with patients in helping them designing reliable studies responsive to their needs that can become a meaningful part of the drug development and approval process.

Introduction

Drug approval in the United States has been heavily shaped by patient activism. A product of the twentieth century, relevant legislation and Food and Drug Administration (FDA) regulations resulted in increasingly tight restrictions on marketing new drugs until the 1980s, when patients' desire to take charge of their medical care and their concern with the length of the approval process led to a rapid reversal in direction. Prior to the twentieth century, drug regulation was in the purview of state and local governments.¹ The first major federal legislation governing the marketing of new drugs was the Food and Drug Act of 1906. The Act did not require pre-market approval and manufacturers could market a new drug as long as it complied with official standards for strength and purity.² Following the Elixir Sulfanilamide incident in 1937,³ Congress passed the Federal Food, Drug, and Cosmetic Act (FD&C Act) of 1938. The new law required that a manufacturer show that the drug is safe prior to marketing.⁴ FDA review, however, remained minimal as the law required pre-market notification rather than approval.⁵ As long as a manufacturer notified the FDA of its intent to market a new drug and the Agency did not respond within sixty days, the drug could go on the market. The next act of Congress came in

¹ For a detailed account of drug regulation history in the United States, see Jeffrey Levi, *Unproven AIDS Therapies: The Food and Drug Administration and dDI*, in BIOMEDICAL POLITICS, 9, 11 (Kathi E. Hanna ed., 1991).

² *Id.*

³ In 1937, a pharmaceutical company in Tennessee created a new, liquid version of sulfanilamide, a drug used to treat streptococcal infections. The company created the liquid version by dissolving the known drug in diethylene glycol—a solvent that is commonly used in antifreeze and was quickly revealed to be highly toxic to humans. Since the Food and Drug Act of 1906 did not require pre-market safety testing, however, the new formulation's safety was never assessed before the drug was released on the market. About a month after the release of the drug, reports of deaths linked to its use began to circulate. Although the FDA acted quickly to retrieve all outstanding prescriptions of the drug, more than 100 people, mostly children, had died before the drug was completely recalled. See Sharon B. Jacobs, *Crises, Congress, and Cognitive Biases: A critical Examination of Food and Drug Legislation in the United States*, 64 FOOD & DRUG L.J. 599, 604, 2009.

⁴ Levi, *supra* note 1.

⁵ *Id.*

1962 and was a response to the thalidomide crisis in Europe.⁶ While the drug's effects in the United States were minimal since the FDA declined to approve it, between 10,000 and 20,000 children in 46 countries suffered severe deformities as a result of the medicine. Congress responded by enacting the Kefauver amendments to the FD&C Act, requiring that manufacturers demonstrate the safety and efficacy of drugs prior to marketing.⁷ The Act also instituted pre-market approval by the FDA. This requirement led to the development of lengthier and more complex clinical trials, typically comprising three phases, and weeding out the vast majority of tested compounds.⁸

Clinical trials attracted much attention and came under intense political scrutiny in the 1980s as the length and complexity of the drug approval process became increasingly frustrating for patients. Particularly, FDA was encountering difficulties in striking a balance between protecting patient safety by demanding comprehensive clinical trial data prior to approval and getting potentially life-saving drugs to the market quickly enough. Patient advocacy organizations, seeking to empower patients and involve them in their own care, expressed concern with the lack of access to medicines during the lengthy testing process, the failure to include women and minorities in clinical trials, and the scarce access to trial results during and after testing.⁹ The AIDS community gave rise to the most vocal patient organizations at the time and the pressure these activists created transformed the nature of clinical trials as well as the

⁶ Thalidomide, developed by a small German company, was originally marketed as an antibiotic. Although it disappointed as such, the drug became known for its sedative properties and quickly became a blockbuster. Various forms of the compound were used to treat nervousness, coughs, and most notably, nausea due to pregnancy. In 1961, reports of a significant increase in birth defects linked to the use of thalidomide began to circulate. Women who had used the drug during pregnancy frequently gave birth to brain damaged and severely deformed children. Due to the discrepancy between the prevalence in side effects in animal studies and human use, the drug was never approved in the United States, however over 2.5 million tablets were distributed to more than 1,000 physicians and patients before trials were halted in 1962. *See Jacobs, supra* note 3, at 608-09.

⁷ *Id.* *See also* Levi, *supra* note 1

⁸ *Id.* at 12-13.

⁹ *See* ARTHUR A. DAEMMICH, PHARMACOPOLITICS: DRUG REGULATION IN THE UNITED STATES AND GERMANY, 96-101(2004).

institutional setting for access to experimental drugs, showing how actively involved patients can be in their own care.

FDA regulations at the time required that new drug applicants submit data from two well-controlled clinical trials. AIDS patients challenged trial structure by questioning selection criteria, the use of placebo control, and the prohibition against taking other drugs while participating in trials.¹⁰ In addition to engaging in direct conversation with regulators, patients challenged the clinical trial landscape by carrying out trials of their own. Community-based trials became increasingly popular, while patients formed “buying clubs,” making experimental compounds available to anyone who wanted them.¹¹ In effect, activists forced regulators to acknowledge clinical trials as a way to access life-saving medicine and to adjust the drug approval process accordingly.¹² Profound changes in clinical trial structure followed. In 1988 the FDA announced a change in regulations allowing the use of historical data rather than denying some patients the use of a potentially effective drug in a trial involving placebo or other treatment.¹³ Also in response to pressure from patients, the FDA created a “parallel track,” allowing patients who were otherwise unable to participate in a full clinical trial to access to the experimental drug.¹⁴ FDA also sped up the clinical trial process by beginning to use surrogate endpoints in assessing the effectiveness of AIDS drugs instead of relying exclusively on long-term survival.¹⁵

¹⁰ *Id.*

¹¹ See Gina Kolata, *Private Doctors Testing AIDS Drugs in Novel Approach*, N.Y. Times, July 9, 1989 at A1 (discussing the prevalence of community-based trials of AIDS medications). See also PETER S. ARNO AND KARYN FEIDEN, *AGAINST THE ODDS: THE STORY OF AIDS DRUG DEVELOPMENT, POLITICS, AND PROFITS*, 71-73, 207-15 (1992) (discussing underground tests of trichosanthin, a Chinese cancer and abortion drug also known as Compound Q, thought to be a potential cure for AIDS).

¹² See generally Thomas C. Merigan, *You Can Teach an Old Dog New Tricks: How AIDS Trials are Pioneering New Strategies*, 323 NEW ENGLAND J. MED. 1341 (1990) (describing the structural changes taking place in AIDS clinical trials as a result of the efforts of the AIDS Clinical Trials Group—a partnership of patients, advocates, and clinical investigators).

¹³ Daemmrich, *supra* note 9, at 98.

¹⁴ *Id.* See also Levi, *supra* note 1 (exploring the emergence of the “parallel track” system and its implications for the drug approval process).

¹⁵ Merigan, *supra* note 12, at 1342.

Additionally, activist pressure led pharmaceutical companies and physicians to start designing trials with broader entry criteria and make efforts to give participants more information on interim findings.¹⁶

Patient activism in the 1980s and 1990s transformed the nature of clinical trials. Patients sought greater involvement in their care, seeking the choice to undertake a course of treatment even if it has yet to receive FDA approval. The advocacy tactics employed by the AIDS community were extraordinarily effective in achieving regulatory and cultural reforms and allowing patients to have a strong voice in their treatment. Yet, the reforms in the 1980s did not end the debate. Despite these regulatory changes, terminally ill patients are once again becoming discontent with what they perceive to be a sluggish and rigid drug approval system that does not focus sufficiently on allowing access to life-saving medication. A new wave of patient activism is on the rise, and it brings the potential for further productive and lasting regulatory changes.

One of the factors that allowed patient activism in the 1980s and 1990s to be a successful reform tool was that the main actors—members of the AIDS community—were unusually unified by the gravity of the crisis they were facing. This allowed individuals to organize easily and efficiently, and to exert collective pressure that the regulatory system of the time could not withstand. While today's patient activism is not brought on by such a crisis, emerging technologies are rapidly fulfilling the unifying role necessary to make patients and advocates participants in the regulatory process.

The advent of advanced communications technologies brought on by Web 2.0 developments have resulted in the formation of patient communities focused around common conditions, interests, and causes. Health-oriented social networks are allowing patients from around the globe to connect with others with similar conditions, discuss treatment options and

¹⁶ Daemmrich, *supra* note 9.

ideas, and harvest collective knowledge, while seeking to become more involved in their own treatments. The slow development of new treatments and therapies is once again coming to the forefront of drug regulation, and frustrated patients, supported by online communities, are taking matters into their own hands.

A striking example of patient activism is the advent of patient-run clinical trials. Recently, patients have attempted, with varying success, to perform underground trials of promising treatments with very limited medical involvement.¹⁷ This development, coupled with the capabilities that new technologies provide, presents a great opportunity for drug regulators and the pharmaceutical industry to once again improve the drug approval process. Drug approval is currently an incredibly costly and lengthy affair. Recent estimates suggest that the development of a new drug requires between ten and fifteen years and costs between \$802 million and \$2 billion.¹⁸ Most of these costs are incurred during the clinical trial stage. The price of performing several phases of clinical testing, involving sometimes thousands of patients in varying geographic locations,¹⁹ has been estimated at \$467 million,²⁰ in addition to \$97 million²¹ for post-release monitoring upon which FDA approval is sometimes conditioned.

If the medical community can make effective use of newly developed technologies and increased patient involvement, drug development costs may be significantly reduced and approval time shortened, while allowing patients necessary access to potentially life-saving medicines. While patient-run clinical trials have been largely underground and unsupervised

¹⁷ See e.g., Catherine Arnst, *Health 2.0: Patients as Partners*, Businessweek, December 4, 2008 (exploring a lithium carbonate patient-run trial on the PatientsLikeMe website); Helen Pearson, *Cancer Patients Opt for Unapproved Drug*, 446 NATURE 474 (2007) (exposing the use of an unapproved small molecule by cancer patients).

¹⁸ Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 141, 167 (2003). See also Mark S. Boguski et al., *Repurposing with a Difference*, 324 SCIENCE 1394, 1394-95 (2009) (analyzing the cost of drug development).

¹⁹ See PETER BARTON HUTT ET AL., FOOD AND DRUG LAW: CASES AND MATERIALS, 624-98 (3d ed. 2007) for a detailed description of the FDA regulatory process.

²⁰ DiMasi, *supra* note 18, at 165.

²¹ *Id.* at 172-73.

affairs to date, therefore yielding no data that the FDA is willing to consider, they can be re-designed in a scientifically rigorous way sufficient to collect the safety and effectiveness data needed for approval and may supplement, or even entirely replace, the expensive and cumbersome company-run trials.

This paper explores the potential of patient-run clinical trials to transform the drug development process. Part I of the paper discusses the technological developments that have led to increased patient interest and involvement in their medical treatment. It focuses on the development and function that health-oriented social networks have played in inciting patient activism and explores the functionality that these networks have made available to their users. This part also examines two examples of patient-run trials as well as the concerns that these trials have raised in the scientific and medical community.

Part II of the paper focuses on the regulatory side of the drug development process, examining FDA requirements for approval, the necessary safety and effectiveness showing, as well as the structure of clinical trials that FDA currently finds acceptable in making that showing. Part III examines the costs and benefits to society of patient-run clinical trials and offers suggestions in resolving the issues that such trials present. The section suggests ways for restructuring the trials in order to make them scientifically rigorous and allow them to fit more comfortably into the FDA regulatory framework. Part IV offers concluding remarks.

I. Health 2.0 and Patient-centered Medicine

Traditionally, healthcare in the United States has conformed to a top-down model: doctors have served as a source of information, and primary decision-makers, while relatively uninformed patients have passively followed doctors' orders without having much real input in

their treatment.²² Technological advances, however, are making great strides in empowering patients and allowing them to take charge of their medical care.²³ Specifically, communications capabilities resulting from the use of Web 2.0 technologies are giving patients the opportunity to easily interact with others with similar conditions, allowing them to harness collective knowledge and become informed about their illnesses.²⁴ Patients can also easily access accurate and up to date medical information, and even personally track the progression of their disease and assess the effectiveness of various treatments.²⁵ As a result, duties that have traditionally belonged strictly to the physician are being democratized.

Health 2.0²⁶, as the recent phenomenon has come to be known, is characterized by “the use of social software and its ability to promote collaboration between patients, their caregivers, medical professionals, and other stakeholders in healthcare.”²⁷ The key driving force is the belief that patients should have greater insight and input into the medical information that they produce. Using available tools on the Internet, thousands of patients are choosing to take an active role in their medical care every day.²⁸

²² Catherine Arnst, *Health 2.0: Patients as Partners*, BUS. WK., December 4, 2008.

²³ *Id.*

²⁴ For a discussion of Web 2.0 technologies' effect on patient care, see Melanie Swan, *Emerging Patient-Driven Health Care Models: An Examination of Health Social Networks, Consumer Personalized Medicine and Quantified Self-Tracking*, 6 INT'L J. ENVTL. RES. PUB. HEALTH, 492, 495 (2009); JANET SARASOHN-KAHN, CAL. HEALTHCARE FOUND., *THE WISDOM OF PATIENTS: HEALTH CARE MEETS ONLINE SOCIAL MEDIA* (2008). See also Arnst, *supra* note 22.

²⁵ Swan, *supra* note 24. See also Jamie Heywood, Chairman, PatientsLikeMe, TEDMED 2009 Presentation: The Big Idea My Brother Inspired (Oct. 2009), available at http://www.ted.com/talks/jamie_heywood_the_big_idea_my_brother_inspired.html.

²⁶ A closely related term, Medicine 2.0, is also frequently used in literature. Because of the ever-evolving nature of the field, academics and practitioners have not reached a consensus on the exact parameters of either term, so the two tend to be used interchangeably. See generally Benjamin Hughes, Indra Joshi, and Jonathan Wareham, *Health 2.0 and Medicine 2.0: Tensions and Controversies in the Field*, 10 J. MED. INTERNET RES. e23 (2008).

²⁷ Sarasohn-Kahn, *supra* note 24, at 2.

²⁸ Recent studies indicate that as of 2008 the Internet is rivaling physicians as a source of health information. Between sixty and eighty percent of Americans use the tools available online to find health information. See Sarasohn-Kahn, *supra* note 24, at 3. See also Letter to the Editor, *The Power of Social Networking in Medicine*, 27 NATURE BIOTECHNOLOGY 888, 890 (2009).

An aspect of the Health 2.0 revolution with profound implications for medical care has been the formation of health-oriented social networks.²⁹ Health-oriented social networks are websites similar to Facebook and MySpace, thematically organized around a variety of health-related topics.³⁰ A network can be general, containing information about a wide variety of ailments, or specific—focused on one or a few related conditions.³¹ There are several services commonly offered by health-oriented social networks, including emotional support and information sharing, virtual contact with physicians and healthcare professionals, quantified self-tracking, and access to clinical trials.³² Each website may offer one or a combination of these services.³³

The most basic service found on the majority of health social networks is emotional support and information sharing. Patients can find information relevant to their conditions, ranging from quantitative and qualitative data posted by other users with similar ailments, to research citations.³⁴ By visiting these websites and becoming a part of the online communities, patients experience emotional support in knowing that they are not alone in their suffering and also by actively doing something—creating a profile, sharing information, educating themselves about their condition—to take charge of their health.³⁵ Additionally, by participating in such health-oriented communities, patients are able to take advantage of the collective knowledge of the group, which is often “smarter than its smartest members.”³⁶

²⁹ Sarasohn-Kahn, *supra* note 24, at 3.

³⁰ Swan, *supra* note 24, at 495.

³¹ *Id.*

³² *Id.*

³³ *Id.* at 501.

³⁴ *Id.* at 496.

³⁵ *Id.*

³⁶ Sarasohn-Kahn, *supra* note 24, at 5.

A second service offered by health-oriented social networks is the ability to interact with physicians online.³⁷ Services can be free or fee-based and patients can pose questions to specific doctors or the medical community at large.³⁸ The inquiries can be public, and therefore accessible to all community members, or private, such that only the patient posing the question and the physician to whom the question is addressed have access to the exchange.³⁹ The willingness of physicians to participate in such patient care is quite surprising. The common belief has been that doctors would not be willing to participate in a healthcare model of that eliminates face to face contact with patients for fear of legal repercussions. However, in reality many doctors are willing to answer patients' questions, recommend treatments, and even provide tentative diagnoses (accompanied by the appropriate disclaimers) using health-oriented social networks, and are reaping reputational and other benefits as a result.⁴⁰ This informal doctor-patient interaction outside of the sterile environment of the doctor's office is making patients active participants in their care, and transforming the role of doctors from arm's length experts to collaborators.⁴¹

Yet another service offered by health-oriented social networks that has been instrumental in helping patients engage in drug trials is quantified self-tracking: "the regular collection of any data that can be measured about the self such as biological, physical, behavioral or environmental information." This functionality consists of data entry capabilities on the web related to conditions, symptoms, treatments, and any other relevant information that patients can track.⁴² The website then displays the data on the patients' profile and, subject to privacy

³⁷ Swan, *supra* note 24, at 497.

³⁸ *Id.*

³⁹ *Id.* at 497, 509.

⁴⁰ *Id.* at 497.

⁴¹ *Id.* at 498.

⁴² *Id.*

controls, makes it accessible to other community members.⁴³ Some websites further aggregate all data of patients with common conditions, making it possible to create predictive models for disease progression and treatment success.⁴⁴ Users can input their own data or use a wearable device with automated data collection capabilities, which uploads the relevant data to the network without further patient involvement.⁴⁵ While the former method is currently much more common, as wearable data collection devices continue to develop and become more affordable, automated uploading will likely become more common. It holds great promise in ensuring data accuracy and authenticity since it essentially eliminates any patient interaction with the raw data.

A social network that has recently attracted a great deal of attention is PatientsLikeMe.⁴⁶ This website, focused on neurodegenerative conditions, is organized into disease-based communities and offers all three services discussed above. Patients can not only obtain information and connect with others in similar health situations, but also have access to robust quantified self-tracking capabilities.⁴⁷ Patients can record their symptoms' severity and progression as well as their treatments, drug regimens, dosages, and other relevant information. The site then converts the data into easy to analyze graphs and progress curves, allowing patients to track drug efficacy and side effects on themselves and other community members.⁴⁸

While this website is enormously useful to patients, it has also served a very important function for the pharmaceutical industry. Firstly, PatientsLikeMe anonymizes collected patient data and, with patient consent, sells it to pharmaceutical companies, universities, and research

⁴³ *Id.*

⁴⁴ *Id.* See also Heywood, *supra* note 25.

⁴⁵ *Id.* at 509-12.

⁴⁶ www.patientslikeme.com (last visited April 11, 2011).

⁴⁷ Editorial, *Calling All Patients*, 26 NATURE BIOTECHNOLOGY 953, 953 (2008).

⁴⁸ *Id.*

facilities.⁴⁹ Companies then use these cheaply and efficiently acquired data to inform their drug development process, reaping significant savings from not having to finance a study and collect the data themselves.⁵⁰ Moreover, frequently, especially in the case of rare diseases, the data are simply not available anywhere else.⁵¹

Social networks also offer pharmaceutical companies a solution to one of the main problems companies encounter in conducting clinical trials—recruitment. A third of all trials fail to recruit a single patient.⁵² Fewer than twenty percent are completed on time, with much of the delays attributable to difficulties in recruiting patients.⁵³ Health-oriented social networks aggregate patients with the same condition in the same place and thus provide an ideal recruitment environment. Drug manufacturers no longer have to approach individual doctors hoping to convince them to refer patients to a clinical trial. Instead, they can simply visit a social network focused on their condition of interest and provide information directly to the relevant consumers.⁵⁴ In fact, in 2008 Novartis used PatientsLikeMe to recruit participants for its multiple sclerosis clinical trial, estimating that the new recruitment method was able to speed up the 1,200-patient study by several months and save the company several million dollars.⁵⁵

While health-related social networks provide pharmaceutical companies with significant efficiencies in clinical trial recruitment, patient involvement in clinical trials need not stop there. Perhaps the most significant cost-saving tool that health-oriented social networks might be able to offer to drug developers is the possibility of patient-run clinical trials. While underground use

⁴⁹ Malorye Allison, *Can Web 2.0 Reboot Clinical Trials*, 27 NATURE BIOTECHNOLOGY, 895, 896 (2009).

⁵⁰ See Sarasohn-Kahn, *supra* note 27 at 12.

⁵¹ Arnst, *supra* note 22.

⁵² Allison, *supra* note 49 at 895.

⁵³ *Id.*

⁵⁴ *Id.*

⁵⁵ Swan, *supra* note 24 at 500. For a discussion of clinical trial recruitment models that are capable of resulting in significant savings for pharmaceutical companies by utilizing health-oriented social networks see Allison, *supra* note 49 at 899.

of unapproved medicines by patients has been historically problematic,⁵⁶ quantified self-tracking capabilities are making it conceivable that patients may one day be able to conduct a scientifically valid clinical trial. While the idea seems far-fetched and problem-ridden at present, the medical community has already witnessed the first attempts at such studies.

The first such trial took place on PatientsLikeMe and was entirely coordinated by network members with amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease. The study was inspired by a publication in peer-reviewed medical journal, reporting that the mood-stabilizing drug lithium carbonate may delay the progression of the disease.⁵⁷ Lithium carbonate is only FDA-approved for the treatment of mood disorders in the United States, but determined patients were able to get it prescribed by their doctors off-label.⁵⁸ The trial was coordinated by a retired engineering professor from the United States, and a Brazilian computer systems analyst, both ALS patients and members of the online community.⁵⁹ The two recruited over 200 ALS patients worldwide to take a specified dose of lithium and answer standardized questions meant to gauge participants' symptoms and disease progression.⁶⁰ PatientsLikeMe provided the tools necessary for data aggregation and analysis.

Figure 1 provides PatientsLikeMe's graphical representation of the aggregated trial data. The default display provides the dosages taken (Figure 1(a)), the duration of the treatment (Figure 1(b)), the side effects experienced by participants (Figure 1(c)), and the perceived effectiveness of the drug (Figure 1(d)). Additionally, graphical representations can be expanded to show the data associated with individual trial participants in the selected category (Figure 2),

⁵⁶ See Arno & Feiden, *supra* note 11 for discussion of underground testing of Compound Q.

⁵⁷ Antonio Paparelli et al., *Lithium Delays Progression of Amyotrophic Lateral Sclerosis*, 105 PROC. OF THE NAT'L ACAD. OF SCI. 2052 (2008)

⁵⁸ *Patient-run Drug Trials Defy Medical Establishment*, FOX NEWS, Nov. 26, 2008, <http://www.foxnews.com/story/0.2933.458009.00.html>.

⁵⁹ *Id.*

⁶⁰ *Id.*

and their full lithium carbonate history (Figure 3). Unfortunately, the data seem to have shown that the drug does not actually slow the progression of ALS and many patients have stopped taking the medication since.⁶¹

Dosages

Top 10 dosages based on patients **currently taking Lithium Carbonate**. See all 21 dosages ▶

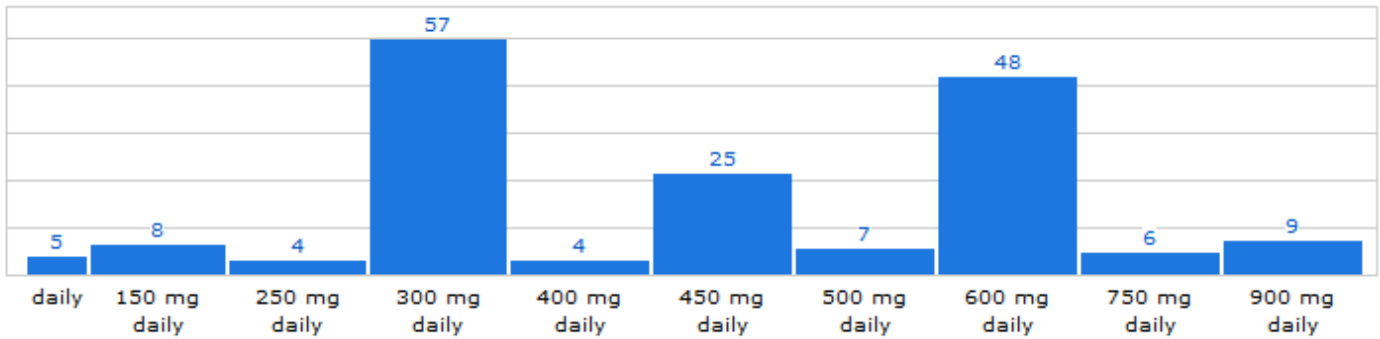


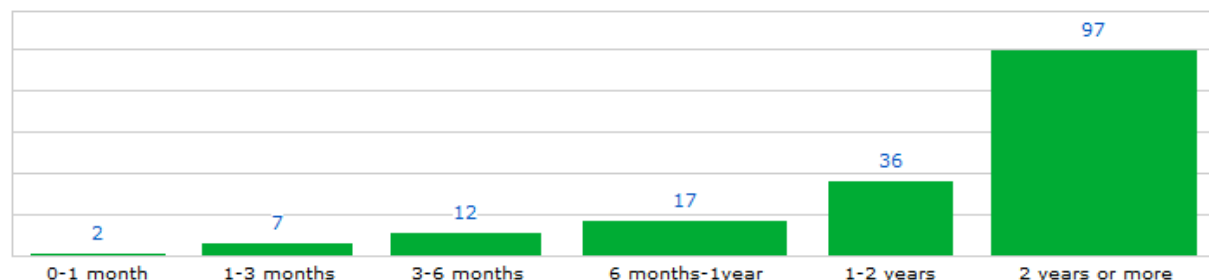
Figure 1(a): Medication dosages taken by PatientsLikeMe trial participants.⁶²

⁶¹ *Id.*

⁶² PatientsLikeMe lithium trial, <http://www.patientslikeme.com/als/treatments/show/777-lithium-carbonate> (last visited Apr. 10, 2011).

Duration [Hide details](#) ▲

Currently Taking Lithium Carbonate



Stopped Taking Lithium Carbonate

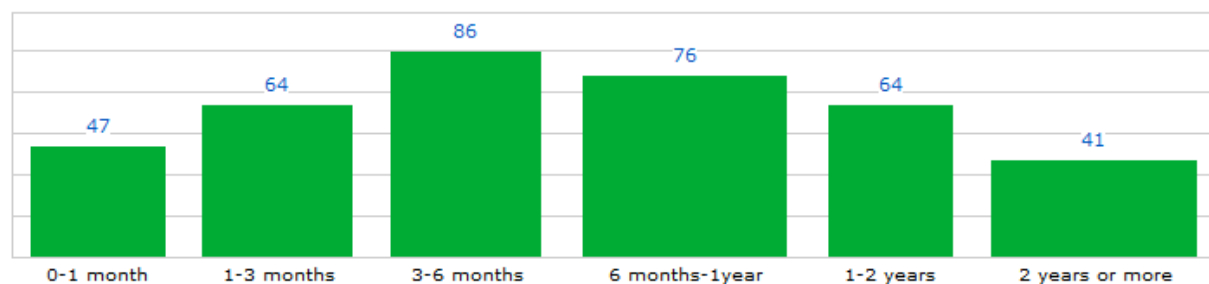


Figure 1(b): Length of lithium carbonate treatment.⁶³

Side Effects

Side effects as an overall problem

Severe	5	6%
Moderate	13	15%
Mild	23	26%
None	47	53%



Most commonly reported side effects

Overall weakness	12	35%
Tremor in hands	10	29%
Urinary frequency	7	21%
Nausea	4	12%
Thirst	3	9%
crying and rage	3	9%

■ Mild ■ Moderate ■ Severe

[See all 35 reported side effects](#) ▼

Figure 1(c): Severity and nature of side effects experienced by trial participants.⁶⁴

⁶³ *Id.*

⁶⁴ *Id.*

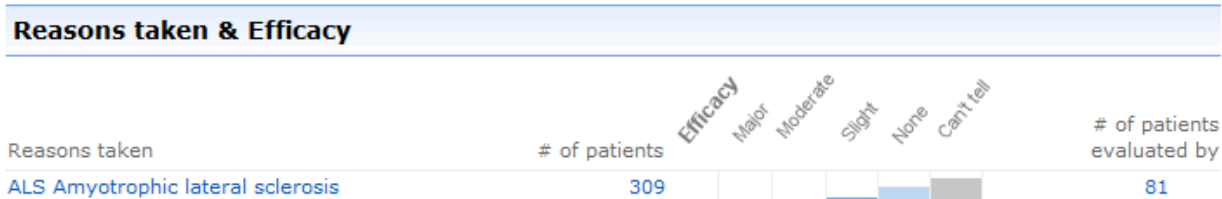


Figure 1(d): Reported effectiveness of the experimental drug.⁶⁵

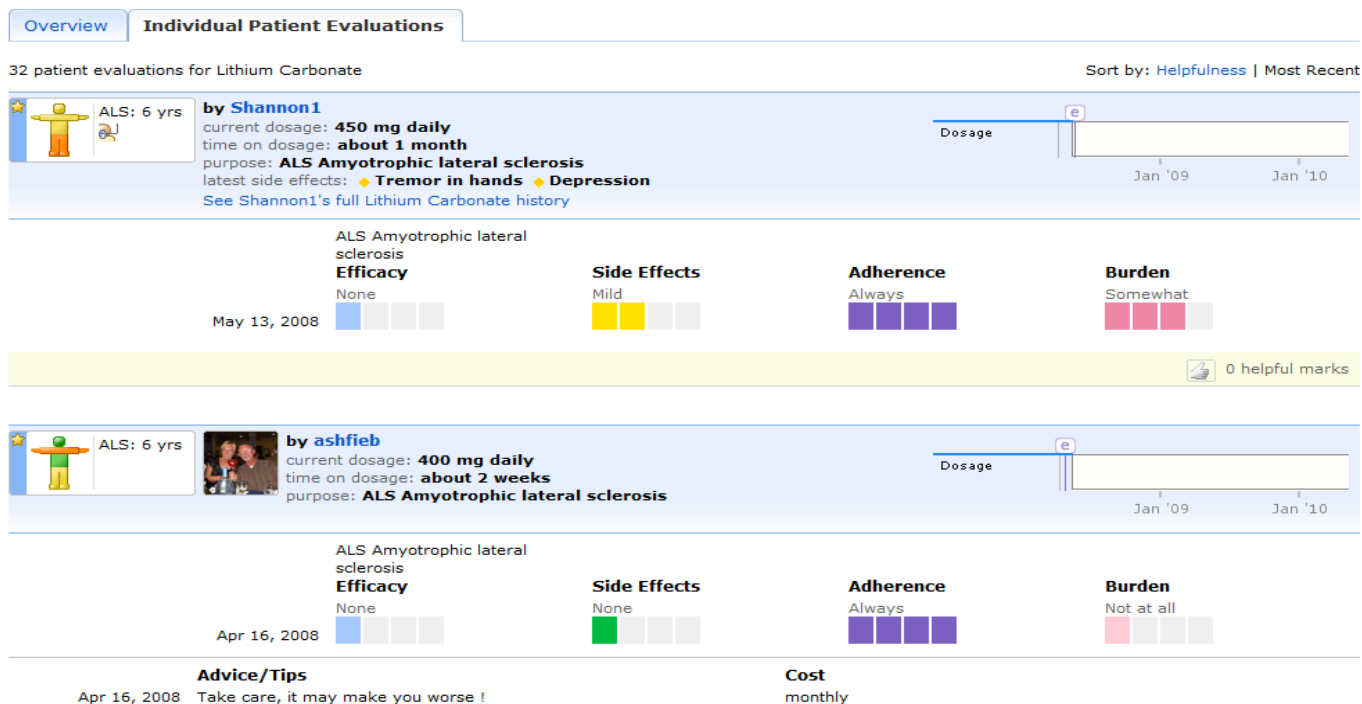


Figure 2: The individual profiles of all participants are accessible by clicking any data parameter in the default graphical display.⁶⁶

⁶⁵ *Id.*

⁶⁶ *Id.*

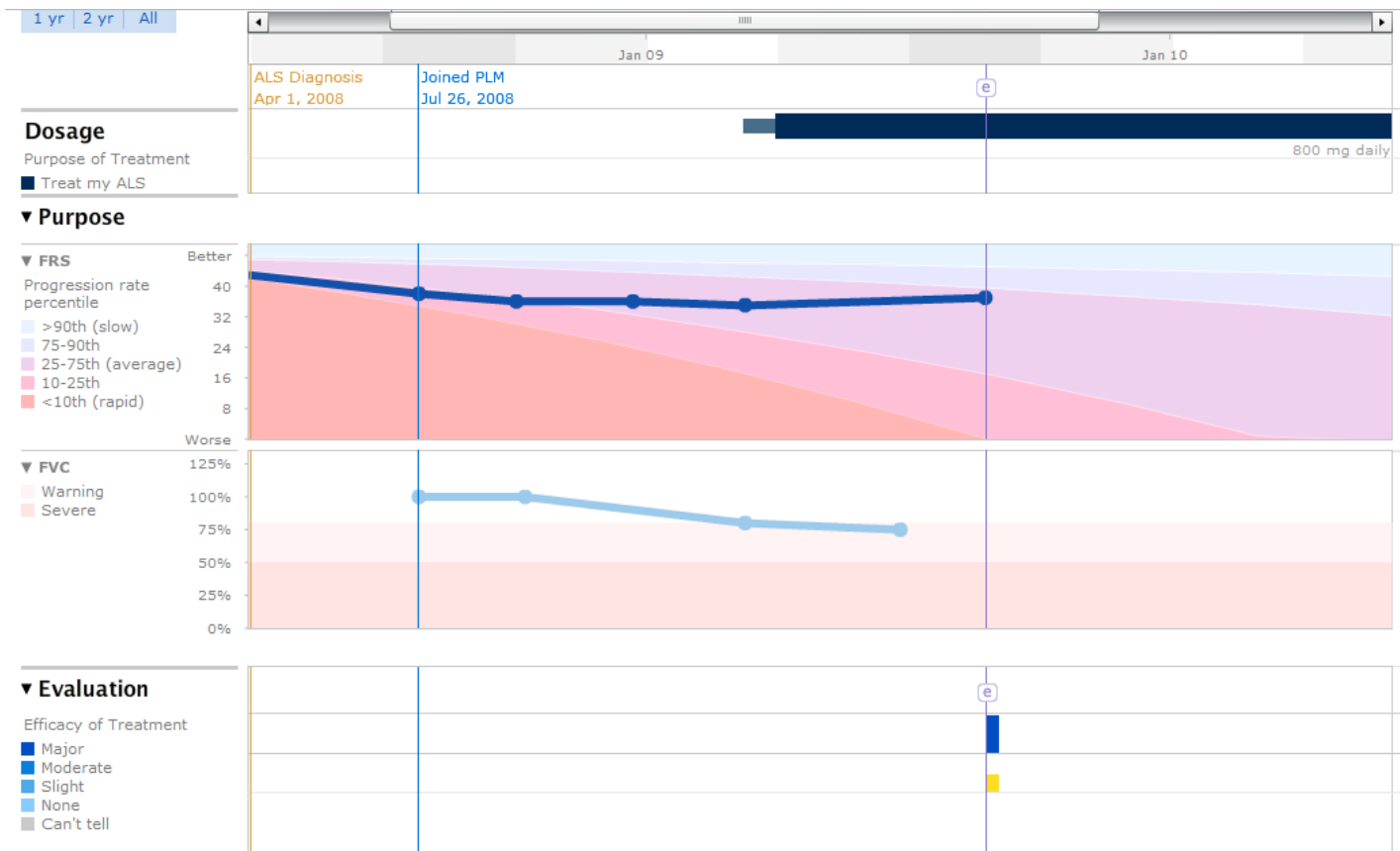


Figure 3: Each patient’s entire history with the particular treatment can be accessed through the patient’s profile.⁶⁷

A similar patient-led initiative occurred in the context of cancer treatments. In 2007, Canadian scientists reported that dichloroacetate, (DCA), exhibited promising anti-cancer properties.⁶⁸ The study reported that the compound shrunk tumors in rats with no apparent side effects.⁶⁹ DCA has long been the subject of clinical trials for mitochondrial diseases in humans, but has yet to be approved even though it has been relatively safe.⁷⁰ Additionally, since the compound is not novel, it cannot be patented, so there is little interest by pharmaceutical

⁶⁷ *Id.*

⁶⁸ S. Bonnet et al., *A mitochondria-K⁺ Channel Axis is Suppressed in Cancer and its Normalization Promotes Apoptosis and Inhibits Cancer Growth*, 11 *CANCER CELL* 37 (2007).

⁶⁹ *Id.*

⁷⁰ Helen Pearson, *Cancer Patients Opt for Unapproved Drug*, 446 *NATURE* 474 (2007).

companies in exploring the molecule's effect on cancer in humans.⁷¹ Frustrated with this lack of action, Jim Tassano, the owner of a pest-control and marketing company in California, decided to take the matters into his own hands. He came across the Canadian rat study while researching alternative cancer therapies to help a dying friend. Teaming up with a chemist, he worked out a way to synthesize the drug and started two websites. At the first one, buydca.com, persons could buy the DCA that Tassano synthesized, labeled for veterinary use.⁷² The second site, thedcasite.com,⁷³ provides patients with information on DCA, as well as the ability to report their progress through the website's chat room or by email. The website is rather rudimentary and does not provide the data aggregation and analysis tools available on PatientsLikeMe but many patients have reported their results to the site. Ultimately, the FDA, determined that Tassano was selling the unapproved compound with the suggestion that it is a cancer treatment and forced him to shut down the buydca.com website.⁷⁴ The second website, however, is still operational and in addition to providing the latest information on DCA, continues to track the progress of patients still using the treatment.

While patient-run trials have the potential to supplement, or even replace the expensive company-run trials used in obtaining FDA approval if structured correctly, several significant issues need to be addressed before that becomes a plausible option. Both the PatientsLikeMe and the DCA studies received strong criticism for failing to meet rigorous scientific standards and were generally not accepted by the medical community.⁷⁵ Unlike properly structured clinical trials, the studies were neither controlled, nor double-blind, which makes it difficult to discern

⁷¹ *Id.*

⁷² *Id.* In the United States, drugs labeled for veterinary use are regulated more loosely than human drugs. Food, Drug, and Cosmetic Act §§ 512-573, 21 U.S.C. §§ 360b-60ccc-1 (2008).

⁷³ www.thedcasite.com (last visited April 11, 2011).

⁷⁴ Linda Geddes, *Illegal "Cancer Drug" Website Shut Down*, *NewScientist*, July 27, 2007.

⁷⁵ Arnst, *supra* note 22.

placebo effects and assess drug effectiveness with any level of confidence.⁷⁶ Further, the studies were fraught with self-reporting bias, the tendency of participants to be influenced by other patients and not report their symptoms objectively.⁷⁷ Moreover, relying on the Internet as a data-collecting tool gives rise to verification issues—both trials lacked a mechanism for ensuring that the participants were who they claimed to be and that the data they contributed was accurate.⁷⁸ Lastly, since these studies were undertaken by patients and were conducted largely without medical supervision, there is a serious concern about patient safety, especially in the case of DCA, which is not FDA approved for any uses.⁷⁹ Scientists are concerned that if participating patients develop harmful side effects because of the insufficient medical involvement in the patient-led trials, the drug would develop a bad reputation and would deter the efforts to perform a proper, physician-lead clinical trial.⁸⁰ While these patient-led initiatives hold great promise, some fundamental changes in their structure are needed before they can fit into the existing FDA drug approval framework and supplement or replace expert-run clinical trials.

II. The FDA Approval Framework

Since 1938 new drugs have had to undergo some form of pre-market review by the FDA before being released on the market. The 1938 the FD&C Act required pre-market notification, but no pre-market approval by the Agency. Prior to marketing a drug, a sponsor submitted a New Drug Application (NDA) to the FDA, and unless the Agency affirmatively disapproved the application within sixty days, the drug could be marketed. The 1962 amendments to the FD&C Act changed this dynamic. Following the passage of the amendments, no drug could be marketed

⁷⁶ Pearson, *supra* note 70.

⁷⁷ For a discussion of the problems posed by patient-run clinical trials, see Allison, *supra* note 49, at 898; Calling All Patients, *supra* note 47.

⁷⁸ *Id.*

⁷⁹ *Id.*

⁸⁰ Pearson, *supra* note 70, at 475.

unless the FDA has found it to be safe and effective for the given indication. Pre-market approval is required for chemical entities introduced on the market for the first time, as well as already approved drugs, sought to be marketed for new indications.⁸¹

The approval process is long and expensive, accounting for about half of the cost of drug development.⁸² The clinical investigation of a new chemical entity can take as many as ten years, and for every 5,000 chemicals screened, five will proceed to clinical testing, and one will receive final approval.⁸³ In order to secure FDA approval, the sponsor must submit to the Agency data indicating, by substantial evidence, that the drug is safe and effective under the criteria established by section 505(d) of the Act.⁸⁴ Such data is most frequently obtained through extensive clinical trials, conducted at numerous sites throughout the country, and sometimes abroad. Section 505(a) of the FD&C Act, however, prohibits the shipment of new drugs in interstate commerce unless they have been approved as safe and effective by the FDA.⁸⁵ In order to facilitate testing and the collection of data, the Act permits the Agency to exempt a drug from the 505(a) prohibition for the limited purpose of conducting clinical investigations by “experts

⁸¹ Food, Drug, and Cosmetic Act § 201(p), 21 U.S.C. § 321(p) (2009).

⁸² See DiMasi, *supra* note 18, and accompanying text.

⁸³ Hutt, *supra*, note 19, at 624.

⁸⁴ “If the Secretary finds, after due notice to the applicant in accordance with subsection (c) of this section and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b) of this section, do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of 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; or (6) the application failed to contain the patent information prescribed by subsection (b) of this section; or (7) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application.” 21 U.S.C. § 355(d).

⁸⁵ 21 U.S.C. § 355(a).

qualified by scientific training and experience⁸⁶ to investigate the safety and effectiveness of the drug.⁸⁷

Prior to conducting a clinical investigation on human subjects, all new drugs are required to go through the Investigational New Drug (IND) process.⁸⁸ The initial step is obtaining approval by the Institutional Review Board (IRB) of the institution where the trial will be performed.⁸⁹ Institutional Review Boards' function is to guard the rights and welfare of trial participants before and during clinical trials. IRBs are necessarily a part of a research institution, and must be composed of at least five members of varying backgrounds and affiliations.⁹⁰ The IRB is responsible for approving the trial prior to its commencement, as well as continuous monitoring of the study, and approving any changes in research activity, unless the changes are necessary to "eliminate apparent immediate hazards to human subjects."⁹¹ In order to approve a clinical investigation, the IRB must determine that the risks to subjects are reasonable in relation to the anticipated benefits to subjects and the importance of the expected knowledge; the risks are minimized by using sound research design; the selection of subjects is equitable, and informed consent is sought from each participant in the study and appropriately documented.⁹² While the FDA can waive the requirement for IRB review,⁹³ absent a waiver, the Agency can decline to consider clinical trial data collected without IRB approval and supervision.⁹⁴

⁸⁶ 21 U.S.C. § 355(d).

⁸⁷ 21 U.S.C. § 355(i).

⁸⁸ 21 C.F.R. § 312.20

⁸⁹ 21 C.F.R. § 312.66 (clinical trial investigators must ensure that their trial is subject to continuing IRB supervision and must inform the IRB of all changes in research activity); 21 C.F.R. § 56.103 (clinical investigations intended to be submitted to the FDA as evidence of safety and effectiveness shall not be initiated prior to IRB approval).

⁹⁰ 21 C.F.R. § 56.107.

⁹¹ 21 C.F.R. § 312.66.

⁹² 21 C.F.R. § 56.111.

⁹³ 21 C.F.R. § 56.105

⁹⁴ 21 C.F.R. § 56.103.

After obtaining IRB review, a sponsor must submit an IND application to the FDA.⁹⁵ The information required to be submitted in the application is set forth in federal regulations and varies depending on the phase of clinical investigation concerned, the drug to be tested, and procedures to be employed.⁹⁶ The Agency always requires the submission of information showing that the drug is sufficiently safe for use in initial clinical studies in humans. If the drug has been studied previously, the sponsor may satisfy this requirement by submitting existing nonclinical data from *in vitro* laboratory or animal studies of the compound, or data from previous clinical testing and marketing in the United States or another country with a relevant population.⁹⁷ If the drug has not been subject to prior investigations, the sponsor must conduct preclinical studies to evaluate the toxic and pharmacologic effects of the drug.⁹⁸ At minimum, the FDA requires that a sponsor “(1) develop a pharmacological profile of the drug; (2) determine the acute toxicity of the drug in at least two species of animals, and (3) conduct short-term toxicity studies ranging from 2 weeks to 3 months, depending on the proposed duration of use of the substance in the proposed clinical studies”⁹⁹ before human trials can be conducted.

In addition to the preclinical toxicity and pharmacological profiles, an IND must contain proposed study protocols. A typical clinical investigation of a previously untested drug consists of three sequential phases. Phase I is a small-scale study, usually involving between twenty and eighty subjects.¹⁰⁰ Because this phase is the drug’s initial introduction into humans, the studies are closely monitored and while they may be conducted in patients, they are usually performed in

⁹⁵ *Id.*

⁹⁶ 21 C.F.R. Part 312.

⁹⁷ FOOD AND DRUG ADMINISTRATION, *The New Drug Development and Review Process*, in THE CDER HANDBOOK (available at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm176522.htm>).

⁹⁸ *Id.*

⁹⁹ *Id.*

¹⁰⁰ Hutt, *supra* note 19, at 630. For a general description of the phases of clinical trials, see also 21 C.F.R. § 312.21.

healthy subjects.¹⁰¹ The main objective of Phase I studies is to determine the metabolism and pharmacologic actions of the drug, and the side effects associated with increasing doses.¹⁰² Sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained during this stage to permit the design of a well-controlled and scientifically valid Phase II study.¹⁰³ Some preliminary effectiveness data can be collected during Phase I studies as well. Phase I studies are usually regarded as the safest phase of clinical testing because they begin with low doses of the tested drug and are conducted under close medical supervision.¹⁰⁴ Phase II studies are intended to evaluate the effectiveness of the drug for a particular indication in patients with the disease or condition concerned, as well as to determine the common short-term side effects and risks.¹⁰⁵ Phase II studies are usually small, involving up to several hundred patients, and are typically well controlled and closely monitored.¹⁰⁶ Phase III studies are performed after sufficient evidence suggesting that the drug is effective for a particular indication has been gathered. They are expanded, controlled and uncontrolled studies, aiming to obtain additional information about "the effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling."¹⁰⁷ Phase III trials tend to be large-scale, long-term studies, involving between several hundred and several thousand subjects and aim to determine the effects of the drug in conditions resembling those of

¹⁰¹ Hutt, *supra* note 19, at 630.

¹⁰² *Id.*

¹⁰³ *Id.*

¹⁰⁴ *But see* Ganesh Suntharalingam et al., *Cytokine Storm in Phase I Trial of the Anti-CD28 Monoclonal Antibody TGN1412*, 355 NEW ENGLAND J. MED. 1018 (2006) (six Phase I study subjects became critically ill after receiving the experimental drug); Steven E. Raper et al., *Fatal Systemic Inflammatory Response Syndrome in a Ornithine Transcarbamylase Deficient patient Following Adenoviral Gene Transfer*, 80 MED. GENETICS AND METABOLISM 148 (2003) (A Phase I clinical trial participant died after receiving experimental gene therapy).

¹⁰⁵ Hutt, *supra* note 19, at 630-31.

¹⁰⁶ *Id.* at 631.

¹⁰⁷ 21 C.F.R. § 312.21. See also Hutt, *supra* note 19, at 631.

its anticipated use.¹⁰⁸ During Phase I clinical trials, the FDA can impose a clinical hold and prohibit a study from proceeding or stop a trial that is already in progress if it finds that the drug is not sufficiently safe to be tested in humans or that the sponsor has not adequately disclosed the risks associated with the study to investigators.¹⁰⁹ In Phase II and Phase III studies the FDA can impose a clinical hold for safety reasons, or because the study is defectively designed and will not accomplish its stated objectives.¹¹⁰

Several decades ago, when the science and practice of drug development limited clinical trial size, three phases of clinical investigation were required to gather sufficient safety and effectively evidence. Thus, most clinical trials followed the standard three-phase model. Today, increased communicational and technological capabilities allow the design of larger clinical trials that supply scientific data to a greater degree of confidence. These developments have allowed sponsors to seek approval without always adhering to the traditional three phase structure. Although the traditional structure is still common, in modern studies the phases frequently overlap since there is no specific regulatory requirement that a sponsor conduct all three phases in order to secure approval. Providing the Agency with substantial evidence of the safety and effectiveness of the drug is sufficient, regardless of the structure of the trial. In fact, the Agency has approved drugs following detailed Phase II studies, as well as drugs that have skipped Phase II altogether.¹¹¹

An IND can be submitted for one or more phases of a clinical investigation.¹¹² It must include a protocol for each planned study, including: a statement of the objectives and purpose of the study; the names, addresses and qualifications of investigators and others working under their

¹⁰⁸ Hutt, *supra* note 19, at 631.

¹⁰⁹ *Id.*

¹¹⁰ *Id.*

¹¹¹ *Id.* at 628.

¹¹² 21 C.F.R. § 312.21.

supervision, as well as the names and addresses of the research facilities involved and the supervising IRB; the criteria for patient selection and exclusion and an estimate of the number of patients involved in the study; a description of the design of the study including the control strategy and methods used to minimize bias; the method for determining doses to be administered as well as the maximum dosage and duration of each subject's exposure to the drug; description of the observations and measurements to be made during the study; and a description of the clinical procedures, laboratory tests and other measures taken to monitor the drug's effect and minimize risk.¹¹³

The detail required in these disclosures varies according to the phase of the study that the IND pertains to. Less detail is required in INDs pertaining to Phase I studies.¹¹⁴ Such disclosures typically provide only an outline of the investigation, the number of subjects, a dosing plan and duration of the study, and safety exclusions.¹¹⁵ Only the elements of the study that are critical to its safety are described in detail.¹¹⁶ Modifications of the study design, unless they impact safety, are reported to the FDA in the sponsor's annual report.¹¹⁷ Phase II and Phase III protocols, on the other hand, describe all aspects of the study in detail.¹¹⁸ The FDA encourages sponsors to design study protocols in such a way that deviations from the study design are built into the protocol. Any additional protocol amendments must be submitted to the FDA before changes in the study can be implemented, unless the changes are necessary to "eliminate an apparent immediate hazard to subjects."¹¹⁹

¹¹³ *Id.*

¹¹⁴ 21 C.F.R. § 312.23.

¹¹⁵ *Id.*

¹¹⁶ *Id.*

¹¹⁷ *Id.*

¹¹⁸ *Id.*

¹¹⁹ 21 C.F.R. § 312.30.

Once the IND has been submitted, the Agency has thirty days to review it. The FDA reviews INDs pertaining to all phases of a clinical trial to ensure that the trial is sufficiently safe for the participating subjects.¹²⁰ A review of an IND pertaining to Phase II and Phase III studies also includes an assessment of the scientific quality of the trial, and the likelihood that the investigation will yield data sufficient to meet the approval requirements of § 505(d).¹²¹ Unless the Agency disapproves an IND within thirty days of its submission, the clinical trial may begin.

The FDA has set forth standards, defining what constitutes a well-controlled clinical trial.¹²² The regulations define a number of criteria that investigators must meet in order for the Agency to recognize the results of a trial as substantial evidence of effectiveness. Although the substantial evidence need not necessarily come from a trial, in practice such studies are the primary basis for drug approval, making compliance with FDA's criteria particularly important.

Firstly, there must be a clear statement of the objective of the investigation and the proposed methods for analyzing results.¹²³ The study must also be able to provide a quantitative assessment of the drug's effectiveness by utilizing an appropriate control mechanism.¹²⁴ Acceptable controls include placebo concurrent control, dose-comparison concurrent control, no treatment control, active treatment concurrent control, or historical control.¹²⁵ Many modern studies involve a combination of these control methods, especially when the severity and nature of the illness make the use of placebo or known treatment controls ethically suspect. Additionally, subject selection methods must ascertain that subjects indeed have the disease or condition being studied, or are otherwise qualified to participate in the trial.¹²⁶ The method of

¹²⁰ 21 C.F.R. § 312.22.

¹²¹ *Id.*

¹²² 21 C.F.R. § 314.126.

¹²³ 21 C.F.R. § 314.126(b)(1).

¹²⁴ 21 C.F.R. § 314.126(b)(2).

¹²⁵ *Id.*

¹²⁶ 21 C.F.R. § 314.126(b)(3).

assigning participants to treatment and control groups must be designed to minimize bias and create roughly comparable groups in terms of patient variables such as gender, disease severity and progression, and use of other treatments.¹²⁷ Most studies accomplish this by using a randomized assignment method, where patients are randomly assigned to a trial arm, much like a lottery, however other methods are possible. Investigators must also take measures to minimize bias on part of both subjects and observers.¹²⁸ This is most frequently done through double blinding, where neither the patients, nor the persons administering the drug know which group is the control and which is a treatment group. In order to provide meaningful results, the study must also define the methods that will be used to assess subjects' response to the treatment, including the variables that will be measured, the methods for measuring those variables, and the criteria used to assess patients response.¹²⁹ The analytical methods employed to assess the effects of the drug must be statistically valid and must take into account the comparability of the different arms of the study.¹³⁰ In addition to these general criteria, FDA regulations set forth good clinical practices (GCP) principles, providing examples and detailed guidance on addressing a variety of issues that may arise at any stage of the drug approval process.¹³¹

Another important aspect of study design is the intensity of quality control and on-site monitoring.¹³² While intense on-site monitoring to ensure high data quality is typical of industry-sponsored trials, the FDA has expressed willingness to be flexible in assessing quality control. In particular, and in accordance with international norms, the Agency has emphasized that

¹²⁷ 21 C.F.R. § 314.126(b)(4).

¹²⁸ 21 C.F.R. § 314.126(b)(5).

¹²⁹ 21 C.F.R. § 314.126(b)(6).

¹³⁰ 21 C.F.R. § 314.126(b)(7).

¹³¹ FDA's website provides access to regulations and guidance documents addressing accepted good clinical practices in different contexts. See Food and Drug Administration, <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm> (last visited Apr. 13, 2011).

¹³² Food and Drug Administration, *Guidance to Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* 20 (1998) (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078749.pdf>).

monitoring of trials should be fact-specific and dependent on factors such as trial design, size, and complexity.¹³³ If a sponsor is able to ensure quality control through means other than close on-site monitoring—by close review of documentation or extensive pre-trial planning with investigators, for example—and the trial conforms to good clinical practices, the FDA has generally been willing to grant both initial and new indication approvals.¹³⁴

Even well-controlled trials that conform to good clinical practices, however, are not without concerns. For a number of reasons, a clinical trial may lead to results that are inconclusive, or worse yet, misleading. For instance, despite the best efforts of investigators, a clinical trial may be subject to undetected systematic biases that may lead to erroneous conclusions.¹³⁵ Additionally, the results obtained at any single investigation site may not be well generalizable because of influence of site-specific or investigator-specific factors that are not truly characteristics of the general population.¹³⁶ Lastly, while small, there is a non-negligible possibility that indications of effectiveness were obtained purely by chance.¹³⁷ Thus, the FDA normally seeks independent substantiation of trial results and generally requires at least two adequate and well controlled clinical trials to recognize effectiveness.¹³⁸ In situations where data pertaining to a drug are particularly convincing, however, data from one adequate and well-controlled clinical investigation may suffice.¹³⁹ There are three main situations where a single clinical trial or alternative evidence may provide substantial evidence of effectiveness to support a given indication.

¹³³ *Id.*

¹³⁴ *Id.*

¹³⁵ Providing Clinical Evidence of Effectiveness, *supra* note 132, at 4.

¹³⁶ *Id.* at 5.

¹³⁷ Statistical treatment suggests that one in forty trials can be expected to give a falsely positive result for effectiveness. While this is a relatively small chance, it becomes significant when considered against the background of the hundreds of clinical trials that take place every year. *Id.*

¹³⁸ Providing Clinical Evidence of Effectiveness, *supra* note 132.

¹³⁹ 21 U.S.C. § 355(d).

In some cases, the effectiveness of a product may be demonstrated by extrapolation from existing clinical studies.¹⁴⁰ This is most frequently applicable for drugs already on the market that are seeking approval for a new indication, rather than entirely new products. For instance, the effectiveness of alternative formulations of an existing drug may be demonstrated by evidence of bioequivalence to the approved formulation.¹⁴¹ The effectiveness of modified-release dosage forms may be extrapolated from immediate-release forms on the basis of pharmacokinetic data linking the two.¹⁴² Lastly, effectiveness information of one dose, dosage regimen, or dosage form may be used to approve another one based on pharmacokinetic data alone, provided that blood levels and exposure are not very different.¹⁴³ Sometimes, when the agency concludes that a disease progresses sufficiently similarly in children and adults, it may approve the use of the drug in children without requiring additional clinical trials.¹⁴⁴

Another situation where the FDA may not require multiple clinical trials in order to approve a drug occurs when the demonstration of effectiveness by a single study of a new use is substantiated by reliable data from related studies.¹⁴⁵ Studies in other populations or in other phases of the disease can be particularly helpful in this context. Additionally, if the FDA has approved the drug for use on its own, a single clinical trial will usually be sufficient to support an effectiveness finding for the drug in combination with other therapies.¹⁴⁶ The FDA may also approve a drug on the basis of a single clinical trial if the drug has been proven effective in

¹⁴⁰ Providing Clinical Evidence of Effectiveness, *supra* note 132, at 7.

¹⁴¹ *Id.*

¹⁴² *Id.*

¹⁴³ *Id.*

¹⁴⁴ *Id.*

¹⁴⁵ *Id.* at 8.

¹⁴⁶ *Id.* at 9.

closely related diseases or in less closely related diseases where the general purpose of the therapy is sufficiently similar.¹⁴⁷

This previous two pathways to approval are more likely to be useful for drugs that are already on the market and are simply seeking approval for new indications. A third pathway to approval that may be appropriate for entirely novel compounds is the use of a large multicenter study that, due to its size and structure, produces particularly persuasive results. In order to constitute substantial evidence of effectiveness, the study must be large and conducted at multiple centers, with patients distributed approximately evenly across test sites. Additionally, approval is more likely for studies conducted on a large number of diverse patients, improving the generalizability of the findings to the general population. Additionally, for studies constructed to include several endpoints involving different events, a sufficient showing of effectiveness may be found where the drug is proven effective on more than one endpoint. The standard for approval, however, is high. In order for the FDA to find sufficient evidence of effectiveness, the data obtained from the single multicenter study has to be extremely persuasive and the FDA is still cautious to consider the possibility of an erroneous result.¹⁴⁸

A vital component to ensuring that the FDA will recognize a clinical trial as well-controlled and therefore the success of an IND or an NDA is early, effective communication between the sponsor and the Agency. Resulting from an agreement between the FDA and the pharmaceutical industry in conjunction with the 1997 reauthorization of the Prescription Drug User Fee Act (PDUFA),¹⁴⁹ the FDA set forth a guidance outlining the three types of meetings

¹⁴⁷ *Id.* at 10.

¹⁴⁸ *Id.* at 10-15.

¹⁴⁹ PDUFA was reauthorized again in 2007, with no significant changes. Prescription Drug User Fee Amendments of 2007, Publ. L. No. 110-85, 21 U.S.C. §§ 379h-1, 379h-2.

possible between the Agency and sponsors of PDUFA products.¹⁵⁰ Type A meetings are ones urgently needed for an otherwise stalled drug development program to proceed.¹⁵¹ Those meetings occur within thirty days of the sponsor's request.¹⁵² Type B meetings are pre-IND meetings, certain end-of-Phase I-meetings, or end-of Phase II/pre-Phase III meetings.¹⁵³ They occur within forty-five days of the written request. Type C meetings are any other meetings pertaining to the development and review of a human drug.¹⁵⁴ Those meetings occur within sixty days.¹⁵⁵ The timeframes for these meetings have frequently been criticized as exceedingly long and costly, especially when follow-up meetings may be necessary, which is frequently the case.¹⁵⁶

Additionally, the FDA Modernization Act of 1997 added section 505(b)(5)(B) to the FD&C Act, requiring the Agency to meet with sponsors who make a reasonable written request in order to reach an agreement on the design and size of clinical trials that will be used as a basis of an effectiveness claim for a new drug.¹⁵⁷ Such meetings occur within forty-five days of the sponsor's request and any agreements reached during the meeting are set forth in writing and are binding on the Agency's review division unless the sponsor fails to follow the agreed-upon protocol, the relevant data presented by the sponsor is found to be false or incomplete, or the "director of the review division determines that a substantial scientific issue essential to

¹⁵⁰ Food and Drug Administration, *Guidance for Industry: Formal Meetings with Sponsors and Applicants for PDUFA Products* (2000) (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079744.pdf>).

¹⁵¹ *Id.* See also Hutt, *supra* note 19, at 626-29.

¹⁵² *Id.*

¹⁵³ *Id.*

¹⁵⁴ *Id.*

¹⁵⁵ *Id.*

¹⁵⁶ Critics argue that the 30, 60, and 75-day waiting periods are grossly mismatched to pharmaceutical manufacturers' decision-making timeframes and result in wasteful spending on the order of several million dollars per meeting. See Hutt, *I* note 19, at 628.

¹⁵⁷ 21 U.S.C. § 355(b)(5)(B)&(C).

determining the safety or efficacy of the drug has been identified after testing has begun.”¹⁵⁸ The agreed-upon protocol can also be altered with the written agreement of the sponsor and the FDA.¹⁵⁹ Meetings pursuant to § 505(b)(5)(B) have become known as Special Protocol Assessments, and are not available once a clinical trial has begun. Although the sponsor can request a meeting with the FDA and an evaluation of a commenced study at any time, once a trial has begun, the meeting is not subject to the forty-five day timeframe set forth in the Act and the results of the evaluation are not be binding on the Agency’s review division. It is important that sponsors take advantage of these opportunities to communicate with the FDA frequently and candidly. Addressing the Agency’s concerns before clinical testing has begun can result in significant cost savings from having to perform follow-up clinical studies or avoiding a clinical hold due to deficient study design once the clinical trial has begun.

In sum, clinical trials are complex creatures that must comply with many requirements before being accepted as valid evidence of safety and effectiveness. It is no wonder that many people dedicate their entire careers to designing and running clinical trials. The legal, scientific, and statistical terrain is complicated at best, and a certain minimum level of expertise is necessary in order to perform a clinical trial that the scientific community and the FDA are willing to recognize as valid and reliable. Yet, patients seem intent on challenging these norms every day. While patients are not expert clinical investigators, they are experts in experiencing the diseases that experimental medications are attempting to treat. The pharmaceutical and scientific communities should acknowledge this unique expertise and embrace and harness patient initiative and wisdom to design the next generation of more efficient clinical trials.

¹⁵⁸ Food and Drug Administration, *Guidance for Industry: Special Protocol Assessment* (2002) (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080571.pdf>).

¹⁵⁹ *Id.*

III. Clinical Trials 2.0

A. The Challenges

While patient-run clinical studies have enormous potential to supplement or even replace expensive clinic-based trials in some contexts, the efforts that we have seen to date present a series of problems that prevent them from serving that function. Trial sponsors must address these challenges before such trials can become acceptable to the scientific and regulatory communities.

The first significant issue that these trials face is that they are, as a general matter, insufficiently scientifically rigorous to be accepted as evidence of safety and effectiveness. The trials have been uncontrolled, relying on patients' abstract account of the drug's effectiveness or lack thereof. Essentially, these trials have had a single treatment arm, and no control group of any sort. Effectiveness, however, is necessarily a relative determination, and unless the results produced by the experimental treatment are compared to something—placebo, a known treatment, or historical data—the trial deviates from good clinical practices as defined by the FDA and the medical community and makes it difficult to make a conclusive effectiveness determination with any level of confidence, especially where complicated biological systems are involved. To make matters worse, patient-run studies have not employed any bias reducing mechanism such as blinding. All participants in the trials' single treatment arm have been aware that they are receiving the active experimental drug—once again a significant deviation from good clinical practices. This lack of blinding makes it challenging to differentiate genuine treatment effects from placebo effects and reduces reliability of the data and therefore the trial's value as a source of evidence for effectiveness.

In addition, in the studies available to date, patients have played the role of study subjects and investigators simultaneously. The current structure has left it up to patients to make and record observations about the progress of their disease and their response to the investigational treatment. This, combined with the fact that aggregate raw data and results are available to patients during the course of the study, gives rise to self-reporting bias. Patients are less able than neutral, trained observers to record observations and results objectively to begin with. Coupled with the access to others' observations during the course of the trial, patients are likely to subconsciously seek to conform to others' experience and are likely to report less accurate and unbiased data. This self-reporting bias is the reason that observing investigators that come in close contact with study participants are usually not made aware of trial results until after the trial has concluded.

Another major concern brought on by these trials is data verification. PatientsLikeMe and thedcasite are open to anyone who wants to participate. Although PatientsLikeMe requires that users create a profile and disclose certain information before they can join the online community and take advantage of the website's full capabilities, patients can provide fairly minimal information that does not necessarily reveal their identity. On the other hand, members of thedcasite need not disclose any information at all, since the site accepts submissions by email or via its blog. In essence, in these two studies it has been impossible to determine with any degree of certainty whether patients are entering accurate and reliable data, or whether they even are who they purport to be. This anonymity is contrary to good clinical practices as a big part of ensuring that trial results are valid and reliable is proper patient selection. Investigators must ensure that trial participants are properly qualified for the trial and actually have the condition that the experimental drug is expected to treat. This is difficult to do without actual contact with

patients, and nearly impossible without a robust identity verification mechanism. Additionally, the anonymity and ease of participation give rise to fraud concerns. One can imagine without too much trouble that a pharmaceutical company who is betting its existence on the success of the tested drug can find ways to enter fraudulent data and skew the results of the trial. Unless there is a way to monitor and control participation and verify patients' identity, these concerns are a major obstacle to obtaining reliable and trustworthy data in patient-run trials.

The medical community is also concerned about patient safety. Normally, trials are conducted under close medical supervision, by clinicians who are well familiar with the drug's potential side effects and in centers that are equipped to deal with possible complications. This is clearly not the case with patient-run trials. In fact, both the PatientsLikeMe trial and the DCA trial were characterized by very limited medical involvement of any kind. Naturally, the concern is that medical oversight is necessary since patients are not normally able to recognize and deal with sometimes serious, yet subtle, side effects on their own. Additionally, without the prior approval of an IRB and formally signed informed consent prior to the start of the trial, it is not clear whether patients understand how risky the experimental therapy is, what side effects they might expect to experience, and how to address any complications that occur as a result of their participation in clinical trials.

Moreover, in the case of internet-based clinical trials, patients are disclosing significant amounts of personal information and storing it online. While online platforms are what is making patient-run trials in the first place, they give rise to strong privacy concerns. Without the involvement of an accredited institution, patients' information is essentially available for all the world to see and use as it sees fit. It is not clear who is responsible for safeguarding data and protecting patients' privacy. Moreover, as is the case with the lack of informed consent, it is not

clear that patients understand the risks they take by opening their health information to the world. For instance, while disclosing ailment details online can be enormously helpful to the patient community, the information is also readily available to employers, who may tacitly take it into account when making employment decisions. While this does not necessarily rule out patient-run trials as a valid clinical model, it is something that patients should be aware of and should actively consider when deciding whether to join an online community and participate in such a trial.

Lastly, the medical and scientific communities are concerned that if an experimental treatment causes serious side effects in patient-run trials, it would be difficult to determine whether the severity of the incident is due to the drug itself or to an essentially incompetently conducted trial due to the lack of medical involvement. Such complications, on the other hand, might give an experimental treatment a bad reputation and lead to reluctance to perform a clinic-based trial, even if closely monitored. In essence, scientists are concerned that patient-run trials gone wrong would deter the scientific community from running properly designed trials and potentially developing a valuable medicine.

B. The Solution: Designing a New Trial

The concerns with patient-run trials hosted by health-oriented social networks largely stem from the decentralized nature of the studies and the lack of medical involvement that is characteristic of these endeavors. While the current design of these trials is not optimal, changes in study structure can alleviate many of the anxieties that the medical and scientific communities have expressed, and transform these patient-run initiatives into legitimate tools for collecting reliable clinical information.

A possible change that would enhance the reliability of clinical data collected in the course of patient-run trials is requiring physician involvement. Yet, while some physician oversight is critical to ensuring a scientifically rigorous trial, a clinic-based setting is not. Rather, a more efficient and cost-effective way of accomplishing the goal of reaching out to the medical community is a shift to a point-of-care system, where the trial is administered by each participant's individual treating physician. In fact, researchers have recently been successful in using point-of-care randomized studies to collect comparative effectiveness data for already approved drugs.¹⁶⁰ This model can be further expanded beyond a comparative effectiveness study to test new indications for approved drugs, as well as drugs that have never been on the market before.

In this novel hybrid clinical trial system, patients would still be the ones initiating studies based on information released by the scientists, doctors, pharmaceutical companies, or other patients. Entrepreneurial patients would continue to use health-oriented social networks as an organizational tool, designing the trial parameters with input from others, and collecting and storing data online. While each health-oriented social network is somewhat different, some are very robust and capable of providing different tools capable of addressing a particular study's needs. PatientsLikeMe, for example, has a permanent staff of modelers and engineers, giving it the ability to be flexible in the tools it develops and to be maximally responsive to patients' needs. Recognizing the fact that no two clinical trials are the same and that major variations could result depending on what the experimental drug is and how it is to be administered, networks that are capable of tailoring their resources to each individual study are the optimal platform for such patient-run trials.

¹⁶⁰ For a description of successful point of care randomized comparative effectiveness trials, see Julia Bownell, *Researchers Devise New Clinical Trial System*, The Stanford Daily, Apr. 12, 2011.

While there seems to be no overarching coordination of the design of the trial and each treating physician is, in theory, free to perform the trial in his or her own way, properly designed study tools can provide some assistance. If the online platform provides tools that incorporate the desired trial and monitoring techniques in the types of information that they call for and the way they allow it to be entered, such platforms could force doctors to work within specified trial parameters, thereby coordinating physician approaches throughout the study. While the argument can be made that each physician still has, to some extent, his or her own subjective way of evaluating patients and collecting the data called for by the health-oriented social network tools, this is true in the clinic-based context as well and is the product of having data collected by multiple investigators. While the decentralized nature of patient-run trials may perhaps exacerbate this source of error, the decentralization minimizes clinic-specific and undetected systematic errors that become significant when a small number of investigators are involved. Additionally, standardized study tools that force doctors to work within the same parameters do, to a large degree, alleviate this decentralization concern.

As a practical matter, the point-of-care model is not difficult to achieve. Once enough patients in an online community are interested in a potential treatment and the online platform has provided them with the appropriate tools for their study, each participating patient would approach his or her treating physicians and enlist the doctor's help in administering the experimental treatment and conducting the monitoring required by the trial. This is relatively easy in the case of approved drugs whose off-label indication is being tested as physicians can simply prescribe the drug for a different use. The case is more difficult for entirely new chemical entities since some coordination with the manufacturer would also be necessary in order to obtain the experimental compound. Yet, various arrangements, including registering with the

manufacturer and having the new drug delivered directly to the participating physician, can be made. Assuming access to the experimental drug however, having agreed to participate in the trial, a treating physician would create a profile on the health-oriented social network where the study is to be conducted, and be ready to enter data. A doctor could be able to enter data for of multiple patients, and patients' identities need not be revealed online.

While at first glance this hybrid patient/doctor trial design seems less optimal than clinic-based trials, a closer examination reveals its many advantages. Firstly, this new model cuts out the currently cumbersome and frequently unnecessary clinical trial bureaucracy, which frequently results in administrative delays and encounters recruitment issues. These delays, responsible for roughly half of the enormous cost of clinical trials,¹⁶¹ are largely eliminated in the patient-run clinical trial context. Moreover, treating physicians frequently already have a relationship of trust with their patients and are well familiar with the condition at issue as manifested in the particular patient. Since most patients rely on a single treating physician and have therefore been in the care of the particular doctor for some period of time prior to commencing the trial, the physician is well aware of the patient's condition and how to effectively manage it. Furthermore, treating physicians, especially specialists, are no less qualified to treat patients' ailments than medical professionals at a trial site who are first becoming familiar with the patients in the context of the trial. If a new drug with which the treating physician is not familiar is being tested, the doctor can be educated on the expected outcomes and potential complications by the developer of the drug with some minimal effort, as is the case with clinic-based medical investigators. While there may be doubt about whether pharmaceutical companies would be sufficiently honest with doctors and willing to disclose potentially serious side effects, the same concern is present in the context of clinic-based trials as

¹⁶¹ DiMassi, *supra* note 18.

well. Because of their familiarity with the trial participants, however, treating physicians would be more capable of noticing and reacting effectively to minor health setbacks that may go long undetected in the larger trial context. Moreover, just as is the case with clinic-based trials, pharmaceutical companies have an incentive to be honest and disclose accurate information in order to see the trial come to completion. Withholding information might result in premature cessation of the trial, or might lead to a bad reputation for the drug and its manufacturer in the medical community—an outcome that pharmaceutical companies strive to avoid at all costs.

Involving treating physicians in patient-run trials also alleviates many of the scientific reliability issues that the medical and scientific communities have had with these endeavors. First, the trials can be made more scientifically rigorous by including a control group. The control can be patients using an alternate treatment, no treatment at all, or even a comparison to relevant historical data. There will inevitably be members of health-oriented social networks that do not partake in any given trial or who choose to take a different medication and who continue to track their condition progress online. Especially if such patients are willing to enlist the help in their treating physicians, their data can reliably be used as a control arm of a trial. Since these patients have already taken the initiative to join the health-oriented social network and derive great benefits from being part of the online community related to their condition, they are likely to be willing to share their information and be participate in the trial, if only as a control mechanism.

Blinding is a more difficult issue to address, since patients, as the ones organizing the trial, are by definition aware of the extent of their participation. Yet, not all clinic-based trials are blinded either, and just as in cases where ethical considerations prevent the use of placebo or alternate treatment, the lack of blinding need not mean that the trial data is entirely without value. While the collected data would have to be statistically analyzed with the awareness of the lack of

blinding in mind, the data can still be very useful to the medical, scientific, and regulatory communities. Additionally, as technologies continue to develop, blinding mechanisms are becoming increasingly within reach¹⁶² and may become the norm in the near future.

Additionally, physicians' involvement essentially eliminates the risk of self-reporting bias. Objective physicians can perform medical tests and evaluations and record resultant data without being influenced by patients' desire to fit in with the group or experience a particular result. While many evaluations performed in the medical office rely on patients' description of their conditions, symptoms, and progress, doctors, based on their training and experience, would be able to make assess the credibility of patients and make these observations impartially and in conformity with medical norms. Under the new paradigm, the risks associated with patients being study participants and investigators at once become essentially moot. Furthermore, online platforms can be structured such that patients have access to the interim aggregated data during the course of the study, while treating physicians do not. In this way, patients would remain aware of their condition—something that patient activists have fought long and hard for—while doctors' medical evaluations would not be biased by premature data exposure. The study design is particularly strong where the variables monitored by the study are objectively testable—pulse, blood pressure, blood test results—rather than relying on patients' description and self-assessment. Even in cases where reliance on self-assessment is necessary, that would also be the case in a clinic-based trial which would be subject to the same bias.

Verification issues are also alleviated by including physicians in the study design. Since physicians in the United States and elsewhere must obtain a professional license before they can practice medicine, ease of identity regulation is improved. For most conditions, there are many fewer physicians than patients and their identity can be ascertained by reference to their medical

¹⁶² Brownell, *supra* note 160.

credential. When creating online profiles, physicians can be asked to provide identifying information and if sufficient doubt exists about the identity or qualifications of a physician, a central authority—be it a patient representative,¹⁶³ the drug manufacturer, or the FDA—can perform further verification, ranging from the request to submit additional paperwork to a site visit. For doctors based abroad, the FDA can rely on foreign licensing medical authorities to authenticate the identity and qualifications of participating physicians. While the Internet’s default setting is anonymity when it comes to patients, once identity is linked to a real-world credential like a medical license, identity becomes harder to hide or fabricate. Thus, regulators can set prerequisite standards of identity verification, and only physicians who are able to make the necessary showing would be allowed to participate. Verifying doctor identities would certainly be easier than verifying the identity of thousands of anonymous patients worldwide. While fraud might still be a lingering concern, given that misconduct could be traced to a specific medical professional, the prevalence of fraud should be no more frequent than in clinic-based trials.

Point-of-care clinical trials also alleviate some of the privacy and informed consent concerns of the medical community. Since physicians are the ones entering the trial data online, it is their identities that are necessarily revealed on the web. Patient identities, on the other hand, can remain hidden, even as patients’ data is aggregated and displayed online. Of course, many patients would choose to reveal their identities in order to retain a sense of belonging in the online community. That is not truly an issue, as long as they are doing so voluntarily and having

¹⁶³ Online patient communities are conducting visits of physicians’ offices in order to assess their services and include them in their network of recommended physicians. This model can easily be extended to involve site visits for the purposes of identity verification. See Clay Shirkey, *Wisdom of the Patients: Should You Trust Crowdsourced Research Over Double Blind Clinical Trials* (2008) (available at: http://trusted.md/blog/hippocrates/2008/12/23/wisdom_of_the_patients_should_you_trust_crowdsourced_research_over_double_blind_clinical_trials#axzz1GoWecvTS).

taken into consideration the possible consequences of the disclosure. While the responsibility can fall on doctors to discuss this informational challenge with patients, health-oriented social networks are perhaps in a better position to lead the conversation. Educational materials on privacy can be presented to the consumer when he or she creates an account and again when he or she chooses to participate in a trial. These materials should be presented in a way that patients are likely to read, and should describe the different privacy options—from disclosing one's identity completely, to remaining completely anonymous, and everything in between—and how a patient might choose between the available alternatives.

Health-oriented social networks should also be completely honest about what they do with the data that their members generate. PatientsLikeMe, for instance, anonymizes patients' aggregate data and sells it to pharmaceutical companies to be used in the drug development enterprise. All PatientsLikeMe community members, however, are aware of this use and have consented to it. People who find the use objectionable have a choice not to participate. Although this may seem somewhat coercive while the given health-oriented social network is the only one dealing with a particular disease or condition—if you want to participate in the trial, you have to share your data, albeit anonymously—as the field develops and becomes more closely populated, competition would likely result in a race to the bottom and a willingness to accommodate users and their privacy and information sharing preferences. Additionally, it is worth noting that many patients actively choose to share their identities and data in participating in such networks, since many of the benefits of participating in such a community are derived from having open, honest interactions with others in a similar health situation. No cause for concern exists, as long as patients are able to make informed decisions about the handling of the data they produce.

Informed consent with respect to the medical consequences of an experimental treatment are traditionally handled by IRBs in the clinic-based context. These Boards are tasked with ascertaining that patients are properly informed of the risks that they are undertaking and able to make an informed decision about taking part in the treatment. While patient-run trials are clearly a patient initiative and it may seem that consent is no longer an issue—patients clearly want to do this, therefore they have consented and we no longer have to worry about patient abuses—the emphasis must be on providing information rather than just obtaining consent. It is important to remember that most patients are not medical experts (though some are), and may not be aware of the sometimes serious risks that they are undertaking in joining a clinical trial. This is particularly true for patients with chronic or terminal diseases, who are the most likely candidates for these trials. Such patients tend to focus on the quantity rather than the quality of life, and may be deceived by the promise of a drug that purports to be a cure regardless of the side effects that patients may suffer.

This phenomenon is well illustrated by the DCA trial, where patients were willing to ignore serious purity concerns and ingest a compound that was made essentially in a stranger's basement, solely because of its promise as a cure for cancer. While the blind desire to be cured is understandable, it is not clear that trial participants were aware of the significant and potentially fatal risks that they were undertaking in taking an unapproved drug. Information matters. Having that information is vital in order for patients to be able to weigh all the alternatives and decide whether they want to take part in an experimental treatment. The answer will not be the same for all patients. Many might still have chosen to take DCA, seeing no prospects of better alternatives in the near future. However the point is not that the answer needs to be the same for all patients,

but rather that every patient should be able to make the choice that is best for him or her, and that can only be achieved through access to sufficient information.

This is where the involvement of treating physicians becomes especially important. Even in the absence of IRB approval, treating physicians can, and should, be required to collect informed consent from participating patients. These doctors are knowledgeable enough to be able to disclose relevant information and likely know their patients well enough to be able to have an honest discussion about the best course of treatment. Since these doctors have no interest in the outcome of the trial and their duties are solely to their patients,¹⁶⁴ they are more likely to focus on the best interest of the patient and his specific form of treatment. Because of their relationship with their patients, these physicians are more likely to make complete disclosure of potential side effects and advise patients not to enter a trial if they believe that a different course of treatment might be in the patient's best interest. This is precisely the purpose of informed consent.

If there is serious concern that treating physicians are not providing patients with sufficient information, the FDA can require that informed consent documentation be submitted along with a new drug application. While IRBs are currently tasked with collecting this documentation and providing it to the Agency upon request, in the new patient/point-of-care paradigm, pharmaceutical companies may standardize informed consent forms and request that they be returned to the company as a condition to providing access to the experimental medicine. While this would be more difficult for patients outside of the United States, a reasonable degree of success can be expected as long as there is a single source of the experimental compound.

¹⁶⁴ Unlike clinical trial contractors or clinics, treating physicians are not paid by pharmaceutical companies for their services. Indeed, they are simply collecting data that happens to have clinical significance in the course of their ordinary treatment of their patients.

Even doctor involvement, however, leaves some challenges unaddressed. While it is possible to make patient-run trials scientifically rigorous, it is more difficult to make them fit into the current FDA regulatory framework. FDA regulations have been promulgated with a centralized, clinic-based framework in mind and are fairly difficult to change. Although the Agency has recently tried to be flexible in what data it will accept as substantial evidence of safety and effectiveness, further cooperation by the Agency is necessary to make this currently developing tool a part of the drug approval arsenal. Firstly, patient-run trials would not be able to comply with regulations requiring the pre-trial approval and continuous monitoring by IRBs. While these regulations permit waiver by the FDA, the Agency has granted such waivers rarely, and certainly not wholesale. This practice would have to be altered if patient-run trials are to be are to serve as acceptable sources of evidence.

Additionally, many FDA regulations envision communication between the Agency and a single entity. While this model is reflective of clinic-based trials where there is a single person in charge that the Agency can communicate with, it does not accurately reflect the reality of the recent patient initiatives. Patient-run trials are decentralized, involve geographically diverse participants, and frequently lack a formal administrator distinct from an entrepreneurial patient who is engaging in patient recruitment. While FDA regulatory changes could address this strain, the current rules are designed to streamline interactions between the Agency and drug developers and to ensure a consistent and efficient line of communication between industry and regulators. Decentralizing this model is, therefore, probably not the optimal alternative. Instead, pharmaceutical companies can should remain involved, and to some extent responsible for experimental uses of their medications. Instead of retaining the clunky bureaucracy of an experimental clinic, however, a single representative responsible for monitoring the progress of

trials and the development of a drug would probably suffice. This individual would be in charge of filing an original IND and registering the clinical trial on clinicaltrials.gov once appropriate. Additionally, once sufficient patient interest has been generated, the pharmaceutical representative would work to maintain communications with the FDA to ensure that the trial design is acceptable to the regulatory community. Additionally, this representative could also work with the appropriate online platforms and health-oriented social networks to come up with the tools necessary to collect the appropriate data and ensure the uniformity of data collected by treating physicians throughout the trial. Since these trials are only relevant where pharmaceutical companies are not taking the initiative and engaging in a clinic-based trial, this pharmaceutical representative would only become engaged once there is sufficient patient interest to be able to conduct a robust trial and collect sufficiently reliable data.

C. Are Patient-run Clinical Trials worth the Trouble?

Given the multiple challenges that stand in the way of patient-run trials, the question becomes whether they are worth the trouble. Would it not be better to just carry on the status quo, which although slowly and at high cost, does bring valuable drugs to the market? It is the author's hope that this paper has convinced the reader to the contrary. Patient-run trials are a valuable drug development tool that, although in its infancy, should not be allowed to remain unexplored. They hold great potential to transform the drug approval process as we know it by reducing the length of typical clinic-based trials by months, or even years and by leading to significant reductions in trial, and subsequently medicine, costs. In addition, allowing patients to drive the drug development agenda ensures that a system with limited resources is focusing its efforts where there is greatest demand. Patients would no longer be victims of a system where promising molecules that cannot be patented fail to be developed because they would not lead to

sufficient profit for manufacturers. Pharmaceutical companies and physicians are not necessarily the most attuned to the needs of patient communities. While these actors do have certain expertise in creating treatments, to them the problems faced by terminally ill patients amount to an investment opportunity or an abstract intellectual challenge respectively. This is markedly different from the way a father of three who has just been told that he will slowly lose control of his body and likely die within a few years experiences the problem. It makes sense to let this father and others like him drive the research agenda. It makes sense to focus healthcare and drug development on their needs, rather than on what seems likely to be the most profitable molecule available in a pharmaceutical company's arsenal.

The FDA is charged with maintaining the delicate balance between keeping unsafe drugs off the market and allowing patients to access potentially life-saving medicines quickly enough. It is a difficult cost-benefit analysis to perform, and a particularly difficult balance to strike in the aggregate. The tipping point is different for different patients. The advantage of patient-run trials and the point-of-care system that this paper proposes is that each patient, with the advice of his own physician, is allowed to perform the cost-benefit analysis on his or her own. The newly acquired flexibility allows each patient to pursue a course of treatment that makes sense in his or her own particular context. It is unlikely that a headache sufferer would undertake a trial of a medication with potentially fatal side effects—they might just resort to taking acetaminophen or another currently available medication. On the other hand, the balance may look quite differently for a terminally ill patient who must choose between an experimental therapy with potentially serious side effects or passively waiting for his time to expire. This flexibility has great social value and should be taken seriously by the medical and scientific communities when considering the merit of patient-run trials.

Patient-run trials that take place on health-oriented social networks further provide a great opportunity to collect well-generalizable data. Since they span large geographic areas, frequently extending internationally, and involve patients with a variety of study-related variables, these studies are akin to large multi-center studies that FDA is willing to consider independently as evidence of effectiveness and safety. Additionally, because of the frequent involvement of international patients facilitated by the Internet, patient run trials can help standardize clinical trials internationally. The current norm is that in order to obtain approval, a drug manufacturer must seek approval in each country independently and must frequently perform studies in each country where approval is sought. If patient-run trials are designed in a way that satisfies most international regulators, perhaps the need for redundant studies would be eliminated. Although the international community has found it difficult to agree on a common set of universal trial criteria, this more decentralized model might provide to be the necessary impetus. Particularly since the new paradigm is the product of patient creativity and entrepreneurship and does not elevate the norms of any single sovereign over others, it may prove to be more politically palatable and may lead to much needed international coordination of clinical trials.

D. Where do we go from here?

Patient-run clinical trials are not the answer to all drug development problems. To be sure, it will take a dramatic regulatory changes as well as change in the mindset of the scientific, medical, and regulatory communities to accept the scientific validity of these studies and to truly harness the full potential of this form of patient activism. Patient activists have been enormously successful in shaping the course of drug development history and may prove to be successful again.

The process will be ostensibly more difficult for novel chemical entities that have never been on the market before. The safety concerns there are particularly noteworthy, since very little is usually known about an experimental drug prior to the commencement of the clinical trial. In order to avoid legal liability, pharmaceutical companies would be eager to retain control of the tested compound and would insist on close physician supervision. Still, provided that treating physicians are sufficiently educated about the new molecule and its potential side effects, patient-run clinical trials are not entirely out of the question. New compounds may still become known and popular to increasingly sophisticated patients who keep abreast of medical and scientific publications, as was the case with both lithium carbonate and DCA. Once sufficient interest has accumulated, a trial is ready to begin. Pharmaceutical companies can, with fairly limited involvement, collect scientifically reliable data to test their new compound. While it is conceivable that not all drugs would generate widespread interest, pharmaceutical companies always have the option of orchestrating a clinic-based trial if they think that it would be more favorable to their interests. Also, because of the general lack of data relating to the new chemical entity, a single patient-run trial, however rigorous, would probably be insufficient to obtain FDA approval. Thus, in this context, clinical patient-run trials are likely to supplement rather than replaced traditional clinic-based trials.

In the case of new indications for already approved drugs, patient-run trials hold even greater promise. Since treating physicians can prescribe the drug for off-label use, patients have relatively easy access to the drug in various dosages. Additionally, the need to visit a doctor to obtain the drug necessarily involves treating physicians in the trial process and makes point-of-care trials the natural next step. With relatively little coordination between pharmaceutical companies, patients, online platform developers, and the FDA, studies can become scientifically

rigorous and a great source of comparative effectiveness data. Additionally, as technology continues to develop, randomization techniques might become possible, making study data even more reliable. Even if the FDA refused to accept such studies as independent, well-controlled clinical trials, it should at least allow them to supplement clinical trials and accept them as supporting information, thereby requiring drug manufacturers to sponsor only one, as opposed to multiple trials. The benefits to the drug development process are fairly obvious.

Lastly, the data collected by patients on health-oriented social networks can be extremely useful to pharmaceutical companies in post-approval monitoring. Currently, while pharmaceutical companies are required to report adverse events to the FDA, the typical mechanism involves patients reporting adverse events to physicians, who in turn may choose to, but are not required to, notify the FDA. It is not surprising that in this long chain of reporting, information frequently falls through the cracks and remains undisclosed. Although patients may choose to report their issues with approved drugs directly to the FDA,¹⁶⁵ this rate of reporting is also fairly low. Instead of relying on this unreliable voluntary reporting mechanism, pharmaceutical companies can gather adverse event data from health-oriented social networks, since the data is already reported and tracked as part of patient-run trials. This saves pharmaceutical companies from having to exert separate efforts and resources to perform Phase IV trials and gather adverse event data, while providing the FDA with accurate evidence of drug safety that can be used to inform subsequent recall decisions.

IV. Conclusion

Patient run clinical trials have great potential to supplement, or even replace expensive, lengthy, clinic-based trials. While some regulatory changes would be necessary to accommodate this developing paradigm, the most important change necessary to make this new model a functional

¹⁶⁵ *See generally*, 21 C.F.R. § 314.80.

equivalent of clinic-based trials is changing the mindset of the scientific, medical, and regulatory communities. While the trials' current designs give rise to a number of problems, most issues are easy to address by incorporating the participation of treating physicians and shifting to a hybrid patient-run/point-of-care model. A trial initiated by patients, but conducted by physicians is much less problematic and much more likely to successfully gain the acceptance of the medical and regulatory communities.

Patient-run trials are valuable social tools, allowing the medical establishment to address the needs of every individual patient—something that collective cost-benefit analysis as performed by the FDA is grossly inadequate at doing. As such, patient-run trials are not only a cost-saving mechanism for drug developers, but also a step in the right direction in striking the balance between safety and access to life-saving medications. While the scientific and medical communities are generally risk-averse and slow to respond to change, they should recognize the tremendous opportunity presented by patient-run clinical trials and once again allow patients' desire to be in charge of their personal medical care shape the drug development and approval process.