

2018

Drug Approval in a Learning Health System

W. Nicholson Price II

Follow this and additional works at: <https://scholarship.law.umn.edu/mlr>



Part of the [Law Commons](#)

Recommended Citation

Nicholson Price, W. II, "Drug Approval in a Learning Health System" (2018). *Minnesota Law Review*. 132.
<https://scholarship.law.umn.edu/mlr/132>

This Article is brought to you for free and open access by the University of Minnesota Law School. It has been accepted for inclusion in Minnesota Law Review collection by an authorized administrator of the Scholarship Repository. For more information, please contact lenzx009@umn.edu.

Article

Drug Approval in a Learning Health System

W. Nicholson Price II[†]

INTRODUCTION

When patients take unsafe drugs, they may die.¹ When patients take ineffective drugs, the drugs won't help them—and they may die. But when patients can't access drugs, those drugs definitely can't help them—and they may die anyway. This is a perennial problem for the Food and Drug Administration (FDA). How much knowledge does FDA need about a drug's safety and efficacy before the Agency can conclude that the drug is safe and effective enough to let the drug on the market?² Where does it draw the line?

This question has been debated vigorously for a long time. Some argue for earlier access with less information required, claiming that individual clinicians and patients are best suited to figure out what works best for them.³ Others prefer a more

[†] Assistant Professor of Law, University of Michigan Law School. For helpful comments and conversations, I wish to thank Ana Bracic, Sam Bagenstos, Nick Bagley, Rebecca Eisenberg, Jaime Staples King, Kyle Logue, Michelle Meyer, Efthimios Parasidis, Kayte Spector-Bagdady, Nic Terry, Patti Zettler, and participants at the UC Hastings Faculty Workshop and *Minnesota Law Review's* Symposium on the Future of the Pharmaceutical Industry. Jacob Flood provided excellent research assistance. All errors are my own. Copyright © 2018 by W. Nicholson Price II.

1. Other bad things may also happen: patients may die a worse death, or they may die sooner, or they may miss the opportunity to take a better drug and not die at all.

2. Use is not the only question. Data about efficacy and safety also influence whether insurers should and will pay for the drug without wasting limited resources. For an analysis of the linkage between approval, data, and insurer reimbursement, see Rachel E. Sachs, *Delinking Reimbursement*, 102 MINN. L. REV. 2307 (2018).

3. See *infra* Section I.A.

cautious approach, in which FDA requires even more information before allowing a drug out into the market.⁴ Still others advocate for a more flexible, intermediate approach, combining earlier access for some drugs and more robust postapproval oversight to gather information after drugs are available.⁵ Such a combination blurs the line of standard FDA approval. Although in one sense approval is still a sharp binary—a drug is either approved for marketing or not—the attendant possibilities about when patients can access drugs and when information is gathered become more complex.⁶ Aspects of this blurring process are taking place at FDA already.

This shift at FDA parallels another blurring going on in the larger health-care system. In a “learning health system” (LHS), data are continuously collected in ongoing clinical care and are then used to learn about and improve that care.⁷ This is a big change from the current system, where systematic learning about health care takes place principally in clinical trials, and not much in clinical care.⁸ True LHSs are still in the future, but some health systems are implementing LHS practices,⁹ and there is considerable policy and scholarly support for the overall

4. See *infra* Section I.A.

5. See *infra* Section I.B.

6. E.g., INST. OF MED., THE FUTURE OF DRUG SAFETY: PROMOTING AND PROTECTING THE HEALTH OF THE PUBLIC 1–14 (2007) [hereinafter INST. OF MED., DRUG SAFETY] (arguing for a “life cycle” approach where evidence about safety and efficacy are gathered both before and after drug approval); Anna B. Laakmann, *Collapsing the Distinction Between Experimentation and Treatment in the Regulation of New Drugs*, 62 ALA. L. REV. 305, 305 (2011) (arguing for a more fluid approach where doctors and patients make decisions based on accumulated experiential knowledge).

7. See INST. OF MED., THE LEARNING HEALTHCARE SYSTEM: WORKSHOP SUMMARY 210 (2007) [hereinafter INST. OF MED., LEARNING HEALTHCARE]. The terms “learning health system,” “learning healthcare system,” and “learning health care system” are all used.

8. *Id.* at 3–6.

9. Geisinger Health System is one prominent example; its ability to use learning-health-system (LHS) techniques is enhanced because it is an integrated health system, which provides both health care and insurance coverage for its members. See, e.g., Tom Foley & Fergus Fairmichael, *Site Visit to Geisinger Health System*, LEARNING HEALTHCARE PROJECT, <http://www.learninghealthcareproject.org/section/evidence/38/63/site-visit-to-geisinger-health-system> (last visited June 18, 2018); Susan D. Hall, *Geisinger Researchers Share Framework for Putting a Learning Health System into Practice*, FIERCEHEALTHCARE (Mar. 13, 2015), <http://www.fiercehealthcare.com/it/geisinger-researchers-share-framework-for-putting-a-learning-health-system-into-practice>.

project.¹⁰ An LHS blurs the line between clinical research and clinical care by tightly intertwining them.

An LHS matters for drug approval for two reasons. First, a LHS enables a set of tools for managing the information landscape around FDA approval. Such a system prioritizes routinely gathering detailed information during clinical care. It also allows simpler and cheaper pragmatic trials embedded in care. FDA can use those tools to gather and use postmarket data on drugs. For some time, FDA has been interested in using real-world evidence from clinical practice to provide continuing oversight of medical devices;¹¹ the 21st Century Cures Act (Cures Act), passed in December 2016, expressly directs the Agency to consider using such evidence to gather postapproval information about drugs.¹² To the extent FDA accordingly promotes or even requires the use of learning health tools, like pragmatic trials embedded in clinical care, FDA not only benefits from an LHS but also can help drive its adoption.

Second, the legal and ethical issues that crop up in implementing an LHS, especially around informed consent and data privacy, shape how FDA or others can use the tools the system creates. Informed consent and privacy doctrines turn on a sharp distinction between research and clinical care; in each, research faces substantially higher burdens than care does. But that distinction depends on being able to define what research is, and how it differs from care—precisely the line that an LHS blurs.

10. Among other things, a new journal has been founded focused exclusively on LHSs. See Charles P. Friedman et al., *The Science of Learning Health Systems: Foundations for a New Journal*, 1 LEARNING HEALTH SYS. 1, 1–2 (2017) (explaining features of LHSs); see also AGENCY FOR HEALTHCARE RES. & QUALITY, DEVELOPMENT OF THE LEARNING HEALTH SYSTEM RESEARCHER CORE COMPETENCIES 2–8 (2017), <https://www.ahrq.gov/sites/default/files/wysiwyg/funding/training-grants/lhs-corecompetencies.pdf> (discussing various methods used to develop LHS competencies); *Agency for Healthcare Research and Quality and Patient-Centered Outcomes Research Institute Learning Health Systems Mentored Career Development Program (K12)*, NAT'L INSTS. OF HEALTH (Sept. 5, 2017), <https://grants.nih.gov/grants/guide/rfa-files/RFA-HS-17-012.html> (calling for grant applications focused on LHSs).

11. See FDA, USE OF REAL-WORLD EVIDENCE TO SUPPORT REGULATORY DECISION-MAKING FOR MEDICAL DEVICES: GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF 8–9 (2017), <https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm513027.pdf> [hereinafter FDA, REAL-WORLD EVIDENCE] (noting that FDA uses real-world evidence “across a wide spectrum, ranging from observational studies within an existing dataset to studies that incorporate planned interventions with or without randomization at the point of care”).

12. 21st Century Cures Act, Pub. L. No. 114-255, § 3022, 130 Stat. 1033, 1096–98 (2016).

Those bright lines thus restrict what an LHS can do and how its tools can be used.

This Article is divided into four Parts. Part I briefly canvasses the ongoing scholarly debate about drug approval, considering both the underlying spectrum between faster access and more knowledge and a set of proposals to help improve the approval process. Part II relates the larger context of a broader move to an LHS, a parallel and connected phenomenon that has been underexplored in the legal literature.¹³ Part III describes how an LHS helps generate postapproval information through both interventional and observational studies, noting the link between drug approval and an LHS. Part IV argues that outmoded bright-line rules on privacy and informed consent hamper and bias both interventional and observational studies. It then suggests that those doctrines may need to change to account for the move to an LHS and the search for a better drug approval process.

I. BALANCING ACCESS AND KNOWLEDGE

The FDA approval process involves balancing access to a drug with knowledge about the drug. The process by which FDA approves new drugs has been described in detail elsewhere.¹⁴ For now, suffice it to say that FDA requires that a company seeking to market a new drug submit reports from randomized clinical trials to generate information about how the drug affects humans;¹⁵ these trials show that the drug is safe and effective for

13. For a significant exception, see Rebecca S. Eisenberg, *Shifting Institutional Roles in Biomedical Innovation in a Learning Healthcare System* 3–10 (Mich. Law Sch. Pub. Law & Legal Theory Res. Paper Grp., Paper No. 560, 2017), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2984905 (describing the generation of knowledge for biomedical innovation in the context of an LHS and arguing that payers, in particular, have a substantial role to play in generating such knowledge once new technologies have been deployed into clinical practice). For an example of government recognition of this link, see Robert M. Califf et al., *Transforming Evidence Generation To Support Health and Health Care Decisions*, 375 NEW ENG. J. MED. 2395, 2396 (2016) (noting, in a joint article by high-level officials across several federal health-related agencies, including FDA, the need for interagency collaboration on data and system design to provide evidence for an LHS).

14. See, e.g., Arthur A. Ciociola et al., *How Drugs Are Developed and Approved by the FDA: Current Process and Future Directions*, 109 AM. J. GASTROENTEROLOGY 620, 621–22 (2014) (describing FDA's drug development and approval process).

15. *Id.* at 621.

specified uses in humans (or not).¹⁶ FDA will then approve (or not) the drug for marketing and sale for specific indications based on this information.¹⁷ After that binary chokepoint, FDA loses some of its control over the drug.¹⁸ FDA doesn't lose *all* control, of course; it still monitors manufacturing quality,¹⁹ collects reports of drug safety problems,²⁰ oversees marketing and advertising,²¹ and can impose limited controls on use²² or remove a drug from the market under certain conditions.²³ But the drug is available for use. And because FDA does not regulate the practice of medicine (or at least, it says it doesn't and many agree²⁴), clinicians can prescribe the drug, even for uses beyond those approved by FDA.²⁵ This off-label use can comprise much of a drug's use.²⁶

16. *Id.* A great many drug candidates, to be sure, are *not* safe and effective for human use, and the attrition rate in the drug development pipeline is quite high. See Michael Hay et al., *Clinical Development Success Rates for Investigational Drugs*, 32 NATURE BIOTECH. 40, 40–41 (2014).

17. Ciociola et al., *supra* note 14, at 622.

18. *Id.*

19. 21 C.F.R. § 211 (2017) (regulating manufacturing practices for finished pharmaceuticals).

20. See *infra* Section I.B.1.c.

21. See 21 C.F.R. § 202 (regulating prescription drug advertising); *id.* § 99 (regulating off-label promotion of drugs). But see Christopher Robertson, *When Truth Cannot Be Presumed: The Regulation of Drug Promotion Under an Expanding First Amendment*, 94 B.U. L. REV. 545, 546–55 (2014) (describing recent cases limiting FDA's authority to regulate off-label promotion); Patricia J. Zettler, *The Indirect Consequences of Expanded Off-Label Promotion*, 78 OHIO ST. L.J. 1053, 1076–97 (2017) (noting potential consequences of those limits).

22. 21 U.S.C. § 355-1 (2012) (regulating with Risk Evaluation and Mitigation Strategies (REMS)); see, e.g., Barbara J. Evans, *Seven Pillars of a New Evidentiary Paradigm: The Food, Drug, and Cosmetic Act Enters the Genomic Era*, 85 NOTRE DAME L. REV. 419, 503–15 (2010) (describing REMS).

23. 21 U.S.C. § 355(e) (describing drug withdrawal procedures); 21 C.F.R. § 314.150 (explaining drug approval withdrawals).

24. See, e.g., Patricia J. Zettler, *Toward Coherent Federal Oversight of Medicine*, 52 SAN DIEGO L. REV. 427, 430 (2015) (“[T]he conventional wisdom among courts, lawmakers, and administrative agencies is that states regulate medical practice, while the federal government regulates medical products.”). But see *id.* at 460–66 (arguing that FDA in fact indirectly regulates medical practice through approval and REMS decisions, and in rare instances directly regulates medical practice).

25. See, e.g., Ryan Abbott & Ian Ayres, *Evidence and Extrapolation: Mechanisms for Regulating Off-Label Uses of Drugs and Devices*, 64 DUKE L.J. 377, 387–88 (2014) (“[O]nce a drug is approved, physicians may prescribe the drug without restriction.”).

26. See, e.g., Randall S. Stafford, *Regulating Off-Label Drug Use—Rethinking the Role of the FDA*, 358 NEW ENG. J. MED. 1427, 1427 (2008) (“A 2003 report

The timing of approval matters not only for the exercise of regulatory powers, but also for FDA's ability to gather information. Drug sponsor motivation changes at approval. Before, sponsors are highly motivated to provide FDA with whatever information it needs to win approval. After, providing information risks raising problems or challenging the profitable status quo. Against this backdrop, when is the right time, along a timeline of increasing information about a drug, to make the drug available for use in the course of patient care? Is the current focus on preclinical trials the best way to learn about the effects of drugs? The following Sections consider the underlying tradeoff between access and information and a set of ways to blur the line of drug approval and thus make that tradeoff less sharp.

A. THE UNDERLYING TRADEOFF BETWEEN ACCESS AND INFORMATION

Some basic details about clinical trials help situate the debate about when to approve drugs. FDA typically requires multiple randomized control clinical trials to establish safety and efficacy.²⁷ But randomized clinical trials have inherent limitations.²⁸ They are necessarily small—even the largest are numbered in the thousands—so while they can show average efficacy and basic safety, they cannot catch rare side effects or subtle differences between different patient groups.²⁹ Trials typically exclude patients with other diseases or who are taking other drugs, which doesn't reflect the reality of many patients.³⁰ Similarly, trials often exclude relevant populations like pregnant women and children.³¹ Patients involved in trials are also

showed that for the 3 leading drugs in each of the 15 leading drug classes, off-label use accounted for approximately 21% of prescriptions.”).

27. Ciociola et al., *supra* note 14, at 621.

28. See Laakmann, *supra* note 6, at 327–30 (listing various limitations inherent to randomized clinical trials (RCTs)).

29. See *id.* at 327–28 (claiming three thousand participants as the typical enrollment in Phase III clinical trials while adverse reactions to drugs occurs at a ratio of one-in-one-thousand, meaning few, if any, participants will statistically suffer from an adverse reaction during such a trial).

30. *Id.* at 327.

31. See, e.g., Patrino H.Y. Caldwell et al., *Clinical Trials in Children*, 364 LANCET 803, 803 (2004) (“In the absence of specific trial-based data in children, clinicians, families and policy-makers are forced to extrapolate from results of studies in adults. This extrapolation is often inappropriate because children have a different range of diseases, and metabolise medications differently, resulting in responses to treatment that are unpredictably different to adults.”); Barbara A. Noah, *The Inclusion of Pregnant Women in Clinical Research*, 7 ST. LOUIS U. J. HEALTH L. & POL'Y 353, 355 (2014) (“Although there has been good

subject to much more careful monitoring than in the real world, so what we see in real-world use may not mirror what we see in trials.³² Last but not least, trials are usually relatively short—they may last for months or years, but this does not tell us how a drug will perform (or its potential safety risks) over the course of decades or a lifetime.³³

Against this backdrop of clinical trials' limitations, an ongoing debate questions how much information should be gathered before drug approval. On one side are proponents for substantially earlier access to new drugs. In this view, FDA's role should be sharply limited; once a drug has been shown to be safe, it should be available for use by patients and providers without additional requirements to demonstrate efficacy.³⁴ The classic case arguing this point is *Abigail Alliance v. von Eschenbach*.³⁵ There, a group of terminally ill patients sued FDA, claiming a constitutional right to access experimental drugs that had been demonstrated "safe" (at least according to the patient advocates) because they had completed Phase I trials, but had not yet been proven effective.³⁶ The D.C. Circuit held en banc in 2007 that no such right exists.³⁷ Five years later, Andrew von Eschenbach—FDA Commissioner from 2006 to 2009 and named defendant in

progress in the inclusion of women in clinical research, the challenges of studying the safety of drugs in pregnant women has caused clinical research with this population to lag, leaving physicians and patients with inadequate data on which to base prescribing decisions.”)

32. See Rachel E. Sherman et al., *Real-World Evidence—What Is It and What Can It Tell Us?*, 375 NEW ENG. J. MED. 2293, 2294–96 (2016) (discussing limitations to clinical trials and real-world evidence).

33. See Rebecca S. Eisenberg & W. Nicholson Price, II, *Promoting Healthcare Innovation on the Demand Side*, 4 J.L. & BIOSCI. 3, 12–14 (2017). The challenge of clinical trial length may also have impacts on incentives for drug development. Longer clinical trials cut more into a drug's patent life, which may lower incentives to develop drugs that require long trials. See Eric Budish et al., *Do Firms Underinvest in Long-Term Research? Evidence from Cancer Clinical Trials*, 105 AM. ECON. REV. 2044, 2044–49 (2015) (showing lower investment for drugs with long clinical trials). But see Vinay Prasad & Stephan Lindner, *Why Is Research in Early-Stage Cancer Research So Low? A Re-Assessment of Budish, Roin and Williams* (2015) (June 15, 2017) (unpublished manuscript) (on file with *Minnesota Law Review*) (questioning this result).

34. Andrew von Eschenbach, *Medical Innovation: How the U.S. Can Retain Its Lead*, WALL ST. J., Feb. 14, 2012, at A19.

35. *Abigail All. for Better Access to Developmental Drugs v. von Eschenbach*, 495 F.3d 695, 707–10 (D.C. Cir. 2007).

36. *Id.* at 697–99.

37. *Id.* at 712–15; see also *United States v. Rutherford*, 442 U.S. 544, 554–59 (1979) (holding that terminally ill patients could not access the unapproved drug Laetrile under the Food, Drug, and Cosmetic Act).

Abigail Alliance—authored a prominent *Wall Street Journal* article arguing that FDA should approve drugs based on safety alone, letting efficacy be proven later by the market.³⁸

This view has at least two problems. First, characterization of a drug as safe depends on whether it conveys a benefit, and is thus tough to disentangle from whether the drug is effective.³⁹ Second, preclinical trials are better at demonstrating efficacy than overall safety (after all, it's what they are designed to do); they can show a lack of immediate toxicity, but they typically cannot show long-term safety or identify rare side effects.⁴⁰ Nevertheless, the argument that FDA should address only safety has considerable power.

The power of the safety-only view has most recently manifested in a spate of right-to-try laws.⁴¹ Thirty-seven states now have laws that purport to allow patients access to experimental drugs before FDA approval.⁴² These laws have had little practical impact in increasing access so far, in part because of limited incentives for drug manufacturers to provide early access to experimental drugs outside of FDA's existing processes.⁴³ But they clearly reflect the view that FDA should serve a more limited role in evaluating efficacy.⁴⁴ Most of these state laws also faced federal preemption concerns when passed,⁴⁵ but Congress has recently passed its own federal right-to-try law.⁴⁶

On the other side of the debate, others defend FDA's caution and suggest that even more may be warranted.⁴⁷ This view has

38. von Eschenbach, *supra* note 34.

39. Indeed, this was FDA's rationale for evaluating drug efficacy well before the Kefauver-Harris Amendments gave it that explicit authority in 1962. DANIEL CARPENTER, REPUTATION AND POWER: ORGANIZATIONAL IMAGE AND PHARMACEUTICAL REGULATION AT THE FDA 140–56 (2011). But this point is not essential to the story this Article tells.

40. See *supra* notes 27–33 and accompanying text.

41. See Patricia J. Zettler, *Pharmaceutical Federalism*, 92 IND. L.J. 845, 881–85 (2017) (explaining the process and purpose behind right to try laws).

42. *Id.* at 882.

43. *Id.* at 893–95; see also *id.* at 881–85.

44. *Id.* at 888–900.

45. *Id.* at 885–88.

46. Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Belina Right to Try Act of 2017, Pub. L. 115-176, 132 Stat. 1372 (2018).

47. See, e.g., Aaron S. Kesselheim & Jerry Avorn, *New “21st Century Cures” Legislation: Speed and Ease Vs Science*, 317 JAMA 581, 582 (2017) (arguing that emphasis on early access could reduce drug efficacy and safety standards and may reduce incentives for manufacturers to develop truly innovative and effective therapies); Chul Kim & Vinay Prasad, *Strength of Validation for Surrogate Endpoints Used in the US Food and Drug Administration's Approval of*

strong historical roots; much of FDA's national and international prestige was cemented by its caution over the antinausea drug Thalidomide and its refusal to approve the drug before a plague of severe birth defects in Europe revealed the drug's teratogenicity.⁴⁸ The Agency has maintained its requirements for extensive evidence in the face of calls for earlier access. This view is supported by safety and effectiveness problems that have resulted from earlier access in some circumstances, as described below.⁴⁹

B. BLURRING THE LINE OF DRUG APPROVAL

Flexible, blended approaches seek to avoid the stark terms of the tradeoff described above by allowing earlier access and promoting later data gathering. Some flexibility in FDA's process has already been enacted into law.⁵⁰ But problems continue to arise in striking the proper balance on when drugs should be available and how, and thus scholars continue to suggest ways to improve the situation. These solutions tend to recognize that FDA approval occupies a somewhat arbitrary place on the slope of increasing knowledge, and they seek, in various ways, to

Oncology Drugs, 91 MAYO CLINIC PROC. 713, 723 (2016); David Gorski, *Donald Trump Versus the FDA: Is the Standard of Evidence for Drug Approval Actually Too Low Rather Than Too High?*, SCI-BASED MED. (Feb. 6, 2017), <https://sciencebasedmedicine.org/donald-trump-versus-the-fda-part-2>; Matthew Herper, *The FDA Is Basically Approving Everything. Here's the Data To Prove It*, FORBES (Aug. 20, 2015), <https://www.forbes.com/sites/matthewherper/2015/08/20/the-fda-is-basically-approving-everything-heres-the-data-to-prove-it>.

48. CARPENTER, *supra* note 39, at 228–97; *see also* R. Alta Charo, *Speed Versus Safety in Drug Development*, in *FDA IN THE TWENTY-FIRST CENTURY: THE CHALLENGES OF REGULATING DRUGS AND NEW TECHNOLOGIES* 252, 253 (I. Glenn Cohen & Holly Fernandez Lynch eds., 2015) (“The turning point [of FDA control] undoubtedly lies in the experience with thalidomide . . .”).

49. *See* Jonathan J. Darrow et al., *New FDA Breakthrough-Drug Category—Implications for Patients*, 370 NEW ENG. J. MED. 1252, 1253–54 (2014) (noting that problems of safety and efficacy occur at a higher rate in drugs approved through accelerated pathways); Nicholas S. Downing et al., *Clinical Trial Evidence Supporting FDA Approval of Novel Therapeutic Agents, 2005–2012*, 311 JAMA 368, 369 (2014); Nicholas S. Downing et al., *Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010*, 317 JAMA 1854, 1854 (2017); *infra* Parts I.B.1, I.B.2 (describing faster approval and earlier access).

50. For a summary of recently approved drugs falling under the blended approach, *see Novel Drugs Summary 2015*, FDA (Jan. 2016), <https://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/ucm474696.htm>.

change the information/access landscape around approval itself.⁵¹ This Section discusses existing approaches to approval flexibility, considers challenges to those approaches, and then identifies a set of scholars' proposals for improvement.⁵²

1. Earlier Access with Postmarket Information

Line-blurring approaches generally aim to get a new drug to patients sooner, while continuing the task of generating data about that drug after it has become available to patients. So far, Congress and FDA have adopted several ways to do this. Ways of getting the drug to patients sooner fall into two buckets: (1) permitting companies to allow certain patients to access the drug before it has been approved; and (2) speeding up the approval process. Gathering information about the drug can also happen in multiple ways, including various types of postmarket drug-safety surveillance and FDA-mandated studies.

a. Faster Approval and Earlier Access

Four mechanisms have been created to let FDA approve drugs faster than normal: (1) accelerated approval; (2) breakthrough therapy designation; (3) fast-track designation; and (4) priority review.⁵³ Accelerated approval explicitly moves the point of approval earlier by deliberately trading earlier information for earlier access by patients, with commitments by the drug sponsor to develop more information later.⁵⁴ This program

51. For an interesting examination of the difference between experimental and nonexperimental treatment in the context of medical care more generally, and the implications of that difference for informed consent in care, see Lars Noah, *Informed Consent and the Elusive Dichotomy Between Standard and Experimental Therapy*, 28 AM. J.L. & MED. 361 (2002).

52. An exhaustive approach to proposed solutions is beyond the scope of this Article. For a description of related approaches not considered here, see, for example, Ryan Abbott, *Big Data and Pharmacovigilance: Using Health Information Exchanges to Revolutionize Drug Safety*, 99 IOWA L. REV. 225 (2013) (arguing for the use of health information exchanges to enable drug surveillance efforts and proposing a bounty for third parties who identify drug safety problems); Abbott & Ayres, *supra* note 25 (arguing for increased reporting and post-market study of off-label uses of drugs and tiered labeling for different uses).

53. See AS Kesselheim & JJ Darrow, *FDA Designations for Therapeutics and Their Impact on Drug Development and Regulatory Review Outcomes*, 97 CLINICAL PHARMACOLOGY & THERAPEUTICS 29, 31–32 (2015). Other mechanisms try to speed up FDA's normal process by providing increased resources and statutory timing mandates; the various Prescription Drug User Fee Acts take this tack. *Id.*

54. See *Accelerated Approval*, FDA (Sept. 15, 2014), <https://www.fda.gov/ForPatients/Approvals/Fast/ucm405447.htm>.

is available for new drugs for serious medical conditions that fill unmet needs.⁵⁵ Under accelerated approval, FDA can approve a drug based on surrogate endpoints instead of true clinical endpoints.⁵⁶ That is, instead of concluding that a drug is effective based on something we care about (e.g., fewer heart attacks), FDA can base its decision on a surrogate that we think is related to the clinical outcome we care about (e.g., lower cholesterol, which is linked to fewer heart attacks). But sometimes this lack of direct information means that the approved drug doesn't actually help achieve the clinical endpoint—that is, it doesn't help patients.⁵⁷ FDA tries to combat this problem by mandating postapproval studies, but these often do not work out as planned.⁵⁸ The other three mechanisms focus on more intense communication between FDA and the drug sponsor or on allocating resources within FDA to focus on a drug of particular interest, and thus do not implicate the information/access tradeoff as clearly.⁵⁹ Nevertheless, these faster mechanisms also come with risks based on their speed and potentially lowered information standards.⁶⁰

A separate set of programs doesn't speed up the FDA approval process, but instead lets more patients access a drug before it has been approved. These programs are collectively known as "expanded access" or "compassionate use," and include both "individual access," where a drug is offered to one patient (or a very small group of patients), and a "treatment IND," where an investigational new drug is used to treat a group of patients.⁶¹ Notably, data from such programs are not generally collected systematically for use by FDA in the drug approval process.⁶²

55. *Id.*

56. *Id.*

57. This lack of efficacy can occur for multiple reasons, including that the surrogate is not a good marker for the clinical endpoint and that long-term effects do not mirror short-term trial results. *See, e.g.,* John R. Johnson et al., *Accelerated Approval of Oncology Products: The Food and Drug Administration Experience*, 103 J. NAT'L CANCER INST. 636, 636 (2011) (concluding that, in a review of oncology drugs granted accelerated approval based on surrogate endpoints, confirmatory evidence of safety and efficacy was eventually developed for about half of the drugs after postmarket studies (twenty-six out of forty-seven), with three removed from the market and trials for the remaining eighteen not yet completed at the time of the review).

58. *See infra* notes 84–87 and accompanying text.

59. *See* Kesselheim & Darrow, *supra* note 53, at 31–33.

60. *See id.* at 33–35.

61. *See* Laakmann, *supra* note 6, at 321–24.

62. *Id.* at 331.

b. *Postmarket Surveillance*

On the other side of the picture, a number of existing mechanisms help FDA gather information about drugs after they have been approved and enter clinical care. Drug manufacturers are required to report adverse events using the FDA Adverse Event Reporting System (FAERS), but this includes only adverse events that are reported to the manufacturer; most are not.⁶³ Clinicians and patients may also report adverse events directly to FDA, but few do.⁶⁴ These systems are passive, in that FDA waits for others to report potential problems. Unfortunately, only around one percent of serious adverse events are reported to FDA through these passive channels.⁶⁵

Under the Food and Drug Administration Amendments Act of 2007 (FDAAA), FDA has vastly increased its own active surveillance capacity.⁶⁶ It created the Sentinel System, which aims to answer postmarket safety questions by surveilling the electronic health records (EHRs) of over 100,000,000 Americans.⁶⁷ Sentinel is federated; data stay on the systems of FDA's partners (hospitals, health systems, and similar entities), which return aggregated data responsive to queries that FDA asks the system.⁶⁸ Although this vastly increases the possibility of verifying potential problems once they come to FDA's attention, the system is much less helpful at actively noticing problems in the first

63. 21 C.F.R. § 314.80(c) (2017) (reporting requirements); Jonathan J. Darrow, *Crowdsourcing Clinical Trials*, 98 MINN. L. REV. 805, 837 (2014) (stating that most adverse events go unreported).

64. See Toshiyuki Sakaeda et al., *Data Mining of the Public Version of the FDA Adverse Event Reporting System*, 10 INT'L J. MED. SCI. 796, 800 (2013).

65. See Efthimios Parasidis, *FDA's Public Health Imperative: An Increased Role for Active Postmarket Analysis*, in FDA IN THE TWENTY-FIRST CENTURY, *supra* note 48, at 286, 289.

66. See Food and Drug Administration Amendments Act of 2007 § 905, 21 U.S.C. § 355(k)(3)–(4) (2012).

67. See *id.* § 355(k)(3) (granting statutory authority to create Sentinel); INST. OF MED., DIGITAL INFRASTRUCTURE FOR THE LEARNING HEALTH SYSTEM: THE FOUNDATION FOR CONTINUOUS IMPROVEMENT IN HEALTH AND HEALTH CARE 259–65 (2011) [hereinafter INST. OF MED., DIGITAL INFRASTRUCTURE] (describing Sentinel and its Mini-Sentinel pilot program). For discussions of privacy and informed consent issues in the context of the Sentinel System in particular, see, for example, KRISTEN ROSATI, AN ANALYSIS OF LEGAL ISSUES RELATED TO STRUCTURING FDA SENTINEL INITIATIVE ACTIVITIES 73–74 (2009); KRISTEN ROSATI ET AL., HIPAA AND COMMON RULE COMPLIANCE IN THE MINI-SENTINEL PILOT (2010); Barbara J. Evans, *Congress' New Infrastructural Model of Medical Privacy*, 84 NOTRE DAME L. REV. 585 (2009) [hereinafter Evans, *New Infrastructural Model*].

68. 21 U.S.C. § 355(k)(3).

place. Someone has to know what questions to ask,⁶⁹ and asking the questions is itself a relatively complex task.⁷⁰ In addition, FDA has limited resources to run studies using Sentinel on its own initiative.⁷¹

c. *Postmarket Studies*

Finally, FDA need not rely on surveillance alone; in certain situations, it can require active studies by drug sponsors after a drug has been approved. The FDAAA authorizes FDA to impose postmarket study requirements as a condition of approval;⁷² alternatively, the drug sponsor can voluntarily agree to conduct such studies to ease the path to approval.⁷³ FDA can also impose such requirements after a drug has been approved in response to new evidence of safety risks, which are defined very broadly.⁷⁴

Section 505(o)(3) of the FDAAA establishes a preference that FDA must follow when deciding what sort of postmarket activity to require.⁷⁵ If the safety question can be answered using FDA's regular resources—including FAERS and Sentinel—FDA must use those.⁷⁶ If those resources “will not be sufficient,”⁷⁷ FDA can order the manufacturer to perform a postmarketing “study,” which includes epidemiological studies, other observational studies, lab experiments, and animal studies—essentially anything that is not a clinical trial.⁷⁸ If that type of non-human-interventional study will not be sufficient, only then can FDA require that the drug sponsor perform a postmarketing clinical

69. See Eisenberg & Price, *supra* note 33, at 43.

70. See Darrow, *supra* note 63, at 841.

71. Barbara J. Evans, *The Ethics of Postmarketing Observational Studies of Drug Safety Under 505(o)(3) of the Food, Drug, and Cosmetic Act*, 38 AM. J.L. & MED. 577, 597 (2012).

72. 21 U.S.C. § 355(o)(3).

73. FDA, GUIDANCE FOR INDUSTRY: POSTMARKETING STUDIES AND CLINICAL TRIALS—IMPLEMENTATION OF SECTION 505(O)(3) OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT 7 (2011) [hereinafter FDA, POSTMARKETING STUDIES] (noting the distinction between postmarketing studies required under the FDAAA and voluntary postmarketing study commitments that do not meet FDAAA statutory criteria for required postmarketing studies and clinical trials).

74. See 21 U.S.C. § 355(o)(3)(B); Evans, *supra* note 71, at 585; see also Parasidis, *supra* note 65, at 293–94 (arguing that new safety information is defined so broadly as to allow the imposition of postmarket studies for essentially all drugs).

75. See 21 U.S.C. § 355(o)(3).

76. *Id.* § 355(o)(3)(D)(i)–(ii); *id.* § 355(k)(1), (3).

77. *Id.* § 355(o)(3)(D)(i)–(ii).

78. FDA, POSTMARKETING STUDIES, *supra* note 73, at 4.

trial, defined as “any prospective investigation[] in which the [drug sponsor] or investigator determines the method of assigning the drug[] or other interventions to . . . human subjects.”⁷⁹ Essentially, postmarket clinical trials are a last resort, to be used only if FDA’s own mechanisms or firm-conducted observational studies are inadequate.

2. Challenges

Line-blurring trades earlier access with less information for the promise of later information. Earlier access brings its own risks—otherwise, what would be the point of the regular process?⁸⁰ More intense postmarket information-gathering is supposed to alleviate that concern. With more information later, FDA can better observe how the drug works, catch problems earlier, and act if necessary.

Unfortunately, it turns out that collecting postmarket information is quite tricky. Drug sponsors don’t have especially good incentives to collect information about drugs that are already being sold and making a profit, especially if that information might reveal safety problems or a lack of efficacy that could hurt sales or result in the drugs being removed from the market.⁸¹ Voluntary submission of data by patients and clinicians is infrequent, patchy, and biased—possibly good for finding previously unnoticed rare side effects and adverse reactions, but not very helpful for gathering evidence of efficacy or safety more broadly.⁸² And Sentinel, while impressive, has relatively limited resources and is better for query-driven safety evaluations than noting new problems or demonstrating efficacy.⁸³

Conducting postmarket clinical trials is even harder than passively gathering information. Drug companies have the same limited incentives to generate potentially negative information about profit-generating drugs, but now those incentives are balanced against the high expense of clinical trials.⁸⁴ Patients often aren’t especially interested in being part of a randomized clinical trial on a drug that is already available for clinical use—why

79. *Id.*

80. *See*, Kesselheim & Darrow, *supra* note 53, at 29.

81. Eisenberg & Price, *supra* note 33, at 4.

82. *See supra* Section I.B.1.b.

83. *See supra* Section I.B.1.b.

84. *See* Eisenberg & Price, *supra* note 33, at 18. Other drug companies have even less incentive, unless they are conducting comparative-effectiveness research—which runs the risk of finding their own drugs less effective. *Id.*

take a fifty percent chance of getting the drug you want through a clinical trial when you could have a 100% chance of getting it through your clinician?⁸⁵ And if the drug has at least some evidence that it works better than alternatives available in such a trial, it may be arguably unethical even to conduct the trial.⁸⁶

As a result of some combination of these factors, postapproval trial commitments have not been a resounding success; a large number are never completed, even when required by FDA.⁸⁷

Finally, even when information *is* gathered that calls for decisive FDA action, the Agency may not act. FDA has a set of tools at its disposal, ranging from making voluntary requests to manufacturers, to requiring changes to a drug's label,⁸⁸ to imposing Risk Evaluation and Mitigation Strategies (REMS)⁸⁹ that can limit how drugs can be used, to requiring withdrawal of the drug from the market.⁹⁰ But it is harder to withdraw approval of a drug once it is already on the market than to delay or refuse approval in the first place because patients are already using it and some—rightly or wrongly—think it is helping them.⁹¹ Once patients are already taking a drug, intense political pressure can weigh against limiting future use of the drug.⁹² Withdrawal from the market does happen—the blockbuster drug Vioxx is a key example⁹³—but it is rare, and typically firms withdraw drugs

85. See Evans, *supra* note 71, at 587–88.

86. See LAWRENCE M. FRIEDMAN ET AL., FUNDAMENTALS OF CLINICAL TRIALS 45 (3d ed. 1996); see also BENGT D. FURBERG & CURT D. FURBERG, EVALUATING CLINICAL RESEARCH: ALL THAT GLITTERS IS NOT GOLD 21 (2d ed. 2007) (discussing the view that withholding a proven beneficial intervention may violate the ethical research standards of the Declaration of Helsinki).

87. See Kevin Fain et al., *The Food and Drug Administration Amendments Act and Postmarketing Commitments*, 310 JAMA 202, 202–03 (2013) (finding low completion rates); Steven Woloshin et al., *The Fate of FDA Postapproval Studies*, 377 NEW ENG. J. MED. 1114, 1114 (2017) (finding the same).

88. 21 U.S.C. § 355(o)(4) (2012).

89. *Id.* § 355-1.

90. 21 C.F.R. § 314.150 (2017).

91. See also Zettler, *supra* note 21, at 1092 (noting pressure on FDA to avoid withdrawing approval for the drug Avastin).

92. See, e.g., Shannon G. Gibson & Trudo Lemmens, *Niche Markets and Evidence Assessment in Transition: A Critical Review of Proposed Drug Reforms*, 22 MED. L. REV. 200, 216–17 (2014) (discussing this challenge in international contexts).

93. See generally Jennifer Couzin, *Withdrawal of Vioxx Casts a Shadow over COX-2 Inhibitors*, 306 SCIENCE 384 (2004).

voluntarily rather than under an FDA mandate.⁹⁴ Limiting an approved drug's use is also hard. FDA can limit the indications for which a drug is approved, but once the drug is available clinicians can readily prescribe it for off-label uses.⁹⁵ In extreme cases FDA may use REMS to limit how a drug is used,⁹⁶ but in run-of-the-mill cases, FDA's ability to control prescribing is quite limited.⁹⁷

In sum, line-blurring approaches to FDA approval are hard. Additions to the approval process have made it easier to get drugs to patients earlier, but the second part of the approach—collecting and using postapproval information—remains challenging.

3. Suggested Improvements

Several scholars have suggested how we might improve the system, especially postapproval information gathering. The five proposals below address different ways to link earlier access with better development of information after approval, whether in the health system generally, through conditional approval with standard evidence generation by firms, by encouraging patients to submit their own data for analysis, or by requiring active study by sponsors of all drugs.

Anna Laakmann argues that “the FDA should formally recognize the blurred line between experimentation and treatment by adopting a more fluid approach to its review of new medical technologies.”⁹⁸ She notes that a tremendous amount of information about drug safety and efficacy goes unrecorded or ignored, some preapproval (when patients ineligible for a trial get access through a different pathway),⁹⁹ but most postapproval (when clinical results are not recorded or are not available for

94. See Eisenberg & Price, *supra* note 33, at 10–12. Even there, FDA was reluctant to take postapproval data, generated by insurers rather than the drug sponsor, into consideration. See *id.*

95. See *supra* notes 25–26 and accompanying text.

96. See Gibson & Lemmens, *supra* note 92, at 212. This approach may face political challenges. See *id.* at 213.

97. See Zettler, *supra* note 21, at 1080–86. Gibson and Lemmens have suggested that insurers could shape drug use by reimbursing only for uses with supporting evidence, though they note political and practical difficulties with this approach. Gibson & Lemmens, *supra* note 92, at 213. Rebecca Eisenberg and I have suggested in a similar vein that insurers should develop information about drug use to save costs on unapproved uses. Eisenberg & Price, *supra* note 33, at 28–29.

98. Laakmann, *supra* note 6, at 305.

99. *Id.* at 331.

study).¹⁰⁰ Accordingly, she argues for the creation of a “central database which serves as a clearinghouse of experiential information on the effects of new drugs.”¹⁰¹ She links this proposal explicitly to those drugs that receive approval through fast-track procedures, but suggests that more drugs could become eligible for such procedures if their manufacturers would commit to her proposed scheme of data collection.¹⁰²

Alta Charo recognizes that many approaches “focus on getting drugs out faster and correcting mistakes later;”¹⁰³ to facilitate this approach, she suggests relying on conditional approval and associated marketing restrictions.¹⁰⁴ In a conditional-approval process, drugs for serious unmet needs are approved only on the condition that the drug sponsors later generate postapproval data by drug companies’ observational studies or clinical trials.¹⁰⁵ Charo suggests that such a system could enable FDA to place limits on marketing—such that drug use could be confined to those for whom strong evidence of safety and efficacy is available—that might otherwise be infeasible.¹⁰⁶ Shannon Gibson and Trudo Lemmens similarly advocate conditional approval, with limits enforced by the use of REMS, especially in the context of niche drugs and pharmacogenomics products.¹⁰⁷ Gibson and Lemmens argue for expanded postmarket data gathering to support these efforts.¹⁰⁸

Jonathan Darrow comes at the blurred line of drug approval from a different direction, relying on patients to share experiential data themselves.¹⁰⁹ He notes that FDA approval—even in the normal order—still leaves many effects of drugs unknown because of the inherent limitations of preapproval clinical trials,

100. *Id.* at 345.

101. *Id.* at 341.

102. *Id.*

103. Charo, *supra* note 48, at 251.

104. *Id.* at 257–59.

105. *Id.*

106. *Id.* at 257–63.

107. Shannon Gibson & Trudo Lemmens, *Overcoming “Pre-market Syndrome”: Promoting Better Postmarket Surveillance in an Evolving Drug-Development Context*, in *FDA IN THE TWENTY-FIRST CENTURY*, *supra* note 48, at 268, 275–78.

108. *Id.* at 278–79. Trudo and Lemmens also note a *third* binary becoming blurred: coverage with evidence development, a scheme in which reimbursement for a drug is tied to the continuing development of evidence for its use. *Id.* at 279–81.

109. Darrow, *supra* note 63, at 826.

and thus that even postapproval use is still essentially experimental for some years after approval.¹¹⁰ This is particularly true in subject populations excluded from the clinical trials, such as pregnant women and children.¹¹¹ Thus Darrow suggests that FDA should grant drugs conditional approval and then conduct “crowdsourced clinical trials,” wherein patients taking the drug provide information about their experience through a widely available web form where they can also learn more about the drug.¹¹²

Efthimios Parasidis would push harder on FDA to require postmarket studies.¹¹³ He argues that FDA has focused almost entirely on premarket evaluations, and that its system of “passive postmarket surveillance” is seriously inadequate.¹¹⁴ Accordingly, he argues that FDA should mandate active postmarket surveillance by sponsors for *all* marketed drugs—either as a condition of approval for new drugs, or as a reaction to the safety concerns raised by off-label use for already-approved drugs.¹¹⁵

4. Information Gathering and the 21st Century Cures Act

Overall, the regulatory pathways and scholarly proposals highlighted above reflect a developing reality for FDA approval. Premarket review is crucial, but has unavoidable flaws: premarket clinical trials have key limitations, and FDA faces strong pressure for access even before those trials can develop what information they are able. The result is a system gradually shifting toward a blended approach—a “lifecycle” approach to developing evidence, in the words of an influential Institute of Medicine report—where information gathering both before and after approval are each key to regulation of drugs.¹¹⁶ Congress has reacted to this shift.

110. *Id.* at 810–11.

111. *See supra* note 31 and accompanying text.

112. Darrow, *supra* note 63, at 826–31. *But see* Ameet Sarpatwari et al., *Crowdsourcing Public Health Experiments: A Response to Jonathan Darrow’s Crowdsourcing Clinical Trials*, 98 MINN. L. REV. 2326, 2329–33 (2014) (noting that FDA’s MedWatcher tool is already relatively flexible, and that self-reported observational studies such as the one Darrow proposes may be vulnerable to self-selection bias).

113. Parasidis, *supra* note 65.

114. *Id.* at 288–90; *see also* Efthimios Parasidis, *Patients over Politics: Addressing Legislative Failure in the Regulation of Medical Products*, 2011 WISC. L. REV. 929, 932–33 (describing the legislative pressures that have resulted in FDA’s prioritization of premarket review over postmarket surveillance).

115. Parasidis, *supra* note 65, at 292–95.

116. *See* INST. OF MED., DRUG SAFETY, *supra* note 6.

In December 2016, President Obama signed into law the Cures Act, which among other things addresses the use of real-world evidence in FDA decisionmaking.¹¹⁷ Section 3022 requires that FDA “establish a program to evaluate the potential use of real world evidence—(1) to help to support the approval of a new indication for a[n approved] drug . . . and (2) to help to support or satisfy postapproval study requirements.”¹¹⁸ The Cures Act defines “real world evidence” as “data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials.”¹¹⁹ Although the Cures Act’s definitions are scanty, “real world evidence” likely includes data derived from studies undertaken in the course of clinical care,¹²⁰ even the randomized interventional studies discussed below, enabled by an LHS.¹²¹ The Cures Act does not require FDA to actually use real-world evidence—only to evaluate its potential use and to issue guidance¹²²—but it clearly contemplates that a broad swath of evidence gathered in the course of clinical care may be used for the purposes of broadening a drug’s approved indications or monitoring safety after approval. These purposes do not capture everything that can be done to evaluate drugs in an LHS, but they encourage substantial FDA involvement.

FDA has expressed its intention to consider real-world evidence, beginning even before the passage of the Cures Act. In a prominent 2016 article, Robert Califf, the outgoing Commissioner of FDA, wrote with his colleagues about the uses of real-

117. 21st Century Cures Act, Pub. L. No. 114-255, § 3022, 130 Stat. 1033, 1096–98 (2016) (to be codified at 21 U.S.C. § 505F (2012)) (amending the Food, Drug, and Cosmetic Act to add § 505F).

118. *Id.*

119. *Id.*

120. Although the Act does not define “clinical trials,” section 2053 refers to “applicable clinical trial[s] as defined in section 402(j) [of the Public Health Services Act].” § 2053, 130 Stat. at 1076. That section, codified at 42 U.S.C. § 282(j) (2012), defines an “applicable clinical trial” to include an “applicable drug clinical trial,” *id.* § 282(j)(1)(A)(i), which in turn is defined as a “controlled clinical investigation, other than a phase I clinical investigation, of [a drug or a biologic],” *id.* § 282(j)(1)(A)(iii)(I), where a “clinical investigation” is defined in the Code of Federal Regulations (CFR), *id.* § 282(j)(1)(A)(iii)(II). Finally, that CFR provision defines a “clinical investigation” as “any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug *except for the use of a marketed drug in the course of medical practice.*” 21 C.F.R. § 312.3(b) (2017) (emphasis added).

121. *See infra* Section III.B.

122. 21st Century Cures Act § 3022.

world evidence in evaluating drugs.¹²³ They noted the possibilities of using data collected during ongoing health care, and the fact that these data can avoid the challenges and disadvantages of relatively small, limited-population, short-term clinical trials.¹²⁴

FDA appears similarly supportive under Commissioner Scott Gottlieb. An August article by FDA officials addressed the definition and gathering of real-world evidence in considerable detail.¹²⁵ In September 2017, Commissioner Gottlieb described the adoption of real-world evidence in regulatory decisions at FDA as a high priority, arguing that the Agency “need[s] to close the evidence gap between the information [it] use[s] to make [its] decisions, and the evidence increasingly used by the medical community, by payers, and by others charged with making health-care decisions.”¹²⁶ He criticized the traditional approach that evaluates a product “based on a data set that speaks to a limited and rigidly constructed circumstance, when the clinical use, and in turn the evidence we might have to evaluate the product, could have been far richer, far more diverse, and more informative[.]”¹²⁷ Finally, he explicitly addressed the blurring of the line between premarket and postmarket evaluation of medical products, and suggested that FDA is embracing this blurring.¹²⁸

This Part has described the development of an approach to FDA approval that broadens the scope of information gathering, focusing not only on premarket clinical trials but also on information developed after approval. This information is useful not only to balance the possibility of earlier access, but also more generally to align what we know about drugs with how they are actually used and how they actually work. So far, so good: this ongoing shift has been recognized before—including by FDA—even if the Cures Act is a new source of statutory impetus and authorization. But how does this shift square with other changes

123. Sherman et al., *supra* note 32.

124. *Id.*

125. See generally Jonathan P. Jarow et al., *Multidimensional Evidence Generation and FDA Regulatory Decision Making: Defining and Using “Real-World” Data*, 318 JAMA 703 (2017).

126. Scott Gottlieb, Commissioner, FDA, Remarks by Dr. Gottlieb to the National Academy of Sciences on the Impact of Real World Evidence on Medical Product Development (Sept. 19, 2017), <https://www.fda.gov/NewsEvents/Speeches/ucm576519.htm>.

127. *Id.*

128. *Id.*

to the health-care system more broadly? Part II addresses this question.

II. A LEARNING HEALTH SYSTEM

Alongside the evolution of the FDA approval system, the broader health-care system is itself slowly evolving into an LHS. The idea of an LHS crystallized in a 2007 report by the Institute of Medicine, which described an LHS as “one in which knowledge generation is so embedded into the core of the practice of medicine that it is a natural outgrowth and product of the health-care delivery process and leads to continual improvement in care.”¹²⁹ Other reports have followed.¹³⁰

Why do we need an LHS? The health system today involves far too much error and unnecessary treatment, with high costs in both money and health.¹³¹ Many provider actions are undertaken with relatively little evidence about how well they work and how they might work best.¹³² Even when there is new evidence of best practices, it takes a long time for improvements to make their way into routine care.¹³³ In large part, this is because clinical trials, with their inherent limits,¹³⁴ simply don’t provide all the information the health system needs to provide the best care.¹³⁵ At the same time, though, the health system itself generates vast amounts of information about how clinical care

129. INST. OF MED., LEARNING HEALTHCARE, *supra* note 7, at 6.

130. See, e.g., INST. OF MED., BEST CARE AT LOWER COST: THE PATH TO CONTINUOUSLY LEARNING HEALTH CARE IN AMERICA (Mark Smith et al. eds., 2013); INST. OF MED., CLINICAL DATA AS THE BASIC STAPLE OF HEALTH LEARNING: CREATING AND PROTECTING A PUBLIC GOOD (Claudia Grossman et al. eds, 2010); INST. OF MED., DIGITAL INFRASTRUCTURE, *supra* note 67.

131. See, e.g., INST. OF MED., TO ERR IS HUMAN: BUILDING A SAFER HEALTH SYSTEM (Linda T. Kohn et al. eds., 2000).

132. INST. OF MED., LEARNING HEALTHCARE, *supra* note 7, at 1–2.

133. See Zoë S. Morris et al., *The Answer Is 17 Years, What Is the Question: Understanding Time Lags in Translational Research*, 104 J. ROYAL SOC’Y MED. 510 (2011) (noting repeated findings that health-care innovations take an average of seventeen years to be incorporated into clinical practice).

134. See *supra* notes 28–33 and accompanying text.

135. INST. OF MED., LEARNING HEALTHCARE, *supra* note 7, at 2 (“[B]eyond determinations of basic efficacy and safety, the dependence on individually designed, serially constructed, prospective studies to establish relative effectiveness and individual variation in efficacy and safety is simply impractical for most interventions.” (citations omitted)); cf. Kayte Spector-Bagdady et al., *Stemming the Standard-of-Care Sprawl: Clinician Self-Interest and the Case of Electronic Fetal Monitoring*, 47 HASTINGS CTR. REP. 16 (2017) (discussing reasons other than a lack of knowledge that evidence-based practices do not diffuse rapidly into clinical care).

works—because clinicians provide care, patients receive it, and how those things happen can tell us how the care is working (or isn't). Unfortunately, we've traditionally ignored that information; the health system doesn't capture it particularly well, and typically doesn't use it well when it is captured.¹³⁶ An LHS could change that.

In an LHS, health-care actors (clinicians, hospitals, pharmacies, and others) systematically capture data about what actually happens in health care—patients' symptoms, how they are treated, and how they do over time—in EHRs.¹³⁷ This part happens to some extent already, though that is quite a recent development, and the transition to EHRs is very much still a work in progress.¹³⁸ In an LHS, data capture is much more systematic and pervasive.¹³⁹ But an LHS need not only observe care. "Practical" or "pragmatic" clinical trials involve actively generating knowledge in the context of clinical care by, for instance, randomizing between different treatments that are all accepted standards of care and measuring the results.¹⁴⁰

An LHS not only generates data, it uses those data to learn. Actors in the system continuously analyze collected data to find new evidence about what works and what doesn't—which patients need surgery and which don't, which drugs work better for whom, what quality improvement mechanisms make a difference, and which standard-of-care practice is superior.¹⁴¹ These results are then fed back into the system, where information-sharing occurs not only through traditional publication but also through updated practice guidelines, presentations, or even automatically, such as when EHRs themselves provide decision support to providers and make recommendations based on the most up-to-date information.¹⁴² The overall goal is to use the

136. See, e.g., Laakmann, *supra* note 6, at 345 ("An additional cost of the FDA's predominate focus on premarketing review is the loss of 'phantom' experiential information that is not effectively captured in the treatment setting.").

137. INST. OF MED., LEARNING HEALTHCARE, *supra* note 7, at 17–18.

138. See generally SHARONA HOFFMAN, ELECTRONIC HEALTH RECORDS AND MEDICAL BIG DATA: LAW AND POLICY (2016) (detailing the challenges and successes of Electronic Health Records systems and recommending approaches for the improvement of such systems).

139. See INST. OF MED., LEARNING HEALTHCARE, *supra* note 7, at 48.

140. See Sean R. Tunis et al., *Practical Clinical Trials: Increasing the Value of Clinical Research for Decision Making in Clinical and Health Policy*, 290 JAMA 1624, 1626 (2003); *infra* Section III.B.

141. See generally Sarah M. Greene et al., *Implementing the Learning Health System: From Concept to Action*, 157 ANNALS INT. MED. 207 (2012).

142. *Id.*

vast troves of data that health care generates to learn more about and improve the process of providing that care—and to do it repeatedly, continuously learning and improving.¹⁴³

Stating the idea is easy, but getting it to work is hard. The 2007 Institute of Medicine report notes several challenges related to data quality, health-data infrastructure, actually conducting studies, implementing changes, and other aspects of an LHS;¹⁴⁴ there is a growing literature around how to actually implement an LHS.¹⁴⁵ The fragmentation of our health-care system—different actors collect different information in different settings—makes the goal harder to achieve.¹⁴⁶ In addition, the ethics of an LHS are also contested.¹⁴⁷ Rather than attempting to address all of these issues—themselves the subject of a substantial literature—this Article focuses on the line-blurring involved in an LHS, the implications of that blurring for gathering and using information about drugs, and related legal complications.

An LHS blurs the line between research and clinical care. The classic model has these two sharply separated: research aims at systematically generating generalizable knowledge, while care aims to improve an individual patient's health.¹⁴⁸ In

143. See, e.g., *id.* at 209–10 (describing the implementation of this continuous cyclic approach).

144. INST. OF MED., LEARNING HEALTHCARE, *supra* note 7, at 1–6.

145. See, e.g., Greene et al., *supra* note 141; Ronald A. Paulus et al., *Continuous Innovation in Health Care: Implications of the Geisinger Experience*, 27 HEALTH AFFAIRS 1235 (2008); Wayne Psek et al., *Leadership Perspectives on Operationalizing the Learning Health Care System in an Integrated Delivery System*, 4 EGEMS 1233 (2016); Wayne A. Psek et al., *Operationalizing the Learning Health Care System in an Integrated Delivery System*, 3 EGEMS 1122 (2015); Glenn D. Steele et al., *How Geisinger's Advanced Medical Home Model Argues the Case for Rapid-Cycle Innovation*, 29 HEALTH AFFAIRS 2047 (2010).

146. See, e.g., Alan M. Garber & Jonathan Skinner, *Is American Health Care Uniquely Inefficient?*, 22 J. ECON. PERSP. 27 (2008) (noting the popular wisdom that the American health care system is exceptionally fragmented); see also W. Nicholson Price II, *Risk and Resilience in Health Data Infrastructure*, 16 COLO. TECH. L.J. 65 (2018) (discussing fragmentation of health data systems).

147. See, e.g., Ruth R. Faden et al., *An Ethics Framework for a Learning Health Care System: A Departure from Traditional Research Ethics and Clinical Ethics*, 43 HASTINGS CTR. REP. S16 (2013); Christine Grady & David Wendler, *Making the Transition to a Learning Health Care System*, 43 HASTINGS CTR. REP. S32 (2013); Nancy E. Kass et al., *The Research-Treatment Distinction: A Problematic Approach for Determining Which Activities Should Have Ethical Oversight*, 43 HASTINGS CTR. REP. S4 (2013).

148. Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 44 Fed. Reg.

fact, an entire strand of literature on the “therapeutic misconception” notes the problems that arise when patients incorrectly believe that research-oriented clinical trials will provide care.¹⁴⁹ On the care side, the purpose is to provide care to individuals, not to generate knowledge. In this model, providers record data principally to note current care, to inform future care, and to facilitate payment.¹⁵⁰

The LHS bucks that model by aiming to capture and use data from health care. In doing this, it transforms care from something that is *only* about providing care to something that is *also* about generating knowledge to improve future care through learning—so much so that Ruth Faden and her colleagues argue that both clinicians and patients have an obligation to contribute to learning.¹⁵¹ This learning should be systematic, in a way that looks much more like research does now. There are still situations, even in an LHS, that are completely distinct. Phase I clinical trials, for instance, are conducted on healthy volunteers to test the safety of a new drug.¹⁵² These studies are not care; they are only research.¹⁵³ But in general, LHSs blur the line between research and care for many situations.

The shift to an LHS shares key characteristics with the shift to a more flexible FDA approval process. Each attempts to improve the way we understand and use health interventions. Each

23,192 (Apr. 18, 1979) (codified at 45 C.F.R. § 46 (2017)); Howard Brody & Franklin G. Miller, *The Research-Clinical Practice Distinction, Learning Health Systems, and Relationships*, 43 HASTINGS CTR. REP. 41, 42 (2013); *but see* Noah, *supra* note 51, at 387–88 (arguing that the Belmont Report and its successors recognize a spectrum from research to clinical care).

149. *See generally* Paul S. Appelbaum et al., *False Hopes and Best Data: Consent to Research and the Therapeutic Misconception*, 17 HASTINGS CTR. REP. 20 (1987). This is not always the case; in some cases, notably pediatric oncology, clinical trials are the principal avenue by which care is provided. *See, e.g.*, Emily A. Largent et al., *Can Research and Care Be Ethically Integrated?*, 41 HASTINGS CTR. REP. 37, 39 (2011).

150. *See* Martha Hostetter & Sarah Klein, *Using Patient-Reported Outcomes To Improve Health Care Quality*, COMMONWEALTH FUND (Jan. 2012), <http://www.commonwealthfund.org/publications/newsletters/quality-matters/2011/december-january-2012/in-focus>.

151. Faden et al., *supra* note 147, at S22. Faden and colleagues do not argue that patients have a duty to participate in experimental research, but others do. *See, e.g.*, John Harris, *Scientific Research Is a Moral Duty*, 31 J. MED. ETHICS 242, 247 (2005); Rosamond Rhodes, *In Defense of the Duty To Participate in Biomedical Research*, 8 AM. J. BIOETHICS 37, 38 (2008).

152. *See* Abigail All. for Better Access to Developmental Drugs v. von Eschenbach, 495 F.3d 695, 698 (D.C. Cir. 2007) (describing the different phases of drug testing).

153. *Id.*

turns on generating information and applying that information in an ongoing process of developing and using those health interventions. And each rejects simple, bright-line distinctions about when that information should be gathered and when it is no longer needed, whether because a drug is already approved or because treatment is offered in a clinical setting rather than a research setting.

The LHS has a broader focus than just FDA-regulated products. An LHS considers—or at least, can consider—the full process of care, including how doctors should interact with patients or which of many interventions (or nonintervention) works best. That may involve determinations that in fact, no drug should be used in a particular treatment plan—something outside FDA’s traditional ambit.¹⁵⁴ Nevertheless, an LHS can help gather more targeted information about drugs as well. The next Part focuses on how information is gathered in an LHS, and how that information and those processes can be used to inform a more flexible FDA drug-approval regime.

III. LEARNING ABOUT DRUGS IN A LEARNING HEALTH SYSTEM

A flexible FDA approval process requires actually generating useful, detailed, postapproval information about drug safety and especially efficacy, which is hard; an LHS system can make it easier. An LHS enables the generation of in-depth information and lowers barriers to access to make such studies accessible to a wider range of researchers and analysts.

Tools to gather information about drugs can be roughly grouped into two sets: interventional and observational.¹⁵⁵ In interventional studies, the researcher (broadly defined) does something deliberate—intervenes—with respect to the object of study and measures the result based on the intervention.¹⁵⁶ Randomized-control clinical trials are the paradigmatic interventional

154. Cf. Rachel E. Sachs, *Administering Health Innovation*, 39 CARDOZO L. REV. (forthcoming 2018) (manuscript at 36–37), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3013895 (describing the need for research on talk therapy as an alternative to drugs).

155. See John Concato et al., *Randomized, Controlled Trials, Observational Studies, and the Hierarchy of Research Designs*, 342 NEW ENG. J. MED. 1887, 1888 (2000).

156. Jarow et al., *supra* note 125, at 703 (“1 or more human research participants are prospectively assigned to 1 or more interventions to evaluate the effect of those interventions . . .”).

study.¹⁵⁷ Observational studies are different; rather than intervening, researchers gather data about what is already happening in the world and try to draw inferences from patterns in those data.¹⁵⁸

Observational studies have some substantial advantages. They are typically cheaper, and they can often use large amounts of data retrospectively without the need to recruit participants.¹⁵⁹ They can bring data together from many sources and, by virtue of the variety and volume of data they can incorporate, they can help identify complex patterns in larger populations.¹⁶⁰ But observational studies typically cannot demonstrate causation; it is challenging to show that a particular patient characteristic or treatment causes an outcome, particularly when the researcher cannot control for other variables.¹⁶¹

Interventional studies can show causation by, for instance, randomly assigning some patients to get one drug and other patients another, or a placebo.¹⁶² The random assignment enables the researcher to avoid selection bias and to conclude that different results are caused by different interventions rather than some other underlying factor.¹⁶³ But interventional studies have their own challenges; they are typically expensive to run and can be hard to fill with subjects.¹⁶⁴ Postmarket interventional studies are especially challenging to conduct. For classic randomized clinical trials, the same limitations as described above apply—smaller sample sets, limited populations, expense, short time periods—with the further limitation that patients don't need to participate to get the drug because they can get it through regular clinical care.¹⁶⁵

157. *Id.* (noting that the clinical trial enterprise is “based largely on randomized clinical trials”).

158. *Id.* (“Studies in which individuals are observed with no attempt to affect the outcome are observational.”).

159. See John Concato, *Observational Versus Experimental Studies: What's the Evidence for a Hierarchy?*, 1 NEURORX 341, 345 (2004) (“[O]bservational studies often are cheaper, quicker, and less difficult to carry out . . .”).

160. See Stuart Silverman, *From Randomized Controlled Trials to Observational Studies*, 122 AM. J. MED. 114, 114 (2009).

161. See Jarow et al., *supra* note 125, at 703.

162. See *id.* (“Randomization within the context of an interventional clinical trial is intended to balance confounders, both known and unknown.”).

163. See *id.*

164. See *supra* notes 28–33 and accompanying text (noting problems with clinical trials).

165. See *supra* notes 84–85 and accompanying text.

An LHS promises to substantially enhance the ability of various actors—FDA, health systems, and drug sponsors alike—to conduct interventional and observational studies. Congress has emphasized the importance of using evidence from ongoing care to improve the FDA information-gathering process in particular.¹⁶⁶ In the Cures Act, Congress required FDA to “establish a program to evaluate the potential use of real world evidence” to conduct postapproval surveillance for drugs.¹⁶⁷ The Sections below explore how this type of real-world evidence could be leveraged to gather information about drugs through both observational and interventional studies in the context of an LHS.

A. OBSERVATIONAL STUDIES

Observational studies find patterns in health data. For instance, in the widely publicized case of the painkiller Vioxx, researchers working at the integrated health system Kaiser Permanente collaborated with FDA’s Dr. David Graham to examine the safety of the drug.¹⁶⁸ They compared health records of Kaiser Permanente patients who took Vioxx with those of patients taking older painkillers and found a higher rate of heart attacks among the Vioxx patients.¹⁶⁹ These findings eventually helped lead to Merck’s withdrawing its drug Vioxx from the market—though only after the findings were confirmed by data Merck reluctantly disclosed from ongoing interventional clinical trials testing whether Vioxx helped prevent another condition.¹⁷⁰ In general, postmarket surveillance today relies on observations rather than interventions—watching to see signs of potential problems (or benefits) and then analyzing existing data to see whether these effects are consistent and predictable.¹⁷¹

166. See, e.g., 21st Century Cures Act, Pub. L. 114-255, § 3022, 130 Stat. 1033, 1096–98 (2016) (to be codified at 21 U.S.C. § 505F (2012)).

167. *Id.*

168. See Eisenberg & Price, *supra* note 33, at 10–11.

169. David J. Graham et al., *Risk of Acute Myocardial Infarction and Sudden Cardiac Death in Patients Treated with Cyclooxygenase 2 Selective and Non-Selective Non-Steroidal Anti-Inflammatory Drugs: Nested Case-Control Study*, 365 LANCET 475, 475–77 (2005).

170. See Robert S. Bresalier et al., *Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial*, 352 NEW ENG. J. MED. 1092 (2005) (concluding that the drug use “was associated with an increased cardiovascular risk”); Eisenberg & Price, *supra* note 33, at 11 (noting Merck’s reluctance to share its data).

171. See *supra* Section I.B.1.b.

LHSs promise to increase the possibilities of interventional and observational studies, because gathering observations comprises much of the core of any such learning system. In an LHS, data are constantly generated about the process of treatment and captured in EHRs and health databases.¹⁷² Ideally, these data can be supplemented from other sources of relevant health data, such as personal health monitors or fitness trackers.¹⁷³

LHS data are deliberately made available for observational studies—indeed, that’s the point.¹⁷⁴ Such studies can note the same sort of problem as appeared in the Vioxx case; indeed, the Sentinel system (itself touted as an example of learning-health-system approaches) is designed to notice just such safety problems, despite the challenges noted above.¹⁷⁵ In a more robust vision of an LHS, such studies would identify not only problems, but also new uses, comparative effectiveness,¹⁷⁶ and differential efficacy among different patients—all of which could potentially feed back into ongoing FDA oversight of drugs.¹⁷⁷

Some observational studies are explicitly mapped out beforehand—which drug of a small set works better, what side effects exist and can be linked to other characteristics, or the like¹⁷⁸—but observational studies can also encompass more complicated possibilities. The availability of very large collections of health data enables a developing subset of observational research: the use of machine-learning techniques to develop “black-box” algorithms that can make predictions and recommendations based on very complex patterns found within the data.¹⁷⁹ This new form of analysis has great potential and raises its own FDA-related questions, both with regard to regulating

172. See INST. OF MED., LEARNING HEALTHCARE, *supra* note 7, at 48 (“Well-designed functionalities will allow generation of data . . . as a by-product of the usual documentation of care.”).

173. See Jarow et al., *supra* note 125, at 703 (hypothesizing the generation of real-world data from “smart devices, social media, meteorological data, census data, and socioeconomic data”).

174. See, e.g., Greene et al., *supra* note 141, at 207–08.

175. See *supra* Section I.B.1.

176. See Robert Temple, *A Regulator’s View of Comparative Effectiveness Research*, 9 CLINICAL TRIALS 56 (2012) (describing comparative effectiveness research and noting the challenges of reaching definitive conclusions).

177. Implementing such oversight, of course, brings its own challenges. See *supra* Section I.B.1.

178. See, e.g., Silverman, *supra* note 160, at 115–16.

179. See W. Nicholson Price II, *Black-Box Medicine*, 28 HARV. J.L. & TECH. 419 (2015) (describing the phenomenon of black-box medicine and noting some of its legal implications).

algorithms and to how algorithms might generate or interpret new drug-related data.¹⁸⁰

Overall, observational studies are a key part of LHSs, and the blurring of clinical and research care promises to generate tremendous amounts of data for those studies, and the chance to use the results of those studies to rapidly improve care.

B. INTERVENTIONAL STUDIES

LHSs can also facilitate interventional studies, though this approach has received somewhat less attention. EHRs, in particular, could make pragmatic trials (that is, trials of real-world interventions in a real-world setting¹⁸¹) much easier to conduct. EHRs can already be used as a source of data for identifying potential trial participants (which makes trials easier), but this is just the first step. To go further, EHR systems could identify patients for a trial in a particular institutional context—perhaps one institution, or perhaps a multi-institutional collaboration—could automatically assign patients to trials, and could even apply the pragmatic randomization, all within the context of the electronic system.¹⁸² (The ethics-focused reader has immediately jumped to the issue of informed consent, which I discuss below).¹⁸³

This is all a bit abstract, so let's take an example. Imagine that we have two drugs, both of which treat chronic migraines: Nonopain and Decapitor. As a profession, clinicians are uncertain which drug is better, a concept known as clinical equipoise.¹⁸⁴ Both are FDA-approved after showing significant decreases in pain in about twenty-five percent of chronic-migraine sufferers, but the clinical trials did not gather enough evidence to predict which patients should use Nonopain and which should use Decapitor. Accordingly, clinicians prescribe one or the

180. See, e.g., W. Nicholson Price II, *Regulating Black-Box Medicine*, 116 MICH. L. REV. 421 (2017).

181. See DUKE-MARGOLIS CTR. FOR HEALTH POLICY, A FRAMEWORK FOR REGULATORY USE OF REAL-WORLD EVIDENCE 11 (2017), https://healthpolicy.duke.edu/sites/default/files/atoms/files/rwe_white_paper_2017.09.06.pdf.

182. See Jarow et al., *supra* note 125, at 704.

183. See *infra* Section IV.A.

184. Benjamin Freedman, *Equipoise and the Ethics of Clinical Research*, 317 NEW ENG. J. MED. 141, 141 (1987). The existence of clinical equipoise is seen by many as an ethical prerequisite to conduct an interventional study; otherwise, the only acceptable ethical path is to provide patients with the better intervention.

other—based on their own perceptions of anecdotal patient evidence or on marketing by companies—and wait to see if it works; if it doesn't, they switch and hope the other works better. This is how we prescribe lots of drugs.¹⁸⁵

Now imagine an EHR-mediated pragmatic clinical trial to determine whether one is actually better. When a patient is newly diagnosed with chronic migraines, the EHR system (into which the treating provider enters the diagnosis) notes that the patient is a relevant participant in the ongoing study, internally randomizes between Nonopain and Decapitor, and recommends to the treating provider that the resulting drug be prescribed—within seconds of the diagnosis being entered. Of course, the provider can reject the recommendation, but by hypothesis she has no a priori reason to do so. The EHR system gathers information about the patient's reactions to the drug over time: are his migraines better, and does he suffer any adverse reactions? These data can come not only from EHRs, but also from self-tracking, as when the patient enters information into his smartphone-based migraine-tracking program.¹⁸⁶ Over time, the system gathers data—systematically—about which patients do better. Maybe Nonopain is actually better than Decapitor across the board (that is, it helps the same group of patients but helps them more). Or maybe Decapitor is better for men and postmenopausal women, while Nonopain is better for premenopausal women—or perhaps some much more complex constellation of characteristics that is better suited for machine-learning-based grouping than straightforward interventional analysis.¹⁸⁷ The point is that this type of study can be tremendously streamlined by integration with EHRs within the context of an LHS, and can consequently become more common, more affordable, and more efficient.

This model is not as far off as it might sound. Derek Angus explores this idea in some depth, arguing that an ideal LHS would fuse randomized trials with big data, because trials are

185. See, e.g., Scott Ely, *Personalized Medicine: Individualized Care of Cancer Patients*, 154 TRANSLATIONAL RES. 303, 304 (2009) (explaining that cancer treatments today are generally instituted on a best-guess, trial-and-error basis).

186. Self-reported data have their own problems with accuracy, consistency, and other issues, but provide at least the possibility of a richer dataset. See, e.g., Florence T. Bourgeois et al., *The Value of Patient Self-Report for Disease Surveillance*, 14 J. AM. MED. INFORMATICS ASS'N 765 (2007) (noting that patient self-reporting tools allow for inclusion of more data elements on individual patients than conventional surveillance data).

187. See *supra* notes 96–97 and accompanying text.

needed to determine causation.¹⁸⁸ He argues that essentially everyone getting treatment should be part of ongoing EHR-mediated clinical trials when the treatment path is uncertain.¹⁸⁹ Angus suggests the idea of adaptive trials: even within the context of an ongoing study, the LHS can take accumulating evidence into account.¹⁹⁰ If evidence suggests that one drug in an ongoing trial is moderately likely to be better than another, though uncertainty remains, the EHR-mediated trial could implement an imbalanced randomization so that patients would be more likely to get the (probably) better drug.¹⁹¹ This has the positive effect that patients in the ongoing trial would, on average, do better than either patients in an equally randomized trial *or* in standard clinical care, where uncertainty would also not yet give them a higher chance of the (probably) better drug.¹⁹² This system, of course, relies on the availability of high-quality, accurate EHRs as well as buy-in by participants in the LHS.

Regulators seem on board with the idea. Califf and his FDA colleagues recognized in 2016 the increasing importance of real-world evidence about drug effects, and emphasized the importance of randomized interventional studies real-world contexts.¹⁹³ They specifically encouraged the expansion of randomized trials outside of academic medical centers.¹⁹⁴ They also noted that the importance of real-world evidence is not in whether it is interventional or randomized, but rather that it takes place in a more generalizable real-world context—precisely the type of evidence enabled by an LHS.¹⁹⁵ Section 3022 of the Cures Act encourages FDA to explore the use of real-world evidence to support fulfilling postapproval study requirements or adding new indications for approved drugs, and these embedded pragmatic trials would fall within that scope.¹⁹⁶

188. See Derek C. Angus, *Fusing Randomized Trials with Big Data: The Key to Self-Learning Health Care Systems?*, 314 JAMA 767, 767–68 (2015).

189. *Id.* at 768.

190. *Id.*

191. *Id.*

192. *Id.*

193. See Sherman et al., *supra* note 32, at 2295.

194. See *id.* at 2296.

195. *Id.*; see also Robert M. Califf, *Remarks of the FDA Commissioner: The Food and Drug Law Institute's 59th Annual Conference*, 71 FOOD & DRUG L.J. 201, 207 (2016) (supporting the idea of clinical trials embedded in clinical practice).

196. See *supra* Section I.B.4.

In fact, to the extent that FDA enthusiastically supports the idea of pragmatic clinical trials in LHSs as a way to fulfill post-marketing study observations—and the Agency seems to be moving in that direction—it may actively help propel the growth and development of LHSs. FDA has already issued guidance on the use of real-world evidence to evaluate medical devices,¹⁹⁷ and it is developing the National Evaluation System for Health Technology (NEST)—a system originally conceived as a safety-surveillance system for medical devices, but has since broadened to include evaluation and evidence collection more generally.¹⁹⁸ Commissioner Gottlieb has stated that FDA’s upcoming guidance on the use of such evidence for drugs, mandated under the Cures Act,¹⁹⁹ will include “a detailed description of [real-world evidence] and its potential applications for satisfying aspects of FDA’s pre- and postmarket requirements.”²⁰⁰ If drug companies are motivated to pursue pragmatic clinical trials, developing the capacity to conduct those trials cheaply and efficiently will also support the capacity to conduct other pragmatic clinical trials—including for purposes beyond those mentioned in the Cures Act, such as comparative effectiveness research, and for deployment by actors other than drug companies themselves.

C. POTENTIAL ACTORS

LHSs also promise to broaden the possible scope of who can conduct studies, whether observational or interventional. Observational studies present the easier case. To the extent that routine, high-quality data collection results in high-quality datasets, those datasets could be made more broadly available to enable observational studies by more than just the few players who can afford the expense of assembling their own datasets.²⁰¹

197. See generally FDA, REAL-WORLD EVIDENCE, *supra* note 11.

198. CDRH Reports: National Evaluation System for Health Technology (NEST), FDA, <https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cdrh/cdrhreports/ucm301912.htm> (last updated Feb. 15, 2018); see also Jeffrey Shuren & Robert Califf, *Need for a National Evaluation System for Health Technology*, 316 JAMA 1153, 1154 (2016); FDA, REAL-WORLD EVIDENCE, *supra* note 11, at 6.

199. 21st Century Cures Act, Pub. L. No. 114-255, § 3022, 130 Stat. 1033, 1096–98 (2016).

200. Gottlieb, *supra* note 126.

201. See W. Nicholson Price II, *Big Data, Patents, and the Future of Medicine*, 37 CARDOZO L. REV. 1401, 1439–44 (2016) (arguing for a government-funded infrastructure model to make data more broadly available in health); cf. Evans, *supra* note 71, at 587–95 (describing hurdles for drug sponsors assembling their own datasets).

FDA could run its own studies, and drug sponsors as well—that's the case now—but so could hospitals, health systems, academics, and others, given access to observational datasets.²⁰² And, less typically, health-care payers could more readily run their own studies to address questions of comparative effectiveness, off-label uses, safety, and cost-effectiveness for existing drugs.²⁰³ This is not to say that these actors don't already run observational studies—some do.²⁰⁴ But more actors could feasibly access data and run studies in an LHS.²⁰⁵ Of course, there are legal and practical challenges around access to data, some of which will be discussed below, but at least the possibility of broader access exists.

Similarly, though to a lesser extent, interventional trials could come within reach for a broader range of actors once those trials can be largely automated through EHR-mediated patient selection and intervention assignment. The sort of trial described above in the Nonopain example could be run not only by drug companies or academics with substantial grants, but also by essentially any health-care system or affiliated actor.²⁰⁶ As Angus writes, at least one possible ideal is that the vast majority of patients receiving care are actively contributing to systematized knowledge—not only through providing data for observational studies, but by a process in which their care itself systematically contributes to generating causal inferences through carefully calibrated (and sometimes randomized) interventions.²⁰⁷

IV. CHALLENGES FROM BRIGHT-LINE RULES

While both FDA flexibility and LHSs blur lines between research and nonresearch—to good effect—some areas of law remain based on bright-line rules that are likely to hamper and bias the development of postapproval information. These bright lines and hard-wired policies create real challenges in moving forward to a system where information is constantly gathered, constantly analyzed, and constantly used to improve the process of regulating drugs and providing health care. Two areas are particularly salient: (1) informed consent rules governing the conduct of care and of research; and (2) privacy rules governing

202. See Eisenberg & Price, *supra* note 33, at 41–44.

203. *Id.* at 14–23.

204. *Id.* at 42–43.

205. *Id.*

206. See Angus, *supra* note 188, at 767–68.

207. *Id.*

the collection, transfer, and use of personal health information.²⁰⁸

A. INFORMED CONSENT

As a default rule, obtaining informed consent of patients and research subjects is both a legal and an ethical duty. The federal Common Rule generally requires that all federally funded research involving human subjects obtain informed consent from participants; many institutions expand this requirement to include all human subjects research, federally funded or not.²⁰⁹ This informed consent must be written and must include several required elements.²¹⁰ FDA separately requires informed consent for interventional studies conducted on drugs, even if the research is non-federally-funded.²¹¹ Because the FDA requirements apply only to “clinical investigations”²¹² that are “experiment[s] . . . involv[ing] a test article,”²¹³ they do not appear to cover purely observational studies.²¹⁴ Waivers of the consent requirements are available in limited circumstances, but can be

208. Another set of substantial hurdles for research involves oversight by Investigational Review Boards (IRBs) more generally, which must approve human subject research. For overviews and criticisms of IRBs as censors of knowledge and research, see generally CARL E. SCHNEIDER, *THE CENSOR'S HAND: THE MISREGULATION OF HUMAN-SUBJECT RESEARCH* (2015) (criticizing IRBs as unaccountable, opaque, and unguided by clear rules); Philip Hamburger, *The New Censorship: Institutional Review Boards*, 2004 SUP. CT. REV. 271 (criticizing IRBs on First Amendment grounds).

209. 45 C.F.R. § 46.101 (2017). For a discussion of the Common Rule, including its scope and purpose, see, for example, Michelle N. Meyer, *Regulating the Production of Knowledge: Research Risk-Benefit Analysis and the Heterogeneity Problem*, 65 ADMIN. L. REV. 237, 243–50 (2013). State law also creates duties to obtain informed consent in the context of clinical care and in some research contexts, though these state requirements exist within the context of medical malpractice law and are relatively underdeveloped in the research context. See Noah, *supra* note 51, at 364–79. Accordingly, this Section will focus on federal law, and the Common Rule in particular.

210. 45 C.F.R. § 46.116 (listing general informed-consent requirements); *id.* § 46.117 (requiring that informed consent be obtained in writing). Consent forms are reviewed by IRBs for compliance.

211. 21 C.F.R. § 50.25 (2017) (listing informed-consent elements); *id.* § 50.27 (requiring that informed consent be obtained in writing).

212. *Id.* § 50.1 (limiting applicable scope of FDA requirements to “clinical investigations”).

213. *Id.* § 50.3(c) (defining “clinical investigation”).

214. See Evans, *supra* note 71, at 591 (arguing that it is unclear whether FDA human-subjects regulations apply to section 505(o)(3) postmarket observational studies).

difficult to obtain.²¹⁵ Until recently, FDA waivers were much more restricted than Common Rule waivers, but those requirements have recently been harmonized by the Cures Act.²¹⁶

A proposed new version of the Common Rule was released in 2017, although the revisions are still under consideration as of this writing. The new draft contains two proposed changes that are especially significant for observational studies of existing information.²¹⁷ First, individuals could give “broad consent” when they provide private information or biospecimens, which would cover a wide range of identified-patient studies going forward; databases made up of information obtained under such broad consent would not require additional consent for later research.²¹⁸ Second, if the researcher’s own use of health information is governed by the HIPAA Privacy Rule,²¹⁹ that use would be exempt from Common Rule requirements.²²⁰

215. Evans, *supra* note 71, at 590. Under the Common Rule, informed consent requirements can be waived by an IRB if: “(1) [t]he research involves no more than minimal risk” (defined as the risks encountered in daily life); “(2) [t]he waiver will not adversely affect the rights and welfare of the subjects; (3) [t]he research could not be practicably be carried out without the waiver . . . ; and (4) . . . the subjects will be provided with additional pertinent information after participation” if appropriate. 45 C.F.R. § 46.116(d). For an ethical defense of informed-consent waivers, see Michelle N. Meyer, *Two Cheers for Corporate Experimentation: The A/B Illusion and the Virtues of Data-Driven Innovation*, 13 COLO. TECH. L.J. 273 (2015).

216. 21st Century Cures Act, Pub. L. No. 114-255, § 3022, 130 Stat. 1033, 1096–98 (2016); see FDA, IRB WAIVER OR ALTERATION OF INFORMED CONSENT FOR CLINICAL INVESTIGATIONS INVOLVING NO MORE THAN MINIMAL RISK TO HUMAN SUBJECTS: GUIDANCE FOR SPONSORS, INVESTIGATORS, AND INSTITUTIONAL REVIEW BOARDS 3 (2017), <https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM566948.pdf> (noting that FDA intends to revise its informed-consent guidelines to allow waivers under the same circumstances as permitted under the Common Rule and announcing FDA’s intention not to object to IRB waivers for those circumstances prior to promulgation of the revised regulations).

217. Federal Policy for Protection of Human Subjects, 82 Fed. Reg. 7149 (Jan. 19, 2017) (to be codified at 45 C.F.R. § 46).

218. *Id.* at 7266. Some biobanks have long taken advantage of the broad consent procedures provided by the Common Rule’s informed-consent waiver provisions by arguing that obtaining only narrow consent makes biobanking infeasible. See *supra* note 215 and accompanying text.

219. See discussion *infra* Section III.B.

220. Federal Policy for Protection of Human Subjects, 82 Fed. Reg. at 7262. This requirement would apply only to data use, and not to data sharing with other parties. *Id.* (explaining that consent is not needed for secondary research “involv[ing] only information collection and analysis involving the investigator’s use of identifiable health information”).

1. Implications

The requirement of obtaining informed consent for research studies creates hurdles that can impact whether and how a study goes forward.²²¹ Obtaining informed consent can cost dozens to hundreds of dollars per subject, can consume substantial time, and can bias the studied population.²²² This is not always a problem for relatively small preapproval studies, but creates a high barrier for large-scale postapproval studies, especially without the incentive of drug approval.²²³ Merely giving drugs to patients in the course of clinical care, on the other hand, requires relatively minimal consent procedures, if any at all.²²⁴ Anna Laakmann quotes one physician pointing out the irony of requiring IRB approval for clinical trials after drugs have been approved by FDA for treatment: “I need permission to give a new drug to half of my patients, but not to give it to them all.”²²⁵ Michelle Meyer describes this broader phenomenon as the “A/B illusion”—“the widespread tendency to view a field experiment designed to study the effects of an existing or proposed practice as more morally suspicious than an immediate, universal implementation of an untested practice.”²²⁶

221. See, e.g., Kass et al., *supra* note 147, at S12 (noting the “burdens and costs of extensive oversight”). Not all agree. See, e.g., Sarpatwari et al., *supra* note 112, at 2329 (“[W]e suggest that the line between research and treatment is inconsequential. In the literature on informed consent, it is well settled that patients and research subjects should alike be informed of all material facts.”); cf. Laakmann, *supra* note 6, at 346 (suggesting that informed-consent rules for observational studies should mirror those used for randomized clinical trials).

222. See, e.g., Fred H. Cate, *Protecting Privacy in Health Research: The Limits of Individual Choice*, 98 CAL. L. REV. 1765, 1789–93 (2010) (discussing costs of obtaining informed consent); Sharona Hoffman & Andy Podgurski, *Balancing Privacy, Autonomy, and Scientific Needs in Electronic Health Records Research*, 65 SMU L. REV. 85, 123 (2012) (reviewing empirical evidence on costs of obtaining informed consent); Sian Noble et al., *Feasibility and Cost of Obtaining Informed Consent for Essential Review of Medical Records in Large-Scale Health Services Research*, 14 J. HEALTH SERV. RES. & POL’Y 77 (2009) (finding costs of approximately \$248 per person to obtain written informed consent); Jack V. Tu et al., *Impracticability of Informed Consent in the Registry of the Canadian Stroke Network*, 350 NEW ENG. J. MED. 1414 (2004) (finding costs of around seventy Canadian dollars per subject to obtain informed consent, but obtaining consent for under fifty percent of subjects and finding substantial selection bias).

223. See, e.g., Mark J. Pletcher et al., *Informed Consent in Randomized Quality Improvement Trials: A Critical Barrier for Learning Health Systems*, 174 JAMA INTERNAL MED. 668, 668 (2014) (“With optimal use of [EHR]s, the administrative costs of a trial need not increase with the sample size; this decoupling of costs and size facilitates large, simple, and inexpensive trials . . .”).

224. See, e.g., Darrow, *supra* note 63, at 820–21.

225. Laakmann, *supra* note 6, at 313.

226. Meyer, *supra* note 215, at 278.

Of course, this could all be perfectly justified. Research is different from clinical care; research aims first to create generalizable knowledge, while clinical care aims first to help the patient, and this distinction is deeply embedded in practice, ethics, and law.²²⁷ One prominent report noted five reasons for the distinction between research and care: (1) the aim for generalizable knowledge; (2) the requirement of systematic investigation; (3) the potential for additional risks to patients in research care (such as extra blood draws); (4) the imposition of research-related burdens not required by clinical care; and (5) the relatively inflexible, protocol-driven nature of care in a research context.²²⁸ Another argument notes that the relationship between patient and provider differs substantially from that between patient and researcher, and that more oversight is thus needed to protect patients in the latter context.²²⁹

Nevertheless, we might think that the standard rules for informed consent don't make as much sense in an LHS where the sharp distinction between research and clinical care becomes blurred.²³⁰ Informed-consent rules and ethical oversight practices were designed to be applied when behavior fits into the traditional box of research. Nancy Kass, Ruth Faden, and their colleagues offer several reasons why the imposition of these rules fits poorly with an LHS.²³¹

For one thing, the type of blended research and care that happens in an LHS may well be just as safe—or safer!—than standard clinical care.²³² If the study is about a quality improvement intervention that we have reason to suspect will improve care (giving a drug at more even interval rather than once daily, for instance), patients should be better off with a fifty percent chance of the intervention than having no chance.²³³ In the type of adaptive clinical trial suggested by Angus, as the system ac-

227. In the Common Rule, for instance, research is defined as “a systematic investigation . . . designed to develop or contribute to generalizable knowledge.” 45 C.F.R. § 46.102 (2017).

228. Kass et al., *supra* note 147, at S6–S12 (listing these reasons and arguing they do not apply sharply in the context of an LHS).

229. *Compare id.*, with Brody & Miller, *supra* note 148, at 45–46 (arguing that Kass and colleagues fail to consider the role played by experimentation in these two relationships).

230. See Kass et al., *supra* note 147, at S4–S5.

231. *Id.* at S11–S12.

232. See Pletcher et al., *supra* note 223, at 669.

233. *Id.*

cumulates knowledge about which drug seems better among alternatives, patients can be randomized to be more likely to get the better drug—again leaving them better off than under the standard of care or a completely randomized trial.²³⁴ And even if we know nothing and instead just randomize among otherwise equal drugs, patients are arguably no worse off than under the standard of care.²³⁵ As Kass, Faden, and colleagues argue, this distinction also cuts the other way—the current system harms patients by *failing* to gather information about currently under-informed clinical interventions.²³⁶ Unlike the classic distinction between research and clinical care where one group (research participants) undergoes research that will eventually benefit a second group (future patients), here, those groups are essentially the same, and all participants of an LHS could potentially reap the benefits of the learning.²³⁷

Finally, the very fact of an artificial distinction about clinical oversight and informed consent is impractical—the Faden/Kass group notes how the distinction creates substantial uncertainty among IRBs²³⁸ and argues that this has problematic dynamic effects on how studies may be conducted:

The fuzziness of the distinction [between research and practice], coupled with the oversight burdens that are required of research but not of practice, creates dubious incentives to redesign quality improvement and comparative effectiveness activities in ways that minimize the likelihood that they will be classified as research, even at the cost of their rigor, utility, dissemination, or value.²³⁹

So what do bright-line informed-consent rules mean for the goal of a more flexible information-gathering regime around

234. See Angus, *supra* note 188, at 768.

235. See generally OFFICE FOR HUMAN RESEARCH PROTS., U.S. DEP'T OF HEALTH & HUMAN SERVS., DRAFT GUIDANCE ON DISCLOSING REASONABLY FORESEEABLE RISKS IN RESEARCH EVALUATING STANDARDS OF CARE (2014), <https://www.hhs.gov/ohrp/regulations-and-policy/requests-for-comments/draft-guidance-disclosing-risk-in-standards-of-care/index.html>.

236. Kass et al., *supra* note 147, at S11 (“[P]atients may have surgery at the hands of surgeons or teams who rarely perform such an operation, despite empirical evidence that low-volume hospitals have worse outcomes than high-volume hospitals. In many respects, these patients are experimental subjects . . . with the indefensible difference being that their experience will not inform the treatment of others.”); see also Darrow, *supra* note 63, at 809–14 (characterizing patient use of recently approved drugs as human experimentation but without informed consent safeguards).

237. See Meyer, *supra* note 215, at 274–79.

238. Kass et al., *supra* note 147, at S11.

239. Faden et al., *supra* note 147, at S16–S17.

FDA approval in an LHS? Essentially, it makes it harder to conduct large-scale interventional studies about drugs (or otherwise) by leveraging the capabilities of an LHS. Automating the process of adding patients to ongoing clinical trials, as described above, and automating their assignment between equally beneficial interventions—or randomly assigning the possibility of an extra, likely beneficial intervention—would require individualized consent, even though such interventions are either neutral or positive compared to the baseline of normal care.²⁴⁰ And informed consent carries costs that scale with the number of participants.²⁴¹ Such a requirement might make frequent, large-scale interventional studies impractical or too expensive to undertake in an LHS.

And for observational studies about drug effects? There, too, the informed consent requirements scale with the number of participants,²⁴² but there are two ways to avoid those costs. First, anonymizing data takes them outside the ambit of the Common Rule (as well as the HIPAA Privacy Rule, described below).²⁴³ However, anonymizing data often results in incomplete pictures because of the difficulty of aggregating data across different sources and especially over time.²⁴⁴ Being unable to aggregate data degrades the ability to observe rare or long-term effects. Anonymizing data also limits access to other useful identity-linked information such as family histories.²⁴⁵ Second, under the proposed revisions to the Common Rule, broad consent could be used to obtain prospective consent for all data-based observational studies. Broad consent eliminates the scaling effects of re-consent costs for *future* studies, but it would help resolve problems with existing datasets, or to lower the burdens of obtaining consent in the first place.

Put together, these requirements push the development of new information about drugs away from what an LHS seeks—a mix of neutral-to-beneficial interventional studies coupled with

240. Faden and colleagues argue that for such research, rather than full informed consent, notice that care is being provided in an LHS should suffice. *Id.* at S24–S25.

241. See *supra* notes 221–23 and accompanying text.

242. See, e.g., Tu et al., *supra* note 222, at 7–10; Hoffman & Podgurski, *supra* note 222, at 123.

243. See 45 C.F.R. § 46.101(b)(4) (2017).

244. See *infra* notes 279–80 and accompanying text.

245. See Roger Allan Ford & W. Nicholson Price II, *Privacy and Accountability in Black-Box Medicine*, 23 MICH. TELECOMM. & TECH. L. REV. 1, 21–24 (2016).

broad ongoing observational studies.²⁴⁶ Instead, it promotes a rocky status quo of limited (or frequently infeasible) postmarket surveillance, often with anonymous data, supplemented by formal clinical trials where FDA firmly requires them. Inflexible informed consent requirements are likely to leave many of the benefits of the LHS on the table. Now, this might be justifiable—Barbara Evans writes,

There is no “research imperative” that compels us, as a society, to proceed with postmarketing drug safety studies merely because they have the potential to save patients’ lives. It is perfectly legitimate to question whether the attempt to save lives is sufficient ethical justification for the unconsented [or less-consented] use of private health data.²⁴⁷

But given the benefits promised by an LHS—that such systems attempt to save lives, whether through better practice guidelines or more effective drug approval—we should explicitly question whether the sharply delimited informed-consent rules constructed decades ago still make sense. The line blurring in an LHS and in the FDA approval process suggest that informed consent, too, could be less rigid.²⁴⁸

2. Potential Improvements

Resolving the informed-consent conundrum presents challenges. Obtaining informed consent protects the value of autonomy (though informed consent as practiced today does not do so especially well).²⁴⁹ But like the privacy rule, imposing the hurdle of obtaining a specific form of informed consent based on a bright line between research and not-research does a poor job of protecting patients in the context of an LHS.²⁵⁰ It seems reasonable to consider the possibility that, at least for research that involves nothing riskier than choosing between standard-of-care options

246. See Sherman et al., *supra* note 32, at 2294–96; Califf et al., *supra* note 13, at 2396.

247. Evans, *supra* note 71, at 605.

248. Faden et al., *supra* note 147, at S24–S25; Pletcher et al., *supra* note 223, at 669.

249. See Jay Katz, *Informed Consent—Must It Remain a Fairy Tale?*, 10 J. CONTEMP. HEALTH L. & POL’Y 69, 84 (1994) (arguing that informed consent as practiced is “largely a charade which misleads patients into thinking that they are making decisions when indeed they are not”); see also Matthew E. Falagas et al., *Informed Consent: How Much and What Do Patients Understand?*, 198 AM. J. SURGERY 420, 432 (2009) (reviewing studies regarding informed consent for surgical interventions and concluding that “adequate overall understanding by the patients . . . was reported in less than one-third of the studies”).

250. See Kayte Spector-Bagdady & Reshma Jagsi, *Big Data, Ethics, and Regulations: Implications for Consent in the Learning Health System*, 45 MED. PHYSICS (forthcoming 2018) (manuscript at 2–3) (on file with author).

in clinical equipoise, the consent we require for medical treatment could also suffice as consent for research participation, perhaps supplemented by general notice provisions in the place of care.²⁵¹

Blending informed consent so that clinical consent does double duty as consent to nonrisky research would face substantial difficulties. The difference between research and clinical care is deeply embedded within American bioethics, as are the preeminence of autonomy and special protections for research participants.²⁵² This would make reforming the legal rules challenging; in addition, some clinicians or clinician groups might conclude that ethical obligations would prohibit participation in such research procedures independent of legal prohibitions. Political economy concerns exist as well; major revisions to the Common Rule were just completed after a years-long process, making another substantial change in the near future unlikely.²⁵³ And even if policymakers were to agree that streamlined or assumed informed-consent procedures may serve for particular benign interventions or for observational studies with identifiable information, the implementation of that decision would rest in the hands of variable and widely distributed IRBs.²⁵⁴ Although this local control brings its own challenges, it does mean that as individual IRBs gain experience with an LHS and become more aware of its benefits and protections, they may be willing to be more flexible and could potentially limit the costs of obtaining informed consent for broad observational or benign interventional studies.²⁵⁵

251. See, e.g., Ruth R. Faden, Tom L. Beauchamp, & Nancy E. Kass, *Informed Consent, Comparative Effectiveness, and Learning Health Care*, 370 NEW ENG. J. MED. 766, 767 (2014).

252. See *supra* note 147 and accompanying text for a discussion of the differences between research and clinical intervention.

253. See Joshua D. Smith et al., *Immortal Life of the Common Rule: Ethics, Consent, and the Future of Cancer Research*, 35 J. CLINICAL ONCOLOGY 1879, 1882 (2017).

254. See SCHNEIDER, *supra* note 208, at xx–xxi (describing the process by which IRBs are appointed, and noting that IRBs have virtually plenary discretion in their decisions and are procedurally insulated from challenges). A separate question is whether locally focused IRBs make sense for broadly distributed observational or interventional studies.

255. For more in-depth analysis of how informed consent could work in a mature LHS, see generally Pletcher et al., *supra* note 223; Smith et al., *supra* note 253.

B. PRIVACY

The law of privacy also has a substantial impact on how information about drugs can be gathered, shared, and used in an LHS. The principal federal rule is the Health Insurance Portability and Accountability Act (HIPAA)²⁵⁶ Privacy Rule,²⁵⁷ although state privacy rules may also come into play.²⁵⁸ The Privacy Rule governs the disclosure and use by “covered entities” of “protected health information,” which includes most individually identifiable health information.²⁵⁹ “Covered entities” includes health-insurance plans, health-information clearinghouses, and most health-care providers; their business associates are also regulated by HIPAA.²⁶⁰ Covered entities cannot use or disclose protected health information except with the authorization of patients or for one of several permitted uses.²⁶¹

1. Permitted Use and Disclosure

The Privacy Rule allows routine use and disclosure of protected health information for specific, normally permitted activities. Permitted uses include treatment and health-care operations; the latter includes “quality assessment and improvement activities[.]”²⁶² But the category of health-care operations specifically does *not* include activities whose “primary purpose” is developing “generalizable knowledge.”²⁶³ That constitutes “research,” which is explicitly not a permitted activity for the use or disclosure of protected health information under the Privacy Rule.²⁶⁴

The Privacy Rule also contains a set of potentially important permissions related to public-health activities. Under 45 C.F.R. § 512(b), “A covered entity may use or disclose protected health information for the public health activities and purposes described in this paragraph to: (i) A public health authority . . . [or]

256. Health Insurance Portability and Accountability Act of 1996, Pub. L. No. 104-191, 110 Stat. 1936.

257. Standards for Privacy of Individually Identifiable Health Information, 45 C.F.R. pts. 160, 164 (2017).

258. Evans, *supra* note 71, at 594.

259. 45 C.F.R. § 160.103.

260. *Id.*

261. *Id.* § 164.502.

262. *Id.* § 164.501.

263. *Id.*

264. *Id.* “Research” is defined in the Privacy Rule as “a systematic investigation . . . designed to develop or contribute to generalizable knowledge.” *Id.*

(iii) [a] person subject to the jurisdiction of the [FDA.]”²⁶⁵ These two exceptions allow disclosures to FDA and to drug companies.

Subsection iii allows disclosure to a person subject to FDA’s jurisdiction—would this ameliorate Privacy Rule restrictions on LHS studies about drugs? Not really. First, the exception applies only to drug companies, and so would not permit the disclosure of protected health information to, for example, academics or nonprofits, limiting the research-democratizing effect of an LHS. Second, the disclosure must be “with respect to an FDA-regulated product or activity for which that person has responsibility.”²⁶⁶ As Barbara Evans has pointed out, this limits the allowable disclosure to data about the drug company’s own drugs.²⁶⁷ This provision fails to enable the comparative work central to an LHS; in fact, as Evans notes, it likely does not even enable firms to conduct postmarket studies mandated by FDA under 21 U.S.C. § 355(o)(3).²⁶⁸ It facilitates updated reports of safety and efficacy to a company about its own drugs, but not much more.

Subsection i allows disclosure to a “public health authority.”²⁶⁹ While this allows disclosure of protected health information to FDA, it does not allow disclosure or use by any other parties, whether drug companies, insurers, or otherwise. Thus FDA could conduct its own “public health investigations” by collecting and using LHS data.²⁷⁰ But again, this allows neither the aggregation of protected health information across sources and time (via data disclosure) nor the wider ability to study drugs by non-FDA entities (via data use). Evans has suggested that once FDA has access to data—in the main, through its Sentinel system—it can facilitate access to those data by routinely contracting with drug companies or others as permitted by section 505(k)(4) of the Food and Drug Amendments Act of 2007, which establishes procedures for “[a]dvanced analysis of drug safety data.”²⁷¹ Whether or not that section allows such a scheme,²⁷²

265. *Id.* § 164.512(b)(1)(i), (iii).

266. *Id.* § 164.512(b)(1)(iii).

267. Evans, *supra* note 71, at 589.

268. *Id.*

269. 45 C.F.R. § 164.512(b)(1)(i).

270. *Id.* § 164.512(b)(2).

271. Evans, *supra* note 71, at 599–602; 21 U.S.C. § 355(k)(4) (2012).

272. Evans argues that sections 505(k)(4)(D)(i)(II)–(IV) allow FDA to enter into contracts with drug sponsors to complete section 505(o)(3) postmarket studies using Sentinel data. Evans, *supra* note 71, at 599–602. While these provisions envision FDA contracting with outside contractors to analyze safety data,

FDA has to date focused on drug safety, rather than on more expansive studies using Sentinel.²⁷³ Overall, section 512(b)'s permitted disclosures do not appear to cover most of the disclosures needed to assemble data for an LHS.²⁷⁴

section 505(k)(4)(H) requires FDA to use “competitive procedures” to enter into such contracts, which suggests that the role conceived under section 505(k)(4) is that of an organization undertaking analysis on FDA’s behalf, rather than drug sponsors using FDA’s Sentinel system to conduct their own section 505(o)(3) studies. *Id.*

273. See Eisenberg & Price, *supra* note 33, at 43. Although section 505(k)(4) focuses on drug safety, because the use of any drug entails a risk-benefit analysis, it is at least a colorable argument that comparative benefit determinations fall within the scope of the collaborations allowed. The case for cost-focused research is less clear.

274. The attentive reader will have noted that section 512(b)(1) permits not only disclosure, but also use: “A covered entity may *use* or disclose protected health information for the public health activities and purposes described in this paragraph to . . .” 45 C.F.R. § 164.512(b)(1) (emphasis added). I have discussed disclosure, but what about use by the covered entity itself? Can a large health system conduct its own research using protected health information to produce generalizable knowledge for public health purposes under the “use” of “use or disclose?” Probably not. This section of the Rule is poorly worded, and any interpretation does some violence to its language, but the most reasonable interpretation does not allow use by the covered entity.

The question is how to determine what the covered entity may “use,” and for what purpose. We could interpret “use or disclose” as a compound verb, modified by “for the public health activities and purposes described in this paragraph,” but then it is difficult to see how the subsequent “to,” immediately following “paragraph,” applies only to one verb and not another. We could (with some creativity) interpret “to” as serving two purposes—one as the preposition connecting “disclose” to its indirect objects that follow (“disclose to” a public health authority, school, etc.), and the other as the first half of a badly split infinitive connecting “use” with various activities (“use to” analyze, interpret, etc.). But no such activities are listed in the following subsections.

We could pull “protected health information for the public health activities and purposes described in this paragraph” from the middle of “disclose . . . to [various entities]” and apply it a second time to the verb “use,” but that is ungrammatical. Furthermore, in the following subsections, each purpose “described in [the] paragraph” is linked to a recipient of disclosed information: a public health authority to control disease, an employer to evaluate workplace injury, a school to check immunization status, and the like. 45 C.F.R. § 512(b)(1)(i)–(vi) (2017). No purpose is described without a recipient, leaving unresolved the purposes for which information could be “used.”

The best interpretation is probably to read “use” out of section 512(b)(1) entirely, since no limitations make grammatical or purposeful sense. Consistent with this interpretation, the immediately following section 512(b)(2), “permitted uses,” states, “if the covered entity also is a public health authority, the covered entity is permitted to *use* protected health information in all cases in which it is permitted to disclose such information for public health activities under paragraph (b)(1) of this section.” (emphasis added). If section 512(b)(2) specifically permits a public health authority to use information it could disclose under section 512(b)(1), reading section 512(b)(1) to allow such use already would make

2. Nonpermitted Use and Disclosure

If the Privacy Rule does not normally allow a particular activity, covered entities wishing to use or disclose protected health information have to work much harder. Under the Privacy Rule, the entity may either obtain authorization from each individual patient or obtain a waiver from a Privacy Board or an IRB.²⁷⁵ The alternative is to rely on information not covered by the Privacy Rule at all, typically by using deidentified data which no longer qualifies as protected health information or the subject of human-subject research.²⁷⁶

Each of these approaches brings its own challenges. Authorization by individual patients is costly and time-consuming to obtain, and may introduce bias: there are systematic differences between those who are willing to give permission for their information to be used and those who are not.²⁷⁷ Waivers are generally hard to get, and, in the case of postmarket studies mandated by FDA under section 505(o)(3), they may be both hard to get and practically unusable.²⁷⁸ And using deidentified data creates its own set of problems (setting aside the contentious question of how well deidentification actually protects privacy)²⁷⁹: without

section 512(b)(2) superfluous. In fact, the parallel section 512(d), “[u]ses and disclosures for health oversight activities,” follows exactly this structure, addressing only disclosure for health oversight activities in section 512(d)(1), with section 512(d)(4) permitting use if the covered entity is itself a health oversight agency. As between vitiating two difficult-to-reconcile words in section 512(b)(1) (“use and”) or the entirety of section 512(b)(2), the better reading is that section 512(b)(1) does not in fact permit use of protected health information.

275. 45 C.F.R. § 164.512(i)(1)(i) (2017).

276. *Id.* § 164.514(a).

277. *See, e.g.,* Evans, *supra* note 71, at 580 (“In large-scale studies of this type, obtaining consent may be impracticable or may bias the dataset in ways that would reduce the scientific validity of the findings.”); Hoffman & Podgurski, *supra* note 222, at 114–19 (discussing the bias introduced by consent requirements).

278. *See* Evans, *New Infrastructural Model*, *supra* note 67, at 591 (“It may be hard to persuade IRBs that releasing data for use in a section 505(o)(3) study entails minimal privacy risk, because it is not clear that there is any regulatory framework in place to provide ethical and privacy protections for people whose data are used in such studies.”); *id.* at 593–94 (noting that even if waivers are obtained because FDA applies its own human-subjects protections to section 505(o)(3) studies to alleviate IRB concerns, those protections do not allow such waivers and concluding that “if drug manufacturers can obtain insurance claims data and healthcare records, they will not be able to use them; if they can use them, then they probably will not be able to get them”).

279. An intense ongoing debate considers how well deidentification works to protect privacy; on the one hand, some reidentification techniques have been strikingly successful; on the other, some question whether there is a meaningful likelihood of any particular individual actually being reidentified. *See, e.g., id.*

identifying information, it ranges from hard to impossible to assemble data across different sources and timeframes to create robust datasets that cover enough time to catch rare or slow-to-arise problems.²⁸⁰

3. Implications

This structure of the Privacy Rule has two important implications for the line blurring involved in an LHS. First, the Privacy Rule explicitly includes a sharp distinction between research and treatment/health-care operations—research is about generalizable knowledge and the other uses are not.²⁸¹ Second, the Privacy Rule privileges the use of data for health-care provision and operations in a way that it absolutely does not privilege the use of data to develop generalizable knowledge.²⁸² The Privacy Rule's sharp line creates a similarly sharp limit on the use of health-care data to improve understanding of health-care interventions, including pharmaceuticals.

In the Privacy Rule context, as in the case of informed consent described above,²⁸³ the bright line results in perverse incentives. As Rebecca Eisenberg and I have previously noted, “one might expect that as the analysis of health outcomes to improve clinical care becomes more scientifically rigorous (and its conclusions therefore more generalizable), it may look less like permissible ‘health-care operations’ and more like restricted ‘research.’”²⁸⁴ If health systems *avoid* learning about generalizable knowledge—if they fail to pursue rigorous randomization protocols, use careful controls, or all of the other best practices for an LHS—then they can pursue “quality improvement” activities or

at 592 & n.124 (listing sources on this issue); Ford & Price, *supra* note 245, at 23 & n.76 (listing sources); Paul Ohm, *Broken Promises of Privacy: Responding to the Surprising Failure of Anonymization*, 57 UCLA L. REV. 1701 (2010) (arguing that deidentification largely fails to protect privacy).

280. See, e.g., Evans, *supra* note 71, at 592 (discussing the need for longitudinal health records in drug safety studies). These effects are somewhat ameliorated in the context of integrated providers that can aggregate data in-house. Some integrated providers, such as the Veterans Administration, are likely to also capture most patient health data over time; but these providers cover only a subset of patients. Eisenberg & Price, *supra* note 33, at 12–13.

281. 45 C.F.R. § 164.501 (2017).

282. Sometimes this line is crossed; quality control initiatives sometimes get published and their insights therefore shared. But at least under the Privacy Rule, generalizable knowledge cannot be the purpose of such activities. See *id.* (drawing a sharp distinction between research and treatment/healthcare operations).

283. See *supra* Section IV.A.1.

284. Eisenberg & Price, *supra* note 33, at 36.

other health-care operations without the need to obtain individual authorizations or pursue difficult-to-acquire waivers.²⁸⁵ It is simply easier, under federal privacy rules governing health information, to avoid collecting and using information in a systematic way to create generalizable knowledge. It is easier, in other words, to avoid learning as a health system, and learning about drugs.

4. Potential Improvements

There is not an obvious consensus solution to the problems with HIPAA's Privacy Rule. Some argue that privacy and control over information should be de-emphasized in favor of greater health-care knowledge.²⁸⁶ Others argue that privacy should not be sacrificed for greater knowledge, and suggest that if privacy limits the course of medical innovation, that is simply the cost we pay to protect the important value of privacy.²⁸⁷ Still others try to find a way around the problem; Evans has proposed that patients form data collaboratives that can manage their own data resources,²⁸⁸ and I have suggested elsewhere with Roger Ford that data should be shared relatively freely within a set of procedural privacy safeguards.²⁸⁹ The problem of balancing data access versus privacy remains a knotty and unsolved one, within the context of an LHS as elsewhere. Nonetheless, the bright line of the Privacy Rule, where information is privileged if it is used

285. Jeremy Sugarman & Robert M. Califf, *Ethics and Regulatory Complexities for Pragmatic Clinical Trials*, 311 JAMA 2381, 2382 (2014). To be sure, there are other ways to avoid the strictures of the Privacy Rule or to use data within them in addition to the paths noted above. Evans, for instance, proposes that FDA should enter collaborative agreements with drug companies to allow them to use the Sentinel system to conduct 505(o)(3) postmarketing studies. Evans, *supra* note 71, at 597–603.

286. See Lawrence O. Gostin & James G. Hodge, Jr., *Personal Privacy and Common Goods: A Framework for Balancing Under the National Health Information Privacy Rule*, 86 MINN. L. REV. 1439, 1455 (2002) (arguing that, in situations where the potential for public benefit is high and the risk of harm to individuals is low, public entities should be able to acquire and use health-care data regardless of individual informed consent or other privacy protections); Hoffman & Podgurski, *supra* note 222, at 124–25 (noting that social benefits may sometimes outweigh informed consent and privacy harms).

287. E.g., Peter D. Jacobson, *Medical Records and HIPAA: Is It Too Late To Protect Privacy?*, 86 MINN. L. REV. 1497, 1499–1500 (2002); cf. Franklin G. Miller, *Research on Medical Records Without Informed Consent*, 36 J.L. MED. & ETHICS 560, 560 (2008) (arguing that practical and scientific considerations militate against requiring consent for population-based observational research).

288. See generally Barbara J. Evans, *Power to the People: Data Citizens in the Age of Precision Medicine*, 19 VAND. J. ENT. & TECH. L. 243 (2016).

289. Ford & Price, *supra* note 245.

in an ad hoc fashion for certain purposes including health-care operations and care but not if used for systematic creation of data, seems to be particularly unhelpful.

The drafters of the Cures Act recognized this problem, and initially chose to prioritize innovation over strong privacy protections. An early draft would have erased the bright line by considering “research” a subset of “healthcare operations” and therefore a permitted use under the HIPAA Privacy Rule, removing the artificial distinction between research and other permitted uses.²⁹⁰ Nevertheless, the provision proved contentious, and the Act as passed does not include it.²⁹¹ Instead, the Secretary of Health and Human Services is directed to convene a working group to examine whether to modify the Privacy Rule to allow research use.²⁹² It remains unclear whether the working group will recommend the move to allow protected health information to be used for health research.

Although a full analysis of the issue is outside the scope of this Article, the creation of a HIPAA exception for research makes at least *prima facie* sense. If we are willing to allow access to health data for a wide range of useful purposes—health care, health-care operations, public health, law enforcement, billing, and quality improvement—why not for research as well? In particular, it seems incongruous to allow access to existing information for the purposes of care, and for the purposes of improving the quality of care in a relatively ad hoc fashion—but not for improving care through the systematic generation of generalizable knowledge.²⁹³ As with informed consent, the argument is that research serves a different set of interests—generalized interests, rather than the specific interests of the patient—but given the existing HIPAA exceptions for public health, law enforcement, and billing purposes, those arguments seem less

290. 21st Century Cures Act, H.R. 6, 114th Cong. § 1124 (2015) (requiring the Secretary of Health and Human Services to “revise or clarify the [HIPAA Privacy] Rule to allow the use and disclosure of protected health information by a covered entity for research purposes, including studies whose purpose is to obtain generalizable knowledge, to be treated as the use and disclosure of such information for health care operations”).

291. See Elizabeth Snell, *Is Health Data Security at Risk in 21st Century Cures Bill?*, HEALTH IT SECURITY: PATIENT PRIVACY NEWS (July 7, 2015), <https://healthitsecurity.com/news/is-health-data-security-at-risk-in-21-century-cures-bill>.

292. 21st Century Cures Act, Pub. L. No. 114-255, § 2063(c), 130 Stat. 1033, 1081–82 (2016).

293. See Eisenberg & Price, *supra* note 33, at 35–36 (noting that it is difficult to distinguish between these purposes).

weighty when compared with the goal of improving health care for patients in general.

C. COMBINED IMPLICATIONS

Combining the restrictions of privacy and informed consent paints a disheartening picture for LHSs in general and for postapproval drug information creation specifically. To be clear: I am not arguing against informed consent or privacy (or, for that matter, for them). They serve important goals, even if imperfectly. But applying them rigidly under a bright-line research-versus-not-research framework leads to real problems in our ability to generate and use information to keep patients safe and to treat them well in an LHS. The privacy and informed-consent rules governing biomedical research were largely formulated decades ago, when research really was quite distinct from care. Now that the two are blending more—at least in certain contexts—it is worth asking whether the benefits of those bright-line rules are outweighed by the costs they impose.

In addition to general barriers described above, these requirements may slant the type of research that does take place. The most straightforward research under both the Privacy Rule and the Common Rule's informed consent requirement is observational research on anonymized data, because neither rule's requirements apply.²⁹⁴ But this type of research results in incomplete pictures of what is really happening.²⁹⁵ We should also expect to see researchers shying away from large-scale pragmatic interventional studies, as consent and privacy costs scale with size (as opposed to a quasi-automated model which limits such cost-scaling²⁹⁶). Where interventional studies *are* needed—whether because of FDA requirements or otherwise—they are more likely to be smaller-scale clinical trials to satisfy FDA requirements, and clinical trials of course bring their own costs and their own risks.²⁹⁷

Informed consent and privacy requirements make it hard to develop postapproval drug information in an LHS, and the best way forward is unclear. What does seem clear is that the artificially bright line between research uses and nonresearch uses is

294. See, e.g., Miller, *supra* note 287, at 560.

295. See *supra* note 280 and accompanying text.

296. See *supra* Section III.A.

297. See Evans, *supra* note 71, at 578 (noting that making observational studies harder increases the need for interventional studies that carry greater costs for participants).

a problematic holdover from an earlier version of medical research and the health system, and one which is unlikely to help FDA, and the health system more generally, do the best by patients. I have briefly suggested that a better path would be to treat research in an LHS more like routine clinical care—allowing access to HIPAA-protected identifiable health information and permitting treatment-focused informed consent to do double duty as research-focused informed consent. Fully fleshing out and defending these possibilities is part of a much broader conversation about how law and ethics should regulate and facilitate an LHS—a conversation in which FDA and the process of drug approval and drug surveillance should be essential topics.

CONCLUSION

The health system is evolving, and the way FDA evaluates drugs is evolving with it. In each context, the sharp lines of the past—between research and treatment, and between unapproved and fully-approved drugs—are becoming blurred as we move to a world where the information created in clinical care is captured, analyzed, and used to improve the way we understand medical interventions going forward. To the extent that FDA allows, promotes, or requires drug companies to use learning-health-system-based trials to fulfill postmarketing study or surveillance requirements, the Agency can help drive the adoption of LHS ideas. This is a development to be welcomed; the health system should learn, and we should continue to develop our knowledge of drugs long after they are approved. And if FDA learns more about drugs based on how they work in the real world, that information should be used to address how drugs are labeled, sold, and used.²⁹⁸ But while FDA and the health system are moving forward, the law hasn't caught up. In particular, the federal law of informed consent and privacy continues to follow bright-line rules separating research from health care. That distinction makes it much harder for health-care system actors, whether drug firms or otherwise, to systematically gather, use, and learn from the data of clinical care. As health care generally, and FDA approval more specifically, evolves, those bright lines need to change with them.

298. See Patricia J. Zettler et al., *Implementing a Public Health Perspective in FDA Drug Regulation*, 73 FOOD & DRUG L.J. 221 (2018) (arguing that FDA has the ability to incorporate many types of information into its regulatory decisions, including real-world evidence of public health implications, and that the agency should take that information into account).