Blurred Lines: The Collapse of the Research/Clinical Care Divide and the Need for Context-Based Research Categories in the Revised Common Rule

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ABSTRACT

Despite its recent update, the Common Rule governing research on human subjects remains fundamentally flawed. Research is still defined primarily in opposition to clinical care so that the Common Rule draws a line dividing the two, a mismatch that fails to appreciate modern developments in healthcare. The historical origins of the Common Rule imbue the regulations with an understanding that research usually involves greater risks than clinical care. This view is perhaps appropriate for old research models like the randomized control trial. However, as modern medicine shifts focus from infectious diseases with common pathways to chronic illness through personalized medicine, research and clinical care draw closer together in ways that defy the assumptions of the Common Rule. New frameworks of precision medicine and learning healthcare are reliant on and work best with data collected through both research and clinical care so useful information that can be used to personalize and improve standards of care is not lost. The same technological advances that enable these changes also make possible more serious abuses of healthcare data than previously imagined. Thus, research models now exist which are both no more risky than clinical care and which are far more dangerous. Conflating different uses of research means that Common Rule simultaneously impedes new frameworks while remaining unable to address new risks. Context-based research categories, each with regulations that appropriately match the set of risks and benefits inherent in each type of research would help to align the Common Rule with reality and better protect research participants.

I. INTRODUCTION

The Federal Policy for the Protection of Human Subjects, better known as the “Common Rule” due to its adoption by twenty federal agencies, finally received an update on January 19th, 2017.1 Unfortunately, this update still fails to bring the Common Rule in line with modern medical research. The Common Rule governs

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federally-funded research done on human subjects and requires researchers who are subject to the Common Rule to utilize certain procedures and safeguards to protect the rights of human research participants. Yet the Advanced Notice of Proposed Rule-Making (ANPRM) that initiated this latest round of updates was first released in 2011, five and a half years before the Revised Common Rule was finalized.\(^2\) That the rulemaking process stretched for so long makes the Revised Common Rule’s failure to address central opportunities and challenges of the modern healthcare research system all the more tragic.

In particular, the update does little to encourage and make way for the precision medicine and learning healthcare model, whereby data and refinements of treatment methods made in the course of clinical care are continuously fed back to improve care of individual patients and contribute to the sum of medical knowledge. Technological advances enable this\(^3\) but the Common Rule’s outdated understanding of the research/clinical care divide will impede efforts to modernize research while also failing to protect research subjects from new research models.\(^4\)

The Revised Common Rule continues to assume that there is a clear divide between research and clinical care, where research is directed toward producing generalizable knowledge\(^5\) and clinical care is directed primarily toward the well-being of the patient.\(^6\) Though these definitions are not in opposition on their face, the division no longer reflects the reality of 21st century healthcare.

Advances in technology, medical knowledge, and research methods are leading to precision medicine and a learning healthcare model in which research and clinical care collapse together in key ways to create better health outcomes. Actions directed primarily toward the well-being of individual patients are able to produce generalizable knowledge while modern research gives rise to new patient care models that are not anticipated or permitted by the Revised Common Rule.

The mismatch between modern healthcare and the regulatory division of research and clinical care may have an erosive effect on the advancement of medicine and the improvement in health outcomes and the protection of human subjects because the Revised Common Rule will impede data sharing that can contribute to a more open, transparent and evidence-based learning healthcare system.

The Revised Common Rule’s definition of research should be modified to accommodate non-traditional research categories and clinical care models. Such modification would require that the Revised Common Rule take into account the fact that different research contexts and clinical care models give rise to very different balances of benefits and risks to human subjects. Because the goal of the Common Rule is to protect human subjects, the Revised Common Rule should more flexibly


\(^{3}\) See generally Heather H. Pierce and Ross E. McKinney Jr., *Opportunities Missed and Created by the New Common Rule*, 17 AM. J. OF BIOETHICS 36 (2017); Liza Dawson, *Common Rule Revised: Opportunities Lost*, 17 AM. J. OF BIOETHICS 46 (2017); Suzanne M. Rivera et al., *Modernizing Research Regulations is Not Enough: It’s Time to Think Outside the Regulatory Box*, 17 AM. J. OF BIOETHICS 1 (2017).

\(^{4}\) See Henry, supra note 2 (the Common Rule has not kept pace with the evolution of modern research).

\(^{5}\) 45 C.F.R. §46.102(d) (2017) [hereinafter COMMON RULE].

balance the various risks and benefits and require restrictions and safeguards that are
more narrowly tailored to various research contexts and clinical care models; otherwise, the Revised Common Rule risks stifling medical innovation and impairing clinical care.

Part II outlines the basic structure, history, and recent revisions of the Common
Rule to illuminate the research/clinical divide. Namely, as a reaction to human subjects
research scandals, the Common Rule aims to protect research participants against
researchers whose interest in producing generalizable knowledge may lead them to
place their subjects at unjustified risk of harm. Part III describes the recent advances
in big data, genomics, and advanced biotechnology that are poised to catalyze
precision medicine and a learning healthcare system, as well as the new risks to which
these advances expose patients. Part IV addresses how the research/clinical care divide
reflected in the Revised Common Rule is ill-suited for modern healthcare practices.
Specifically, it discusses the failure to account for how the shift in health research from
a linear model based on discovering treatments appropriate to the average statistical
patient to an iterative, circular process that centers the individual and which feeds
clinical data back into research changes the balance of benefits and risks in research
and clinical care. In addition, it details how agglomerating research activities with very
different balances of risk and reward leads to an overreliance on informed consent to
the detriment of health data privacy rights. Part V proposes context-based research
categories that better accommodate the advances in research and in clinical care.

II. THE COMMON RULE AND THE 2017 UPDATE

a. Basics of the Common Rule

The Common Rule, codified by the U.S. Department of Health and Human Services
(HHS) at 45 CFR part 46 (HHS Regulations), requires that federal funded research
involving human subjects undergo IRB approval and obtain the informed consent of
the subjects. The regulation is so named because it is shared by twenty federal
agencies. It applies to research involving human subjects conducted or funded by a
federal agency, and to research otherwise subject to regulation by an enacting agency,
for example, research conducted at institutions (such as universities) that have
accepted federal funds with a condition that research performed with such funds
comply with the Common Rule.

The Common Rule defines “human subject” as a “living individual” about whom a
researcher obtains either “data through intervention or interaction with the individual”

7 FEDERAL POLICY FOR THE PROTECTION OF HUMAN SUBJECTS ("COMMON RULE"),
[https://perma.cc/45UG-JXW7 ] (The agencies are: Department of Homeland Security, Department of
Agriculture, Department of Energy, National Aeronautics and Space Administration, Department of
Commerce, Social Security Administration, Agency of International Development, Department of
Housing and Urban Development, Department of Justice, Department of Labor, Department of Defense, Department
of Education, Department of Veterans Affairs, Environmental Protection Agency, Department of Health
and Human Services, National Science Foundation, Department of Transportation, Office of the Director of

8 Victoria Berkowitz, Common Courtesy: How the New Common Rule Strengthens Human Subject

9 Mark A. Rothstein, Ethical Issues in Big Data Health Research, 43 J.L. MED. & ETHICS 425, 425
or “identifiable private information,”10 and defines “research” as “systematic investigation . . . designed or developed to contribute to generalizable knowledge.”11

If research falls within the purview of the Common Rule, it is generally subject to two main requirements:12 informed consent by the human subjects and Institution Review Board (IRB) review and approval.13

Legally effective informed consent must allow the prospective human subject adequate opportunity to make a considered decision about whether to participate in the research.14 The researcher may not coerce the participant and must provide an informed consent form that the prospective subject can understand.15 The informed consent form must include an explanation of the purpose of the research study, reasonably foreseeable risks, foreseeable benefits, contact information for questions, be in writing and be approved by the IRB.16 Before a human subject participates in research, the human subject must sign the informed consent document, but the human subject may revoke such consent and withdraw from the research at any time without penalty.17

An IRB is a group of individuals who have the “professional competence necessary to review specific research activities” and must (i) consist of at least five members who have some diversity in background, with at least one member from a scientific background, at least one member from a non-scientific background, and at least one member who is not affiliated with the institution or individuals proposing the research, and (ii) not include any member who has a conflicting interest in the proposed research.18

Except in limited circumstances for categories of research that are likely to pose only a minimal risk to human subjects,19 any research that is subject to the Common Rule must be approved by an IRB before the research may begin, and ongoing research must be reviewed and approved by an IRB at intervals appropriate to the degree of risk related to such research (and no less than one time each year).20 The reviewing IRB will inform the researcher in writing of the IRB’s approval or disapproval of the research, including any necessary modifications to the research that would be needed to achieve IRB approval.

When reviewing research, the IRB is responsible for ensuring that (i) risks to subjects are minimized, (ii) risks to subjects are reasonable in relation both to the anticipated benefits to the individual subjects who participate in the research and to

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10 COMMON RULE, supra note 5, § 46.102(f).
11 Id., § 46.102(d).
12 There are some exceptions to the requirements of informed consent and IRB review/approval. But the exceptions are nuanced and narrow, and have little relevance to the subject matter on which this article is focused. Accordingly, the exceptions are not explored in-depth in this article.
13 Berkowitz, supra note 8, at 940.
15 COMMON RULE, supra note 5, § 46.116.
16 Id., § 46.116(a)(1)-(8).
17 Id., § 46.116(a)(8).
18 Id., § 46.107(a)-(f).
19 Id., § 46.101(b).
20 COMMON RULE, supra note 5, § 46.103(b).
the importance of the knowledge that may result from the research, (iii) selection of subjects is equitable, (iv) informed consent is sought from prospective subjects and appropriately documented, (v) if appropriate, the research plan requires monitoring of research data to ensure the subjects’ safety, and (vi) if appropriate, adequate protections are in place to protect the privacy of subjects and the confidentiality of data.21 Outside of these rather broad requirements, each IRB establishes its own policies and procedures for how it will discharge its responsibilities under the Common Rule.22

Thus, the basic structure of the Common Rule is simple: federally funded research involving human subjects requires the informed consent of the subjects and IRB approval.

b. The Research/ Clinical Care Divide

Due to the Common Rule’s historical origins in the Belmont Report,23 explained below, the Common Rule applies to “research” but not to clinical care. As such, the Common Rule establishes a dividing line between clinical care—where ethical responsibility, professional duties and legal restrictions are judged adequate protection for patients—and research—activities theoretically carried out for general knowledge might expose individual or small groups of human subjects to unacceptable risks or harm.24 A brief examination of the history of the Common Rule helps elucidate the reasons for, and contours of, such clinical care/research divide.

i. Origins of the Divide: the Belmont Report

The history of human subject research is littered with examples of immoral, sometimes downright horrifying behavior.25 Wartime examples such as the atrocities committed by Nazi26 and Japanese scientists27 during the Second World War readily come to mind. Closer to home is the Tuskegee Syphilis Study, a forty year study in which researchers followed African American men infected with syphilis.28 Researchers violated their ethical duties by not only failing to inform the men of their condition or of the increasingly accessible cures, but by actively obstructing them from coming into contact with people and institution who could assist them, all in the service of being able to observe the stages of the disease.29 Many of the men died from syphilis though cures were readily available by the conclusion of the study. The

21 Id., §46.111(a)(1)-(3).
23 Berkowitz, supra note 8, at 934–935.
28 Lenrow, supra note 14, at 24.
documents of one the doctors involved with the Tuskegee study included evidence of a companion study performed in Guatemala. In that study, researchers not only failed to treat the syphilis patients, but, in some cases, intentionally infected the men in the first place, ultimately leading to debilitating disease and death.

These studies, and others like them, were performed in the open and discussed at academic conferences while the lead investigators were toasted as valued contributors to the sum of human knowledge. Thus it was not a problem of isolated rogue scientists but of the commonly understood ethics of the healthcare profession.

In the wake of the revelations about the Tuskegee syphilis trials, the ethical importance of human subject research garnered substantial attention, culminating in the Belmont Report. The Report was written in 1978 after four years of work by a National Commission formed to study the protection of human subjects in biomedical and behavioral research. The U.S. Secretary of Health, Education and Welfare (the precursor to the U.S. Department of Health and Human Services) tasked the Commission to identify the boundary between research and clinical care, determine the role of risk-benefit analysis in human subjects research, recommend guidelines for selecting subjects, and outline requirements for informed consent.

The resulting report, called the Belmont Report, was short but complex, and its content heavily influenced subsequent human subject research regulations, including the Common Rule. A brief preamble notes that the Belmont Report outlines three core principles stated at a “level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects” that provide “an analytical framework that will guide the resolution of ethical problems.”

The first principle is “Respect for Persons”: individuals should participate in research only if they are fully informed about, and voluntarily agree to participate in, such research.

The second principle is “Beneficence”: researchers should maximize possible benefits while minimizing possible harms.

The third principle is “Justice”: the selection of human subjects who participate in research should be a fair and representative sampling of individuals, without regard to social, racial, sexual, or cultural biases.

The second half of the report is devoted to how these three principles should be applied in the context of research. Most important among these practical applications


31 Id.

32 Jones, supra note 25, at 5.

33 Berkowitz, supra note 8, at 934.


35 BELMONT REPORT, supra note 6, Preamble.

36 Javitt, supra note 24, at 48.

37 BELMONT REPORT, supra note 6, Preamble.

38 Id., at Part B.1.

39 Id., at Part B.2.

40 Id., at Part B.3.
are informed consent procedures and the development of systematic assessment of risks and benefits, both of which were adopted in the Common Rule and discussed above.

ii. The Misleading Universalism of the Belmont Report Definition of Research

The first part of the Belmont Report is devoted to elucidating the Boundaries Between Practice and Research, and sets up a divide with clinical care on one side and with research on the other. The Belmont Report defines “research” as “an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships).” In contrast, the Belmont Report defines “practice” (referred to in this article as “clinical care”) as “interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success.”

By not clarifying that these definitions are bounded to a particular time period, level of technological sophistication, and model of research, the Belmont Report makes an implicit claim of universal applicability. This is a problem because the assumptions underlying the Belmont Report’s vision of how research and clinical care are conducted have in fact changed with the passage of time. Defining “research” and “clinical care” in opposition to each other draws an unjustifiable dividing line and presents a false dichotomy that has become increasingly problematic as changes in healthcare priorities and advances in methodology mean that research is often now part and parcel with clinical care, and clinical care can be used to contribute to generalized knowledge.

The Common Rule was adopted in 1981 with the Belmont Report and its three core principals as the “foundational background” and the definition of “research” under the Common Rule closely mirrors that under the Belmont Report. Given the regulatory history of the Common Rule, and the similar definitions of “research,” it appears that the Common Rule envisions a similar, if not identical, division between research and clinical care. Therefore, to better understand the limits of the research/clinical care divide outlined in the Common Rule, it is important to understand two significant shortcomings of the Belmont Report’s implicit claims to universal applicability.

First, the Belmont Report failed to provide either a detailed account of what ethical human subjects research should look like or a comprehensive framework to guide it. Instead, the Belmont Report recommended three core principles, with only a few paragraphs of justification for each one. It is possible these principles were chosen because there could be broad consensus on them between stakeholders who approached the problems of human subjects research from different directions.

41 Berkowitz, supra note 8, at 940.
42 See supra Section II.a.
43 BELMONT REPORT, supra note 6, Part A.
44 Id.
45 Id.
46 FEDERAL POLICY FOR THE PROTECTION OF HUMAN SUBJECTS, supra note 7.
Second, just as the Belmont Report does not provide much explanation regarding the assumptions underlying the three core principles, the Belmont Report does not explain how assumption that medical research and clinical care function entirely separate from one another, or the practical implications of the research/clinical care divide. Specifically, the Belmont Report assumes a linear research model in which information flows in one direction—from researchers to clinical care providers—which ignores the feedback loop that is inherent within a successful healthcare system.

Fundamentally, the Belmont Report, and arguably the Common Rule, assume that a doctor performs only research or clinical care at any given moment. But, as discussed more fully in Part III, this is simply no longer accurate as medicine pushes into new boundaries where clinical care often necessitates research and research often evaluates the health outcomes of clinical care. And if the clinical care/research divide no longer maps onto our modern healthcare system, it not only means that the Common Rule is not optimized for protecting modern “research” participants (who are often patients undergoing clinical care), but that the Common Rule may even be an impediment to progress since it is attempting to enforce a false division.

c. 2018 Revisions

Despite high hopes for the Revised Common Rule, it failed to tackle some of the key problems in the Common Rule, including the research/clinical care divide. Nevertheless, the update is evidence regulatory bodies recognize greater clarity is needed and that the Common Rule itself must adjust to changes in healthcare research. For one thing, Revised Common Rule introduced limited IRB review and broad consent for the storage of information and bio specimens, which can be used to help drive structural improvements in modern healthcare research. However, the problem is that these are rather awkwardly tacked on as either research exempt from regulation or research exempt from regulation except for some limited required procedures. Not only does this not meaningfully move the Common Rule away from its adherence to a research/clinical care divide, these categories are themselves ill defined. The reasons why explicitly named research activities fall into them are not explored. This gives the regulatory structure the kind of uncertainty and apparent capriciousness that is detrimental to innovation. Thus, while the Revised Common Rule attempts to address some of the issues brought to the forefront by changes in the healthcare research paradigm, it does little to address the fundamental mismatch between the reality of medical research and the Common Rule’s understanding of the division between research and clinical care. As this work focuses on research/clinical divide, only those changes most relevant to that distinction are discussed.

i. Major Updates

Addition of Not Research and Exempt Research Categories

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49 Pierce, *supra* note 3, at 37.

50 Final Update, *supra* note 1, at §____,104(d)(7)-(8).

51 Id.
The pre update Common Rule divided proposals into two different categories: research exempt from regulation and research that is not exempt. This update adds two additional categories. The first is an explicit listing of four activities that do not count as research at all to assist IRBs: a limited set of academic and journalistic activities that focus on individuals rather than communities, public health surveillance, criminal justice activity, and authorized operations in service of national security. The update also modifies and adds certain exemptions but attaches conditions such as limited IRB review. The result is that there are functionally two groups of explicitly exempt research, some with additional conditions and the others without.

Changes to the Informed Consent Form

In terms of informed consent, the Notice of Proposed Rulemaking (NPRM) included certain strict categorization of information that would need to be included with the informed consent form and proposed that technical information be relegated to appendices to reduce confusion. However, information must be presented at sufficient detail to allow the subject to consent. In addition to the existing categories of required information, the final rule requires the informed consent form include:

- Whether biospecimens collected as part of research will be used or distributed for future research, even if identifiers are removed;
- Whether specific technology can generate identifiable private information or identifiable biospecimens will be used;
- A statement that subjects’ biospecimens may be used for commercial profit and whether the subject will share in this profit; and
- A statement regarding whether clinically relevant research results will be disclosed to subjects.

Introduction of Broad Consent

In addition, for the first time, the Revised Common Rule supports the use of broad consent for the storage, maintenance and use of identifiable information or biospecimens. The broad consent form must still contain sufficient information for a reasonable person to understand the types of secondary follow up research that might be possible. For instance, the researcher must include a description of reasonably foreseeable risks, potential benefits both to the subject and to third parties, whether whole genome sequencing will be involved, how long the information or bio-

52 P. Pearl O’Rourke, The Final Rule: When the Rubber Meets the Road, 17 AM. J. OF BIOETHICS 27, 28 (2017).
53 Id.
54 FINAL UPDATE, supra note 1, at § _____.102(i).
55 Id., at 23.
56 Jerry Menikoff et al., The Common Rule, Updated, 376 THE NEW ENG. J. MED. 613, 614 (2017).
57 FINAL UPDATE, supra note 1, at § _____.116.
59 O’Rourke, supra note 52, at 30.
specimens will be stored including if that time period is indefinite, and if it will be used for commercial profit.\textsuperscript{60}

\textbf{Other Updates}

The update also requires that clinical trials that fall under the purview of the Revised Common Rule post online a copy of the consent forms approved by their IRB.\textsuperscript{61}

Finally, the update introduces some changes in the way research will be reviewed when multiple institutions are involved. Multisite research will have to be reviewed by a single IRB as a condition of receiving grants, the net effect of which will be to centralize review of large scale, multisite research efforts.\textsuperscript{62}

\textit{ii. Potential Impact of Updates}

The basic structure of the Revised Common Rule remains largely unchanged and there was no change in the definition of “research.”\textsuperscript{63} The 2018 Revisions thus reflect the same core assumptions about the way research can and should be done.\textsuperscript{64} Commentators have pointed out that the questions asked and answered by the update were bounded by the existing contours of the Common Rule framework and thus did not truly touch on how principles such as informed consent should be updated for 21st century research.\textsuperscript{65}

\section*{III. \textsc{Changes in the Healthcare Model}}

The way healthcare is delivered depends upon available technology. Rapid transit enables the extension of critical medical services to more people all around the world than ever before. Vaccines lead to the eradication of diseases that once plagued the population. Advances in biosciences and protein modeling have allowed for a more precise drug design process.\textsuperscript{66} Modern medicine relies upon a cycle of experimentation and implementation where the efficacy of drugs and wellness regimes is repeatedly tested against a control to isolate its effect upon an illness.\textsuperscript{67} This is an evidence-based regime which might be why medical experts are increasingly convinced that existing models of medical research are seriously flawed.\textsuperscript{68} For instance, researchers are discovering that randomized control trials cause trouble when their results, which

\begin{itemize}
  \item Sugarman, supra note 58, at 25.
  \item Menikoff, supra note 56, at 614.
  \item FINAL UPDATE, supra note 1, at §____.102(l).
  \item Berkman, supra note 48, at 8; Rivera, supra note 3, at 1.
  \item Henry, supra note 2, at 386 (describing scholarship that posits whether the Common Rule is deficient on its own terms); Pierce, supra note 3, at 37; Rivera, supra note 3, at 1.
  \item See generally Chun Meng Song et al., Recent advances in computer-aided drug design, 10 BRIEFINGS IN BIOINFORMATICS 579 (2009).
  \item See e.g., id.; John P. A. Ioannidis, Why Most Published Research Findings Are False, 2 PLOS MED 696 (2005).
\end{itemize}
come from averaging patients together are then applied to individuals who depart from the mean.69

Modern technology is poised to change healthcare via precision medicine, mass clinical trials, big data analysis of existing health data, and rapid genomic sequencing. These changes have the potential to vastly improve health outcomes, perhaps especially for minority populations. These populations are underrepresented in the medical profession and study participation70 which means that the results are not well targeted for them. Big data and other large scale analyses may eliminate some of these biases. Thus, the modern healthcare revolution will be good for patients. But it may also be dangerous because the digitization of healthcare and healthcare relevant information presents real risks.71 The Revised Common Rule cannot adequately grapple with these risks because its definition of “research” does not accommodate the technology-driven changes to clinical.

a. Changes in Technology

The subsections below detail some of the key innovations changing the way healthcare research is done and the way treatment is delivered.

i. Big Data

In its colloquial usage, big data refers to the use of predictive analytics on a large data set sufficient to reveal novel information unattainable through traditional statistical analysis.72 The defining feature of big data is that it reveals trends and relationships that are not obvious on their face, correlations that perhaps no one could have predicted.73 This can help detect diseases at earlier stages, manage population level health and predict outcomes based on existing data.74 The limitation of big data in its current form is that the data is unstructured and can potentially produce false correlations.75 Nevertheless, big data is an increasingly powerful tool in healthcare, where diagnosis and treatment depends on integrating data points to create a

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71 See generally Barbara J. Evans, Power to the People: Data Citizens in the Age of Precision Medicine, 19 Vand. J. Ent. & Tech. L. 243, 244–45 (2016) (describing one danger- that identifiers are needed in the big data analysis process); PRESIDENT’S COUNCIL OF ADVISORS ON SCIENCE AND TECHNOLOGY & EXECUTIVE OFFICE OF THE PRESIDENT, BIG DATA AND PRIVACY: A TECHNOLOGICAL PERSPECTIVE (2014) [hereinafter PCAST REPORT] https://www.whitehouse.gov/sites/default/files/microsites/ostp/pcast_big_data_and_privacy_-_may_2014.pdf.

72 VICTOR MAYER-SCHONBERGER & KENNETH CUKIER, BIG DATA: A REVOLUTION THAT WILL TRANSFORM HOW WE LIVE, WORK, AND THINK 6 (2013).


74 Wullianallur upathi & Viju Raghupathi, Big Data Analytics in Healthcare: Promise and Potential, 2 HEALTH INFO SCI. & SYS. 1, 2 (2014).

reasonable hypothesis about patients’ illnesses. As will be discussed further below, the addition of genetic data will permit the revelation of more and more details about individual pathologies.

ii. Mobile Medicine and EHRs: The Proliferation of Data

The rise of wearable devices, some of which have more or less direct health uses, means that more than ever before, clinically relevant information can be collected outside of a formal clinical setting. Some of these devices are worn pursuant to formal medical treatment such as when a doctor instructs a patient to monitor their heart rate at different times of the day. More often, these devices are worn for fitness or are primarily communication devices. Nevertheless, the data they collect can be clinically relevant, especially with the application of big data methods.

Formal health records are also increasingly stored electronically. In 2009, the federal government earmarked $27 billion dollars to incentivize hospitals and health providers to switch from paper records to electronic records.

While many of the programs hospitals use are clunky and not intuitive, electronic health records have many advantages over their paper counterparts. They are safer from the elements, more easily transported, and best of all, more easily linked with other sources of data to create new information.

Together, these new sources of data make it possible to obtain a richer and more complete record of information about each individual’s daily patterns and other clinically relevant health information.

iii. Genetic Sequencing and Analysis

At the start of the Human Genome Project, sequencing an entire human genome was projected to take nearly twenty years and $3 billion dollars. Today, commercial labs are able to sequence an entire genome for less than $1000. New techniques and technologies are constantly in development such that this price point is unlikely to

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76 Raghupathi, supra note 74, at 2.
78 Evans, supra note 78, at 244–45.
79 Yasser Khan, Monitoring of Vital Signs with Flexible and Wearable Medical Devices, 28 ADVANCED MATERIALS 4373, 4373 (2016).
83 Raghupathi, supra note 74, at 4.
85 The Cost of Sequencing a Human Genome, NATIONAL HUMAN GENOME RESEARCH INSTITUTE (Jul. 6, 2016) [https://perma.cc/4JQ9-VTSS].
stand for long. In fact, recent reports indicate that companies believe that the cost will drop to less than $100 within three to five years.86

Note too that this price reflects a full sequencing of the approximately 3 billion base pairs in human DNA. Many consumer facing companies have developed procedures for a more limited sequencing to discover those genes thought to be linked to specific health conditions or those that help to reveal ancestry which is cheaper still. As of this writing, a commercial DNA testing kit can be obtained for less than $100. The natural result of the rapid decline in the cost of DNA sequencing is that it will increasingly become a part of routine healthcare.88 This is important because each individual has a unique genetic makeup as well as different environmental circumstances which affect the expression of those genes, the pathways of disease can differ widely.89 Effective treatments will increasingly require examining the genetic information of the individual for clues as to what sorts of interventions will work best.90

b. Changes in Healthcare Delivery and Research Caused By Technology

From a bird’s eye view, changes in technology are poised to revolutionize the approach to healthcare research in many different ways.

i. At the Technical Level

By extending the precision and range of the treatment techniques that can be employed. The technological advances noted in the section above will lead to the development and proliferation of many novel techniques. For instance, cancer patients can have their genomes sequenced to help determine what treatments will work best for them.91 These tests have the capacity to determine which molecular and genetic triggers might be most responsible for the unchecked cellular differentiation that characterizes cancer.92 The monitoring and data collection advances also allow doctors to do around the clock monitoring in a way never before possible such that they can hope to develop a clearer picture of their patient’s illness.

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87 Lydia Ramsey, I’ve taken Ancestry DNA, 23andMe and National Geographic genetics tests – here’s how to choose one to try, SCIENCE (Nov. 24, 2017) [https://perma.cc/WZE9-WC2T].

88 See generally Carla G. van El et al., Whole-Genome Sequencing in Health Care, 21 EUR. J. OF HUM. GENETICS 580 (2013).

89 Jens Mogensen, Current Role of Next-Generation DNA Sequencing in Routine Care of Patients with Hereditary Cardiovascular Conditions, 36 EUR. HEART J. 1367, 1368 (2015).


92 Aronson, supra note 90, at 336–337.
ii. At the Methodological Level

By encouraging the development of new experimental techniques and data collection in settings other than classical clinical care. Consider, for instance, mass mobile clinical trials. In the traditional model, research subjects are recruited from a limited geographical area. With the rise of mobile devices and the increased ease of programming applications for download onto smartphones, some researchers have begun to cast wider nets in searching for research subjects. In the notable mPower study, Sage Bionetworks enrolled thousands of patients in a mobile Parkinson disease study. Subjects who downloaded the application were put through an informed consent process within the application with multiple choice quizzes designed to ensure comprehension. Mediated through the app and through the use of sensors such as the accelerometer, participants could enter information directly or do activities designed to test their memory or their reflexes. In this way, researchers were able to collect data with relative ease compared with the labor and time it would have taken in classical clinical settings.

iii. At the Data Production and Analysis Level

By permitting the formation of large-scale databases with genomic and other types of data. One good example of this is the establishment of biobanks. These are collections of data or bio specimens, often centered around a specific disease. Rather than having to track down new subjects every time, researches can access the biobank data to do follow up studies or original research with existing data. For instance, Sage Bionetworks, the non-profit that facilitated the mPower study, asked participants to allow their data to be used by researchers beyond the initial study. More than three-fourths agreed to share their data with any researcher who qualified under Sage’s screening process. Through studies like these, Sage is attempting to build up a

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93 See generally, Yeshe Fenner, Web-Based Recruiting for Health Research Using a Social Networking Site: An Exploratory Study, 14 J. OF MED. INTERNET RES., iss 1 e20
94 See generally, Deborah Estrin & Ida Sim, Open mHealth Architecture: An Engine for Health Care Innovation, 330 SCI. 759 (2010).
95 Charles Moore, 6-Month Data from Parkinson’s mPower App Study in 9,500 People Released to Researchers, PARKINSON’S NEWS TODAY (Mar. 7, 2016).[https://perma.cc/JP3B-CFWF]
96 Brian M. Bot et al., The mPower Study, Parkinson Disease Mobile Data Collected Using ResearchKit, SCIENTIFIC DATA 1, 2 (2016).
97 Id., at 2–3.
98 Id., at 2.
100 Holly Fernandez Lynch et al., Confronting Biospecimen Exceptionalism in Proposed Revisions to the Common Rule, HASTINGS CENTER REPORT, Jan.-Feb. 2016, at 4, 5 (illustrating some of the uses).
101 Aronson, supra note 90, at 340.
103 Id.
database so that researchers unconnected with the initial study can verify the study or do secondary research to discover connections the primary investigators missed.104

Databases like Sage’s can reduce the barriers to entry for rare diseases but they have broader implications for secondary research and analysis.105 After all, there are more than 300 million human specimens being stored in the United States alone.106 Along with electronic records and data, these bio specimens can be analyzed through big data techniques to discover nonobvious linkages and correlations.107 As described above, big data allows the discovery of interactions that operate on a deeper level than the traditional bevy of statistical metrics, allowing combined datasets to be “more than the sum of the parts.”108 Collections of data from different studies can be linked together and analyzed to better isolate confounding factors.109 Big data also allows the integration of data without obvious health implications but that nevertheless reveal relevant information such as lifestyle habits.110

c. The Benefits of a Changed Research Paradigm: A Learning Healthcare System and Precision Medicine

Technological change is driving changes in the healthcare research model and how care is delivered: two examples of this are “precision medicine” and a “learning healthcare system.” Per the Precision Medicine Initiative, precision medicine is “an innovative approach that takes into account individual differences in people’s genes, environments, and lifestyles.”111 The Institute of Medicine defines a learning healthcare system as one in which “science, informatics, incentives, and culture are aligned for continuous improvement and innovation, with best practices seamlessly embedded in the delivery process and new knowledge captured as an integral by-product of the delivery experience.”112 Together, they permit healthcare professionals to consider the unique characteristics of each individual and permits them to funnel what they learn back into the system to better inform healthcare decisions and improve health outcomes.113 Together, these can supplement and refine the results from the randomized control trials which much medical research currently leans on.

In the past, the gold standard of medical research was double-blind randomized control trials with placebo and the use of large cohorts, large enough so that differences would average out and statistical anomalies that might skew the results are

104 Id.
105 Id.
107 Raghupathi, supra note 74, at 2–3; Thorpe, supra note 73, at 171.
108 PCAST REPORT, supra note 71, at 24.
109 Raghupathi, supra note 74, at 5.
112 Integrating Research and Practice: Health System Leaders Working Toward High Value Care, INST. OF MED., xi (2015).
113 Aronson, supra note 90; Deven McGraw, Paving the Regulatory Road to the “Learning Healthcare System”, 64 STAN. L. REV. ONLINE 75 (2012).
These results inform not only the approval of new drugs but the clinician’s standard of care for the use of those drugs and other wellness regimens. However, randomized control trials have some blind spots and are well suited to linear, one-way processes where research defines clinical care and which does not easily make room for the feedback loops that define a learning healthcare system.

First, randomized control trials are incredibly costly, which both makes them inaccessible for under-resourced researchers as well as difficult to perform at large scales. In addition, due to uneven recruitment as well as historical mistrust of research science in certain minority populations, there is often some bias in patient populations that sign up for randomized control trials. Next, due to a combination of the way journals process submissions for publication, flaws in research methodology and some unscrupulous professionals, there is a bias toward positive results. There is evidence that some pharmaceutical companies actively suppress negative data about leading drugs. So a study is far more likely to be published if it shows that the drug or regimen it is testing has a beneficial effect on the patients involved. Add to this the reality that researchers must publish if they are to maintain their positions and to advance their careers and there is ample potential for biases to prejudice the literature. Most clinicians no longer consider themselves researchers, which, along with their large workload, leads to a concurrent lack of attention to the evolving medical literature such that even specialists may use outdated standards of care.

Randomized control trials can also be a poor tool to aid in precision medicine, which aims to tailor treatments to the individual. The randomized control trial usually aims toward the most common form of a disease and the end result works best for average, standardized patients. Precision medicine recognizes the reality that these average or standard patients do not truly exist. Though randomized control trials remain a useful part of healthcare research, the linear model of research they are best suited for leaves on the table a treasure trove of data produced through every day clinical interactions. Taken in aggregate, the daily interactions of doctors with their patients can offer the equivalent of real-world randomized control trials, ones targeted not for

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114 Susan Salmond, Randomized controlled trials – Methodological concepts and critique, 27 ORTHOPAEDIC NURSING 116 (2008) (article describes the principles and rationale of RCTs).
117 When researchers have connections to the company producing the drug, the findings are four times as likely to support the drug. Marcia Angell, THE TRUTH ABOUT THE DRUG COMPANIES (2004).
119 Pasquale, supra note 82, at 679–90.
120 Ioannidis, supra note 68, at 697–98.
121 See Seema Rawat and Sanjay Meena, Publish or perish: Where are we heading?, 19 J. OF RES. IN MED. SCI. 87 (2014).
122 Bothwell, supra note 115, at 2177.
124 Id.
average patients but for individuals. Our data processing capabilities have advanced to the point that useful, actionable information can be derived from this.

It is also true however, that many of the medical challenges of the 21st century are not the sort that can be easily addressed by randomized control trials, even bolstered by the addition of clinical data. That is because randomized control trials work best for medical issues that have consistent symptoms, activity pathways, and infection profiles. This is not how many modern health challenges such as heart disease or cancer operate. For these types of medical challenges, the unique genetic makeup and medical histories of each individual patient affect their response to various treatments in unique ways. Thus, individualized healthcare will require extensive modifications from the one size fits all research model. There is therefore a lot of room for precision medicine and a learning healthcare system to add value to the medical research.

In recent years, genomics and biotechnology have become sophisticated enough to allow individualized care that takes into account specific risk factors, lifestyle and genetic history. Additionally, due to the advent of the internet, human beings are producing more health data than ever, even beyond clinical care interactions through personal monitoring devices. Through the use of big data processes, this information can reveal important information about the efficacy of clinical interventions in general as well as the efficacy of specific regimens for individuals. All of this in conjunction can help catalyze a learning health care system that improves healthcare through constant feedback loops. It can also be harnessed to reorient the healthcare system away from the illusory average patient and toward personalized medicine. New technology permits and encourages the integration of research and clinical care in a way likely to produce better healthcare outcomes for individuals.

d. The Risks of Participating in the New Healthcare Model

The advances in technology that can improve healthcare delivery also produce new risks. One set of risks comes out of participating in the new systems of routine data sharing. The other set of risks stems from novel commercial applications of the same data collection and analysis capabilities driving precision medicine.

i. Risks of Participating in Public Data Sharing

To fuel a learning healthcare model to work, data sharing should occur at the population level. Researchers and clinicians will have more data with which to test

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125 Id (see box 2 for a description of how large scale heterogeneous data can be used as controls).
126 Id.
128 Mogensen, supra note 89, at 1367.
129 Id.
131 Huber, supra note 127.
132 Evans, supra note 78, at 244.
133 Cf. McGraw, supra note 113, at 76.
134 See generally Hiller, supra note 81.
their hypotheses. This is one of the reasons that some scholars have called for a duty to share data. Yet real risks do remain.

For one thing, big data does not necessarily mean better data. Innovative and conceptual thinking is still necessary for breakthroughs as big data alone, without the structures of analysis and organizations, is not actionable knowledge. Even worse, thoughtless application of new techniques without a full understanding of their limitations can lead to more bias and inaccuracy.

Increasing digitization and the creation of links between different buckets of data also means there are additional points of entry for those with ill intentions. These risks are important to address not just for the safety and peace of mind of the individuals they affect but also for safeguarding the revolution in healthcare that modern technology can enable. Data breaches or misuses of data can erode trust, which may lead to a retreat away from the kinds of broad data sharing and processing most helpful for modern healthcare research.

All of these problems are made more acute with the increasing prevalence and indeed, relevance of genetic data to personalized healthcare. Genetic data is unique and as the means of analysis becomes more sophisticated, it becomes more difficult to disentangle identity from data.

**ii. Additional Risks from Commercial Applications of Human Subjects Research**

The Revised Common Rule applies only when the research is funded by the federal government. Activity not funded by the federal government but otherwise falling under the Revised Common Rule’s definition of research is not subject to it. Though the measure was not ultimately adopted, NPRM initially proposed that the Common Rule be extended to clinical trials that are not federally funded as long as the institution conducting them receives federal funding. Thus, the NPRM recognized adequately protecting human subjects requires turning outside the band of research directly funded by the federal government.

The economic incentives to exploit the new types and new volumes of health and health relevant data that can be collected and processed with new technology have

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135 Evans, supra note 78, at 257; Rosamund Rhodes, In Defense of the Duty to Participate in Biomedical Research, 8 AM. J. BIOETHICS 37, 37–38 (2008).

136 PCAST REPORT, supra note 71, at 8.


138 See Choong Ho Lee & Hyung-Jin Yoon, Medical Big Data: Promise and Challenges, 36 KIDNEY RES. & CLINICAL PRAC. 3, 9 (2017) (for the proposition that big data shares the limitations of observation studies and cannot test causality).


140 Gearhart, supra note 77.

141 Rothstein, supra note 9, at 425.

already led to instances of abuse. The lack of an oversight structure or a mechanism by which to develop norms that might mitigate harms invites further risks. This section traces a few case studies in order to elucidate risks presented by commercial applications of information technology driven human subjects research.

**Data brokers and the risk to privacy**

As of 2016, according to a Newsweek report from that year, there were anywhere between 2500 to 4000 data broker companies. One of these companies, “Acxiom has at least 1,600 pieces of information about 98% of US citizens.” These brokers scrape information from public sources such as government records. Public facing data on social media sites, online retailers who possess information on purchase patterns as well as other companies that offer online services are also sources. Data brokers then make money by selling the profiles, which often are attached to identifying information. They might sell to individuals seeking leverage over another person as well as to political campaigns and advertising companies. Just nine brokers generated over $400 million in annual revenue. None of this activity is legally forbidden.

Yet aggregating this data to form comprehensive profiles raises significant privacy concerns. Due to the sensitivity of medical information, these problems are particularly acute in the health data context, raising issues of discrimination and stigma.

**The Facebook Contagion Study and risk of intentional manipulation of behavior**

In 2012, Facebook effectively enrolled nearly 700,000 of their users in a study to see how increasing or decreasing emotional content would affect them. Researchers manipulated newsfeeds and measured the emotional content in subsequent posts. Facebook justified its actions on the basis of a provision within its consent documents

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145 Pasquale, supra note 82, at 721.


148 Id.

149 Id.


151 Rostow, supra note 146, at 675.


added four months after the study. While much coverage focused on the lack of consent, perhaps just as important, the study provided evidence that emotional states could be affected by the posts a user encountered.

Other published studies have also indicated that manipulation, emotional or otherwise, is possible online. This, alone, is no surprise. The difference is that online, companies are able to track and follow up with increasing precision. Sophisticated companies today can collect and analyze data regarding how many times a consumer had to see an ad to make a purchase, which placements were most successful and even how much time the consumer spent looking at the ad. And much as treatments are personalized to have the biggest impact on the health of the individual patient, ads and other media web designs may become targeted precisely to better manipulate the individual. To refine these manipulations, companies will be relying on trial and error. In other words, they will be performing experiments on human subjects but since it is not federally funded, this activity is not covered by the Common Rule.

23andMe and the risks of re-identification
Consumers of 23andMe pay about 100 dollars and receive a DNA test kit in the mail. They send a sample back to the company which sequences the genetic information within and churns out a report with ancestry information and likelihood of disease. Thereafter, the genetic information is stored in a database. One profile of the company noted that “23andMe wants to do for health what Google has done for search: make massive quantities of information digital, accessible, and personal.”

23andMe is therefore an information broker with the ability to financially capitalize on access to the database. The incentives certainly exist as individual health information is sometimes more valuable than traditionally trafficked information such as credit card data. This information can be dangerous for privacy in that it can still be traced back to the individual even if it is stripped of identifying information. Advances in technology and data analysis make it more and more difficult to truly de-

identify data.\textsuperscript{161} Even Netflix reviews can be linked back through the application of big data on the vast amounts of information each one of us leaves on the web.\textsuperscript{162} So it stands to reason that many studies have demonstrated that it is possible to link health data and especially genetic data with an individual by combining it with publicly available info.\textsuperscript{163} Indeed, 23andMe’s own privacy statement recognizes that it “cannot guarantee confidentiality and security of this information due to inherent risks associated with storing and transmitting data electronically.”\textsuperscript{164}

This is not to say that health information should never be kept in private hands. In fact, note the similarity of the 23andMe model to that of Sage Bionetworks, mentioned above, a non-profit that stores research data to permit secondary research. Whether the storage of patient data that third parties can access is a sign of beneficial changes in healthcare research or a reason for concern depends upon the context in which this is done. For one thing, Sage Bionetworks and other healthcare oriented non-profits are either already required under the Common Rule or voluntarily run through their consent procedures through an IRB review process.\textsuperscript{165} In addition, non-profits are subject to rules and regulations that may have nothing specifically to do with health data privacy but nonetheless subject them to oversight. Finally, because commercial enterprises are motivated by profit, they are subject to certain bad incentives in a way non-profits are not. As the examples above have shown, there is a lot of money to be made in the various uses of health data. Advancements in big data, proliferation of health data and innovation to take advantage of these will tend to increase these financial pressures, especially since many of the money-making strategies, while morally dubious, would not be illegal.

Yet even extending the Revised Common Rule to research conducted without federal funds is insufficient to curb potential abuses because the way it defines research as something opposite to and apart from clinical care misunderstands the different balances of risks and rewards.

IV. THE MISMATCH BETWEEN THE RESEARCH/CLINICAL CARE DIVIDE AND NEW FORMS OF HEALTHCARE RESEARCH

The aim of this Part is to first describe precisely how the oppositional research/clinical care divide envisioned by the Revised Common Rule fails to map onto the way research and clinical care relate to each other, especially given recent

\begin{footnotesize}
\begin{enumerate}
\item[164] Privacy Highlights, 23ANDME, https://www.23andme.com/about/privacy/ [https://perma.cc/3GCG-BM39].
\item[165] Sage Bionetworks, http://sagebase.org/ [https://perma.cc/5XM6-MEBZ].
\end{enumerate}
\end{footnotesize}
technological advances and new understandings of the flaws in healthcare research. Then, it attempts to lay out exactly why this mismatch is detrimental, namely by encouraging over-reliance on informed consent and by acting as an impediment to the potential of precision medicine and a learning healthcare system.

To reiterate, the Revised Common Rule defines research as “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.”166 Based on the Common Rule’s origins in the Belmont Report, this is in contrast with clinical care which are interventions “designed solely to enhance the well-being of an individual patient.”167

a. The Research/Clinical Care Divide Fails to Account for the Way the Two Increasingly Collapse Together

Consider two clinicians. Each has a patient suffering from high blood pressure who does not respond to intervention using standard care. Common practice dictates the patients should be prescribed either of two other drugs which have different pathways of efficacy. Neither physician is certain which of the two drugs will work best for their patient but they take different routes to determining which is more suitable.

Based on past experience, physician one thinks that Drug A will be more effective for her patient so she prescribes a dose. When this doesn’t appear to work after one week, she prescribes Drug B. After one week of this regimen, there are some benefits but the physician realizes that these improvements may be due to the lag time for Drug A to take effect. The physician discusses with her patient and returns him to Drug A, which appears to help. Subsequently, the physician thinks her experience may be helpful to others so she writes a case study and publishes it to assist other physicians with treating their patients.

Physician two takes a slightly different approach. Since she has no standard of care to determine whether Drug A or B will work better for her patient, the two treatments are said to be in equipoise. Therefore, she sits down with her patient and designs an N-of-1 study with him, which takes an individual as its subject. Such studies usually seeks to reproduce the benefits of a randomized control trial in miniature by toggling back and forth between regimens.168 This is necessary to reduce the effect of confounding factors and rule out the effects of lag times.169 In an experimental structure where A is tested for one week and then B is tested the next, the patient may appear to have a better result under B even though it is really because A took a longer period of time to kick in.170 Based on this, physician two and her patient agree to use an ABA structure for their N-of-1 study. Drug A ends up being more effective for the patient. The physician subsequently publishes the results of the N-of-1 study, along with some patient characteristics that are non-identifying but would better enable other researchers to determine if this N-of-1 study is relevant.

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166 Common Rule, supra note 5, § 46.102(d).
167 Belmont Report, supra note 6, Part A.
170 AGENCY FOR HEALTHCARE RES. & QUALITY, supra note 168, at 5.
Functionally, physician one and physician two have done substantially similar things. Faced with uncertainty about which of two regimens to prescribe their patient, the two physicians each decided to perform an experiment in miniature to determine the best procedure and ended up publishing their results. How might the Revised Common Rule deal with these two situations? Probably very differently.

Physician one is undoubtedly in the clear. Her actions at each phase of the process followed standard of care, she did not conceive of the idea to publish the case study until afterwards, and a case study is not commonly regarded as research. However, physician two may run afoul of the Revised Common Rule. An N-of-1 study is after all a systematic investigation, usually designed in such a way that it is able to contribute to generalizable knowledge.\(^{171}\) Note that this is the case, even though, as here, the physician conceived of the study solely for the well-being of her patient and followed standard of care. Note as well that the actions and results of both processes were substantially similar since both physicians switched their patient from Drug A to B and then back again. The difference is simply that physician two conceived of the process as an N-of-1 study and the plan developed at the beginning better resembles traditional research processes. That these two practices (N-of-1 research + case study) which are functionally equivalent should have diverging requirements illustrates a fundamental flaw in the Common Rule’s definition of research. Even worse, the more rigorous practice, the one more likely to benefit the healthcare system as a whole, is discouraged.

As the example above illustrates, miniature experiments undertaken solely for the benefit of the patient in question but capable of generating generalizable information are increasingly possible. Technological advances and new models of healthcare not only make these sorts of activities easier, but also more and more necessary.\(^{172}\) As it becomes increasingly clear existing standards of care are not sufficiently individualized to the unique circumstances of each patient, the standard of care may not be single regimen but instead a recommendation to conduct an N-of-1 study.

So little research to inform standard of care exists for rare cancers that innovative experimental techniques are sometimes required.\(^{173}\) For certain types of hereditary cardiovascular diseases, guidelines recommend genetic testing.\(^{174}\) Doubtless this would count as research under the Common Rule definition as it is “a systematic investigation . . . designed to develop or contribute to generalizable knowledge” since the results offer information other patients can use. Yet it is also clearly clinical care as the process is oriented primarily toward improving the well-being of the patient in question. So what does it mean for an intervention if it is simultaneously research and clinical care?

The difficulty of answering this question under the Revised Common Rule stems from the simple fact that while research and clinical care increasingly tend to collapse together and overlap, the requirements of the Common Rule apply only to activities that fall within its rigid definition of research.

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\(^{171}\) Aronson, supra note 90, at 340.

\(^{172}\) Schork, supra note 116, at 611.

\(^{173}\) See Jan Bogaerts, Clinical Trial Designs for Rare Diseases: Studies Developed and Discussed by the International Rare Cancers Initiative, 51 EUR. J. OF CANCER 271, 274–75 (2015).

\(^{174}\) Mogensen, supra note 89, at 1367.
A reasoned answer would consider the original rationale for the Common Rule. The procedural requirements under the Common Rule were not meant to be an administrative roadblock to innovation. Rather, they were an attempt to reduce the dangers that attend participation in research. It is critical to remember that the model of research the drafters had in mind was randomized control trials which are impersonal and require a significant portion of patients to receive either useless placebos or else unproven treatments. While ethical researchers no doubt cared about the well-being of each participant, their allegiance and duty was to the generalizable knowledge and greater good that could be produced by an unbiased study. In this model, research and clinical care have reasonably distinct balances of risks and benefit so the increased burden upon doctors as researchers vis a vis doctors as clinicians makes sense.

Large scale clinical trials remain a useful tool and will continue to occur. Thus, the dynamic of competing duties and conflicts of interest also exists. Increasingly however, new forms of research will go hand in hand with clinical care, in more personal, collaborative settings where the competing duties do not exist, where research is the most beneficial path for the individual as well as the community. Yet the Revised Common Rule does not make space for this nuance, indicating there is a mismatch in the way it conceptualizes the relationship between research and clinical care and the way they interact in practice.

b. The Problems Presented by the Mismatch

i. Impediment to Precision Medicine and the Learning Healthcare System

If N-of-1 studies and other small-scale systematic investigations are considered research under the Revised Common Rule and subject to the same requirements as large-scale clinical trials, doctors will be far less likely to conduct them. Most clinicians are unlikely to have time to shepherd each miniature study through the IRB process. This however, does not mean experimentation and trial and error will cease. Given the diversity of human beings, a degree of uncertainty is inevitable in medical interventions. More modern understandings of molecular biology reveal that individuals have unique responses to treatment. Clinicians, much like physician one in the scenario above, will continue to move their patients on and off specific treatment regimens. Wary of being taken to task for doing human subjects research however, they are likely to do this in a less systematic fashion. Not only does this mean they are far less able to contribute to general knowledge that would decrease uncertainty over time, not following best research practices will also make it harder to discover what works best for the patient in question. The confusion and uncertainty created by the Common Rule’s definition of research could slow the rise of precision medicine.

175 Angela Ballantyne, In Favor of a No-Consent/Opt-Out Model of Research with Clinical Samples, 15 AM. J. OF BIOETHICS 65, 66 (2015).
176 Lois Shepherd & Margaret Foster Riley, In Plain Sight: A Solution to a Fundamental Challenge in Human Research, 40 J. L. MED. & ETHICS 970, 971 (2012).
177 Id. at 971–72.
178 Ballantyne, supra note 175, at 66.
179 In fact, even the top-ten highest grossing drugs help only between one in 25 and one in four people who take them. Schork, supra note 116, at 609.
because it will be more difficult for physicians to tailor treatment to the individual as well as more difficult to publish data in a way that assists other clinicians attempting to tailor treatment.

In other words, whereas the Revised Common Rule’s requirements are an attempt to guard patients against activities that might contribute to generalizable knowledge but harm them personally, they may now instead serve as an impediment to activity that both benefits the patient personally and contributes to generalizable knowledge. As described in Part III, electronic health records as well as advanced data analysis make it possible to examine the efficacy of clinical interventions not just through traditional randomized control trials but through aggregating the data collected during every day patient-physician interactions. The data from these clinical interventions could have enormous positive effects on health outcomes, especially for patients whose treatment-relevant individual characteristics vary greatly from those of participants in drug trials. Real world data that demonstrates the effectiveness of those interventions could combat some of the fundamental weaknesses in healthcare research identified in the work of Ioannidis. Yet the more systemized, the more generalizable and therefore more useful this information is, the more likely it is to fall under the Revised Common Rule’s definition of research even though no patients are put at extra risk.

A fundamental difference of the emerging health care system as it pertains to the research/clinical care divide is that the two do not happen sequentially but side by side. Research does not only inform clinical care, it will often be an equal and necessary part of the clinical care process. Information does not flow in a linear fashion from researchers to clinicians but rather iteratively and cyclically such that new information and new discoveries during clinical care can be fed back to improve the accuracy and precision of treatments. Yet the Revised Common Rule has no space for the hybridization of research and clinical care made possible by new technology and which is so critical to improving medical research.

ii. Overreliance on Informed Consent

As the range of what constitutes research has expanded into activities both more and less risky to the patient than randomized control trials, the Common Rule has improperly leaned on informed consent as a cure all. This is true for instance, in the latest update, which adds broad consent for a limited subset of actions mostly having to do with the storage, maintenance and use of identifiable information. However, relying upon informed consent alone is dangerous for patient rights. Informed consent may become little more than a meaningless gesture given the threats of data breaches as well as the increased sophistication of big data. The broad

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180 McGraw, supra note 113, at 75.
181 See generally Deven McGraw & Alice Leiter, A Policy and Technology Framework for Using Clinical Data to Improve Quality, 12 HOUS. J. HEALTH L. & POL’Y 137, 141–42 (2012) (explaining how clinical data can be used for this purpose).
182 Ioannidis, supra note 68, at e124–25.
183 McGraw & Leiter, supra note 181, at 142.
184 § 104(d)(8); Sugarman, supra note 58, at 24–25.
scope of some informed consent forms is couched in legal language and sometimes
does more to protect practitioners than to inform patients.\textsuperscript{186} Informed consent is a
procedural right, not a substantive one. It shifts the burden for protecting privacy onto
patients who often do not read consent forms or else do not understand them.\textsuperscript{187}
Moreover, even truly informed consent does not guarantee data security or
confidentiality.\textsuperscript{188}

The substantive values informed consent is intended to support and the protection
it is intended to offer is easy to do an end run around, especially since informed consent
is really only rarely a thoughtful, thorough decision-making process.\textsuperscript{189} The
introduction of broad consent into the Revised Common Rule is a nod to the pressures
discussed in the previous section. Many scholars worried about the roadblock the
Common Rule might present to the advancement of evidence based medicine have
pushed to move toward broad consent for the use of bio specimens and identifiable
information.\textsuperscript{190} Others have even argued for a no consent or a duty to donate model.\textsuperscript{191}
This may seem self-serving but these scholars are arguing in good faith, aware that
many of the procedures and advances that accompany the precision and learning health
revolution pose no additional risks to patient and have the potential to catalyze
significant improvements in healthcare outcomes. Indeed, there is also some support
in the survey literature that patients are satisfied by broad consent.\textsuperscript{192}

While broad consent and other models may be appropriate in the context of a patient
working closely with their doctor on cutting edge cancer research or for a researcher
conducting secondary analysis on clinical data to verify the efficacy of a drug regimen,
they may not be appropriate in other contexts. In situations where patients already have
substantive protection, either because of the existence of other protective regulation or
due to standards of medical duty, informed consent, broad consent or even a no consent
model may offer enough protection.

The problem is that as the forms of research diverge and change, the kind of
informed consent required in the Revised Common Rule becomes simultaneously too


\textsuperscript{188}Dawson, \textit{supra} note 3, at 47–48.

\textsuperscript{189}See Botkin, \textit{supra} note 186, at 48.


\textsuperscript{191}See generally Ballantyne, \textit{supra} note 175, at 65 (arguing that a no consent model is appropriate for
samples given the value to medical science); Rhodes, \textit{supra} note 135, at 38 (discussing why there should be
a duty to donate given the potential benefits to healthcare advances).

\textsuperscript{192}See generally D. Chen et al., \textit{Research with Stored Biological Samples: What do Research Participants Want?} 165 Archives of Internal Med. 652, 655 (2005) (discusses survey data that patients
are satisfied by broad consent); Thomas Ploug & Soren Holm, \textit{Going Beyond the False Dichotomy of Broad or Specific Consent: A Meta-Perspective on Participant Choice in Research Using Human Tissue}, 15 Am. J of Bioethics 44, 45 (2015) (discusses several survey studies of patient views on consent); Ussha Pillai, \textit{Factors that May Influence the Willingness of Cancer Patients to Consent for Biobanking}, 12 Biopreservation & Biobanking 409 (2014) (uses survey data to discuss what characteristics may
influence patients to consent biobanking)
stringent for some kinds of research so as to form a barrier for progress as well as too weak to offer protection against more acute threats.

iii. Lack of Attention to More Tangible Threats to Patient Privacy

The Revised Common Rule fails to protect patients and human subjects against the new risks outlined in Part III both because of its lack of attention to how the context of the research affects the risk of abuse as well as the scope of the regulation. Because the Common Rule applies only to federally funded research, many commercial companies who profit off data brokering, aggregation of health data and other potentially abusive practices, fall outside of the framework.193

Yet even if commercial companies are required to follow the proscriptions of the Revised Common Rule, the over-reliance on informed consent means that the substantive values it means to protect are not actually guarded. Consider the privacy notification and terms of use of 23andMe. Though the company is not subject to the Revised Common Rule, its practices are an example of how a company might be able to comply without truly increasing the safety or rights of their consumers. The privacy notice appropriately delineates potential privacy risks including the risk that third parties might use partial genetic sequences to identify individuals through comparisons with published research results.194 It also describes the ways in which the company plans to use consumer data, much like the Revised Common Rule informed consent requirements.195 One of the uses of consumer data is research. Even declining to allow 23andMe to use genetic and personal information for research still permits it to use the information for activities such as targeted marketing.196 The company also collects details about the consumer as well as the online behavior.

The ubiquity of clickwrap shows the average consumer does not parse through consent language. They should not be expected to. Human subjects research regulations exist because we have made a reasoned determination that individual rights need to be protected. If this remains true, then the rights ought not to be so easy to circumvent.

Thus, the result is to lay procedural and bureaucratic barriers in the way of precisely those parties already under the most stringent oversight and which already have the motive to bend their research toward the common good rather than profit. None of this is to say that healthcare institutions and healthcare professionals should be deregulated. Even those who believe themselves working in service of the common good may be blinded to the ethics of their actions. The point is simply that parties with explicitly less altruistic goals ought to at least be held to the same standards as the people dedicated to improving health outcomes of the community. If nothing else, healthcare researchers aim to publish results and incorporate them into standards of care. Therefore, they are pushed towards greater openness and transparency. Evolving norms also tend to nudge researchers in that direction. Healthcare oriented commercial enterprises likewise face some of these pressures.

193Rothstein, supra note 9, at 425–26.
195Drabiak, supra note 158, at 156–57.
196Id. at 157–58.
Commercial companies engaging in human subjects research on the other hand, especially those not oriented toward healthcare, have an obvious incentive to keep their activities hidden. As techniques become more sophisticated and the financial incentivizes become more extreme, there will also be corresponding pressures to re-identify data. The ease with which re-identification can occur in an era of advanced statistics will have differential effects on these activities and on the public health-oriented research that is likely to be subject to the Revised Common Rule. The Revised Common Rule, as well as other privacy regulations, rely upon identifiability to restrict access to data. Parties covered by the Revised Common Rule will often have to remove personally identifiable information in order to do the sorts of cross cutting, cohort wide secondary research studies that are needed to verify treatments and contribute to a learning healthcare system. Yet as re-identification procedures become more sophisticated, these parties will have to remove more information, much of which is actually useful, even critical, when attempting to do this type of analysis. Thus, the Revised Common Rule imposes restrictions on healthcare-oriented research to the detriment of improving healthcare outcomes while simultaneously doing nothing to prevent the same activity by parties whose activities are less transparent and less directed toward public interest.

This may also end up shaping the healthcare sector. If companies not subject to re-identification restrictions under the Revised Common Rule are able to access data collected by public and private healthcare institutions, they will have an undeniable advantage even if healthcare is neither their aim nor expertise. New healthcare paradigms will increasingly become determined by those private companies which have a profit motive for secrecy and closed systems even as researchers start to adopt some of the practices of businesses. All this will serve as structural barriers to the types of open data sharing that is needed to revolutionize healthcare. If private, profit motivated entities that do not have prior commitments to improving healthcare end up in control of the information most critical for precision medicine, the equity issues that already exist will become acute. While a closed system may continue to work well for those with the funds to purchase access, those without the means will be subject to the risks that come from re-identification without the rewards. In some ways, this offers a vision of the worst-case scenario. On the one hand, patient privacy will be routinely violated by parties with profit motives while on the other, the aggregated, de-identification information is kept privately such that it cannot be used to improve healthcare.

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197 See, e.g., Hiller, supra note 81, at 300.
198 See generally Paul Ohm, Broken Promises of Privacy: Responding to the Surprising Failure of Anonymization, 57 UCLA L. Rev. 1701 (2010).
199 Id. at 1740–45.
200 Pasquale, supra note 82, at 683.
201 Michele Pagano, Don’t Run Biomedical Science as a Business, 547 NATURE 381, 381 (2017).
202 Hiller, supra note 81, at 301.
V. A WAY FORWARD: CONTEXT BASED RESEARCH CATEGORIES

a. Goals of Healthcare Regulation

Understanding how an altered approach to regulating human subjects research might be formulated first requires understanding what a system of regulation should aim to encourage and incentivize.

First and foremost, the human subjects research regulation regime should aim to ensure research leads to better health outcomes for all patients. At the moment, that means the regulations should support the reorientation of the healthcare system toward precision medicine and a learning healthcare system where valuable data producing during clinical care is recaptured and fed back into research.

Second, regulation should encourage greater openness and transparency, the better to promote trust in medical care and those who provide it. Past scandals have revealed that researchers have not always acted in the best interests of their patients, abided by ethical rules or respected the autonomy of their research subjects. The result is an unfortunate yet understandable reluctance by some populations to participate in much needed research. Fostering trust may go a long way to undoing some of the damage that is a legacy of earlier misdeeds. Trust, however, is not just a problem for populations with a troubled history in medical research. As the expertise and skill of doctors and researchers has increased such that these professions are more technical than ever, the process of obtaining medical treatment has become more opaque. The sophisticated algorithms, learning models and complex biological principles that animate modern medicine are not accessible to the average patient, the average donor of health data. They may not even be accessible to the doctors who apply standard treatments, especially as they are less likely to be familiar with research science. Meanwhile, commercialization of medicine, while perhaps effective at mobilizing resources to mass produce cheaper drugs, may also create perverse incentives in the marketing and production of drugs. Even with advanced protein modeling and vast databases of drug precursors with potential medicinal uses, drug development is very difficult. The existing drug trial system relying on randomized control trials and to determine efficacy of a given drug is well understood to be flawed. Innovative research methods that help to avoid those flaws should be encouraged.

203 See Cadigan, supra note 161, at 4 (transparency involved in asking for consent bolsters trust in the research enterprise); Kathryn L. Braun et al., Cancer Patient Perceptions about Biobanking and Preferred Timing of Consent, 12 BIOPRESERVATION & BIOBANKING 106 (2014) (for a study which explores how communication and collaboration leads to trust and greater participation in research); Rivera, supra note 3, at 2.


205 Hiller, supra note 81 Error! Bookmark not defined., at 290; David E. Lanfear et al., Factors Influencing Patient Willingness to Participate in Genetic Research After a Myocardial Infarction, 3 GENOME MED. 39 at 1 (2011).

206 Sayeeda Rahman et al., Physician Participation in Clinical Research and Trials: Issues and Approaches, ADVANCES IN MED. EDUC. & PRAC., Mar. 2011, at 85, 86.

Related to the second point, regulation should not stand in the way of new methods of partnership between doctors and their patients. In fact, regulations should be formed and interpreted in such a way as to encourage cooperation and active participation. Collaboration builds trust, which in addition to increasing the likelihood of patient participation in needed research,\textsuperscript{208} may have ripple effects on patient compliance to treatment regimens as well as readiness to report symptoms or anomalies their physicians need to know about. Active dialogue with patients and treating them like stakeholders makes it more likely that patient concerns will be addressed in meaningful ways\textsuperscript{209} resulting in a system that is more respectful and equitable for all.

\textit{b. Context-Based Research Categories}

All of these goals mediate in favor of a context based human subjects research definition. Such a definition would have to be detailed enough to take into account the factors that contribute to real risks but flexible enough to adapt to the new forms of research developed in response to technological advances and known flaws with the existing research paradigm. Due to the fast paced nature of changes in medical research, it may be best to require these categories undergo review periodically to ensure they match the progress and new risks presented by human subjects research.\textsuperscript{210}

To take into account the variable risks and rewards of different types of research both to the individual and to the healthcare system at large, the Common Rule should not define research in opposition to clinical care. Rather, it should outline different general categories of research, some of which should be subject to minimal procedures when performed in conjunction and in line with clinical care, some of which should be subject to more stringent procedures, when the parties involved are not bound by standards of care and other ethical or legal constraints. Exemptions for secondary research in the Revised Common Rule are a step in the right direction but the regulatory system needs to incorporate more context specific protections to promote systems level change while protecting patients from risks.

The context-based categories of research should be evidence based in that they should be shown to represent a meaningfully distinct balance between risk and reward. An evidence based inquiry of this nature is beyond the scope of this study. However, dealing with generalities and based on some of the evidence already discussed above, it is possible to outline some factors that should be weighed and some basic context-based categories to serve as a point of departure.

In evaluating the risks to the patient, it matters who is conducting the research. A primary care physician or anyone who is acting in a clinical capacity is ethically and otherwise bound to prioritize their health and safety in a way that is not true of specialists at a research institute responsible for running a large scale trial. The latter in turn are likely to be under legal and ethical constraints researchers at a private corporation are not. Further if the corporation is oriented toward medical care, they are likely to be regulated in ways that companies that are not part of the healthcare industry are not. Therefore, the Revised Common Rule should take into account the

\textsuperscript{208}TL Albrecht et al., \textit{Influence of Clinical Communication on Patients' Decision Making on Participation in Clinical Trials}, 16 J. CLINICAL ONCOLOGY 2666 (2008).

\textsuperscript{209}Garrett, \textit{supra} note 185, at 57.

\textsuperscript{210}See Berkman, \textit{supra} note 48, at 8 (for the proposition that revisions are necessary to keep up with advances in medical research)
differential burdens and responsibilities of the target researchers to complement them and respond appropriately to risk.

The motives of the organization or the individual also matter. This is necessarily an amorphous factor but can be evaluated through a combination of stated motives, organizational orientation and an examination of actual behavior. An institution or an individual researcher may always hold themselves out as being primarily interested in the advancement of the healthcare system and the welfare of their research participants. This would likely be true of academic research centers, healthcare institutions and individual clinicians. Other actors such as pharmaceutical companies and other private parties in the healthcare industry of course aim to improve healthcare outcomes and to better serve customers. However, due to their private nature, they face financial conflicts of interest as well as perhaps pressure from shareholders or investors interested in returns.\(^{211}\) Still other institutions lie outside the healthcare system all together. Rather than prioritizing health either on an individual level or a system wide level, they may elevate information transparency, democratizing access to personal information or simply profit. The restrictions and the care context-based research categories should take depends on how closely the motives of the regulated parties track with the goals of the Common Rule. As the Common Rule has its origins in the protection of individuals against the potential risks of engaging in human subjects research, even if it is oriented toward the public good, it should prioritize participant welfare. Therefore, those institutions and parties whose stated motives, organizational orientation and actual behavior do not exhibit a commitment to these values should perhaps be required to comply with more restrictions designed to protect research subjects.

Keeping in mind that patient outcomes are driven both by whether the clinician follows the standard of care as well as how well the standard of care works for them, contributions to the learning healthcare system should also be a factor in forming categories. The key to catalyzing a learning healthcare system is data, shared with the parties who will use it to verify the efficacy of existing treatments and analyze to discover new information.

This process will be most effective if it happens in an open, transparent and collaborative way. Quality improvement and verification programs will certainly be helpful even if they happen on a small scale, for instance within a single research institute. Yet if this information is siloed and not linked together, the learning healthcare model will not be able to harness the full potential of all the data patients produce as they move throughout the healthcare system and as they live their daily lives. Allowing the data to languish in separate buckets is not only a waste of useful data, it is detrimental to health outcomes, the improvement of which should be the goal of the healthcare system. Therefore, whether the regulated entity plans to share the data in a way that enables its use for promoting the learning healthcare system should also be taken into account. This needs to be dealt with carefully. After all, the same ability to link seemingly unrelated data together that makes it powerful in the health data context also introduces new risks. So, while data sharing should be encouraged, it also matters who the data is shared with, in what form and with what sort of precautions.

\(^{211}\)See generally Kubiak, supra note 22.
c. Some Preliminary Categories

Having set out some general factors, this section lays out a few context-based categories that could be adopted. This is not meant to be comprehensive and indeed, further study and consideration should be completed so the final categories are based on evidence of meaningful distinctions in the balance of benefits and risk. Nevertheless, this section attempts to offer a guide toward the considerations that would justify a new context-based research category by example.

i. Individualized Research

One category should include low risk individual research with no IRB review and minimal oversight. This might include self-experimentation by physicians such as those who test out wellness regimens, physician guided self-experimentation as well as N-of-1 research done in collaboration with a physician. The latter should include both instances such as the miniature blood pressure trial described above as well as more complicated genetic biomarker analysis that represent the future of molecular level precision medicine. These methods are distinguished by the fact that they occur concurrently and as a critical part of clinical care. The Common Rule is designed to protect human subjects from researchers who may put their individual health at risk for the sake of the general good. A physician led N-of-1 study done in a clinical setting where the doctor has the usual duties of care is not the kind of situation that the Common Rule should heavily regulate. Since the Revised Common Rule otherwise presumes that a clinician does not need the particular types of oversight it mandates, a clinician who simply seeks to individualize and make sure that their treatments are based in evidence should not be treated differently. If anything, such behavior should be encouraged.

ii. Quality Improvement Programs

This category would include programs which involve testing the factors and activities that surround care with the goal of improving healthcare outcomes. For instance, a hospital monitors changes in infection rates when they move to requiring physicians run through a checklist when placing catheters.\(^\text{212}\) Though the systematic way effects are recorded in these programs may make them appear to approach randomized control trials, they more closely resemble administrative reorganization, especially as they often involve the implementation of practices prior research has shown to produce better results.\(^\text{213}\) Such investigations are sometimes published as case studies rather than research.\(^\text{214}\) Critically, they put patients in no more risk than they would be in otherwise if the hospital implemented changes to their procedures without relying upon evidence of changes in outcomes. This is apparent in the checklist case as the alternatives would have been either no change to the existing system, responsible for causing avoidable infections or simply changing over to a new


system without tracking the impact. Actually, tracking the response to various administrative changes such as altering nurse schedules or posting signs reminding doctors to wash their hands is extremely helpful in the verification and spread of best practices to improve health outcomes for the specific patients involved as well as patients generally.215

iii. Public Health Oriented Cohort-wide Research

This category would consist of the large scale verification and analysis projects that will help to drive the learning healthcare model. A typical research project might combine data sets from a variety of sources to discover new correlations between individual characteristics and drug response. Or else the goal of the study might be to verify the efficacy of the top three treatments for a particular disease. Since these are the types of studies that will help to close the loop in the healthcare research model by feeding data derived through clinical care back into research, they should be encouraged through expedited procedures. Though healthcare oriented institutions both public and private should be able to perform this type of research, perhaps researchers must promise to publish their result in a way such that they can be verified and contribute to learning healthcare. Otherwise, this will simply reproduce the incentives for secrecy that exacerbate flaws in the randomized control trial driven clinical research.216 The risks to patients with this type of research are really privacy risks. To the extent the Revised Common Rule cannot cope with them, that is largely a problem with the health data privacy regulations. The latter also need updating to fit the modern healthcare system but that is outside the scope of this paper.217

iv. Non-health Related Commercial Research 218

One final category should include human subjects research either driven by commercial interests outside healthcare, the end result of which is to produce data retained and kept hidden by a private party. This category is distinct for reasons already discussed in part IV(b)(iii).219 It is in the commercial context where the need to protect human subjects against divergent interests of the researcher that may have adverse effects for the individuals involved is strongest. Therefore, particular caution is warranted. Some scholars have suggested an IRB equivalent called Consumer Subject Review Boards which would be responsible for evaluating the ethics of data use.220

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216 See generally Pasquale, supra note 82.


218 Legislative action may be required to reach this type of research. A full discussion of this point is beyond the scope of this paper and the category is included here because it is a necessary part of thinking about healthcare as an interconnected ecosystem.

219 Supra Section IV.b.iii.

VI. CONCLUSION

Modern medical science has advanced so quickly since its inception in the wake of the world wars\textsuperscript{221} that it is sometimes hard to remember how much further it has to go. Digital technology and all the advances that come with it have revolutionized many aspects of life. They have the potential to catalyze more precise, evidence based medicine, the result of which is better health outcomes, particularly for underserved communities.\textsuperscript{222}

Unfortunately, the Revised Common Rule is not optimized to encourage this revolution in healthcare. The 2016 update did not meaningfully engage these core problems even if it made incremental improvements to the existing regime. This is because it defines research in opposition to clinical care. The result of this is an overly broad and general definition of research that swallows many different activities and tries to fit them into the same regulatory regime based on the fact that they are all systematic investigations. Yet this research/clinical care divide no longer describes a reality in which the two must increasingly collapse into each other as healthcare professionals begin to recognize the flaws in the existing medical research paradigm.

Given the history of the Common Rule, the initial division between research and clinical care was perhaps important to help drive home the importance of patient autonomy and respect, particularly for those persons vulnerable to exploitation. Moreover, it made more sense when the pattern of information flowing from research to actual clinical care was linear. Now however, changes in technology and increasing awareness among healthcare professionals of the inadequacy of the current state of medical literature means that the relationship between research and clinical care will and should change. Namely, the relationship between the two will be or should be circular, reiterative and relational instead of a one-way inquiry.

The fundamental mismatch between this reality and the way the Revised Common Rule conceptualizes the boundaries and form of research is an impediment to precisely those changes in the healthcare research model. By painting all forms of research with a broad brush, it discourages conscientious researchers who wish to follow the law from performing beneficial research that would help to improve health outcomes for individuals for whom standard treatments should be adjusted. Yet, at the same time, it encourages the overbroad use of informed consent in a perfunctory and procedural form that unscrupulous researchers can easily circumvent, which eases the path of lucrative activities that potentially put patient privacy and health at risk. Thus, the Revised Common Rule, far from protecting patients from researchers who may have interests that diverge from their own, actually serves to advantage precisely those parties who are more likely to engage in risky behavior. What the Revised Common Rule is missing, is a context-based approach to research, taking into account the relative balance of risks and benefits of each type of research activity in order to determine what type of procedures and regulatory measures are appropriate.

\textsuperscript{221}See generally Beth Linker, The Great War and Modern Health Care, 374 NEW ENG. J. MED. 1907, 1907 (2016).

\textsuperscript{222}Ballantyne, supra note 175, at 66.