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Rethinking ethical oversight in the era of the learning health system☆

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ABSTRACT

Opportunities to advance science increasingly arise through investigations embedded within routine clinical practice in the form of learning health systems. Such activities challenge conventional approaches to research regulation that have not caught up with those opportunities, often imposing burdens generalized from riskier research. We analyze the rules and conventions in the US, demonstrating how even those rules are compatible with a much more flexible approach to participant risk, institutional oversight, participant consent, and disclosure for low-risk learning activities in all jurisdictions.

Health care around the world suffers from missed opportunities to learn from changes in real-life practice. A fundamental principle of a learning health system is that processes to generate new knowledge should be embedded in the delivery of care. Electronic medical records and other digital data systems make data collection easier, offering the promise that health systems can become efficient laboratories to advance the science of health care delivery. A challenge is that the methods one might use to rigorously evaluate real practice—everything from observational analyses to randomized trials—are identical to the methods of human participant research that in other settings are subject to regulation. And yet, reasonable regulations or conventions that surround clinical research are often unreasonable inside the operations of functioning health care facilities. Those rules can be both burdensome and self-defeating when applied to the evaluation of operational improvements in the context of ordinary clinical practice, potentially dissuading learning in settings where it could instead flourish.

The rules surrounding research involving human participants aim to protect those participants against risk—including to their physical or psychological well-being—and to allow people to participate in activities that are consistent with their values and priorities. In the US, federal regulations define research as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge."[1] The best learning health system activities similarly use systematic approaches to develop generalizable health care insights and look so much like typical research endeavors that old distinctions between research and quality improvement activities now seem false.[2] An idealized learning health system would use state of the art research methods to evaluate its clinical practices and would publish and disseminate its findings to help other health systems improve as well. By that standard, learning health systems look just like laboratories. However, what distinguishes learning health systems from laboratories is that, in the absence of specific consent to do otherwise, they remain bound by the norms, standards, and fiduciary obligations of clinical practice, and so are constrained to provide care that is consistent with that practice.[3] The existence of these guard rails justifies a different approach to ethical oversight from that classically applied to biomedical research.

Here, we discuss the nature of participant risks in a learning health

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system. We also discuss what review and oversight mechanisms, including the use of institutional review boards (IRBs) or other mechanisms, are appropriate to ensure those risks are addressed as well as what kinds of consent or disclosure fit the nature of the activities they pursue. We include a table of key regulatory authorities and considerations.

1. Does a learning health system activity increase risk?

All patients receiving health care face risk. Risks directly attributable to involvement in learning health system activities are those that rise above the risks patients would face if they were not involved in those activities. Frequently, the incremental risks of participating in learning activities are minimal.[4] Consider this case:

> Conventional diabetic retinal screening involves referral to an ophthalmologist or optometrist, but completion rates are low because screening requires an extra visit, bright lights, and pupil dilation that blurs vision for hours. New non-mydriatic cameras, used in some practices, can image the retina without need for pupil dilation or examination by a specialist. Both systems are used clinically. However, the cameras are expensive and require changes in patient flow. Before switching, XYZ health system buys one camera. It then randomly assigns some patients to an appointment with a specialist and the others to same-day examination with the camera. They measure overall examination completion rates, including assessment of vulnerable subpopulations, the disease burden discovered in the two groups, and patient satisfaction. Based on the results, they decide whether to buy cameras for all diabetic patients and they publish the findings for other systems to benefit.

The example illustrates what learning health systems can contribute. The organization faces a choice. It has the patients, the naturalized setting, and the technical resources to learn what approach works better and for whom. Rather than just implementing an approach, it systematically varies the approach and measures the results.

Whenever a health system implements something of uncertain benefit without evaluation, it forgoes an opportunity to learn what works. The XYZ health system, in contrast, takes a more rigorous approach. Because both approaches to retinal screening are clinically acceptable, the choice of one or the other introduces no incremental risk. Randomization does not introduce additional risk beyond what patients might face in the absence of the learning activity, in terms of quality of diagnosis, physical discomfort, wait time or other measurable experience, because a patient might have encountered a physician with either screening approach. Replacing a haphazard process with a deliberately random one is better for learning and no worse for patients.

The same is true of many drug formulary comparisons. If a health system might keep on formulary either of two drugs within a homogeneous class of established diuretics, quinolones, or statins, no incremental harm is introduced by randomizing between them, particularly if clinicians can exercise their professional judgment and expertise to override the formulary default. The underlying risk of the drug is not the issue. Given that patients could reasonably be prescribed either drug, being part of this randomized learning activity imposes no incremental risk.

Beyond the risks of the interventions, a learning health approach could increase risk if it is burdensome or invasive. In the hypothetical cases described above, however, evaluation involves only a review of data we would expect any health system to collect, including satisfaction measures that require seeking patients' feedback.

XYZ health system's randomized clinical trial not only looks like systematic research with generalizable findings, it is exactly that. However, the participants face no more risk than they would have if the system had merely used the same approach for everyone, or if individual sites idiosyncratically chose different approaches.

In sum, systematic evaluation, including randomization of individual patients, introduces no incremental risk if system leaders could have adopted the alternative approaches in regular practice, the choice between interventions is not preference-sensitive, and the evaluations used to measure outcomes do not themselves add significant burden or risk.

2. Does this learning health system activity need oversight?

In the US, if the XYZ health system's project is federally funded or regulated by the U.S. Food and Drug Administration (FDA), then Institutional Review Board (IRB) oversight is legally required by the Common Rule[5] or its FDA analog.[6] Most learning health system activities, however, are not federally funded. Effective January 2019, institutions have flexibility to choose their method of ethical oversight of research activities that are neither federally sponsored nor FDA-regulated.

In our view, all intervention and evaluation activities should receive some form of external oversight.[7,8] Those proposing a study should not decide whether their approach is appropriate, because they may not recognize when their approaches are too risky, too far from clinical norms, or too burdensome to patients. For many settings, oversight and review might conveniently remain with an IRB, or the IRB might provide an intake and triage function to direct more detailed review elsewhere. However, given that learning health system activities are typically embedded within existing clinical practices with their own conventions and standards, appropriate oversight could be as simple as approval by the institutional leader or committee that normally approves the policy, procedure, or regimens being evaluated. Alternatively, institutions may wish to establish a separate committee, operating with a different set of policies from those used by the IRB, to oversee health system learning activities that fall outside IRB jurisdiction. In any event, we believe a key component to oversight of these investigations is input from a health system leader who is familiar with the usual delivery of the kind of care under consideration. This person's core responsibility should be to determine whether system leaders could have chosen either of the alternative approaches in regular practice, and whether the choice between interventions, e.g., hospital formulary listing, is one that is usually not made by patients together with their clinicians.

3. Does this learning health system activity need participant consent?

Informed consent is the traditional mechanism to ensure respect for persons in research and clinical care. Consent allows individuals to exercise autonomy and promotes transparency and trust.[9]

However, informed consent may compete with learning health systems' pragmatic goals and is not always necessary.[10] Are the patients in the XYZ health system randomized to conventional versus non-mydriatic camera screening owed the opportunity to give or refuse "informed consent?" The XYZ health system would have been ethically justified in providing either approach to all patients without additional consent. Using random rather than arbitrary assignment introduces no incremental risks to safety or autonomy. Thus, it introduces no additional need for consent.

Still, one might argue that seeking consent promotes transparency and trust and is respectful. In regular practice, however, informed consent of this type isn't natural. Patients referred for eye examinations typically aren't given choices about one approach or the other. Furthermore, consent requirements that go beyond the clinical norm can bias an evaluation by excluding patients who would be subject to the intervention outside of a learning framework. For example, if the trial evaluates only the most motivated patients—those willing to consent to a trial and to randomization—it might find fewer differences between in-chair retinal screening and camera-based retinal screening, because highly motivated patients might be willing to get their eyes screened either way. Conventional trial designs in which patients must affirmatively enroll with opt-in consent study a narrower, less inclusive,

population than trial designs with a presumption of inclusion and opt-out consent.[11,12] Both approaches are likely to examine populations more selected than those with no research consent at all—the approaches that will be used once programs are implemented in clinical practice. Tests of these programs using consent rules typical of conventional research will not reflect the clinical practice they intend to model if that clinical practice would use different rules. The advantage of pragmatic research is that it models what would happen in conventional practice, outside of research settings. Those conventional practices carry with them a set of processes and conventions that address human protections, including community standards for consent.

Not only do consent processes in these settings reduce the fidelity and relevance of the study, they reflect an unrealistic ideal. It is understandable to feel more comfortable with a randomized trial with consent than one without consent. However, the relevant counterfactual for randomized trials without consent is not a trial with consent—rather, it is the roll out of one approach or the other, with neither consent nor rigorous evaluation. Faced with the superficial question, "would you rather have patients consent or not?" it's easy to side with consent. But it's easier to endorse a trial that doesn't involve traditional research consent when faced with the more realistic question, "given that patients won't be offered the opportunity to consent anyway, would you rather have an intervention rolled out for everyone or would you rather do a trial so we can learn something?"

In the US, the Common Rule anticipates this concern, allowing consent waivers when research involves no more than minimal risk and the research could not "practicably be carried out"[13] without the waiver. Thus, many federally sponsored minimal-risk studies may be conducted without consent. Many assessments of value to learning health systems meet these criteria. Importantly, the Common Rule explicitly directs IRBs to consider only the incremental risks of research participation.[14] Although the regulations do not define practicability, authoritative commentary suggests that feasibility of obtaining consent should not be the sole criterion.[15] Once minimal risk is established, the critical determinants in deciding whether or not to waive informed consent are *both* the logistical burden of obtaining that consent and the implications of consent for the study's validity. Imposing consent requirements that would not be imposed in practice often threatens the validity of learning health system activities.

4. Should this learning health system activity be disclosed to patients?

Even when consent is impracticable, a presumption of disclosure seems wise to support trust and transparency. Disclosure might take various forms, including summaries of ongoing evaluations posted on a website, leaflets placed in patient care areas, or point-of-care discussions between clinicians and patients.[16] Despite the conceptual appeal of disclosure, however, its practical value and effectiveness may be limited. Learning health systems evaluate a wide range of activities, from operations like scheduling, communication, and patient flow, to alternative care practices or choices of routine devices and common medications. Calibrating the extent and form of disclosure to the nature of the activity, so that disclosure is neither merely cosmetic nor inappropriately intrusive, requires judgment and merits study.

Although a presumption of disclosure is reasonable, disclosure, particularly at the point of care, can threaten the validity of a learning activity. For example, disclosure of random assignment to generic versus culturally tailored colorectal cancer screening reminders might change patients' screening behavior. In such circumstances, withholding disclosure when a health system would disclose nothing had they merely adopted one approach or the other may be appropriate. As with waivers of informed consent, decisions to withhold disclosure on validity grounds require justification and oversight.

Table 1
Key US regulatory considerations for learning health systems.

Regulatory Consideration	Relevant regulatory language	Citation
The Common Rule, and its FDA analog, apply only to federally funded or FDA-regulated research	"[Unless exempt], policy applies to all research involving human subjects conducted, supported, or otherwise subject to regulation by any Federal department or agency that takes appropriate administrative action to make the policy applicable to such research."	45CFR46.101(a)
	"This part applies to all clinical investigations regulated by the [FDA] under sections 505(i) and 520(g) of the Federal Food, Drug, and Cosmetic Act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the [FDA]."	21CFR50.1(a)
The Common Rule requires that IRBs consider only the incremental risks and benefits of research, over and above those of background care, in making approval decisions	"In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research)."	45CFR46.111(a)[2]
If the requirement for informed consent poses a threat to the validity of a study, the IRB may take that threat into account along with other considerations in determining whether obtaining informed consent is "practicable" and therefore whether a waiver or alteration of the informed consent requirement may be granted.	According to the Secretary's Advisory Committee on Human Research Protections, "IRBs should consider the following points when determining whether research could not practicably be carried out without the waiver or alteration…[the possibility that] scientific validity would be compromised if consent was required…. Practicability should not be	January 31, 2008 SACHRP letter to HHS Secretary: Recommendations related to waiver of informed consent and interpretation of "minimal risk." Available at https://www.hhs.gov/ohrp/sachrp-committee/recommendations/2008-january-31-letter/index.html

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Table 1 (*continued*)

Regulatory Consideration	Relevant regulatory language	Citation
	determined solely by considerations of convenience, cost, or speed."	
Publication or intent to publish does not, by itself, satisfy the definition of research or trigger the need for IRB oversight.	"… Planning to publish an account of a quality improvement project does not necessarily mean that the project fits the definition of research; people seek to publish descriptions of nonresearch activities for a variety of reasons, if they believe others may be interested in learning about those activities. …"	Quality Improvement Activities FAQs https://www.hhs.gov/ohrp/regulations-and-policy/guidance/faq/quality-improvement-activities/index.html#nodequeue_14-page_8-5

Abbreviations: FDA, Food and Drug Administration; IRB, institutional review board.

5. Learning health system lessons for research: the importance of incremental risk

These considerations of oversight, consent, and disclosure are premised on the minimal risks of typical learning health system activities. The development and testing of new drugs, devices, or novel surgical procedures typically present substantially more risk and so require substantially stronger human protections. But much of what would be considered research, federally funded or not, consists of testing alternative but conventional approaches to advance patient care that remain minimal risk.

Much effort has been devoted to defining which activities constitute research versus quality improvement.[17] That long-held distinction has been a source of continuous confusion and is increasingly recognized as false.[18] The best quality improvement activities and the best research activities use the same rigorous methods; both intend to inform practice; and both offer the same social value when their results are disseminated to others. By those standards, research and quality improvement do not differ.

The distinction has seemed important because many institutions use their IRB to review all research, not just federally funded research, and those institutions understandably want to prevent their IRBs from having to review every new approach. We believe all of these activities need some form of oversight; the important distinction is not whether they are labeled research or quality improvement, but the extent of incremental risk they create. When incremental risk is minimal in the judgment of the evaluation's designated decision maker or review process, the approaches to consent and disclosure we advocate for learning health system activities are relevant whether the activity is federally funded or not, reviewed by an IRB or through some other process, or labeled as research or quality improvement. (See Table 1)

6. Conclusion

The promise of the learning health system comes from embedding the practice of learning into the rhythms of care, so that every patient encounter creates an opportunity to make the next encounter better.[19] realizing that promise requires that learning health systems' human protections conform to the protections of routine care. Community standards surrounding routine care already tolerate substantial haphazard and arbitrary variation in clinical practices. Setting higher protective standards for systematic variation—especially when doing so doesn't benefit patients in any meaningful way—hinders learning and worsens outcomes for all.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper: Dr. Asch owns stock in Berkshire Hathaway; is a partner in and part owner of VAL Health; and has received compensation and/or travel support for speaking, writing, or consulting from the following organizations: AFYA, MTS Health Partnership, GSK, Cosmetic Boot Camp, Meeting Designs, Capital Consulting, Healthcare Financial Management Association, TED MED, Deloitte, MITRE.

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