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Controversies in Clinical Research Ethics

Guest Edited by Robert M. Sade

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Cover image ©Getty Images

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INTRODUCTION: **Controversies in Clinical Research Ethics**
Robert M. Sade

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Drawing the Line at Age 14: Why Adolescents Should Be Able to Consent to Participation in Research
Robert Schwartz

This article argues that teenagers become fully capable of consenting to participation in most IRB-approved research involving human subjects at age 14, four years earlier than they are allowed to consent under virtually all states' laws, and, consequently, four years younger than they are able to consent under currently applicable federal regulations. In determining the age at which person is old enough to have decision-making authority, legal institutions look at the intellectual and emotional maturity of someone of the age of the decision-maker, the risks and benefits of allowing the decision to be made by someone of that age, and the risks and benefits of denying a person of that age the authority to make the decision. Given the high level of safety of participating in IRB approved research, the value of doing so for both the society and the teenage subject, and the psychological and neuropsychological research on the specific nature of emotional and intellectual development during the teen years, the balance comes out in favor of allowing younger teens, by the age of 14, authority to consent to participate as subjects in IRB approved research. The current process requiring both teen assent and parental permission should give way to a process that requires only a teen's consent.

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Mark J. Cherry

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Rosamond Rhodes

In this paper I argue for recognizing the moral duty to participate in research. I base my argument on the need for biomedical research and the fact that at some point studies require human participants, what I call collaborative necessity. In presenting my position, I argue against the widely accepted views of Han Jonas and all of those who have accepted his declarations without challenge. I go on to show why it is both just and fair to invite and encourage people to participate in studies. It is just because research participation is the necessary means to achieve the broadly shared goals of preventing and curing disease and alleviating disease symptoms. Mutual love requires us to be willing to do for others what we would want them to do for us. It is fair because the approach treats similarly situated people in the same way. Research participation is morally required because failing to do one's part in the collaborative project of advancing biomedical science would be free-riding. People who exempt themselves from participation while eagerly accepting benefits from others doing their part are taking advantage of their compatriots and treating themselves as more deserving than others when they are not.

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Mark Yarborough

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Susan M. Wolf

Developing ethical standards for clinical use of large-scale genome and exome sequencing has proven challenging, in part due to the inevitability of incidental or secondary findings. Policy of the American College of Medical Genetics and Genomics (ACMG) has evolved but remains problematic. In 2013, ACMG issued policy recommending mandatory analysis of 56 extra genes whenever sequenc-

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ing was ordered for any indication, in order to ascertain positive findings in pathogenic and actionable genes. Widespread objection yielded a 2014 amendment allowing patients to opt-out from analysis of the extra genes. In 2015, ACMG published the amended policy, providing that patients could opt out of the full set of extra genes, but not a subset. In 2016, ACMG enlarged the set and indicated planned expansion of the roster of extra genes to include pharmacogenetic findings. ACMG policy does not protect the respect for patient choice that prevails in other domains of clinical medicine, where informed consent allows patients to opt in to desired testing. By creating an expanding domain of genomic testing that will be routinely conducted unless patients reject the entire set of extra tests, ACMG creates an exceptional domain clinical practice that is not supported by ethics or science.

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Margaret R. Moon

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Lois Shepherd

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Informed Consent for Comparative Effectiveness Research Should Not Consider the Risks of the Standard Therapies That Are Being Studied as Risks of the Research
John D. Lantos

There is a debate at the highest levels of government about how to classify the risks of research studies that evaluate therapies that are in widespread use. Should the risks of those therapies be considered as risks of research that is designed to evaluate those therapies? Or not? The Common Rule states, "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)." (CFR 46.111 (a)(2)). By contrast, the Office of Human Research Protections, in a proposed "guidance" states, "The reasonably foreseeable risks of research include already-identified risks of the standards of care being evaluated as a purpose of the research." (emphasis added).

In this paper, I argue that the Common Rule got it right and OHRP got it wrong. When treatments are in widespread use, the risks of those treatments are ever-present for all patients. By enrolling in formal studies that use rigorous methods to compare one treatment with another and that carefully monitor outcomes and adverse events, patients are protected from the risks of idiosyncratic practice variation. Their risks are decreased, rather than increased.

If OHRP's approach becomes the law of the land, patients will be misinformed about the relative risks of treatment and research in ways that undermine autonomy rather than promoting it and that make truly informed consent impossible.

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Susan S. Ellenberg and Steven Joffe

The random]ized clinical trial is widely accepted as the optimal approach to evaluating the safety and efficacy of medical treatments. Resistance to randomized treatment assignment arises regularly, most commonly in situations where the disease is life-threatening and treatments are either unavailable or unsatisfactory. Historical control designs, in which all participants receive the experimental treatment with results compared to a prior cohort, are advocated by some as more ethical in such circumstances; however, such studies are often highly biased in favor of the new treatment and frequently yield misleading results. Alternative controlled designs motivated by the desire to maximize the number of patients with the treatment ultimately determined to be superior have been proposed, but have been challenged on both methodological and ethical grounds. Debates about appropriate and ethical study designs recurred during the recent Ebola Virus Disease (EVD) epidemic in West Africa. Despite its devastating nature, the EVD epidemic showed the ongoing necessity of conducting randomized trials to obtain convincing evidence of the safety and efficacy of therapeutic interventions.

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The Moral Case for Granting Catastrophically Ill Patients the Right to Access Unregistered Medical Interventions
Udo Schuklenk and Ricardo Smalling

Using the case of Ebola Virus Disease as an example, this paper shows why patients at high risk for death have a defensible moral claim to access unregistered medical interventions (UMI), without having to enrol in randomized placebo controlled trials.

A number of jurisdictions permit and facilitate such access under emergency circumstances. One controversial question is whether patients should only be permitted access to UMI after trials investigating the interventions are fully recruited. It is argued that regulatory regimes should not prioritise trial

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recruitment over patient access, even if this results in drug research and development delays.

We describe how the moral duty to rescue impacts on others' duties to oblige patients seeking emergency access to unregistered medical interventions. The view that eligible patients are owed the provision of access to UMI regardless of their willingness to enrol in a randomised controlled trial (RCT) is defended.

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Maxim Gakh and Lainie Rutkow

The Health in All Policies (HiAP) approach aims to integrate health into decisions across sectors to address the social determinants of health and enhance health equity. Jurisdictions interested in implementing this approach may seek clarification about how to operationalize it. Public health legal preparedness provides useful lessons for HiAP. While there are important differences between these two areas, there are also critical similarities. These similarities are particularly important because HiAP and public health preparedness are complementary. Law has been essential in advancing public health preparedness by helping to: (1) prioritize planning; (2) allocate responsibility; (3) enhance collaboration and coordination; (4) establish responsive funding; and (5) emphasize the needs of vulnerable populations. Law can be used similarly to advance HiAP.

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The Medical Surrogate as Fiduciary Agent
Dana Howard

Within bioethics, two prevailing approaches structure how we think about the role of medical surrogates and the decisions that they must make on behalf of incompetent patients. One approach views the surrogate primarily as the patient's agent, obediently enacting the patient's predetermined will. The second approach views the surrogate as the patient's custodian, judging for herself how to best safeguard the patient's interests. This paper argues that both of these approaches idealize away some of the ethically relevant features of advance care planning that make patient preferences so inscrutable and surrogate decision-making so burdensome. It proposes a new approach to surrogate decision-making, the Fiduciary Agency Approach. On this novel approach, the surrogate has authority to not only act on the patient's behalf as the patient's agent but also to decide on the patient's behalf as the patient's fiduciary. One upshot of this new approach is that surrogates must sometimes go against the expressed dictates of the patients' advance directives not necessarily because doing so would be in the patient's best interest but rather because doing so would best represent the patients' will.

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Parent Beliefs about Chronic Traumatic Encephalopathy: Implications for Ethical Communication by Healthcare Providers
Emily Kroshus, Sara P.D. Chrisman, and Frederick P. Rivara

The objective of this study was to assess the beliefs of parents of youth soccer players about Chronic Traumatic Encephalopathy (CTE), concussion, and retirement from sport decisions and compare them to those of concussion-specialized clinicians. An electronic survey was completed by parents of youth club soccer players (n=247/1600, 15.4% response rate) and concussion-specialized clinicians (n=18/47, 38.3% response rate) located in a large U.S. urban center. Parents believed more strongly in the causal relationship between concussions and CTE, and between CTE and harm than did clinicians. Parents who themselves had participated in sport at a high level had more conservative beliefs than other parents about the number of concussions after which an athlete should retire from contact or collision sport. Results are discussed in the context of ethical risk communication between clinicians and parents. This includes the importance of communicating information about CTE to parents and youth athletes in an understandable way so that they can make informed choices about contact and collision sport participation. Further research is encouraged to evaluate approaches of communicating evidence about CTE to a diverse population of families of youth athletes.

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Facing the Need: Screening Practices for the Social Determinants of Health
Joanna Theiss and Marsha Regenstein

Despite evidence that social factors can result in poor health outcomes, and the emergence of payment models that encourage the use non-medical interventions to improve health, many health care providers do not identify the social determinants of health within patient populations through routine screening. This Article explores the possible reasons for this inconsistency by considering screening practices in medical-legal partnerships (MLPs), the health care approach most concerned with identifying and treating the social determinants of health. Through an analysis of the results of a national survey and qualitative interviews with MLPs, we discovered that screening is not operationalized or consistent within many MLPs. We conclude that although health care providers may recognize the value of screening, they are not yet embracing the practice, perhaps because of an unspoken fear that fulsome screening identifies so many unmet social and legal needs that community-based resources cannot satisfy demand. This fear is unfounded. Approaches such as MLP demonstrate that social and legal needs can be efficiently treated through collaboration with other professionals, often within the health care setting. Nevertheless, providers must first operationalize screening to truly understand the scope of the need in their patient populations and collaborate to address those needs.

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Columns *are written or edited by leaders in their fields and appear in each issue of JLME.*

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Healthcare Provider Limitation of Life-Sustaining Treatment without Patient or Surrogate Consent
Andrew Courtwright and Emily Rubin
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