The American Journal of Bioethics

ISSN: 1526-5161 (Print) 1536-0075 (Online) Journal homepage: http://www.tandfonline.com/loi/uajb20

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To cite this article: Kirstin Borgerson & Joseph Millum (2010) A Third Way: Ethics Guidance as Evidence-Informed Provisional Rules, The American Journal of Bioethics, 10:6, 20-22, DOI: 10.1080/15265161003702881

To link to this article: http://dx.doi.org/10.1080/15265161003702881

A Third Way: Ethics Guidance as Evidence-Informed Provisional Rules

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How should ethics guidance documents be conceived? Benjamin Sachs (2010) suggests that there are two possibilities: They may be attempts to state absolute ethical rules, or they may be recommendations for policies that regulatory bodies should adopt. Since there are cases of clinical research that appear ethical but are inconsistent with the rules, Sachs rejects the first possibility and embraces the second, arguing that ethics guidance should therefore be evidence-based. However, we do not think that this exhausts the ways in which ethical guidance can be helpfully understood, nor do we think that his proposed evidence base for its evaluation is sufficiently broad.[1]

Rather than attempt to state exceptionless ethical requirements, ethics guidance documents might be better understood as a set of provisional rules for assessing the ethics of particular research proposals, derived from general ethical principles. Sponsors, investigators, and research ethics committee (REC) members can use sets of such rules to help them think systematically through the ethics of a project. But principles frequently have to be balanced against each other, and provisional rules inevitably admit of particular exceptions. Thus, for example, *all else being equal*, we think that risks to research participants should be minimized. But sometimes all else is not equal: Perhaps the data obtained in a study would be much more robust if participants' cerebrospinal fluid were analyzed, adding the risks of a lumbar puncture. Whether such exceptions are permitted is a matter of moral judgment. Understood in this way, ethics guidance documents would be making ethical claims, not policy recommendations. But, since they would also admit of exceptions to the rules they state, a case of ethical research inconsistent with a rule would not entail that the rule should be rejected. Instead, a rule should be rejected only if it is shown not to be a good default position or rule of thumb.

Suppose that Sachs accepted our third way to understand ethics guidance documents. He might respond that his point about evidence would retain its force. He thinks that statements of policy recommendations can be assessed on the basis of the effects the policies would have if implemented. Likewise, our statements of ethical principles and their interpretations could be assessed on the basis of their effects; for example, does the use by RECs of this particular list of ethical rules of thumb help or hinder the protection of human research participants and the clinical research enterprise?

We agree that empirical evidence has a role to play in the evaluation of ethics guidance. But whether you accept our conception or Sachs's policy view, the appropriate use of empirical evidence requires more detailed consideration. First, conceptual analysis must still play a necessary role, both in assessing whether general ethical principles are correct and in developing their best interpretation in the research context. It is hard to see, for instance, how the requirement of Valid Design could be assessed except through conceptual work. Advancements in our understanding of the scientific validity of elements of research methods such as blinding, control, and randomization have come about as a result of detailed accounts of causation developed by philosophers of science, developments in the debates between Frequentist, Bayesian, and other statisticians, and theoretical debates about, for instance, the validity of pragmatic rather than efficacy trials in clinical epidemiology.[2] The moment we try to empirically assess our standards of validity, we get caught in circular discussions about the best (most valid) way to perform such an assessment.

Second, empirical evidence is not all of a piece: We must consider what sort of data we need. One option would be to seek the sort of evidence valued most highly by the

Acknowledgments: The opinions expressed are the authors' own. They do not reflect any position or policy of the National Institutes of Health, U.S. Public Health Service, or Department of Health and Human Services. The authors thank Danielle Bromwich for her helpful comments on an earlier version of this commentary.

1. The understanding of ethics guidance documents we develop here is not the only alternative, either. Sachs does not consider the possibility that the "canonical pronouncements" of research ethics might not be only policy recommendations but also direct attempts to influence people's behavior. The very fact that the World Medical Association proclaims that some act is morally required is likely to affect whether that act is performed even when the regulations governing research are unchanged. Hence, following Sachs's general argumentative strategy, we could evaluate the Declaration of Helsinki not just on the basis of whether its recommendations would make good policy, but on the basis of whether its recommendations actually have good effects.

2. See, for instance, Cartwright (2007), Anderson (2006), Grossman and MacKenzie (2005), Borgerson (2009), and Zwarenstein and Treweek (2009).

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evidence-based medicine (EBM) movement, as suggested by Sachs's title and his claim that the position he outlines involves "embracing the idea of evidence-based rules in the arena of human subjects research."[3] But a simplistic insistence on basing policy rules on empirical evidence would fail to attend to the fact that, in response to 18 years of critical literature, even the most ardent EBM proponents have tempered their enthusiasm for empirical evidence (and, specifically randomized controlled trials [RCTs]) as a panacea for medical decision making. For instance, it is widely recognized today that empirical evidence should inform but not provide the sole basis for medical decisions and policy recommendations. Furthermore, depending on the issue under discussion, different types of evidence will be better suited to inform a decision—from average patient data on clinically relevant outcome measures drawn from large-scale RCTs through to detailed, context-specific narratives drawn from individual interviews.

Fortunately, a commitment to a direct relationship between empirical evidence and policy is not necessary for Sachs's argument. Recognition of the need for integration of such elements as conceptual analysis, individual and social values, and a wide range of empirical evidence, as well as attention to the challenges of this type of integrative policy-making, could be helpfully added to his account. Resources for the construction of a more nuanced position on the role of evidence in shaping guidance documents include not only positions taken in the debates over evidence within evidence-based medicine, but also the specific literature on evidence-based policy.[4]

Once we have attended to the role of nonempirical research (including conceptual research) and the range of forms the empirical evidence might legitimately take, we can ask what particular forms of empirical evidence would be most useful for the specific questions Sachs wants answered. As he acknowledges, there are formidable obstacles in the way of prospective randomized controlled trials of, for instance, research ethics committees following different rules. The only other suggestion considered by Sachs—hypothetical surveys—is also likely to have limited utility. For example, consider the rule of Post-Trial Access. Like Responsiveness and Reasonable Availability, it is not required by regulations. However, like them, it is widely endorsed as an ethical requirement in developing countries,[5] and there are very different interpretations of what it entails.[6] A hypothetical survey would presumably involve asking investigators or REC members how they would behave if this requirement were different. But even if someone's particular interpretation of the requirement could be established in a survey, if she considered it an *ethical* requirement, she would be unlikely to say that her behavior would change if the guidance documents did.

Rather than looking outside current practice for opportunities to gather evidence, we suggest taking current practice as a starting point and asking: What sorts of evidence do RECs already have access to and how might this evidence be better used? In the context of research ethics review, RECs are by their nature faced with particular cases of research studies for evaluation. Evidence presented about individual cases is used to justify exceptions to the usual ethical rules governing research (though not the regulations, of course). For example, researchers might acknowledge that the products they are testing are unlikely to be available to people in the community hosting research, but show that there are other expected benefits to local health care and research infrastructure that might justify their study.[7] Moreover, the persistent identification in a range of proposed trials of the need for a trade-off between, for instance, risk minimization and informed consent might provide some reason to revisit the scope and limitations of each requirement. Thus, rather than conducting surveys of people's hypothetical choices, perhaps we should make use of the resources already presented to RECs on a regular basis.

In order to avoid lapsing into practice-as-usual, such an approach would require that RECs explicitly attend to and collectively reflect on the patterns that arise in the application of ethical rules. Over time, the accumulation of data from individual cases may help us in amending our guidance documents. This would be a practical and straightforward way to make use of evidence that might otherwise be lost but that is already built into the review of research.

Sachs's insightful paper has the potential to broaden discussion about the proper role of ethics guidance documents. We have suggested two amendments to his position. First, we need not conceive of these documents as either the statements of exceptionless ethical rules or as policy recommendations: there are intermediate conceptions. Second, we should in any case take a more nuanced view of the types of evidence that can be useful. An inclusive account of empirical evidence would allow us to make use of the information we are already given. ■

3. Sachs (2010, 3). This call for empirical evidence echoes similar comments made by Ezekiel Emanuel in a recent address to the annual meeting of the American Society for Bioethics and Humanities (ASBH) in October 2009. If the call for evidence-based everything is a trend in bioethics, it would benefit from closer attention to the hard-earned lessons about the limits of evidence-based approaches in medicine.

4. See, for instance, Greenhalgh and Russell (2009), Goodman (2005), and Klein (2000).

5. See Kass and Hyder (2001).

6. See Millum (in press).

7. Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries (2004).

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An Absence of Evidence in "Evidence-Based Rulemaking"

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In the last paragraph of a very interesting paper about the normative status of the consensus rules protecting human subjects participating in research, in which he establishes an important distinction between ethical and policy rules, Sachs (2010) asserts that "the *policy-oriented approach is the scientific approach*, and we should hope that the research community will embrace the scientific approach to regulation as wholeheartedly as they already embrace the scientific approach to medicine. . . *Until we have the answers, our rules remain unproven*" (3, emphasis added).

Despite the paper's title, Sachs says little about how and what evidence should be generated, and even less about how that evidence should be evaluated and incorporated into the rules of human subjects protection. He relegates consideration of this matter to two footnotes, describing in vague terms possible prospective or survey studies that could be mounted to determine whether or not there is evidence providing "robust support" (3) or justification for the policy recommendations.

Specifying the purpose and design of empirical research is critical to an evidence-based approach. We must be clear what combination of research goals and designs are best suited to informing policy recommendations. Whether we conduct or evaluate cross-sectional, observational, or experimental studies matters a great deal to whether and what kind of inferences or conclusions we are able to make.

Sachs states that the empirical research "should endeavor to establish *causal connections* between the enacting of policy and the production of some benefit for an interested party" (3) and seemingly rejects a priori or ethical reasoning as a basis for such an inference. If we are to rely exclusively on empirical evidence, then we must be clear and precise about the kind of evidence that we need.

Let us consider a rule that Sachs claims requires empirical support: the requirement for research to have a valid design. How exactly would such a study be constructed? His first footnoted suggestion is that this be done with randomization between users and nonusers of the rule. Why randomization? Presumably because a randomized study is known to be most valid for establishing causality. The circularity is apparent. The validity of randomized designs is based on theoretical considerations; it cannot be established empirically. So it might be difficult to convince an institutional review board (IRB) (or submitting researchers) to abandon this requirement. He then suggests an observational alternative: asking what a researcher would have done without this requirement. Would any result from such a design supersede what we know theoretically?

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