The ethics of promulgating principles of research ethics: the problem of diversion effects

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ABSTRACT

There is an important distinction between ethical standards for the conduct of research with human subjects and the ethics of promulgating principles of research ethics. Those who promulgate ethical standards for the conduct of research have an ethical responsibility to consider the consequences to which those promulgations give rise. In particular, they must consider whether their promulgations will give researchers incentives not to conduct research or not to conduct research in locales in which participants would benefit from participation. I first show how such ‘diversion effects’ are possible and then examine four principles of research ethics in that light. I then consider several objections to the argument that those who promulgate principles of research ethics should consider diversion effects.

KEYWORDS: Research ethics, regulation, promulgations, standard of care, incentives

INTRODUCTION

The purpose of this article is to argue that those who promulgate ethical standards for the conduct of research with human subjects have an ethical responsibility to consider the consequences to which the promulgation of those standards give rise.

There is a wide range of consequences to which promulgations should be sensitive. For example, if a state wants people not to exceed 75 mph on the highway, it may be best to set the speed limit at 65, not 75. Those who promulgate principles of ethical research should similarly consider whether researchers or institutional review boards (IRBs) are likely to ‘overshoot’ or ‘undershoot’ those principles. For example, given possible definitions of ‘minimal risk’, are the relevant actors likely to interpret this standard too
loosely, thereby putting subjects at excessive risk? Or are they likely to interpret this standard too rigidly, thereby preventing important and ethically justifiable research that poses little or no risk to subjects? It would be important to know.

In this paper, I focus on the incentive effects of promulgations. It is relatively uncontroversial that regulation and public policy must be sensitive to unintended incentive effects, but it is more controversial and less well understood that much the same is true for the promulgation of ethical standards for the conduct of research with human subjects.

To give my argument greater specificity, I will argue that several principles that are contained in one or more guidelines for the ethical conduct of research may give rise to what I will call diversion effects. These include (1) the principle that research in low- and middle-income countries (LMICs) should be responsive to the health priorities of the host country, (2) the principle that subjects in the control arm of a trial should receive the standard of care for the disease in question, and (3) the principle that subjects should receive post-trial access to treatments shown to be effective in trial. A fourth principle—that researchers have obligations to provide ancillary care to subjects—has not yet been incorporated into any standard promulgation. But it, too, gives rise to a similar problem.

I will argue that the promulgation or advocacy of such principles may give researchers or sponsors incentives not to engage in research from which possible subjects would have benefitted or to shift the location of their research with similar effects. This is a consequence that is particularly worrisome in locales where participation in research is often the only means by which people receive treatment for a disease or where participation enables subjects to receive important collateral benefits. Promulgators should consider whether their promulgations would have such effects.

FOUR EXAMPLES OF DIVERSION EFFECTS
To fix ideas, consider four examples of possible diversion effects.

Child Safety Seats (On Planes)
Whereas all states require that children in automobiles below a certain weight be placed in a child restraint (and, otherwise, in a seat belt), the Federal Aviation Authority (FAA) does not require that infants on planes be placed in a child safety seat (CSS) in their own seat. Adults flying on commercial aircraft with children younger than two years old are permitted to hold infants on their laps and need not buy a separate seat for them.

In the wake of several plane crashes in the late 1980s and early 1990s in which children on the laps of adults were fatally injured, the National Transportation Safety Board (NTSB) recommended that the FAA mandate the use of CSSs for all children younger than two years during take-off and landing. The FAA has refused to adopt this recommendation. It argued that mandating the use of CSSs would actually result in an increase in deaths and injuries to infants from the diversion from plane travel to automobile travel. It argued that if parents are required to purchase a separate ticket for their children, a significant number would choose to drive rather than fly. And being held on an
adult’s lap in an airplane is safer than being placed in a child seat in an automobile.\(^1\) So if the FAA’s claim is empirically correct and if the point of the proposed policy is to save the lives of infants tout court—not just the lives of infants on planes—then the FAA was right to reject a mandatory CSS policy (even if it were primarily motivated to serve the interests of the airline industry).

The proposed regulation (and its rejection) gave rise to considerable controversy. For example, the NTSB complained that the FAA’s policies were inconsistent. It noted that whereas adults are required to stow their baggage or computers during take-off and landing, infants and toddlers need not be restrained, somehow ignoring the fact that because one need not buy a ticket for one’s baggage, this regulation has no diversion effect. In general, I suspect that the inclination to take diversion effects seriously reflects the mental images one brings to the problem (and vice versa). From this perspective, supporters of mandated CSSs focus on the contrast between (1) a child in a safety seat and (2) a child on a parent’s lap and find it easy to prefer (1). By contrast, opponents of mandated CSSs focus on the contrast between a child on (2) a parent’s lap in a plane and (3) a child in a car seat in an automobile, and hence prefer (2) to (3).

There are other issues raised by the example that are relevant to research ethics. There is a question as to whether different governmental agencies have moral and institutional reason to worry about some consequences but not others. Moreover, even setting aside the diversion effects of mandating CSSs, there is a genuine question as to whether the projected benefits would justify its costs. One estimate suggests that a mandatory CSS regulation would cost $1.3 billion (in extra tickets) per infant life saved on planes. There are also genuine issues as to how to weigh the value of different lives. If a mandatory CSS policy would have a diversion effect, it will generate additional injuries and deaths to passengers of all ages in those cars as well as to passengers in other cars and to pedestrians. After all, every additional car on the road generates some risk to others.

But none of these complexities disturb the central claim that an ethically defensible safety regulation must be sensitive to incentive effects. I know of no critic of the FAA’s decision who has argued, in effect, ‘Yes, mandating child safety seats on planes will result in more deaths of infants but it should be required nonetheless.’

**Cigarette Taxes**

In an effort to reduce the number of people who smoke and raise revenue, some states have enacted very high taxes on cigarettes. In addition to the (approximately) $1.00 per pack Federal Tax, the per-pack tax in New York is $4.35 and New York City has an additional tax. By contrast, Virginia’s tax is $.30 per pack and North Carolina’s tax is $.45 per pack. The disparity among the state taxes on cigarettes has given rise to illegal diversion along the I-95 corridor. Some estimate that about a third of all the cigarettes sold in New York City are smuggled whereas others estimate that it has much as 57%.\(^2\)

Suppose that one were a New York State policymaker who was concerned to maximize the revenue of New York State from cigarette taxes. In the absence of more

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1 Thomas B. Newman et al., *Effects and Costs of Requiring Child-Restraint Systems for Young Children Traveling on Commercial Airplanes*, 157 ARCHIVES PEDIATRIC ADOLESCENT MED. 969 (2003).

2 Cigarette Smuggling Increase Prompts Crackdown by States, [http://www.bloomberg.com/news/2014-03-25/cigarette-smuggling-increase-prompts-crackdown-by-states.html](http://www.bloomberg.com/news/2014-03-25/cigarette-smuggling-increase-prompts-crackdown-by-states.html) (accessed Oct. 27, 2014).
effective enforcement (which would, of course, be costly in its own right), the optimal tax for New York will take into account the revenues lost to illegal diversion, where the state collects no tax at all. Set the tax too high, too much smuggling. Set the tax too low, less revenue than possible. One wants the tax rate that will maximize revenue given a rate’s concomitant level of smuggling. And the same would hold true if one’s main objective were to reduce cigarette consumption by raising the effective price.

State Income Taxes
There is great variation among the states in the United States with respect to taxation of income. Some states, such as New Hampshire, Texas, and Florida have no state income tax. Other states, such as New York, New Jersey, and Vermont tax individual income with varying degrees of progressivity. For example, the highest marginal tax rate in California is over 13% of taxable income, whereas the highest marginal tax rate in New York is 8.82% and the highest marginal tax rate in North Dakota is 3.22%.

Suppose the New York State legislature wants to generate greater tax revenues from high-income earners. It behooves policymakers to consider whether increasing tax rates on high-income earners would cause many of them to move to a lower tax state, thereby depriving New York of tax revenue. In this case, it turns out that the diversion effect is very small, in part because the neighboring states also have relatively high taxes. As this example indicates, it is always an empirical question as to whether a policy that might have a diversion effect actually has such an effect. But it is uncontroversial that tax policy must be sensitive to such effects.

India’s Compensation Policy
In the wake of concerns about unethical clinical trials, inadequate consent, and numerous adverse events, India passed new regulations in January, 2013. The government wanted to insure that the sponsors of clinical trials were not taking unfair advantage of poor and illiterate people. Among other things, the new regulations required that subjects in clinical trials receive compensation for research-related injuries. The new policy required that subjects should be provided with free treatment for any ailment that develops during the course of a trial whether or not the illness was caused by the tested intervention or was the result of an underlying (or other) condition. In addition, the policy required that compensation be paid in case of injury or death if the subject received a placebo or if the experimental intervention did not have its intended effect. Although the policy has now been altered, it exemplifies the way in which well-intended policies can have a self-defeating diversion effect.

Although there are legitimate questions as to the wisdom and fairness of several elements of the policy, it quickly became event that the policy was having a substantial diversion effect. The National Institutes of Health (NIH) pulled 40 incomplete trials from India, and whereas there were 500 approvals for clinical trials in 2011, the number dropped to 19 in 2013. Munshi and Thatte comment that ‘insisting on the

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3 Wealthier New Yorkers Aren’t Fleeing the City for Tax Havens, New York Times, July 20, 2014, http://www.nytimes.com/2014/07/21/nyregion/wealthier-new-yorkers-arent-fleeing-the-city-for-tax-havens-a-study-says.html (accessed Oct. 27, 2014).
4 Jeremy Sugarman et al., India’s New Policy to Protect Research Participants 346 BMJ f4741 (2013).
5 Ibid.
compensation clause may act as a deterrent to undertaking non-industry sponsored academic research as making such provisions may be beyond the means of individual investigators, academic groups of investigators and many academic institutes. But the diversion effect also applies to commercial research. After all, it is no surprise that for-profit corporations are sensitive to costs. Although international pharmaceutical corporations might have had the resources to comply with the regulations, they don’t have to conduct their clinical trials in India—Shoibal Mukherjee, chief medical officer of Quintiles, one of the world’s largest contract research organizations remarked that ‘they are happy to move abroad and conduct the clinical trials elsewhere.’

This diversion (or cessation) of clinical research in India had several untoward and unintended consequences. First, it entailed an economic loss for the nation, as sponsors invested less in clinical research in India. Second, it may have reduced research into diseases that are a health priority in India. Third, given that India requires evidence of local efficacy before it allows new drugs to be marketed in India, the policy would have prevented useful drugs from being sold. Fourth, and of greatest relevance to the present project, the reduction in trials meant that impoverished people who would have benefitted from participation in trials did not have the opportunity to do so. It is true that the background conditions of impoverished patients were certainly unfortunate and may well have been grossly unjust. Nonetheless, the fact remains—and it, too, is an important moral consideration—that many such people ‘begged to be included in trials because that was their only affordable means of getting any medical care.’ It is possible, of course, that some or even most of these people were badly mistaken: they may have thought that it was in their interest to participate in clinical trials, even though the risks of participation may well have outweighed the benefits. But if they were not mistaken, then the India Compensation Policy was hurting precisely those people that it was designed to help.

**BENEFICIAL RESEARCH**

For present purposes, I am concerned about the diversion effects of promulgation only in cases of net-subject-benefit research, or, for short, beneficial research. In these cases, the totality of expected benefits to the subject from participation exceeds the totality of the expected risks, harms, and burdens of participation. By contrast, net-subject-risk research refers to those cases in which the totality of expected risks to the subject exceeds the totality of the expected benefits to the subject. In my view, the expected benefits in beneficial research may include access to the experimental treatment or the treatment offered in the control arm (if any). It may also include collateral benefits such as access to medical screening that would otherwise be unavailable to the subject, access to ancillary care, satisfaction of curiosity, and the warm glow of contributing to a worthy cause. And, more controversially, it may also include the value of payment.

I am quite aware that my definition of what counts as a benefit of participation is broader than others would accept. Consider a ‘challenge’ study of an experimental cholera vaccine. My local medical center paid $3000 to people who agreed to be

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6 Renuka Munshi & Urmila Thatte, *Compensation for Research Related Injury*, 4 PERSP. CLINICAL RES. 61 (2013).
7 Kripa Mahalingam, *Critical Condition*, OUTLOOK BUSINESS, Mar. 1, 2014.
8 Jacob Puliyel, *Compensation for Victims of Clinical Trials: A discussion on How Current Indian Rules and Guidelines are Hurting India*, 6 J. CLINICAL DIAGNOSTIC RES. 1367 (2012).
The ethics of promulgating principles of research ethics

randomized to receive the experimental vaccine or a placebo. The subjects were subsequently exposed to the cholera pathogen (or ‘challenged’) and were required to spend 12 days in the hospital under round-the-clock medical supervision. Although at least half the subjects (those in the placebo group) were virtually certain to experience a bad case of diarrhea, the disease’s biggest danger is dehydration that is easily monitored and remedied in a controlled hospital setting. In my definition, this is a case of beneficial research if the subjects could reasonably regard $3000 as more than adequate compensation for the inconvenience and burdens of participation, including research-related procedures such as blood draws, stool samples, and the like.

It is virtual black letter law in research ethics that IRBs should not regard payment as a benefit for the purpose of risk/benefit assessment or the like. As the Department of Health and Human Services (HHS) policy puts it, ‘Direct payments or other forms of remuneration offered to potential subjects as an incentive or reward for participation should not be considered a “benefit” to be gained from research.’ I have argued elsewhere that this view is mistaken. The principal practical upshot of my view is that IRBs should approve research that has low social value so long as participants can expect to benefit and give robust consent. I set that argument aside for present purposes. We can assume that the research in question has sufficient expected benefit to others to justify giving prospective subjects the opportunity to participate. Within that context, I am arguing that if a subject can reasonably regard participation as a net benefit, including collateral benefits such as payment, then we can regard participation as beneficial.

Whether a person benefits from participation, all things considered, depends on the person’s pre-participation position or baseline. Consider Phase I oncology research. If a subject has exhausted all available treatments and can otherwise expect to die relatively soon, he might reasonably expect to benefit from participation in a Phase I trial even if there were no evidence that the intervention would be effective and safe. If there were a 0% chance of surviving 3 months without any new treatment and a 5% chance of benefitting from the experimental intervention, a subject could reasonably decide that the totality of the benefits from participation exceeds the totality of the risks.

Much the same holds true for people who participate in research because their background conditions are miserable and participation in research constitutes their only access to medical care or screening or ancillary health care (treatment for diseases unrelated to the disease being studied) or because the value of the payment for participation is greater than the disvalue to them of the risks and burdens of participation. It might be objected that desperate people don’t have good judgement about the relative value of the risks of participation and the benefits they can expect to receive, that they tend to overestimate the value of payment or underestimate the disvalue of the risks and burdens of participation. I see no reason to accept the premise of this argument, but even if this is so, it remains the case that if a reasonable assessment of the value of the

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9 Ken Picard, UVM Will Make People Sick to Test an Experimental Cholera Vaccine, SEVEN DAYS, Aug. 14, 2013, P. 3.

10 Institutional Review Board Guidebook (1993), http://www.hhs.gov/ohrp/archive/irb/irb˙chapter3.htm#e1 (accessed Oct. 27, 2014).

11 Alan Wertheimer, Is Payment a Benefit? 27 BIOETHICS 105 (2013).
benefits—in the subject’s objective position—is greater than a reasonable evaluation of the risks and burdens of participation, then this is a case of beneficial research.

Although my evidence is purely anecdotal, I suspect that most research ethics professionals assume that most subjects are at net risk when they participate in research. If so, then the key questions become whether they have given robust consent to participate and whether the anticipated benefits to others justify placing the subject at net risk, whether the risks are minimized, and so forth. I believe that this assumption is highly questionable. The proportion of research that is beneficial must be reasonably high unless subjects are typically more altruistic than I am inclined to think or unless they frequently and mistakenly believe that they are likely to benefit from participation when they are not. In the latter case, participation is extremely problematic, because it implies that the subject’s consent is seriously defective. Still, I think it quite unlikely that many impoverished people in LMICs are participating in research principally for altruistic reasons. Rather, they are participating because they expect to benefit all things considered.

Whatever the proportion of beneficial research, my argument is limited to such cases. And with respect to such cases, the diversion effect of promulgations would be a serious matter, for it means that many people may not have the opportunity to participate in research from which they counterfactually would have benefitted if it had taken place in their locale.

THE ETHICS OF REGULATION: THE IMPORTANCE OF INCENTIVES

Although I am ultimately concerned with the ethics of the promulgation of principles for the conduct of research with human subjects, it is best to start with the ethics of regulation or policy that has the force of law. As a general proposition, regulators must surely consider whether a possible regulation or policy will have undesirable unintended consequences. It is well known, for example, that regulations and policies must be sensitive to ‘moral hazard’ and ‘adverse selection’. We have a moral hazard effect when someone is more likely to take a risk when others will absorb the costs of that risk. And so it was argued that the government should not have bailed out banks or investment companies during the financial crisis because that would encourage them (or others) to take more risks in the future. It is argued that the government should not subsidize flood or hurricane insurance for those living in flood prone areas, lest it encourage people to take excessive risks in locating their homes. We have an ‘adverse selection’ problem when buyers and sellers have asymmetric information about risks. It is argued, for example, that if we do not mandate that all people join a health insurance pool, then those who do not expect to need expensive medical care will refuse to join whereas those who expect to need such care will sign up and this will result in sky-high premiums.

It is sometimes sensible to adopt a policy despite its moral hazard effects. For example, it is possible that free needle exchange programs may encourage more use of illicit drugs because it makes it safer to use such drugs. At the same time, it is possible that benefits of the program—such as reduced infection with HIV and hepatitis—well exceed such undesired effects. The point remains that—as a general proposition—a sound approach to regulation and policy must be sensitive to the incentives to which regulations and policies give rise.
I am concerned with the particular question as to whether a regulation advances the interests of the persons it is designed to advance given the incentives to which it gives rise. Conservatives often argue that many government regulations and policies are self-defeating in just this way. What Albert Hirschman mockingly refers to as the ‘perversity thesis’ maintains that public policies always or at least often fail to achieve their objective because of the way people respond to such policies. For example, conservatives frequently argue that a robust ‘safety net’ for the poor leads to more poverty because it gives people an incentive not to work—a moral hazard. It is often argued that minimum wage laws do not serve the interests of low-income people because potential employers will refuse to create jobs or hire people if they are required to pay those wages. What is often referred to as the Peltzman effect maintains that many safety regulations fail to achieve their objective because the target population compensates by taking more risks. For example, it is claimed that anti-lock braking systems in cars do not reduce accidents because drivers take more risks if their cars are equipped with such systems.

I am decidedly not claiming that all regulations are self-defeating in this way. Although it is possible that the beneficial effects of mandatory seat-belt laws are somewhat offset by the Peltzman effect, there is no doubt but that mandatory seat-belt laws save lives, all things considered. Nonetheless, regulations and policies sometimes do have incentive effects such that they fail to achieve their objectives in ways that set back the interests of precisely those persons or the class of persons that the regulations were designed to serve.

The actual effects of a policy or regulation are always an empirical matter. But incentive effects are real and an ethical approach to policy and regulation must take them into account. As Max Bazerman and Ann Tenbrunsel put it, policymakers ‘must try to take the perspective of those whose behavior they are trying to influence and think through their likely responses’. And as Dan Brock puts it,

Whatever we think about the responsibilities of bioethicists or philosophers, persons who directly participate in the formation of public policy would be irresponsible if they did not focus their concern on how their actions will affect policy and how that policy will in turn affect people.

The present argument does not claim or assume that regulations or policies should be based on some kind of aggregate consequentialism. Policymakers might reasonably decide that some consequences should weigh more heavily than others. And so our criminal justice system treats the conviction of the innocent as worse than the non-conviction of the guilty. Lawmakers might also decide that some deontological moral principles trump certain consequences, barring torture for moral reasons even when it is thought that torture might generate more good than harm. That said, I am arguing that it is the ethical responsibility of regulators to consider the consequences of a regulation

12 Albert O. Hirschman, The Rhetoric of Reaction (1991).
13 Sam Peltzman, The Effects of Automobile Safety Regulation, 83 J. Pol. Econ. 677 (1975).
14 Steven D. Levitt, The Difference Between 'Theoretically Possible' And 'Important', http://freakonomics.com/2006/12/09/the-difference-between-theoretically-possible-and-important/ (accessed Oct. 27, 2014).
15 Max Bazerman & Ann Tenbrunsel, Blind Spots: Why We Fail To Do What’s Right And What To Do About It 109 (2011).
16 Dan Brock, Life and Death 409 (1993).
and that is so even though others are responsible for the way in which they respond to those regulations. Even if parents should choose to spend the extra money for a seat on an airplane rather than drive, those who make regulatory policy should consider the way in which others actually respond to a regulation, and this is particularly so when their response affects innocent third parties such as infants.

FROM REGULATION TO PROMULGATION

Some documents of research ethics, such as The Common Rule and FDA regulations, are examples of pure regulation. They have the force of law. I regard other codes or documents—what I refer to as promulgations—as quasi-regulatory. These promulgations are not just aspirational. Rather, they are intended to influence the behavior of sponsors, researchers, and IRBs, etc. These promulgations include The Declaration of Helsinki, The Belmont Report, and The CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects, and The Nuffield Council’s Report on The Ethics of Research Related to Healthcare in Developing Countries. Although these documents may not have the force of law, they may influence regulations as when an EU directive says that ‘all clinical trials shall be carried out in accordance with ethical principles laid down in the current revision of the Declaration of Helsinki’. In addition, and as a Nuffield Report adds, ‘Even though [The Declaration] is not a regulatory device, it has far more influence than a document that merely formulates aspirational ideals.’

The promulgation of a principle has behavioral consequences for its targets through what I shall call acceptance and conformance. First, those who want to act ethically but who are unsure as to what that might entail may accept a principle advanced in a promulgation as a guide to ethical behavior. Second, even when the targets of a promulgation are not motivated by ethical considerations, they may choose to conform their behavior to a principle for prudential reasons, such as not wanting to be perceived by others as acting unethically. Promulgations may have a diversion effect because the duties of researchers are mostly conditional obligations. They refer to what researchers must do if but only if they engage in research in a given locale. Researchers will not violate these principles by not engaging in research or engaging in research in a locale in which they do not violate such duties.

17 45 CFR § 46 (2009).
18 U.S. Food and Drug Administration, http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm (accessed Oct. 27, 2014).
19 World Medical Association, The Declaration of Helsinki, last amended 2013, http://www.wma.net/en/30publications/10policies/b3/ (accessed Oct. 27, 2014).
20 The Belmont Report (1979), http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html (accessed Oct. 27, 2014).
21 Council for International Organization of Medical Sciences, International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002), http://www.cioms.ch/publications/layout_guide2002.pdf (accessed Oct. 27, 2014).
22 Nuffield Council on Bioethics, The Ethics of Research Related to Healthcare in Developing Countries (2002), http://nuffieldbioethics.org/wp-content/uploads/2014/07/Ethics-of-research-related-to-healthcare-in-developing-countries-1.pdf (accessed January 12, 2015).
23 See Nuffield Council on Bioethics, The Ethics of Research Related to Healthcare in Developing Countries: A follow-up Discussion Paper 64 (2005), http://nuffieldbioethics.org/wp-content/uploads/2014/07/HRRDC_Follow-up_Discussion_Paper.pdf (accessed January 12, 2015).
The ethics of promulgating principles of research ethics

Given that promulgation and advocacy of principles of research ethics influence the behavior of investigators, sponsors, IRBs, and the like, the ethics of writing such guidelines is similar to the ethics of drafting regulations. The task of the promulgators is not confined to articulating ethical ideals or telling the various actors what they should do if they were motivated to act ethically. The task is to determine what the promulgations should advise people to do given how the various actors are likely to respond to those promulgations and the effects of those responses on the people whose interests the promulgations are designed to advance.

The core principles of research ethics maintain that the pursuit of otherwise legitimate and important research objectives should be constrained by appropriate concern for the autonomy and welfare of research subjects. As the Declaration of Helsinki puts it, 'While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.' This concern has become particularly prominent in international collaborative research in LMICs in which many or most citizens do not have access to adequate medical care. Alex London rightfully observes that researchers in LMICs may 'have the knowledge and training to prevent some of the harms they encounter as a result of [the subject’s] vast, unmet healthcare needs.' Because research designs typically allow researchers’ considerable latitude and discretion with respect to the care that they could provide without compromising their scientific goals, London claims that ‘the researchers and agencies that sponsor clinical trials are responsible for the ramifications that trial designs have on the welfare of the people who submit themselves to scientific study.’

This is potentially a very bold claim about the scope of the responsibility of researchers. But is it correct? We must be careful. A teacher is responsible for the grades that she assigns to students and may have great discretion over those grades, but it does not follow that the teacher is responsible for or should even consider the ‘ramifications’ of her grades on the student’s prospects for graduate school. Just because employers have discretion as to the salary schedules they offer to employees, it does not follow that they are blameworthy just because the offered salary is not sufficient to provide for the needs of an employee’s family. Similarly, just because researchers may have the knowledge and maybe even the resources to provide for people’s medical needs does not, in itself, tell us what researchers should do. Are they responsible only for the effects of their ‘trial design’ as opposed to all the actions that they could take? If so, why? Are they responsible for the effects of their decisions only on those ‘who submit to themselves to scientific study’ or do they also have responsibilities towards those that are not included in the study because they do not meet the inclusion criteria or, say, because of the sample size? Or should they refrain from using resources on current subjects in order to pursue other research projects from which others would benefit?

But my present point is not so much to quarrel with London about the specific responsibility of researchers, but to adopt his perspective with respect to the

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24 WMA Declaration of Helsinki—Ethical Principles for Medical Research Involving Human Subjects, http://www.wma.net/en/30publications/10policies/b3/ (accessed January 12, 2015), Principle 8.
25 Alex London, The Ambiguity and the Exigency: Clarifying 'Standard of Care' Arguments in International Research, 25 J. MED. PHIL. 379 (2000).
26 Ibid.
promulgation and advocacy of principles of research ethics. If those involved in conducting and approving research are ethically responsible for the ramifications that trial designs have for the welfare of research subjects, then those who promulgate or advocate principles of ethical research are similarly responsible for the ramifications of their promulgations on the welfare of research subjects. And if promulgations and advocacy of ethical principles do not actually serve to advance the interests of the relevant persons, then the wisdom of advancing such promulgations is in doubt. What's sauce for the goose is sauce for the gander.

Actually, the sauce for the gander is thicker than the sauce for the goose. The scope of the responsibility of investigators or sponsors is quite unclear. It is surely not obvious that investigators can reasonably be expected to provide for the ‘vast unmet healthcare needs’ of the communities in which they conduct their research simply in virtue of their capacity to help and their proximity to those in need. By contrast, those who promulgate principles for the protection of subjects cannot so easily limit their responsibility for the effects of those promulgations on the welfare of subjects and possible subjects. And here things get complicated. Just as requiring that infants be placed in CSSs in airplanes may actually put those infants at risk given the diversion effects to which the regulation gives rise, promulgating that researchers provide certain sorts of benefits to research subjects may work to the detriment of possible subjects if such promulgations lead researchers to abandon the research from which possible subjects would have benefitted or shift the research to a different location.

Of course a possible subject is not an actual subject. And this raises a crucial issue about the proper scope of the principles of research ethics and the responsibilities of promulgators. Although it is obvious that promulgators should be concerned with the consequences of their promulgations for those who become research subjects, should their concern also extend to those who would counterfactually become subjects if the research had been conducted? I suggested above that it was a mistake to think that transportation regulators should be concerned about the safety of infants on planes but that they need not be concerned about those infants who are not on planes as a result of their regulations. If this is right, is it more plausible to argue that those who promulgate principles of subject protection should be concerned exclusively with the welfare of those persons who are actually included in trials as opposed to the effects of those promulgations on those who do not become subjects in beneficial research as a result of the promulgations? More plausible, perhaps. Plausible, I don’t think so.

Now it is often perfectly reasonable for a decision maker to be held responsible for some consequences of his decisions but not others. A moral division of labor is often justifiable when a decision or policy or role affects different persons. Within the framework of an adversarial system of justice, it is perfectly legitimate for a criminal defense lawyer to advance the interests of his client to the detriment of the public’s interest in the conviction of his client. It is perfectly legitimate for environmental regulators to be (much more) concerned with those who are adversely affected by air pollution while remaining (relatively) unconcerned with the interests of coal producers, coal miners, and utility companies. It is perfectly legitimate for some people to lobby for resources for research on breast cancer when doing so adversely affects the resources available for research on prostate cancer (and vice versa). And it is entirely plausible to advocate for the protection of research subjects when doing so adversely affects the interests of
The ethicsof promulgating principles of research ethics

13

researchers or even the public’s interest in seeing that the research is undertaken and completed. These ‘different persons’ cases raise no deep problems about the scope of one’s responsibilities. By contrast, it is more difficult to justify actions or policies that seek to advance the interests of a group of persons when doing so adversely affects some of those very persons.

It is not always easy to distinguish between ‘different person cases’ and ‘same person cases’. Admittedly, there is a sense in which infants in cars are different infants from those on planes, but they are the same infants if they counterfactually would have been on the planes in the absence of a mandatory CSS policy. Similarly, if a promulgation seeks to advance the interests of the class of people that includes research subjects and possible research subjects, then if a promulgation deters research from taking place when the class of possible subjects would benefit if the research did take place, then they are members of the same group of people that the promulgation is trying to help.

We can make the contrast in slightly different terms. Some regulatory activity recognizes a conflict between the interests of those it is designed to advance and those who will be hurt. Such policies are typically defended on the grounds that the interests of one group outweigh the interests of another or that the decision makers have special role obligations. By contrast, airplane safety regulations are motivated by a concern for the safety of persons. No thought is given to the claim that the interests of plane passengers outweigh the interests of possible plane passengers. It would seem that a similar logic applies to promulgations of research ethics. The promulgators of principles of research ethics cannot avoid responsibility for the effects of their promulgations on possible subjects on the grounds that—‘If they’re not in the trial as a result of our promulgations, they are not our problem.’

As we shall see in more detail below, promulgations of principles of research ethics may give rise to a diversion effect because researchers and sponsors can comply with or avoid violating such principles by simply choosing not to engage in a particular line of research or deciding not to engage in research in a particular locale. For the most part, promulgators seem to have ignored this possibility. I see no mention of this issue in the Declaration of Helsinki. The Nuffield Council is concerned that ‘researchers may forego conducting valuable research because sponsors in developed countries or review committees in sponsor countries may judge it incompatible with provisions of guidance’, but here the concern seems to be that researchers will forego research that is valuable to the prospective host country not that it will forego research that is valuable to the participants themselves.27 As I noted above, critics of the Indian Compensation Regulations pointed to its adverse effects on public health and the economy, but did not focus on its potential adverse effect on possible subjects who did not get the opportunity to participate in beneficial research.

FOUR PRINCIPLES OF RESEARCH ETHICS

In this section, I will argue that three commonly promulgated principles of research ethics may well give rise to diversion. In addition, the principle that researchers have ancillary care obligations has not yet been incorporated into any of the standard

27 Nuffield Council on Bioethics, supra note 22, at 11.
guidelines, but is on its way to becoming widely accepted in research ethics and is subject to the same worries.

A preemptive strike: I am not claiming that any or all of these principles should be rejected. On balance, it is entirely possible that they should be retained. But I do want to insist that a decision as to whether they should be retained should consider whether they give rise to untoward diversion effects and, if they do have such effects, whether the ‘price’ of those effects is acceptable.

The Responsiveness Principle

It is accepted wisdom that clinical research in LMICs—but not necessarily in developed countries—should be ‘responsive’ to the health care needs of the community in which research takes place. The questions asked should concern a health priority of the developing country. Call this the ‘responsiveness principle’ (RP). In most formulations, RP does not claim that researchers are under a positive moral requirement to conduct research in LMICs that is responsive. It is generally not claimed, for example, that it would be wrong for NIH or Pfizer to conduct research on Alzheimer’s disease in the United States where the research is not responsive to the needs of people in LMICs, where Alzheimer’s is not a health priority. The main thrust of RP is negative: it is wrong to conduct research in LMICs that does not satisfy RP.

Versions of RP appear in many documents. Guideline 10 of CIOMS Ethical Guidelines for Biomedical Research states: ‘Before undertaking research in a population or community with limited resources, the sponsor and the researcher must make every effort to ensure that the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out.’ The Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries say that it is ‘widely accepted’ that clinical research ‘should address a health problem of the developing country population’. Recommendation 1.3 of the National Bioethics Advisory Commission states: ‘Clinical trials conducted in developing countries should be limited to those studies that are responsive to the health needs of the host country.’

Despite its wide acceptance, RP is deeply puzzling. We do not appeal to anything like RP in standard economic contexts in which people in the developed world benefit from the labor of people in LMICs so long as the workers benefit (enough) and consent to their employment conditions. No one argues that Nike should locate production plants only in countries where the need for athletic shoes is a priority. It may be thought that medical researchers have responsiveness obligations that do not apply to ordinary manufacturers. But even if that is so, promulgating a principle such as RP can still give rise to troublesome diversion effects.

Consider a benign hypothetical case in which Pharma, a major US drug company, proposes to conduct a randomized controlled superiority trial of a new hypertension drug, Q, in Uganda, where hypertension is (for the sake of argument) not a health priority (the example is stylized in order to isolate the alleged importance of

28 The Council for International Organizations of Medical Sciences, International Ethical Guidelines for Biomedical Research Involving Human Subjects, http://www.cioms.ch/publications/layout˙guide2002.pdf (accessed January 12, 2015).
29 Fair Benefits for Research in Developing Countries, 298 SCIENCE 2133 (2002).
30 http://govinfo.library.unt.edu/nbac/clinical/execsum.html (accessed January 12, 2015).
The ethics of promulgating principles of research ethics

The trial enrolls subjects who exhibit hypertension, but who are not receiving medication. Half the participants would receive Q and half would receive an existing drug, R. Although Pharma offers to provide Q or R (whichever is more effective) to all participants when the trial is complete, Pharma intends to market Q in developed nations. Pharma could run the trial in the United States, but it prefers to conduct this trial in Uganda because Uganda has more ‘treatment naive’ subjects and because other research-related costs are significantly lower.

It would appear that the proposed trial of Q would not be compatible with RP if hypertension is not a health priority in Uganda as, say, contrasted with the need for interventions to control infectious diseases. So if a promulgation motivates Pharma to conduct the research in, say, the United States, then possible participants in Uganda do not get the opportunity to benefit from participation. Assuming that all Ugandans who would participate in this research can expect to benefit from participation, it is surely paradoxical to claim that it would not be wrong to conduct this research in the United States, in which case no Ugandans benefit, but that it would be wrong to conduct this research in Uganda where some Ugandans benefit.

Given the possible diversion effect, what explains the consensus in support of RP? First, it is entirely possible that promulgators just didn’t think about it. Second, it is possible that most promulgators assume that most participation is non-beneficial or net-risk in which case the issue doesn’t arise. Third, promulgators could accept the claim that RP has diversion effects, but see this as an acceptable price for the benefits to which RP will give rise. It might be argued that even if participation in non-responsive research is beneficial to the possible subjects, it typically has negative effects on the host societies or, put differently, that barring non-responsive research will have positive effects for the society. It might be argued that most research imposes health costs on the community—using resources for research rather than for medical care—and that insisting on responsiveness is a way to off-set or compensate the society for the burdens imposed by research. It might also be argued that because non-responsive research uses resources that would otherwise be used for responsive research, a policy of making it more difficult to conduct non-responsive research will motivate or incentivize researchers to use their resources in ways that will benefit the people of LMICs. By denying possible subjects (eg Ugandans with hypertension) the opportunity to participate in research to their benefit, RP seeks to advance the interests of others at risk for higher priority diseases such as malaria.

These claims provide a coherent defense of RP, but it is an empirical question as to whether research typically imposes net burdens on communities or provides net benefits. It is also an empirical question as to whether such ‘blocking’ strategies will have positive effects. As the Nuffield Council suggests, even non-responsive research can actually offer ‘considerable indirect benefits to host countries in the developing world because of the potential for strengthening the national capacity in research, in the form of improved infrastructure and training’. Moreover, it is a normative question as to whether the interests of current possible subjects should be sacrificed in order to secure gains to society. In any case, while the aggregate effects of insisting on RP are an empirical question—and the results may well go either way—the general point remains

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31 Council for International Organization of Medical Sciences, supra note 21, at 29.
that promulgators must consider whether RP has a diversion effect that works to the
detriment of possible subjects.

**Standard of Care**

It is commonly thought that it is unethical for researchers to test an intervention against
a placebo when proven effective treatment is available unless, perhaps, a placebo-
controlled trial is necessary to generate the relevant scientific information and there
is little risk to the subject in not receiving the intervention. The Declaration of Helsinki
contains the canonical statement of this principle: ‘The benefits, risks, burdens and ef-
ficacy of a new intervention must be tested against those of the best proven inter-
vention(s),’ except in special circumstances that we can safely ignore here. I assume
that ‘best proven’ must appeal to a world-wide rather than a local standard. The world
medical association (WMA) could hardly have thought it unproblematic if researchers
were to provide those in the control arm with a placebo just because no useful inter-
ventions were available in a given locale.

Consider the (in)famous Surfaxin Trial. Respiratory distress syndrome (RDS) is a
common and potentially fatal disease in premature infants that is caused by insufficient
surfactant in the lungs. Several replacement surfactants have been approved by the US
Food and Drug Administration since the 1990s. Surfactant replacement therapy is the
standard treatment for RDS in the developed world where it has sharply reduced neo-
atal mortality from RDS. In LMICs, however, infants do not typically have access to sur-
factant therapy or ventilator support, both of which are quite expensive.

In 2000, a private US drug company, Discovery Labs, proposed to conduct a Phase
III clinical trial of a new synthetic surfactant, Surfaxin. The principal target market for
Surfaxin was the United States and Europe, as it would prove unaffordable in LMICs.
Although Discovery could have proposed to conduct (and eventually did conduct) an
active-controlled trial in which Surfaxin was compared with an approved surfactant
therapy, it preferred to conduct a placebo-controlled trial in LMICs because it would
be quicker, cheaper, and require fewer subjects in order to generate the required level
of statistical significance. Moreover, FDA regulations do not require that an interven-
tion be shown to be better than or compared with existing interventions; they require
only that an intervention be shown to be safe and effective.

Discovery proposed to conduct a randomized placebo-controlled trial involving 650
premature infants with RDS in Bolivia and three other countries in South America. On
this trial design, Discovery agreed to provide endotracheal tubes, ventilators, and an-
tibiotics for all participants. Half the infants would receive air suffused with Surfaxin
and half the infants would receive (‘sham’) air without any drug. Note that while in-
fants in the control group would not be receiving surfactant therapy, they would also
not be denied a treatment to which they would otherwise have had access. Indeed, venti-
lator support with sham air was superior to the treatment generally available to Bolivian
infants. Parents of infants with RDS would be asked to give consent for their babies to
participate. And under the circumstances, it would have been perfectly rational for them
to do so. A 50% chance of life-saving therapy is better than none.

32 U.S. Food and Drug Administration, *supra* note 18, Principle 33.
33 See the description of the Surfaxin Trial in JAMES V. LAVERY et al. (eds.) ETIcal ISSUes IN INternational BIomedical RESEARCH: A Casebook 151, 159 (2007).
The proposed Surfaxin Trial was clearly not compatible with the Declaration of Helsinki because it involved withholding proven effective therapy from participants in the control group. No such trial would be permitted in a developed society, not to mention that parents in the developed world would never consent to participate if surfactant therapy were otherwise available. It’s not hard to see the problem with Discovery’s proposed protocol. To allow this study to go forward is to allow researchers to stand right next to a very sick child and choose not to administer life-saving surfactant therapy when they have the capacity to do so. As Peter Lurie and Sidney Wolfe pointedly put it, ‘... the provision of placebo. .. to the 325 infants in the control group will result in the preventable deaths of 16 infants’, an estimate of the number of infants in the control group who would not have died if they had received traditional surfactant therapy.\(^{34}\)

In the face of intense criticism, Discovery altered the protocol. Rather than conduct a placebo-controlled trial at sites where surfactant therapy was not available, it conducted an active-controlled trial at a variety of sites, most of which were located in a variety of developed and less developed countries where ventilator support and surfactant therapy were ordinarily available.\(^{35}\) But note the consequence! Because Discovery shifted the location of the research, no infants in the original proposed sites received the benefit of surfactant therapy from Discovery or, for that matter, the hospital care that would have been provided with the administration of ‘sham air’. Following Lurie and Wolfe’s logic, the diversion of Discovery’s research from the sites of its original proposed research resulted in the preventable deaths of approximately 16 infants who would have received surfactant therapy under the original placebo-control trial design.

What explains the arguable indifference to the possible diversion effect of the Standard of Care principle by the WMA or by critics such as Lurie and Wolfe? First, I suspect that it was not given much thought. Second, and as with the CSS example, one’s views about such cases reflect the mental images that one brings to this sort of situation. Those who favor the standard of care principle may have been focusing on the contrast between (1) the image of a patient having a 50% chance of receiving beneficial treatment and a 50% chance of receiving a placebo, and (2) the image of patients in the control arm receiving the standard of care. And (2) is better than (1). They did not focus on the contrast between (1) and (3) a child receiving no medical care, where (1) is better than (3).

But suppose that the problem occurred to the promulgators. How might they defend their principle? They might claim that the promulgation should be concerned with the welfare of those who are actual subjects and need not be (much) concerned with the welfare of possible subjects. This is a difficult ethical row to hoe and Lurie and Wolfe do not try to till it. A more plausible strategy is to argue that while insisting on the standard of care may have short-term costs to those who would benefit from participation in a placebo-controlled trial, it will eventually serve to benefit people in LMICs. Insisting on a universal standard of care may prevent a ‘race to the bottom’ among LMICs.

\(^{34}\) Peter Lurie & Sidney Wolfe, Letter to Tommy Thompson, THE PUBLIC CITIZEN, Feb. 22, 2001, http://www.citizen.org/publications/publicationredirect.cfm?ID=6761 (accessed January 12, 2015).

\(^{35}\) Fernando Moya et al., A Multicenter, Randomized, Masked, Comparison Trial of Lucinactant, Colfosceril Palmitate, and Beractant for the Prevention of Respiratory Distress Syndrome Among Very Preterm Infants, 115 PEDIATRICS 1018 (2005).
competing to be used for research that does not provide the standard of care. The ‘long-term’ argument should be taken seriously. But it ultimately rests on both empirical and normative considerations. Lurie and Wolfe provide no evidence for the claim that the long-term health of people in developing countries will be ‘better served by... a higher standard’ and one cannot evade the very real loss to the infants who would have benefitted from participation in the original proposal for the Surfaxin Trial by assuming that the long-term effects will go one’s way. Moreover, it is at least questionable as to whether it is justifiable to sacrifice the interests of those infants even if the long-term effects are likely to be positive.

Finally, it might be claimed that the standard care principle could be understood as a deontological constraint on researchers rather than as a principle designed to advance the interests of subjects. In this view, it might be claimed that it is wrong for researchers to take advantage of the subjects’ unjust background conditions (where no surfactant therapy was available) even if the researchers bear no moral responsibility for those background conditions and, most importantly, even if the subjects would be better off if they did so. Moreover, it might be argued that Discovery’s ‘offer’ of a 50% chance of receiving surfactant therapy should not be compared with the subjects’ status quo ante, but against a normative baseline that reflects what Discovery could have provided if it had been motivated to act ethically. I think that this argument will not work and will say more about it below. For present purposes, I will simply note that no defender of the standard of care principle has argued in that way.

Post-Trial Treatment
If a clinical trial shows that an intervention is effective and superior to other interventions, it will typically be available (in time) as part of standard medical care in developed countries. Not so in LMICs, where the intervention may be generally unaffordable at least in the short run. CIOMS states that it is unethical to conduct research if there is good reason to believe that a product developed or knowledge generated by research is unlikely to be reasonably available to, or applied to the benefit of, the population of a proposed host country or community after the conclusion of the research. The Declaration of Helsinki states: ‘At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.’ Note that whereas the CIOMS statement concerns post-trial availability to the community, the Declaration of Helsinki is concerned about post-trial availability to the subject. In any case, requiring that researchers provide post-trial benefits to either subjects or to the community could give rise to a diversion effect. As a general proposition, if it is more expensive for people or organizations to do something, they’re less likely to do it.

Researchers are generally not legally required to provide post-trial treatment. Indeed, some researchers are precluded from doing so. For example, NIH policy states that because it is ‘statutorily authorized to support and conduct biomedical research’,

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36 The Developing World as the ‘Answer’ to the Dreams of Pharmaceutical Companies: The Surfaxin Story in Lavery et al., supra note 33, at 166.
37 Nuffield Council on Bioethics, supra note 27, at 53.
38 U.S. Food and Drug Administration, supra note 18, paragraph 33.
its resources cannot be used for treatment following the completion of a trial (strictly speaking, the premise does not entail the conclusion). But not all researchers are subject to such regulations, and acceptance of or conformance with the post-trial treatment principle may exert its own force with researchers and IRBs. In addition, NIH policy may be wrong. And so we need to ask whether research ethics should press for this principle.

I am not concerned here to consider the merits of the argument for the principle of post-trial treatment on its own terms, except to note that even if subjects should receive post-trial treatment because they were subjects (as opposed to being people who need treatment), it is another question as to who has the obligation to provide it: the researchers? The state? But if such promulgations lead some sponsors or researchers not to conduct beneficial research or to conduct it in a locale where providing post-trial treatment is not an issue, then these promulgations give rise to a diversion effect. True, some research projects would be undertaken anyway in the same locale and those subjects will benefit from the requirement or promulgation. And this is particularly so if the research generates significant profits and the researchers would do better conducting the research at that locale and providing post-trial treatment than shifting the research to another locale. But, at the margin, increasing the cost of research will deter at least some research from being undertaken at all, and, in still other cases, it is likely to cause sponsors to shift the location of research from LMICs to developed societies where such treatment would be covered by insurance or provided by the national health system.

Some ethicists seem sensitive to this possibility. The National Bioethics Advisory Committee says ‘It has been pointed out that expecting industrial sponsors to provide expensive drugs free of charge after a trial is over might curtail interest among companies in developing interventions specifically for diseases prevalent in developing countries.’ But it’s not just that this expectation might work to the detriment of the populations in developing countries; it might also work to the detriment of possible trial participants themselves. The NBAC did not say whether it thinks that this argument has merit or take a position on its force. It says only that this worry ‘has been pointed out’. But the point is quite crucial. If the NBAC or similar organizations seek to influence the conduct of research, then it would be important to determine whether the promulgation of a principle will in fact motivate investigators to abandon research from which possible participants can expect to benefit and to which they would consent.

At least one group of prospective subjects voiced their objection to being excluded from a trial on this basis. In 1997, the rate of HIV infection in South Africa was extraordinarily high and anti-retrovirals were not provided by the South African public health services. Multinational drug companies wanted to conduct research in South Africa because of its combination of a ‘large infected population and proven medical

39 The National Institutes of Health, Regarding Guidance for Addressing the Provision of Antiretroviral Treatment for Trial Participants Following their Completion of NIH-Funded HIV Antiretroviral Treatment Trials in Developing Countries (emphasis added), http://grants.nih.gov/grants/policy/antiretroviral/QndA.htm (accessed Oct. 27, 2014).
40 National Bioethics Advisory Commission, Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries, c. 4, (2001) 65, http://bioethics.georgetown.edu/nbac/clinical/Chapter4.pdf (accessed Oct. 27, 2014).
expertise'. Research Ethics Committees (the equivalent of IRBs) in South Africa were considering whether to approve protocols for combinations of experimental drugs with approved drugs. The sponsors said that they would provide the ‘cocktail’ free for two to three years, but without any guarantee that the treatment would be continued at the conclusion of the trial, in part, because that would require the sponsor to buy expensive drugs produced by other companies.

The ethics committee maintained that ‘it is not ethical’ to do such research unless post-trial treatment is assured and that it had the responsibility ‘to ensure that patients are not exploited’. In response to these worries, AIDS activists argued that, for them, the trials ‘are seen as treatment rather than research—and are often the only way in which [they] have any access to treatment...’ If the researchers would, in fact, not engage in the research if they were required or expected to provide post-trial treatment, then the requirement or expectation effectively deprives possible subjects from benefiting from participation. In effect, the activists claimed that they would rather be ‘exploited’ than excluded. For them, half a loaf was better than none.

Of course, a promulgation about post-trial treatment may advance the interests of some actual subjects (who receive post-trial treatment) while adversely affecting the interests of some possible subjects (because of diversion). As an analogy, consider minimum wage laws. Such laws may raise the income of actual employees while deterring the employment of potential employees when an employer believes that the economic value of a potential employee’s work is less than the minimum wage. What then? The obvious and correct answer is that we have to choose. If minimum wage legislation causes a significant increase in non-employment, then such laws would be hard to justify even if they helped some workers. On the other hand, if the principal effect of minimum wage laws is to raise the income of low-paid employees without significantly reducing employment, then such laws are much easier to justify unless we give great priority to the interests of the unemployed because they are arguably the worst off. Similarly, promulgations requiring researchers to provide post-trial treatment may benefit some communities and subjects while adversely affecting only a small number of possible subjects. These are all empirical questions and the case for such promulgations cannot be settled in the absence of evidence about its effects.

Ancillary Care

The view that researchers have an obligation to provide ancillary care to subjects has not yet been widely endorsed in regulations or the most well-known promulgations. But such a view has been advocated by bioethicists who clearly hope to influence those who do fashion regulations and promulgations. There is a genuine question as to whether scholars who advance philosophical arguments for ethical principles need to worry about the consequences of the acceptance and promulgation of those principles. Perhaps scholars get a pass. Nonetheless, those who might come to promulgate the principle that researchers have ancillary care obligations must consider whether doing so would give rise to diversion effects.

41 Peter E. Cleaton-Jones, An Ethical Dilemma: Availability of Antiretroviral Therapy After Clinical Trials With HIV Infected Patients Are Ended, 314 BMJ 887 (1997).
42 Ibid.
43 Peter Busse, Strident But Essential: The Voices of People with Aids, 314 BMJ 888 (1997).
In their seminal article, Richardson and Belsky define ancillary care as treatment provided to a subject that is ‘beyond what is necessary to implement a study’s design safely and validly’, and is also beyond any (contractual) treatments that investigators may offer in order to recruit and enroll a sufficient number of participants. For example, in the course of conducting research on malaria in Africa, investigators may find that some participants have schistosomiasis, a serious and debilitating parasitic disease that is caused by drinking contaminated water. They may also be in a position to provide care for that disease. To the extent that the researchers have ancillary care obligations, they need to treat participants with schistosomiasis even if doing so uses resources that would otherwise be devoted to other research projects and even if treating the participants for schistosomiasis is not required in order to get scientifically valid results for the research on malaria.

In his article with Belsky and in his more recent (sole-authored) book, Richardson argues for a ‘limited entrustment’ model on which investigators have an obligation to provide ancillary care if it would not unduly strain the research effort. The core idea is that because researchers benefit from their use of the research subjects and access to private information and people’s bodies, researchers should strive to provide ancillary care as a form of reciprocity.

But what does reciprocity require? One cannot argue, as does James Lavery, that participation ‘warrants some special gratitude or recognition, over and above the potential benefits inherent in a given research design’ simply by citing a principle of reciprocity or gratitude, because it is precisely the content and force of reciprocity that is at issue. But even if we assume that investigators do acquire ancillary care obligations in the course of research, the question arises as to whether researchers and subjects should be able to ‘contract around’ such obligations. Assuming that the researchers are not required to engage in research, and assuming that they would prefer not to saddle themselves with costs that are not related to their research aims, should we prefer an approach that allows them to ask possible participants to waive claims on ancillary care as a condition of participation rather than simply decide not to engage in the research?

Richardson is quite aware that acceptance or conformance with the view that researchers have non-waivable ancillary care obligations can give rise to a diversion problem.

Suppose that a group of researchers working on extremely drug-resistant (XDR) tuberculosis would not be able to afford to do their study in such a poor district, so terribly lacking in health infrastructure, if they had to provide ancillary care, but that without having to do so, they could afford it. It is possible that by choosing to do their research in such a district, they would be doing the people of the district a favor, at least by giving them temporary access to some non-ancillary medical care—perhaps more medical care than they otherwise would have had—and by doing something to boost the local economy. It is also possible, however, that in choosing to locate their research in such a district while not providing

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44 Henry Richardson & Leah Belsky, The Ancillary-Care Responsibilities of Medical Researchers, 34 Hastings Ctr. Rep. 25 (2004).
45 Ezekiel Emanuel et al. (eds.), The Obligation to Ensure Access to Beneficial Treatment for Research Participants at the Conclusion of Clinical Trials, in The Oxford Textbook of Clinical Research Ethics 701 (2008).
ancillary care that would otherwise be obligatory, these researchers would be criticizably tak-
ing advantage of the injustices that have put these people in such difficult straits.⁴⁶ (Emphasis added)

Richardson acknowledges that the possible subjects would be better off if the re-
searchers were to conduct the research without providing ancillary care and that it
would be reasonable for them to waive any claims on ancillary care they might oth-
erwise have in order to encourage the researchers to conduct the research. Moreover,
as Richardson presents the example, it’s not just that the researchers might choose not
to engage in the research if they had to provide ancillary care. Rather, his hypothetical
assumes that the researchers could not go ahead with the research.

Still, Richardson says that ‘it is possible’ that these researchers would be criticizable
for taking advantage of these impoverished people even though the alternatives, ex hypo-
thesi, are for them (1) to take advantage of these people to the benefit of the subjects
or (2) not to conduct the research and, therefore, not to provide them with any benefits
at all. I concede that there is a sense in which the researchers would be ‘taking advan-
tage’ of the injustices that have put people in such difficult straits. But just as auto-body
repairmen are not criticizable for earning a living from other’s misfortunes, and just as a
lawyer is not criticizable for earning a living from the injustices suffered by his clients,
I just do not see why the researchers would be ‘criticizable’ for taking advantage of people
in this way. As I have argued elsewhere, there is an important distinction between ‘tak-
ing advantage of injustice’ and ‘taking unjust advantage of injustice’.⁴⁷ The researchers
didn’t cause the injustice. They can’t do more for the subjects. So if ‘ought implies can’,
it’s hard to see how they could have obligations to provide ancillary care if they were to
go ahead with the research.

In my view, Richardson’s hypothetical makes the case for waiving ancillary care obli-
gations too easy precisely because the researchers do not have the resources to con-
duct beneficial research and to provide ancillary care. But even if the researchers do
have the resources to provide ancillary care, the question still remains as to whether re-
quiring them to do so will have diversion effects that work to the detriment of possible
subjects.

Taking Stock

Just as requiring parents to buy a separate ticket for their infants on planes gives them
an incentive to choose less safe forms of travel, I have argued that promulgating some
principles of ethical research may give investigators and sponsors an incentive to make
decisions that are detrimental to possible participants. Just as the regulators were right
to be mindful of the consequences of requiring CSSs for infants on airplanes, those who
promulgate or advocate principles of the ethical conduct of research should be mindful
of the consequences of acceptance of or conformance with the principles they promote
or advocate.

Once again, and repeating for emphasis, I have not argued that any or all of the prin-
ciples of research ethics that I have discussed should not be promulgated. The validity of
that claim would depend upon a range of normative and empirical considerations that

⁴⁶ HENRY RICHARDSON, MORAL ENTANGLEMENTS 153 (2012).
⁴⁷ ALAN WERTHEIMER, EXPLOITATION 298 (1996).
remain unsettled. It is possible that the diversion effects of these principles are relatively small. It is possible that the long-term benefits of promulgating such principles exceed the cost of the diversion effect, in part because it strengthens public trust in the research enterprise. It is possible that if the promulgations under discussion were deleted or significantly changed, then the document as a whole—which may do a lot of good—would lose legitimacy. It is possible that if guidelines were changed so as to make them more palatable to some researchers, this would give them incentives to push for even laxer standards.

To pursue the previous point, those who promulgate principles of research ethics are right to worry about allowing or encouraging a ‘race to the bottom’. The Declaration of Helsinki may have been right to maintain that ‘No national or international ethical, legal, or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this declaration.”48 For if one community were allowed to reduce such protections by X amount in order to attract research that benefitted participants or the community, then another community might reduce such protections by 2X amount and so forth.

In any case, I have not argued against any of the standards set forth in any of the well-known promulgations. I have argued that a plausible defense of the promulgation of these principles must consider the likely diversion effects of such promulgations with respect to beneficial research.

**OBJECTIONS**

In this section, I consider several objections to the argument that promulgators should consider diversion effects.

**ETHICS IS NOT REGULATION**

It might be objected that my analysis doesn’t attend to the distinction between regulation and ethical promulgation. It may be argued that while ethical regulators have to focus on the consequences of the policies, it is not sufficient or perhaps even important for them to ask whether the content of a regulation captures or reflects the ethics of individual behavior. On this view, the FAA (or some other agency) should be concerned with what happens to infants under various policies and not exclusively with what parents ‘should’ do.

By contrast, it may be thought that when organizations or individuals promulgate or advocate what are understood to be ethical principles that do not have the force of law, the principal question is whether the articulated principles capture or reflect the relevant ethical behavior. We should not ask the World Medical Association to worry about whether bad things will happen if people take the Standard of Care principle seriously or to take those consequences into account in deciding which principles to promulgate. They should ask only what researchers should do.

Considered from a wider perspective, this objection exemplifies a recognized problem in practical ethics. With respect to an ethical principle, we can ask three questions: (1) Does a principle capture the moral truth? (2) Is it best that people believe the principle? (3) Should ethicists argue for the principle? Although one might expect that the

48 [http://www.wma.net/en/30publications/10policies/b3/](http://www.wma.net/en/30publications/10policies/b3/), Principle 10 (accessed Oct. 27, 2014).
answers to these questions would always be the same, these are different questions and can admit of different answers. Assuming that a principle is true, it does not follow that it is also best that people believe it or that ethicists should argue for it.

For example, it is commonly accepted that even if some version of utilitarianism is the correct theory of right action or states of affairs, there may be good utilitarian reasons for not promoting utilitarianism as a decision procedure. In other words, people may produce better consequences if they do not believe in or act on the principle that they should attempt to maximize good consequences and, instead, act on the basis of (relatively firm) deontological rules or principles. As Sidgwick put it, ‘a Utilitarian may reasonably desire, on Utilitarian principles, that some of his conclusions should be rejected by mankind generally; or even that the vulgar should keep aloof from his system as a whole’.49

Just as the truth of a principle does not entail that it should be believed, that it is desirable that people believe a principle does not entail that it should be promulgated or advocated. Consider this question: How much should affluent Americans give for the purpose of alleviating worldwide poverty? Peter Singer argues that affluent Americans should give a large proportion of their income—say 70%. Assuming that Singer is correct, it would be best if affluent Americans believed that this were so. But suppose that for various psychological reasons, those who encounter Singer’s argument will be highly resistant to its demands. They will be highly motivated to find reasons to dismiss his arguments and, as a consequence, they will come to believe that they need to donate no more than 5% of their income to the alleviation of poverty. By contrast, if Singer advocates a more moderate contribution, say 20% of one’s income, to the alleviation of poverty, the proposal generates less resistance and, as a consequence, people will devote 10% of their income to the alleviation of poverty. Although it would be better if people believed in the 70% principle, Singer argues that it is better if he advocates a donation rate that is likely to yield the highest donation rate.50 If Singer is right and if the ethics of conducting research and the ethics of alleviating poverty are analogous in this respect, then those engaged in the promulgation of principles of ethical research should advocate the principles whose promulgation will have the best consequences in terms of the values and interests the promulgations are attempting to promote.

In sum, I see no reason to think that promulgators of ethical principles are free to ignore the consequences of their promulgations just because they are not technically engaged in regulation. It is sufficient that their promulgations are intended to—and do—have effects on the decisions that others make.

ACCOMMODATING ETHICALLY SUBOPTIMAL OR WRONGFUL BEHAVIOR

It may be thought that taking diversion effects seriously is ethically problematic because it implies that promulgators should adjust ethical standards to the ethically sub-optimal or wrongful behavior of others. I believe this line of objection fails. First, it is important to note that we regard much sub-optimal behavior as morally permissible. It may be better if parents travel with their infants by plane and use CSSs, but we do not think that

49 Henry Sidgwick, The Methods of Ethics 489, 490 (1907).
50 Peter Singer, The Life You Can Save 152 (2009).
they act *wrongly* if they choose to drive, if only to save some money. It would be better if pharmaceutical companies used their resources to develop treatments for malaria rather than to develop new drugs for rare forms of cancer, but we do not think that they act wrongly or impermissibly if they do the latter. We may think it better that pharmaceutical companies conduct their research on malaria drugs in LMICs and provide post-trial treatment to subjects, but we do not think that they act impermissibly if they conduct the research in locales where post-trial treatment is ordinarily provided by the national health care system and thus would not be a burden on the company.

But even when diversion effects cause others to act wrongly, I believe that there is no general ethical bar to accommodating or appearing to condone such wrongful behavior. Consider several public policy programs. Providing free needles to drug addicts has been shown to be a very successful way to reduce communication of infectious diseases such as hepatitis and AIDS. Some critics of such programs maintain (1) that the program effectively condones or is complicit with the illicit use of drugs or (2) that the program is likely to promote such behavior in the long run. Although (1) and (2) are often conflated, they are independent arguments. With respect to (2), it is not clear that needle exchange programs do promote drug use. Maria Szalavitz says that ‘no study has ever found that needle exchange increases drug use or that it prevents users from quitting. On the contrary, these programs encourage many addicted people, who were formerly isolated, to get help and recover’. But suppose that such programs do increase drug use. It is still likely that the long-term effects of such programs are immensely positive, and that the benefit of reduced infections greatly outweigh the harm of somewhat increased drug use. If the principal goal of drug policy is to minimize aggregate harm, we would have to take the wrongness of complicity very seriously to think that such policies are unethical.

Or consider a recent study in which sexually active teenagers in St. Louis were offered the option of long-term contraceptives such as intrauterine devices. Most chose that option and it turns out that ‘pregnancy and abortion rates plunged to less than a quarter the rates of sexually experienced teenagers nationally, the group most comparable to those in the study’. Although the results of the program seem (almost) unequivocally positive, it could be argued that the government should not be encouraging sexual activity among teenagers. Although the benefits to society and to the teenagers seem to outweigh the harms of encouraging early sexual activity (if the program actually leads to more sexual activity and if such activity really is harmful), here too I would be disinclined to reject such programs on the grounds that it renders the state complicit with such activity. Better to have 10 cases of safe sex than 9 cases of unsafe sex.

Or consider tax policy. Recall the example of state income tax policy in an environment where citizens can move from state to state with relative ease. Suppose that Vermont legislators propose to increase the state income tax rate on those who earn over $200,000 per year in order to better fund public schools, welfare, health care, and

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51 Clean Needles Saved My Life. Now Congress Wants to Ban Funding for Needle Exchange, TIME, Dec. 16, 2011, http://healthland.time.com/2011/12/16/clean-needles-saved-my-life-now-congress-wants-to-ban-funding-for-needle-exchange/ (accessed January 12, 2015).

52 NEW YORK TIMES, Oct. 1, 2014, http://www.nytimes.com/2014/10/02/science/teenage-pregnancy-and-abortion-rates-plummet-with-long-acting-female-contraception-study-says.html (accessed January 12, 2015).
unemployment compensation and because they believe that such tax rates are also just. But also suppose that the evidence indicate that if such a tax were enacted, Vermont’s tax revenues would actually decline because some high-income people would move to states with lower tax rates or somehow arrange to change their official residence. It would be unwise for the legislators to insist on higher taxes for the rich as a matter of justice if doing so actually increases the tax burden on lower income people. If the state lowers tax rates in order to give high-income people an incentive not to move, is it complicit with injustice? Perhaps. But given the hypothesized facts, it seems clearly best that they aim for the tax rate that maximizes (within the limits of justice) the tax income received from high-income citizens given their response to varying tax rates.

Now the previous claim does not maintain that a tax rate is just if it maximizes the well-being of the poor given the sub-optimal or unjust behavior of the rich. It maintains only that it is the most ethical tax rate, all things considered. Along these lines, Gerald A. Cohen has argued that John Rawls is wrong to endorse the difference principle as a principle of justice. As is well known, Rawls argues that even though the more talented or able do not deserve their abilities, the difference principle allows for inequalities that gives the talented incentives to use their talents in ways that work to maximize the position of the least well off. If many talented people would prefer to be philosophers than physicians, but would serve the least well off better by becoming physicians, then the difference principle would countenance paying doctors more than philosophers in order to increase the supply of physicians.

In response, Cohen has argued that allowing for such incentives is not just because such incentives would not be necessary if the talented were themselves committed to the principle of equality that underlies the difference principle. After all, if the talented were motivated to act justly, they could simply choose to use their talents and labors in ways that serve the least well off without being given incentives to do so. After all, a person who chooses to become a physician rather than a philosopher at the same pay would still have a pretty good life. Cohen does not deny that—given the world as it is—it may be ethically best to provide incentives to the talented so that they use their talents in ways that work to the advantage of all. But Cohen is at pains to argue that the principles of justice and the best principles for regulating society answer different questions.

Along similar lines, I suggest that ethically sound promulgations for conducting research also need to take account of the need to provide the appropriate mixture of incentives given the world as it is. I think a similar point applies to Henry Richardson’s approach to ancillary care obligations. As I noted above, Richardson is very reluctant to abandon his strong commitment to ancillary care obligations in the face of its diversion effects even though he acknowledges the problem. And he seems willing to insist on adherence to this principle even if it entails that some possible subjects are left worse off than if the research were to take place.

Is Richardson wrong to adopt this view? On consequentialist grounds, it depends. It is possible that if a promulgation to the effect that researchers have ancillary care obligations were to build in too many exceptions and were too easy to avoid, then it would never acquire much long-term ethical force and the benefits of promulgating that view

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53 Gerald A. Cohen, Rescuing Justice and Equality (2008).
54 David Estlund, Utopohobia, 42 Phil. Pub. Aff. 113 (2014).
would then be lost. That said, I don’t think that it makes sense to say that that researchers have non-waivable obligations to provide ancillary care or other benefits if—even in the long run—doing so is bad for the people whose well-being we are concerned to promote.

I have argued, in effect, that if Regulation or Promulgation X is better for a class of people than Regulation or Policy Y because of diversion effects, then to the extent that we are concerned about that class of people, and other things being equal, we should prefer Regulation or Policy X. But how far should we go in this direction? Suppose that insisting on minimal safety standards in industrial production in LMICs would divert investment to better off countries, thus making (prospective) workers in LMICs worse off. Given their background conditions, and unfortunate as it is, it may well be that unsafe jobs are better than no jobs. Does this tell in favor of relaxing safety standards for those communities or populations that would be better off if we did so?

Here a lot turns on the phrase ‘other things being equal’. If people in a given society would in fact be better off if we relaxed safety standards, I think that does tell in favor of relaxing those standards. I am prepared to bite that bullet. But we may also be concerned about the long-term effects of relaxing such standards. And it is entirely possible that—in the long run—even people in LMICs will be better off if we insist on a certain level of safety standards. Once again, it is an empirical question as to whether the long-term effects of minimal safety standards outweigh the short-term loss of jobs to those who would otherwise be employed. But that I think is where the case for such standards must be made. So, too, for standards of ethical research.

SUBJECTS AND POSSIBLE SUBJECTS
I have argued that the promulgation of principles of research ethics should take the consequences for possible subjects as well as actual subjects into account just as regulators should consider the effects of a CSS requirement on possible airplane passengers as well as actual airplane passengers. It might be objected that the two contexts are not analogous. It may be argued that the purpose of promulgating ethical principles for the conduct of research is to protect only those who actually become research subjects, and that, unlike transportation regulators, these promulgators need not be concerned about the effects of their actions on those who would or might have become subjects but for their promulgations.

I have not suggested that any particular agency needs to be concerned about the diversion effects of a CSS requirement. As I argued above, there is room for a moral division of labor. It might be quite appropriate for the FAA to be concerned about safety on airplanes while some other agency—perhaps the NTSB—be concerned about the safety of all travelers given diversion effects (although, in fact, these roles were reversed). Nonetheless, I would maintain that some agency or authority should be prepared to consider the diversion effects of such policies when they are likely to harm those same persons. Similarly, it may be appropriate for IRBs to ignore the diversion effects of their decisions; their job is to apply and implement the relevant standards of subject protection. But those who fashion the standards that IRB members are meant to apply cannot escape responsibility for considering diversion effects of their promulgations on those people who would have the opportunity to participate in research to their benefit. If not the WMA, then who?
Still, it might be argued that whereas the purpose of safety regulators is to promote safety, the purpose of promulgating principles of ethical research is to establish a framework for the pursuit of generalizable knowledge in ways that respects the rights and welfare of research subjects. At the same time, it may be argued that the purpose of such promulgations is not to promote the interests of subjects and possible subjects per se. But that move won’t do. If there are two alternative policies—both of which would serve to generate scientifically valid data—but one of which would do more to advance the well-being of people in LMICs because of diversion effects, I see no basis for claiming that promulgators are free to ignore those effects, particularly given that many of the principles contained in those promulgations seem designed precisely to advance the interests of people in LMICs.

**TOO CONSEQUENTIALIST**

It might appear that the soundness of my argument turns on whether we should adopt a purely consequentialist approach to research ethics. Not so. First, I have not argued for any sort of aggregate consequentialism in which the benefits to some can outweigh the harm to others. My argument does not deny that there may well be deontological constraints on the pursuit of generalized knowledge. For example, the principle of informed consent bars researchers from enrolling people as subjects without their valid consent even when the aggregate benefits of doing so exceed the aggregate harms. I have argued only that if a principle effectively denies possible subjects an opportunity to participate to their benefit and to which they would give valid consent, then that is a cost to which those who promulgate those principles should be sensitive.

Second, even if the corpus of research ethics includes some principles such as informed consent that have a deontological form (whatever their ultimate grounding), the principles under consideration do not have that form. In the current context, the whole point of the ‘responsiveness principle’ or ‘standard of care’ or ‘post trial access’ or ‘ancillary care’ is to promote the well-being of the community or research subjects. If so, then there is little case for promulgating such principles if and when such promulgations fail to serve those ends.

More generally, appeals to deontology seem out of place in the present context. Deontological principles are typically advanced as side constraints on agents that serve to protect the targets of actions against harms or rights violations that could otherwise be justified on consequentialist grounds. For example, we can’t paternalistically impose treatment on a competent adult against her will even if she would be better off if we did so. We can’t kill one person to redistribute her organs to save five others. But such constraints have absolutely no bearing on cases which involve an interaction between researchers and subjects from which the subjects will benefit and to which they consent.

It might be objected that principles of fairness or justice can also serve as deontological constraints on research as, say, in the proposed Surfaxin trial. In this view, it is wrong for researchers to exploit subjects even when subjects benefit from being exploited and consent to be exploited. Along these lines, Richardson claims that ‘the opportunities to [waive claims on ancillary care] permissibly would be sharply limited by considerations
The ethics of promulgating principles of research ethics

I accept the claim that researchers can be acting wrongly if they do not treat subjects fairly, even when subjects would benefit from and consent to participation on unfair terms, just as sellers can be acting wrongly when they engage in ‘price gouging’ even though buyers benefit from the transaction and consent to it. The question is whether regulations or promulgations should seek to prevent such unfair transactions in beneficial research just to insure that researchers are not acting wrongly. Here things are more complicated. We do not observe the constraint of fairness for the sake of the constraint or to honor some abstract principle. We observe it for the person’s sake. It is wrong for A to treat B unfairly because we think that B would be better off if treated fairly. There are contexts in which it makes sense to prohibit unfair Pareto superior transactions for the sake of the exploitee, namely, when prohibiting unfair transactions is likely to result in a fairer transaction rather than no transaction. But I think that it would be an ethical mistake to attempt to deter or prevent such cases of unfair treatment when doing so is not better for the prospective subject or for anyone else.

Finally, it may be argued that promulgations of the principles of research ethics serve an important expressive function that is not reducible to the consequences of those expressions. As Lurie and Wolfe put it, ‘ethical standards have unique value as a statement of the equality of persons and are therefore themselves important to maintain’. I agree that promulgations as well as laws have an important expressive function. Prohibiting racial discrimination not only seeks to deter such discrimination through the coercive powers of the state, but also serves as an expression or signal of society’s values—a message that we hope will be heard and that will be integrated into the moral psychology of society’s members. On examination, however, I believe that the expressive value of promulgations ultimately reduces to its effect on the relevant parties: Does the expression of those values serve to promote the realization of those values?

Recall the example of state income tax policy in an environment where citizens can move from state to state with relative ease. It would be crazy for the legislators to say: ‘Let’s use our tax rates to make “a unique and valuable statement” about the taxes that people should pay as a matter of justice even if this shifts the tax burden to lower income people.’ In this case, the expressive function of tax rates should clearly give way to an acknowledgement of diversion effects. In other cases, the long-term effect of signaling certain values may serve to promote the values at stake. It is possible that insisting on certain standards of research ethics will—over time—serve to educate various parties about their obligations and will ultimately promote the well-being of research subjects. That is an empirical question. Ultimately, however, the value of expressing values is a function of the effects of such expression on the realization of those values.

**DOUBLE STANDARD?**

My line of argument implies that given the importance of diversion effects, it may be ethically justifiable to promulgate that researchers should provide the appropriate standard of care when research is conducted in a developed country but that they need

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55 Ezekiel Emanuel et al., supra note 45, at 151.

56 The Developing World as the ‘Answer’ to the Dreams of Pharmaceutical Companies: The Surfaxin Story, in Lavery et al. (eds.), supra note 33, at 166.
not provide that standard of care when research is conducted in a developing society. Bioethicists frequently claim that it simply can’t be right to employ a ‘double standard’ in evaluating the ethics of research, that such a view is incompatible with a commitment to the equal moral worth of all persons. If taking diversion effects seriously implies that we should accept a double standard, then so much the worse for taking diversion effects seriously.

Unfortunately, there is much confusion about the alleged wrongness of double standards. We don’t have a morally problematic double standard just because a principle might allow for research in one locale that it would not allow in another. For present purposes, we can ask two questions: (1) Is the alleged double standard justified? (2) If so, should a promulgation (or policy) accept the ‘double standard’? With respect to (1), the question is not whether we are treating X differently than we are treating Y but whether we are justified in treating X differently than we are treating Y. A university would use an unjustified double standard if it demanded higher math SAT scores from women than men, but it might be using a justified double standard if it demanded higher math SAT scores for those applying to its College of Engineering than to its College of Arts and Sciences.

Consider medical care. We think that it might be legitimate for physicians to provide medical care in LMICs that is not up to the standard that we would expect in the United States. We would applaud—not condemn—an American physician working in a refugee camp in an impoverished area who is providing beneficial medical care that would be considered unacceptable in the United States. We would hardly accuse him of using an unjustifiable double standard.

Consider the use of a vaccine for rotavirus. Rotavirus is a leading cause of severe childhood diarrhea and a frequent cause of death in developing societies. At the same time, few children in developed societies actually die from the disease because it can be treated in a hospital environment. In 1998, the FDA approved the use of a vaccine for Rotavirus—‘RotaShield’—which was then administered to 600,000 in the United States. In 1999, several infants suffered a serious intestinal complication—intussusception—after receiving the vaccine and the CDC demanded an immediate halt to its use. The risks of the vaccine raised an important question: If the risk of complications from RotaShield was unacceptable in the United States given that death from rotavirus was rare here, would it be acceptable to use RotaShield in India where hundreds of children might be saved for each complication? This appears to be a no-brainer. An Indian official reportedly remarked: ‘I know this vaccine would save 100,000 children in my country.’ The benefit/risk ratio for RotaShield was much more favorable in India than in the United States.

The basic problem with appeals to the notion of ‘double standards’ is that it typically fails to specify the level at which the relevant principles or standards are meant to operate. A researcher does not apply a double standard if he regards it as permissible to do a blood draw on X but not on Y if X consents to participate in research whereas Y does not. Here we have a simple single standard—the principle of informed consent—that has different upshots in the two cases. Similarly, we would not necessarily be applying a double standard if we say that it is impermissible to do a placebo-controlled trial in a

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57 Roger Glass, New Hope for Defeating Rotavirus, 294 Sci. Am. 46 (2006).
location where it would be unreasonable to consent to participate because treatment is otherwise available, but that it is permissible to conduct such a trial in a location where it would be reasonable to consent because treatment is not otherwise available. I am not claiming that informed consent is sufficient to justify such trials. I am claiming that no wrongful double standard would be at work with regard to informed consent.

Or consider the assessment of risks and benefits in research. The Common Rule states that the risks of participation must be ‘reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result’. Although this provision implies that IRBs can approve research when the importance of the knowledge and its benefit to others outweighs the risks to the subject, let’s ask what would happen if we focus on whether participation is of net benefit to the subject, setting aside benefits to others.

The fact is that participation in a trial may be beneficial to subjects in LMICs whereas it would not be beneficial to subjects in developed countries. Recall the proposed placebo-controlled version of the Surfaxin Trial. Given that possible subjects in LMICs would receive no treatment in the absence of the proposed Surfaxin Trial, participation is beneficial because a 50% chance of receiving surfactant therapy is better than a 0% chance, not to mention that those in the control arm would have the benefits of hospitalization and antibiotics. By contrast, if we apply that principle in a developed society where subjects could expect to receive the surfactant therapy outside of the trial, then the risks of participation to the subjects may well be less than the anticipated benefits. Once again, I am not arguing that the placebo-controlled version of the Surfaxin trial passes ethical muster in LMICs. I am arguing that a single-standard approach to the benefit/risk ratio for subjects might allow for such a trial in LMICs but not in developed countries and that appeals to the notion of double standards are simply not helpful.

But even if it were legitimate or sensible to allow researchers to provide lesser benefits to subjects in LMICs than in developed countries because of diversion effects, it does not follow that promulgations should explicitly allow for research in LMICs that it would condemn in more developed countries. The Indian official who thought it was clearly sensible to use RotaShield in India remarked that if he were to have allowed the its use, ‘when the first case of intestinal blockage occurred, I would not be forgiven for allowing a vaccine that had been withdrawn in the United States to be used in my country’. The double-standard argument can exert emotional and political pull even when it should be rejected on its own terms. And if endorsing what appears (wrongly) to be unjustified double standards is likely to compromise the legitimacy and force of the entire promulgation, then this is also a consequence that promulgators must consider. It may be best not to promulgate a perfectly justified ‘double standard’.

**CONCLUSION**

I have argued that the ethics of promulgations requires that promulgators need to think not only about what researchers, sponsors, and others should do. They need to think about what promulgations should do in attempting to get researchers to do what researchers should do. We cannot arrive at a view about the standards that should be

58 45 FCR §46.111.
59 LAVERTY et al., supra note 56, at 54.
promulgated on the basis of philosophical or moral arguments alone. We cannot say ‘we should promulgate the principle that researchers should do X for subjects because researchers should do X for subjects’ without taking into account the consequence of promulgating that researchers do X for those subjects.

Put somewhat differently, there is a distinction between the ethics of conducting research and the ethics of promulgating the ethics of conducting research. The claim that researchers have a prima facie obligation to provide post-trial treatment to the community concerns the ethics of research. It is analogous to asking whether parents who take their children on planes should spring for the extra ticket and use CSSs. It is another question whether it is ethical to promulgate that researchers guarantee that post-trial treatment will be provided as a condition for approval of a trial if doing so encourages researchers to ‘drive’ rather than ‘fly’. Those who are responsible for the major promulgations of research ethics need to systematically consider the consequences of their promulgations.

What should promulgators do in the absence of evidence about the consequences of their promulgations? I do not know. At a minimum, however, promulgators must at least be sensitive to the problems I have identified to proactively evaluate whether the promulgations are accomplishing their intended and aims, and be willing to consider revisions when they are not.

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