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Peer Commentary

Diversion effects, incentive effects, and the goals of research ethics promulgations

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ABSTRACT

It was with great sadness that the philosophical and ethical communities noted the recent passing of Alan Wertheimer. It is not possible to engage in serious work regarding international research ethics (nor much of political philosophy more broadly) without encountering and wrestling with his careful contributions. He was welcoming of discussion and generous with his intellectual energies. Ongoing work in these areas will be so much the poorer for his absence.

KEYWORDS: incentives, intellectual property, research ethics

Alan Wertheimer makes a strong case for the claim that those who promulgate ethical standards for the conduct of clinical research have a concurrent responsibility to consider the consequences to which such promulgations give rise. Specifically, promulgators should consider whether compliance with their promulgations may have so-called "self-defeating diversion effects" (4) on research from which participants can be expected to receive a net benefit, causing trials to be relocated or forgone altogether due to the increased costs associated with promulgation compliance. This possibility is of particular concern in lower- and middle-income countries (LMICs) because

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"participation in research is often the only means by which people receive treatment for a disease" or access to other ancillary care.[1]

Although compelling, Wertheimer's case that such promulgations are self-defeating depends upon a particular, undefended view of the motivation behind research ethics promulgations (REPs), a view which ignores alternative, legitimate goals for REPs. Moreover, this view of the goal of REPs seems closely linked to an underlying mischaracterization of the goals of the research enterprise itself. Given that REPs can have other legitimate goals, I argue that Wertheimer's concerns about diversion effects are at best overstated, and at worst misplaced. Moreover, we must also consider what I refer to as "incentive effects" of non-promulgation. Specifically, we should consider whether the absence of such guiding principles among the standards offered by the world's major research ethics advisory groups might reinforce incentives that function to maintain existing levels of inequality, including the lack of access to needed healthcare in LMICs.

The diversion effects about which Wertheimer is concerned are specifically the higher costs borne by sponsors who meet criteria such as conducting research which is responsive to the health needs of host communities, providing established standards of care to research participants, ensuring that interventions shown safe and effective are made available to participants and/or host communities after the conclusion of a trial, and providing ancillary care to participants in LMIC research to which they would otherwise lack access. Insofar as complying with such promulgations would increase the costs of conducting research in LMICs, Wertheimer reasons, this will divert resources away from the conduct of additional trials which could benefit additional research participants.

In assessing REPs, we should clearly distinguish between two different claims about diversion effects which might be defended:

> **Strong Resource Diversion Effects:** Promulgators of REPs have an ethical responsibility to consider the consequences to which their promulgations give rise, and in particular whether those promulgations are self-defeating insofar as they hurt precisely those people they are designed to help.

> **Weak Resource Diversion Effects:** Promulgators of REPs have an ethical responsibility to consider the consequences to which their promulgations give rise, regardless of whether those consequences are related to the goals informing such promulgations, or in what way.

As I interpret him, Wertheimer seeks to defend Strong Resource Diversion Effects. In particular, Wertheimer defends the claim that REPs are intended to "promote the interests and autonomy" of both actual and prospective research subjects, and that such promotion entails ensuring that the greatest number of impoverished individuals possible has the opportunity to benefit from participation in clinical research.

This is not an uncontroversial understanding of what is entailed by promoting the interests and autonomy of research subjects. Nor is it clear that the goal of such promulgations is to promote the interests and autonomy of research subjects at all, rather than

[1] Alan Wertheimer, *The Ethics of Promulgating Principles of Research Ethics: The Problem of Diversion Effects*, 2 JLBIOS 2, 32 (2015).

to simply *protect* them. While this may seem a minor linguistic point, it actually tracks an important distinction in how we conceptualize the proper aims of clinical research itself. Wertheimer conceives of clinical research as ultimately a transaction between researcher or sponsor and research participant, with protections such as prospective risk/benefit assessment justified only due to the inability of otherwise competent adults to protect their own interests in clinical trials given their lack of biomedical knowledge.[2] But clinical research is actually a social endeavor, with an explicitly social goal: the production of valuable knowledge for the purpose of benefiting future patients and healthcare systems. Investigators not only don't conduct research with the primary goal of promoting the interests of research subjects, but they *ought not* insofar as the promotion of research subjects' interests undercuts the ability of a clinical trial to generate socially valuable knowledge.[3] Gold standard methodologies such as blinding to treatment allocation and randomization, for example, could never be ethically justified were clinical trials conducted for the purpose of benefiting trial participants.

Rather, the entire body of research ethics promulgations can be viewed as reflecting a desire to balance the goal of producing generalizable knowledge which can inform and improve the care of future patients against the need to protect research subjects from harms they might suffer as a result of a myopic focus on the value of research outcomes. Conceiving of clinical trials as a transaction merely between researcher and participant obscures this social function, and contributes to the problematic misconception of research as primarily about advancing the interests of *current* participants, rather than *future* patients. When we are explicit about the goals of clinical research in generating socially valuable knowledge, it becomes clearer how the goals of REPs may be very different from ensuring that benefits devolve to the greatest number of potential research participants. Because the goal of research is not to benefit research participants, a more accurate representation of the goal of REPs is the protection of actual research participants from practices which serve the fundamental goal of clinical research, but which if left unchecked might do so at an unjustified cost to the health and well-being of trial participants. But note that if this is the goal of REPs, the existence of diversion effects would not make REPs self-defeating, since such effects do not undermine the goal of protecting those subjects who are enrolled in research from a bias in favor of experimentality.

This shows that Wertheimer's argument in defense of Strong Resource Diversion Effects misses its mark. But what about Weak Resource Diversion Effects? Insofar as it is not predicated on a particular view of the goals of REPs, Weak Resource Diversion Effects is on face a more defensible claim. But Weak is also consistent with the idea that concerns for diversion effects should be balanced against existing goals of REPs. In fact, we might attribute various aims to the promulgation of research ethics standards other than advancing the interests of research subjects and prospective research subjects by ensuring maximal access to beneficial research. We might think, for example, that one goal of research ethics promulgations is to ratchet up local standards of care through the implementation of progressive improvements in the healthcare of research

[2] Alan Wertheimer, *Is Payment a Benefit?*, 27 BIOETHICS 105 (2013).

[3] Samuel Hellman & Deborah S. Hellman, *Of Mice But Not Men: Problems of the Randomized Clinical Trial*, 324 NEW ENGL. J. MED. 1585 (1991).

participants.[4] LMIC communities often bear the burdens of biomedical research even when those same communities are unable to benefit from the resultant knowledge due to entrenched poverty, lack of infrastructure, or other complex vulnerabilities. One interpretation of the aim of promulgations calling for responsiveness, the use of best proven standards of care and prevention, access to treatments after the conclusion of a trial, or the provision of ancillary care is that such provisions function to promote incremental progress in health systems which otherwise might remain stagnant given competing claims on local funding.

Wertheimer might reply that the claim in Weak still applies: insofar as REPs generate increased costs and reduce the number of trials that can be conducted, there will be fewer opportunities to use research as a tool for ratcheting up care. This may be correct, but what it demonstrates is a need to balance the values of improving care within host communities and the number of communities in which such improvements can occur. Absent REPs, research may very well never function to ratchet up care, suggesting that if such ratcheting is a worthwhile goal, REPs are a necessary step in promoting it.

Another plausible goal of research ethics promulgations is the protection of research subjects from exploitation by research sponsors, contract research organizations (CROs), and investigators. The same incentives which drive sponsors and CROs to seek host communities in LMICs provide powerful incentives to cut the costs associated with conducting research in those communities as much as possible. Absent constraints governing research interactions which demand a greater share of benefits for research participants – whether through post-trial access, ancillary benefits, or other mechanisms – communities and participants will rapidly race to the bottom with regards to the benefits they're willing to accept in exchange for participation in research.[5] Such a race to the bottom should be of concern insofar as we think that the distribution of the social surplus generated through clinical research ought to be informed by considerations of fairness and justice rather than merely by the relevant bargaining power of the individual parties involved in negotiating terms.

Even if we don't think that justice or fairness ought to play a role in the distribution of the social surplus generated in research, however, we might have additional reason to want to reduce or eliminate exploitation in LMIC research which provides yet another potential goal for REPs. Specifically, we may have independent reason to protect the reputation and social capital of the research enterprise itself. The ability of researchers and sponsors to engage in the various self-interested activities which together combine to result in the generation of socially valuable biomedical knowledge depends in large part on continued social support of clinical research. That support comes in the form of continued funding of research through government agencies and charitable giving, the high esteem accorded to active research institutions and the researchers who populate them, and the willingness to participate in research as subjects.[6] This social capital can be threatened in many ways, including via growing public awareness of a research

[4] K Shapiro & SR Benatar, *HIV Prevention Research and Global Inequality: Steps Towards Improved Standards of Care*, 31 J. MED. ETHICS 39 (2005).

[5] Alex John London & Kevin J.S. Zollman, *Research at the Auction Block: Problems for the Fair Benefits Approach to International Research*, 40 HASTINGS CTR. REP. 34 (2010).

[6] Alex John London, *A Non-Paternalistic Model of Research Ethics and Oversight: Assessing the Benefits of Prospective Review*, 40 J. LAW MED. & ETHICS 930 (2012).

enterprise in which many actors apparently fail to adequately respect the interests of research subjects. Because the average citizen is not well-equipped to distinguish between those actors who tend to ensure a proportionate share of research benefits are passed on to appropriate parties and those who do not, the loss of social capital devolves to all research stakeholders, and not only those involved in exploitative research. The upshot can be a loss of public or philanthropic funding for research, a loss of willing participants, or perhaps most troubling, the imposition of new legal regulations at the state-level which ultimately make research even more costly and potentially preclude more valuable research from occurring.

For example, Wertheimer highlights recent Indian regulation requiring research sponsors to pay for research-related and other injuries and illnesses occurring to research participants while on protocol as an instance of a counterproductively diversionary regulation. But it is reasonable to think that this regulation was a direct result of a growing lack of public trust of the research enterprise within India given a growing awareness of significant exploitation in industry-sponsored trials in that country. Thus the lack of broader enforcement or regulation on the basis of existing REPs resulted in more demanding regulation, and ultimately created an even larger impediment to the conduct of valuable research. Moreover, this example shows not what Wertheimer believes it to show, that the imposition of REPs will have diversion effects. Rather, it shows that a regulatory approach to REPs will have diversion effects *insofar as it lacks sufficient reach.* For REPs to effectively serve diverse goals such as protecting subjects from exploitation and ratcheting up care within local contexts, they must be established in a way which provides incentives to a broad enough swath of researchers and sponsors.[7]

Although Wertheimer's defense of Strong Resource Diversion Effects depends upon a problematic understanding of the goals of REPs and the research enterprise itself, Weak Resource Diversion Effects is more plausible. However, Weak is consistent with the existence of a plurality of values which REPs might be said to seek to promote. Thus even if promulgators ought to be concerned about diversion effects, those effects must be considered as weighed against the other legitimate goals of REPs. Moreover, there is reason to think that Wertheimer's concern about diversion effects is overstated where there are possibilities for extending the reach of the incentives thereby generated, i.e. through mechanisms which will impact a large enough proportion of research sponsors so as to preclude the race-to-the-bottom-style mentality of the CRO chief medical officer Wertheimer cites.

Alternatively, Wertheimer might have defended the following claim:

> **Research Diversion Effects:** Promulgators of REPs have an ethical responsibility to consider the consequences to which their promulgations give rise, and in particular whether those promulgations are self-defeating insofar as they limit the number of important research questions which might be answered.

Research Diversion Effects is more plausibly a concern about the counterproductivity of REPs, given that it is more faithful to the underlying goals of the research enterprise. But a concern for Research Diversion Effects is likewise consistent with the

[7] Danielle M. Wenner, *Against Permitted Exploitation in Developing World Research Agreements*, Dev. World Bioethics (2015) DOI:10.1111/dewb.12081.

recognition of a plurality of motivations behind REPs which might outweigh Research Diversion in terms of their importance to the overarching goal of biomedical progress. This is again a matter of balancing competing values: in the absence of REPs, the research enterprise might be undermined to such an extent as to have an even greater negative impact on the number of important questions that can be answered.

Finally, both Weak Resource Diversion Effects and Research Diversion Effects are consistent with the following:

> **Incentive Effects:** Promulgators of REPs have an ethical responsibility to consider the consequences to which the absence of such promulgations might give rise, and in particular whether the lack of promulgations might generate incentives which entrench existing disparities in access to health and healthcare.

Specifically, we might think that the guidance documents published by international organizations such as the World Medical Association, the Council for International Organizations of Medical Sciences, and the Nuffield Council on Bioethics serve an important social function by drawing the attention of sponsors, researchers, and the public to the kinds of ethical concerns which can arise in LMIC research due to a background context of vast inequality. In drawing public attention to these concerns, such promulgations provide incentives in the form of social approbation to research sponsors who might otherwise strongly prefer to cut costs by ignoring ethical obligations to research subjects and host communities, and generate the race to the bottom that occurs absent constraints on research agreements.

Consider, for example, the costs associated with conducting a vaccine trial on a population with access to the best proven means of prevention versus conducting it on a population without such access. For any vaccine to be shown effective, sufficient numbers of participants must contract the study disease in order to show a statistically significant difference between the intervention and control arms. Access to the best proven means of prevention will therefore drastically increase the necessary sample size, as well as associated costs. Given this cost differential, profit-seeking research sponsors have a vested interest in the ability to locate populations who lack such access, and this interest generates incentives to ensure the continued existence of such populations.[8]

Moreover, industry sponsors wield a disproportionate ability to influence the availability of effective interventions at an affordable price within LMICs. One of the most direct means of exercising this influence is via the active promotion of robust intellectual property protections which prevent the development of inexpensive generics. These stringent protections present significant barriers to the ability of LMICs to address local health deficits, entrenching the very lack of access to effective interventions which allows research sponsors to continue to conduct research in LMICs at a steeply discounted cost.

Without consistent regulation, the conspicuous absence of REPs demanding higher standards of care, responsiveness, ancillary care, and post-trial access may generate new or reinforce the existing incentives which operate on research stakeholders (and in particular, industry sponsors) to ensure ongoing barriers to access for populations

[8] Thomas Pogge, *Testing Our Drugs on the Poor Abroad*, *in* Exploitation and Developing Countries: The Ethics of Clinical Research 105 (Jennifer S. Hawkins & Ezekiel J. Emanuel eds., 2008).

in LMICs. Should governance bodies and international organizations refrain from the promulgation of ethical standards for international research, this would amount to the removal of some of the very few existing *disincentives* to the continued support of an intellectual property regime which serves precisely this end.

Wertheimer's claim that research ethics promulgators ought to be concerned about the possible diversion effects of their promulgations can be interpreted in at least three ways. The interpretation that Wertheimer defends, Strong Resource Diversion Effects, does not accurately represent the goals of research ethics promulgations or those of the research enterprise. There are two more plausible interpretations of Wertheimer's claim, Weak Resource Diversion Effects, and Research Diversion Effects, but they are each consistent with a plurality of motivations behind REPs and the possibility that any diversion effects are outweighed by the values associated with those motivations. Finally, while either of the alternative versions of Wertheimer's claim may be accurate, promulgators ought also to consider the potential incentive effects of failing to issue such promulgations.