Book Review

Rationally Defensible Standards for Research in Developing Countries

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Review of *Double Standards in Medical Research in Developing Countries* by Ruth Macklin (Cambridge University Press, Cambridge, UK 2004).

Debates on ethical requirements for conducting international collaborative medical research in developing countries have achieved considerable prominence in recent years. The stark implications of the HIV/AIDS pandemic, major escalation of clinical research in developing countries, and the imbalance of only 10% of world medical research expenditure on diseases causing 90% of the global burden of disease have rekindled concern about relationships between researchers and their subjects.

Information gained from clinical trials conducted efficiently and expeditiously in developing countries has the appeal of allowing early registration of drugs, thus considerably enhancing profits. Growing sensitivity to the potential for exploitation has been associated with the expectation that profits should also benefit the citizens of developing

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countries in which research is undertaken. This underpins claims that, in addition to the direct benefits for individuals within the study, benefits should include the linkage of otherwise unavailable health care to research projects, provision of proven treatments following completion of trials, as well as community empowerment.

The intensity of the debate surrounding revision of international guidelines on research ethics and the considerable stakes involved make it most timely to have a full-length book detailing both substantive and procedural aspects of the debate. Ruth Macklin's active involvement in many of these international deliberations combined with her critical insight and philosophical analysis make her an ideal author for such a text.

The main thrust of Macklin's book is to review whether local or universal standards should apply to research in developing countries. The opening chapter outlines recent controversies in international research ethics. Subsequent chapters address such issues as how to maintain ethical standards in research, striving for justice in research, avoiding exploitation (one of the best chapters written on this topic), and the provision of safeguards through informed consent and review of research. How to make drugs affordable, the suggestion that respecting, protecting, and fulfilling human rights is the way ahead, and provision of a single standard for research are the topics of the final three chapters. Throughout the book, Macklin makes extensive reference to all the major international guidelines for medical research, and comparisons are drawn between these in relation to controversial issues. There is no other comparable text, and this book will be of great value to all interested in the ethics of international research.

Some criticisms and comments are offered from this reviewer's perspective to broaden the debate. The book's discussion on justice fails to acknowledge the extent to which power struggles affect the way in which justice is perceived. The abuse of power and the extent of self-interest are, however, alluded to in the author's comment about the April 1, 2002, revision of US Food and Drug Administration's (FDA) regulations: "One can only wonder at the motives of those

responsible for the elliptical misleading account provided by the nation's drug regulatory agency." While criticism is leveled at the "incoherent" views of the Pharmaceutical Research and Manufacturers of America (PhRMA) on the provision of health benefits as inducements and at the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement on protection of profits from drugs for asthma and cancer, the "coherence" of these approaches is evident when viewed through a lens that depicts research and health care as commodities. Macklin appropriately recommends the repeal of TRIPS prohibitions against the export of generic and patented drugs and medicines. She also mentions numerous factors, besides lack of money, that hinder access to drugs in many developing countries, and she correctly identifies the need for capacity-building. Her chapter on making drugs cheaper fails, however, to draw attention to the upstream causes of poverty and ill-health and to the dominant economic paradigm that thrives on economic growth with little concern for distribution and even less for the powerful economic forces that keep poor countries in poverty and that underpin the behavior of the pharmaceutical industry.[1,2] She acknowledges the important role of philanthropy but fails to note that sustainable independence and self-generating capacity-building can only be achieved if poor countries are liberated from the powerful oppressive economic forces that sustain their impoverishment. Reducing dependence on philanthropy will be crucial to achieving sustainable access to essential drugs.[3]

Macklin's evaluation of a human rights approach to greater equity in health care acknowledges both its strengths and some of its weaknesses. A shortcoming of a rights approach is that insufficient attention is given to identifying the range of duty bearers required to give effect to the achievement of rights. Greater emphasis on duties to citizens and the vulnerable would add another important dimension to the language of morality and would facilitate the achievement of the right to share in scientific advancement and its benefits, as described in Article 27 of the Universal Declaration of Human Rights (UDHR). Excessive reliance is placed on the responsibilities of states to uphold

rights without considering how impoverished states are kept economically weak and unable to meet these duties to their citizens. Calls for benchmarks against which to measure the effectiveness of weak states' protection of their subjects' human rights should be matched by calls for benchmarks against which to monitor efforts by wealthy states to reduce poverty and enhance human rights.

While it is generally accepted that there is a need for universal ethical standards and not double standards for research on humans, there is much less agreement on what should constitute such universal standards and how these can be justified. Macklin abhors double standards, but acknowledges that different standards may be legitimate. However, she admits to failing to identify an adequate example of a different standard that is legitimate. The controversial study of prevention of mother-to-child transmission (MTCT) of HIV may be such an example.

The AIDS Clinical Trials Group Study 076 (ACTG 076) established that MTCT could largely be prevented by giving antiretroviral drugs to pregnant women orally for 8 weeks or more prior to childbirth (median 14 weeks) and intravenously during labor, as well as to the newborn child for 6 weeks in the absence of breast feeding.[4] There is no reason to believe that such a regimen would not work in developing countries if it could be applied. Use of the full ACTG 076 regimen is precluded, however, not only by its extremely high cost, but more relevantly when women do not present early enough in pregnancy to receive this intensive regimen, are anemic and malnourished, are not able to stop breast-feeding, and have difficulty providing treatment to a child for a six-week period. Under such circumstances, a different research question needs to be asked and answered: To what extent can mother-to-child transmission of HIV be prevented in resource-poor settings where pregnant mothers only present to clinics a few weeks or hours before labor, are often anemic and malnourished, and where breast-feeding cannot be avoided? Here the balance of benefits and harms, and the feasibility of introducing a widespread preventive regimen, could be very significantly different than in the original studies. When few women present early enough to

be treated with the full ACTG 076 regimen, the legitimacy of a different study design would be based on the different research question being asked in a totally different social context with very different implications for the local society. Important relevant differences include inability to enroll enough women presenting early enough to receive the ACTG 076 regimen (those few who do could receive it), inability to prevent breast-feeding, and the great public health value of obtaining an answer as rapidly as possible, in the face of a major pandemic, to allow early implementation and the saving of many lives. So, if we agree that different standards are acceptable because of contextual differences and that consideration of relevant differences is part of the moral reasoning process, then we can agree that different standards may not be ethically double standards.

I take this argument one step further. In the ACTG 076 study in wealthy countries, the researchers did not have to treat their research subjects for malaria, tuberculosis, or other concomitant diseases that may afflict them during the study, as treatment for these would be available to them through locally available health services. In developing countries, however, it would surely be unethical of researchers not to treat their research subjects for such conditions if treatment were not otherwise available to them. So researchers would be required to provide a broader and different standard of overall care in these two research situations. This is not an example of double standards, but of morally legitimate different standards.[5] The morally objectionable double standard that really needs to be addressed is the one of doing research with the knowledge that the results will be regularly translated into health care practice in wealthy countries, while this outcome is seldom achieved or given high priority for many poor countries.

Macklin concludes that the best hope for future improvements in heath care in resource-poor countries lies in public-private partnerships. I agree and cite the examples of the Global TB Alliance and the US Agency for International Development (USAID) providing resources to implement HIV/AIDS prevention, care, and support programs in developing countries, and sponsorship of research on the preven-

tion and treatment of HIV/AIDS by the US National Institutes of Health, the US Centers for Disease Control and Prevention, and private foundations. Collaborations with bilateral and multilateral funders, implementers, and technical agencies such as the World Health Organization, the World Bank, private and philanthropic foundations and NGOs, and with pharmaceutical companies could also be explored.

A shift from considering ethics *in* research in developing countries to considering the ethics *of* research in developing countries reveals the need to improve the links between research and health care delivery and to promote social and economic processes that could begin to reverse global disparities in health.

References

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