

Responsibilities in international research: a new look revisited

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EDITOR'S
CHOICE

Following promulgation of the Nuremberg code in 1947, the ethics of research on human subjects has been a challenging and often contentious topic of debate. Escalation in the use of research participants in low-income countries over recent decades (stimulated by the HIV pandemic and the need to carry out clinical trials expeditiously on large numbers of patients), has intensified the debate on the ethics of international research and led to increasing attention both to exploitation of vulnerable subjects and to considerations of how the 10:90 gap in health and medical research (ie, 90% of resources being spent on 10% of the problems) could be narrowed.

In 2000, prompted by the discussions over several years that led to the US NIH launching a capacity building programme on research ethics for members of research ethics committees in developing countries, we advanced a 'new look' for the ethics of international research.¹ Since then progress has been made on several fronts.

First, our ideas—considered somewhat radical and impractical at the time—have been provocatively addressed by scholars who have either contested them or advanced similar conceptions of what obligations international researchers have to research participants and communities in low income countries before, during and after clinical trials. Second, those researchers who have been sympathetic to our ideas have either endeavoured to put these into practice or have investigated the feasibility of doing so. Third, the intractability of the 10/90 gap and the escalation of interest in global health have sensitised many to the need to amplify the uptake of these ideas in practice.

Here, we briefly review the conceptual and practical developments in international research ethics. While much conceptual progress has been made (and the concepts are now appearing in practice), we advocate for intensification of endeavours to link research to improvements in health-care and health and to build the capacity and independence of local researchers.

Intensification of controversies in international research ethics began with Marcia Angell's vehement criticism in 1997 of exploitation and double standards in the placebo controlled studies undertaken to develop rapidly an affordable and effective method of preventing mother to child transmission of HIV infection in developing countries.²⁻³

Since then debates on ethical aspects of international research ethics have progressed from assertions as to what is ethical in research to: (a) well argued consideration of what the 'standard of care' (SOC) should be¹⁻⁴⁻⁵ and how this could be ratcheted upwards through the development of strategic alliances and partnerships with other stakeholders¹⁻⁶; (b) the development of such concepts as fair benefits⁶ and ancillary care⁷⁻¹⁰; (c) encouragement of community engagement¹¹ and a broader understanding of what it means to do research on poor people from other cultures¹²⁻¹³; and (d) how, using such concepts, research could be linked to improved healthcare and greater social justice.¹⁴⁻¹⁷

Underpinning all these debates has been an intense controversy on what constitutes exploitation in international clinical research.¹⁸ Instead of attempting here to summarise the complex philosophical debate on exploitation we refer readers to a simple description that provides practical guidance.¹³ We also acknowledge that escalating demands on researchers for additional healthcare benefits in association with their research have been constrained by the need to set limits in order to avoid hampering research,¹⁹ and that research in developing countries may contribute to the brain drain.²⁰

It was dissatisfaction with a SOC defined merely in relation to the drug used

in the control arm of a clinical trial that led to our proposal almost a decade ago for a broader understanding of SOC through a new look at international research ethics linked more closely to health benefits and with enhanced community engagement.¹ Our purpose was also to draw attention to the extent to which vulnerable populations benefited very little from much of the research in which they participated. In addition, we promoted the idea that if researchers understood that ongoing poverty and poor health in many countries were related to powerful system forces in which they were indirectly implicated,¹² this could help reshape the ethics and practice of research by linking research to improved healthcare through strategic alliances with sponsors, and cooperative ventures with local Ministries of Health and philanthropists.¹⁻²¹

Other significant simultaneous endeavours to avoid exploitation included development of the concepts of fair benefits⁶ and ancillary care.⁷⁻¹⁰ Within the framework developed for fair benefits and ancillary care the responsibility of researchers to provide such additional care is determined by the independently variable strength of four components of the underlying relationship with participants. Consideration of these components provides a range of possible pre-trial, in trial and post-trial benefits, the mix of which could be agreed on through negotiations between researchers and participants. While these approaches are of value, they have been criticised as being focused on micro-conceptions of exploitation and thus limited to a thin conception of justice (procedural in nature) to be applied on a case-by-case basis and without taking account of background conditions of injustice.²²

A necessary, but not sufficient way to begin to rectify the latter shortcoming is through fuller engagement with communities. In seeking to be more understanding of local conditions, research groups undertaking long-term planning for HIV microbicide and vaccine trials have led the way in achieving more inclusiveness by establishing trusting working relationships with communities and negotiating standards of care or fair benefits that exceed those set in the past. An excellent example is the Vulindlela clinical research centre, part of CAPRISA's Women and AIDs Programme based at the University of KwaZulu Natal, where a longstanding relationship with the local community is the precondition of, and basis for all research conducted in true

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partnership.²³ Although community advisory boards have been formed and used constructively, participation of communities in the design of trials largely remains an unfulfilled aspiration,²⁴ except for isolated examples.^{23 25}

While these endeavours could be seen to be more socially fair, they are not based on any agreed-to substantive concept of justice but rather on a commitment to co-operation that could be of greater benefit to vulnerable populations.^{26 27} The recent work of Powers and Faden strengthens the arguments for more substantive justice approaches to public health and research.²⁸

Why is there so much continuing controversy and disagreement on ethical dilemmas in research? Ruth Macklin, writing from her extensive participation in updating international guidelines on research ethics, came to the conclusion that while general agreement could be reached on several hotly contested aspects of international research ethics, deeper intractable disagreements would persist within each agreement category.²⁹ A practical example of these remaining controversies is the recent rejection by the US Food and Drug Administration of the latest modification to the Declaration of Helsinki, probably because this has more stringent ethical requirements than they are willing to commit to—including disclosure of potential conflicts of interest, responsiveness to host country's health needs and provision of post-trial benefits.³⁰ We have argued that more nuanced considerations of social relations could allow resolution of some of these intractable controversies.¹³

It is significant that these ethical debates are taking place *pari passu* with scientific and technological advances that enhance medical practice (eg, development of anti-retroviral preventions and treatments) while, paradoxically despite such advances, health outcomes globally are generally either deteriorating or not improving. In part, this is due to the fact that the global medical research agenda remains skewed away from the needs of poor people despite concerted philanthropic global health endeavours over the past 10–15 years to narrow the gap. More importantly, the gap remains because the health of whole populations, especially in developing countries is more dependent on the social determinants of health than on medical treatments that benefit individuals.³¹

While these powerful upstream forces cannot be easily or rapidly reversed by medical researchers, as we pointed out almost a decade ago,¹ attempting to

achieve a closer and more direct linkage between health research and healthcare services is the least that privileged researchers can do to alleviate the plight of people in poor countries.

By 2005 descriptions of at least three trials in developing countries had been published showing application of the extended ethical responsibilities we have advocated, and which, stimulated by the ongoing debate about the obligations of researchers, some researchers were adopting and applying.²¹ More recently a large study in Mwanza²⁵ has been explicitly driven by the core principles of equity, beneficence and social justice that were implicit in our 'new look' article in the *BMJ*,¹ and that we articulated in greater detail subsequently.²¹

The challenge now is to amplify these new approaches, especially in the context of the currently evolving global economic crisis that involves job losses, escalating food prices, and cutbacks in social services that adversely affect the health of poor people disproportionately.^{32 33}

We suggest that amplification of the new approaches that address the linkages between research ethics, health and social justice could be advanced by focussing on two overarching principles that encapsulate the ethical requirements for research associated with moral progress and enhanced social justice in developing countries. These principles may seem self-evident, but unfortunately they are seldom put into practice. Adherence to these principles and their promotion by international researchers sensitive to wide disparities in health and increasing interdependence globally, could give practical effect to these new ideas.

Based on the surely uncontroversial idea that the ultimate purpose of research is to improve healthcare and health, the first principle is that research undertaken in poor countries should contribute to improved health care in the community in which the research is undertaken. While benefits should flow to all stakeholders (participating individuals, communities, researchers and sponsors), every effort should be made to ensure that benefits for sponsors (academic institutions and pharmaceutical companies) do not overshadow benefits for participants and communities. Again we emphasise that striving for such goals should be viewed as a progressively upward ratcheting process to be achieved not merely by burdening researchers with all these responsibilities but through encouraging and assisting them to develop the partnerships and strategic alliance that have been demonstrably effective.²¹

Such new ideas require advocacy in order to be accepted and further effort is required to progressively implement them. The Global Campaign for Microbicides group is an excellent example of strong advocacy for attention to the full range of health and social needs that participants face during clinical research. This groups' comprehensive study in seven large-scale microbicide effectiveness trials, to evaluate what SOC was being provided, has gratifyingly shown that creative and innovative means are being explored by several research teams to implement a more broadly defined SOC in developing countries.³⁴ This supports the notion that higher standards can indeed be implemented in an upward ratcheting manner.²¹ Other projects exploring and implementing community engagement include studies of tuberculosis in the South African mining industry³⁵ and previously mentioned examples.^{25–27}

An example of directly countering background social conditions that oppress research subjects has been the application by Lavery and colleagues of measures to reduce social and gender discriminatory pressures on the lives of the sex workers who were their research subjects. From their experience they propose that researchers in developing countries should develop a framework that includes attempts to relieve at least some of those short-term, remediable, work-related oppressive conditions (unpublished work). If that framework could be expanded and more broadly applied through fairer and more compassionate ways of linking economic growth to reductions in inequity,³⁶ this would enhance the credibility of much research in the eyes of research participants in the developing world.

At the level of health systems, Hyder and colleagues have recently pointed out that health research system goals have been defined as the advancement and use of scientific knowledge to improve health equity.³⁷

Even further upstream, it needs to be recognised that ongoing poverty and poor health in poor countries are aggravated and sustained by trade and other economic policies that continue to favour economic growth in wealthy countries even though this is at the cost of ongoing oppression of the poor.^{16 38}

The second principle is that research should enable host country researchers to solve their own research problems in the future. The response of Indonesia to sharing influenza virus samples illustrates the danger of ignoring the ability of host

researchers to solve their own problems.³⁹ While we do not endorse some of the claims made by the Indonesians, the argument that Indonesia will not share samples since they cannot be guaranteed access to any resulting vaccine, highlights the need to pay attention to issues of research self sufficiency in the South.

Over and above attention to the much neglected social determinants of health, improvements in healthcare in developing countries can be achieved through advances in medical knowledge and in the ethics of how these advances are applied. Progress, albeit slow and inadequate, is indeed being made on both conceptual and practical fronts as illustrated with five examples.^{40–47}

These amplificatory approaches open up ambitious opportunities to replace a narrow research ethics framework, focused on protection of vulnerable participants, with a broader framework that could emancipate them and their communities, improve inadequate healthcare systems, promote social justice, and foster development. In 2001 we expressed the view that strengthening ethics capacity would advance the cause of ethical research in the world far more than another revision of the Helsinki Declaration, and ultimately, by facilitating health research, help redress one of the greatest ethical challenges in the world—the unconscionable inequities in global health.⁴⁸ Promoting a participatory framework that, through dialogue and cooperation uplifts people from dependence and facilitates self-sufficiency, could ensure that people are being helped from their own perspectives in addition to those of researchers.^{13 21 49}

We suggest that the most important value driving this new paradigm, and underpinning these two principles, is 'solidarity', which can be defined as attitudes and determination to work for the common good across the globe in an era when interdependence is greater than ever and in which progress should be defined as enhancing capabilities and social justice rather than sustaining dependency. Strengthening solidarity requires an understanding of the range of social relations within different cultures and recognition of how much different people have in common, rather than how they differ.^{13 36}

The two principles we promote here build on and augment our previous arguments for the need to expand the discourse on international research ethics beyond interpersonal ethics and civil and

political rights, (based on the ideas of individual rights and freedom) to the ethics of how institutions operate and interact, the ethics of public health and social and economic rights (based on concern for equity) and the ethics of international relations (based on solidarity) that affect whole populations.³⁶

Achieving the goals of these principles in an interdependent world, where the poorest suffer most from systemic forces adversely affecting health, will need to be underpinned by promotion and achievement of solidarity with all as global citizens, and political efforts to move towards new paradigms of thinking and action that could begin to narrow widening economic disparities that threaten both our humanity and global security.^{36 38 50} It is important to note that our proposals, and the central value of solidarity underpinning them, are consistent with accountable private sector engagement in global health.

Since we wrote our original article a decade ago, significant conceptual progress has been made, but less translation into practice than we had hoped. We remain cautiously optimistic that our proposals for research to be linked to improvements in health and sustainable capacity building in research—based on an overarching value of solidarity—could contribute to an ongoing paradigm shift in thinking from research as merely a means of acquiring new knowledge, towards a much broader goal encompassing beneficial impacts on health, healthcare delivery and independence in poor countries.

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REFERENCES

1. Benatar SR, Singer PA. A new look at international research ethics. *BMJ* 2000;**321**:824–6.
2. Angell M. The ethics of clinical research in the third world. *N Engl J Med* 1997;**337**:847–9.
3. Varmus H, Satcher D. Ethical complexities of conducting research in developing countries. *N Engl J Med* 1997;**337**:1003–5.
4. London AJ. The ambiguity and the exigency: clarifying 'standard of care' arguments in international research. *J Med Philos* 2000;**25**:379–97.
5. London AJ. Equipoise and international human-subjects research. *Bioethics* 2001;**15**:312–32.
6. Emanuel E, et al. Moral standards for research in developing countries. From "reasonable availability" to "fair benefits". *Hastings Cent Rep* 2004;**34**:17–27.
7. Richardson HS, Belsky L. The ancillary care responsibilities of medical researchers. *Hastings Cent Rep* 2004;**34**:25–33.
8. Belsky L, Richardson HS. Medical researchers' ancillary clinical care responsibilities. *Br Med J* 2004;**328**:1494–6.
9. Richardson HS. Gradations of researchers' responsibilities to provide ancillary care for HIV/AIDS patients in developing countries. *Am J Public Health* 2007;**97**:1956–61.
10. The ancillary-care obligations of medical researchers working in developing countries. *PLoS Med* 2008;**5**:e90.
11. Lo B, Bayer R. Establishing ethical trials for treatment and prevention of AIDS in developing countries. *BMJ* 2003;**327**:337–9.
12. Benatar SR. Some reflections and recommendations on research ethics in developing countries. *Soc Sci Med* 2002;**54**:1131–41.
13. Benatar SR. Towards progress in resolving dilemmas in international research ethics. *J Law Med Ethics* 2004;**32**:574–82.
14. Benatar SR. Justice and medical research: a global perspective. *Bioethics* 2001;**15**:333–40.
15. London AJ. Justice and the human development approach to international research. *Hastings Cent Rep* 2005;**35**:24–37.
16. Macklin R. Global justice, human rights and health. In: Green RM, Donovan A, Jauss SA, eds. *Global bioethics*. Oxford: Oxford University Press, 2008:141–60.
17. Meslin EM. Achieving global justice in health through research ethics: supplementing Macklin's "top-down" approach with one from the "ground up". In: Green RM, Donovan A, Jauss SA, eds. *Global bioethics*. Oxford: Oxford University Press, 2008:161–77.
18. Hawkins JS, Emanuel EJ. *Exploitation and developing countries*. Princeton: Princeton University Press, 2008.
19. Gbadegesin S, Wendler D. protecting communities in health research from exploitation. *Bioethics* 2006;**20**:248–53.
20. Benatar SR. An examination of ethical aspects of migration and recruitment of health care professionals from developing countries. *Clin Ethics* 2007;**2**:2–6.
21. Shapiro K, Benatar SR. HIV prevention research and global inequality: towards improved Standards of care. *J Med Ethics* 2005;**31**:39–47.
22. Ballantyne A. 'Fair Benefits' accounts of exploitation requires a normative principle of fairness: response to Gbadegesin and Wendler. *Bioethics* 2008;**22**:239–44.
23. *Women and aids programme*. University of Kwa Zulu Natal. http://www.capriza.org/Projects/women_and_aids.html (accessed 14 Dec 2009).
24. UNAIDS/AVAC. *Good participatory practice*. Geneva: US AAIID, 2007. <http://www.unaids.org> (accessed 14 Dec 2009).

25. **Vallely A**, Shagi C, Lees S, *et al*. Achieving equity and social justice in HIV prevention trials in developing countries: engaging the community in the standard of care debate in a vaginal microbicide trial in Mwanza, Tanzania. In *4th International AIDS Society Conference Sydney, Australia*. Abstract No. WEPEC047; 2007.
26. **Tindana PO**, Singh JA, Tracy CS, *et al*. Grand challenges in global health: community engagement in research in developing countries. *PLoS Med* 2007;**4**:e273. doi:10.1371/journal.pmed.0040273.
27. **Slevin KW**, Ukpong M, Heise L. Community engagement in HIV prevention trials: evolution of the field and opportunities for growth. http://www.path.org/files/aids2031_comm_engage.pdf (accessed 14 Dec 2009).
28. **Powers M**, Faden R. *Social justice*. New York. Oxford University Press, 2006.
29. **Macklin R**. After Helsinki: unresolved issues in international research. *Kennedy Inst Ethics J* 2001;**11**:17–36.
30. **Kimmelman J**, Weijer C, Meslin E. Helsinki discords: FDA, ethics and international drugs trials. *Lancet* 2009;**373**:13–14.
31. **Social Determinants of Health**. World Health Organization. 2008. http://www.who.int/social_determinants/en/ (accessed 14 Dec 2009).
32. **Chan M**. Impact of the global financial and economic crisis on health: statement by WHO Director-General 12. November 2008. <http://www.who.int/mediacentre/news/statements/2008/s12/en/index.html> (accessed 14 Dec 2009).
33. *The Global Economic Crisis and HIV prevention and treatment programmes: vulnerabilities and impact*. The World Bank Global HIV Program and UNAIDS, June 2009.
34. **Heise L**, Shapiro K, Slevin KW. Mapping the standards of care at microbicide clinical trial sites. Executive summary. Global Campaign for Microbicides. <http://www.global-campaign.org/clientfiles/SOC-ES.pdf> (accessed 5 Mar 2010).
35. Thibela TB project. <http://www.tbhiv-create.org/about/studies/thibela> (accessed 14 Dec 2009).
36. **Benatar SR**, Daar A, Singer PA. Global health ethics: a rationale for mutual caring. *Int Aff* 2003;**79**:107–38.
37. **Hyder AA**, Dawson L, Bachani AM, *et al*. Moving from research ethics review to research ethics systems in low-income and middle-income countries. *Lancet* 2009;**373**:862–5.
38. **Benatar SR**. Moral imagination: the missing component in global health. *PLoS Med* 2005;**2**:e400. <http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.0020400> (accessed 14 Dec 2009).
39. **Fidler DP**. Influenza virus samples, international law, and global health diplomacy. *Emerg Infect Dis* 2008; [serial on the Internet]. <http://www.cdc.gov/EID/content/14/1/88.htm> (accessed Jan).
40. **Fogarty International Center**. International research ethics education & curriculum development award. http://www.fic.nih.gov/programs/training_grants/bioethics/ (accessed 14 Dec 2009).
41. **Advancing Science for Global Health**. Fogarty International Center. http://www.fic.nih.gov/news/publications/fogarty_40th_brochure.pdf (accessed 14 Dec 2009).
42. **Duffy P**, *et al*. Protective immunity against severe malaria in children. <http://www.grandchallenges.org/NEWWACCINES/CHALLENGES/LEARNABOUTIMMUNOLOGICALRESPONSES/Pages/Malaria.aspx> (accessed 14 Dec 2009).
43. **Plummer FA**. Comprehensive studies of mechanisms of HIV resistance in highly exposed uninfected women. <http://www.grandchallenges.org/NewVaccines/Challenges/LearnaboutImmunologicalResponses/Pages/HIVResistance.aspx> (accessed 14 Dec 2009).
44. *The Teasdale-Corti Global Health Research Partnership Program*. http://www.idrc.ca/en/ev-134225-201-1-DO_TOPIC.html (accessed 14 Dec 2009).
45. **Anon**. Strengthening research capacity in Africa [Editorial]. *Lancet* 2009;**374**:1.
46. **Whitworth JAG**, Kokwara G, Kinyanjui S, *et al*. Strengthening capacity for health research in Africa. *Lancet* 2008;**372**:1590–3.
47. EDCTP Forum. <http://www.edctp.org/Home.162.0.html> (accessed 14 Dec 2009).
48. **Singer PA**, Benatar SR. Beyond Helsinki: a vision for global health ethics. *BMJ* 2001;**322**:747–8.
49. **Benatar SR**, Fleischer TE. Ethical issues in research in low-income countries. *Int J Tuberc Lung Dis* 2007;**11**:617–23.
50. **Benatar SR**, Gill S, Bakker IC. Making progress in global health: the need for new paradigms. *Int Aff* 2009;**85**:347–71.