

# Ethical and Policy Implications of Clinical Drug Trials Conducted in Developing Countries

*Solomon R. Benatar, MBChB, FRCP and Theodore E. Fleischer, JD, LL.M*

The intense debate on many ethical dilemmas associated with an expanding program of clinical research in developing countries has failed to resolve all controversy. We suggest that many contested issues could be addressed through greater attention to different worldviews on the relationship between research and clinical care and by defining policies that both progressively improve the standard of care in research and link research to improved delivery of health care in developing countries.

## Introduction

Stimulated by the pharmaceutical industry's desire for new, marketable drugs, clinical research has become a burgeoning activity in recent years. In industrialized countries, pharma's goal of developing large profitable markets for drugs has

led to the proliferation of only marginally advantageous research on versions of existing drugs, so-called "me too" drugs, for the primary purpose of capturing market niches.<sup>1</sup> Pharma needs large numbers of research subjects and often finds it easier and more economically favorable to recruit them in developing countries where costs are lower, ethics committees may be more lenient and underprivileged subjects are eager to participate regardless of any benefits or the standard of care offered. Such advantages enable the medical-industrial complex to easily meet the requirements of the US federal authorities that new drugs be tested against a placebo to ensure that they provide at least a marginal benefit over no treatment at all.

Drug research is mainly focused on developing drugs that can be sold for a profit to the most affluent quintile of the world, which can afford expensive new drugs and technology. Although widely accessible

.....  
*Solomon Benatar is Professor of Medicine and Founding Director of the University of Cape Town's Bioethics Centre. He is Visiting Professor in Public Health Sciences and Medicine at the University of Toronto and a past President of the International Association of Bioethics. Theodore Fleischer is Deputy Director of the Bioethics Centre, University of Cape Town, and Senior Lecturer (Hon) in the Department of Medicine and the Faculty of Law.*

benefits have occasionally resulted from research produced by pharma or from the recently renewed attention to tropical diseases, the multinational pharmaceutical industry operates like any other business. It responds primarily to economic demands for investor profits, rather than to social or human needs.<sup>2</sup>

In this profit-driven environment, new drugs often fail to meet the health needs or priorities of local populations in developing countries where much of the research is done. This disparity raises serious ethical questions about the relevance and benefit of such research in the developing world. Recent controversies over proposed revisions to the Helsinki Declaration – the premier, internationally accepted guidelines for research ethics – have stimulated renewed interest in the ethics of clinical research in developing countries. Some believe these revisions to be motivated by the desire to facilitate exploitative research in developing countries.<sup>3</sup> Defenders of the revisions respond that they would not weaken the Declaration but rather permit research around the world to the benefit of global health needs.

These contentious debates are mirrored in tensions between researchers and subjects and between researchers and Institutional Review Boards (IRBs). We believe that these tensions can be explained in part by different worldviews, or perceptions of the world and of the relationship between research and health care. Researchers largely share a scientific worldview and have a primary interest in advancing knowledge. However, this motivation is often accompanied by a consideration of the financial, personal and/or institutional benefits pharmaceutical companies in search

of profit may confer. This may prompt some researchers to direct their energies to the development of marginally useful “me too” drugs. Underprivileged and deprived research subjects within traditional cultures, on the other hand, tend to share a non-scientific worldview, are less wedded to foreign imposition of market rules that seem not to benefit them and have a predominant interest in receiving care for their illnesses.<sup>4</sup> Although these differences lie along a spectrum and many values may be shared, the extent of such divergence is not trivial. These discrepancies are of practical importance in developing ethical policies for research.

We briefly review here the issues that arise when these worldviews clash. We then propose guidelines to help resolve these contentious issues in a practical way that will lead to both scientific and ethical progress in research done in developing countries. Finally, we look at the need to implement these proposals in structural policy changes.

### **Ethical Considerations**

In her recent review of controversy in international research ethics, Ruth Macklin concludes that, despite seeming agreement in several areas, different viewpoints persist on fundamental issues and that such disagreements will not be easily resolved.<sup>5</sup> In response to Macklin, one of us (SRB) has argued that disagreements may be explained in part by differing perceptions of social relations adhered to by various participants within the research context and by a failure to use moral reasoning to identify the rational middle ground between

ethical universalism and moral relativism.<sup>4</sup> It has also been proposed that progress can be made towards resolving contentious issues in international research ethics if we acknowledge the many points of agreement and develop a framework for understanding the different perspectives on life by researchers and vulnerable subjects that could facilitate rational responses to the areas of disagreement Macklin outlined.<sup>4</sup>

We summarize an approach to resolving these disagreements by posing and answering a series of questions.

*What research should be undertaken in developing countries, and how should priorities be decided?*

Most would agree that clinical trials conducted by overseas sponsors in developing countries should be relevant to the health needs of the host country. To ensure that the host nation's health priorities are considered, host country researchers and IRBs must be involved in the design, review and conduct of trials. Health administrators and policy makers will also frequently play a role. Before a trial is approved by the host country IRB, these participants should determine and agree with overseas investigators a means by which study findings and other benefits that result from the research will be incorporated into local healthcare systems. Only through advance collaboration can host country researchers, subjects and health systems benefit in ways that significantly improve local research processes and build capacity for the public health sector that often provides research subjects.

*What sorts of study designs are acceptable? Can placebos be used, and what comparative arms should be included?*

Whether it is ethical to use placebos in

a particular research project cannot be deduced simply by examining a few sentences in broad clauses in research ethics guidelines. General principles, whether in law or ethics, are not self-interpreting. Moral reasoning always requires consideration of context in the process of applying general, universally applicable principles. Each study in which a placebo arm is anticipated should be considered on its merits, taking into account the research question posed, how this could best be answered, potential harms and benefits, ethics principles and relevant local circumstances.

Where morally valid reasons can be mounted for placebo-controlled trials, and where such studies are designed specifically for the benefit of local populations rather than as surrogates for acquiring information for wealthy countries (e.g., studies of "me too" drugs), the use of a placebo may be justified on rational grounds. We caution, however, that utilitarian calculations for the benefit of whole groups of people, even with their agreement, should almost never be used to justify a placebo arm when this may result in unnecessary suffering, avoidable injuries or death. We contend that our recommendations do not imply moral relativism. The arguments for this have been explicated in greater detail elsewhere.<sup>4</sup>

*How do we avoid exploiting research subjects in developing countries?*

Exploitation in the research context should be defined to include the following acts or omissions:<sup>4</sup>

- To take advantage of power differentials to meet the researchers' goals through any means they choose without first giving serious

consideration to the harms that may be perceived and experienced by research participants or their communities;

- To use research subjects as a means to achieving only the ends of researchers, e.g., advancing knowledge and in many cases the commercial interests of pharma, when the benefits of the research will not be relevant, affordable or easily available to research participants and their communities;
- To undertake studies in which minimal benefits accrue to participants and large benefits, especially financial, may accrue in the long term to research sponsors, thus failing to ensure fair balance of benefits and burdens to sponsors/researchers and research participants over the long term;
- To deny participants post-trial use of therapies identified as safe and beneficial in environments where such treatments would not otherwise be affordable and available to subjects in the public health sector.

To avoid exploitation, priority should be given to trials that will provide useful knowledge for the host country, result in a fair distribution of the benefits and burdens and ensure that the results of research flow into healthcare settings. While individual subjects' safety and gain are always important, community and national health priorities must be identified and negotiated with relevant authorities rather than with individual subjects, the IRB, or the local researcher. In no event should

existing disparities be further entrenched by deflecting local human or material resources away from healthcare systems in host countries towards research that fails to advance subject, community or national health priorities.

*What is the standard of care? How is this defined, and how can it be justified?*

Attempts to resolve the vexed question of what standard of care must be provided for research in developing countries by applying arguments based on a single worldview are unlikely to convince those who have a different perspective on social relations and how these should influence social policy in research.<sup>4</sup>

We believe that a well-reasoned universal standard of care could be translated into feasible local practices. We also argue that a universally applicable ethical framework for a standard of care in research must acknowledge practical and morally relevant differences between countries. In order to apply universal principles to the context of a specific research project in a particular place, we suggest that researchers:

- Avoid exploitation as indicated above;
- Conduct research with the same respect for the dignity of all subjects wherever they are in the world, always treating them as ends in their own right and not using them merely to acquire knowledge that could only benefit others;
- Obtain authentic informed consent that reflects the realities of the economic, social, linguistic and cultural framework of research subjects and their communities;

- Provide care for other diseases concomitantly afflicting the subjects and for which treatment may not otherwise be available.

The recommendations above require that researchers, IRBs and the subjects shape an acceptable standard of care for a particular study through a deliberative, respectful process of moral and scientific reasoning, not merely political haggling.<sup>7,8</sup> In this way, health care could be improved through successive research projects that would increase the standard of care in research towards an acceptable universal level. Such progress requires researchers and IRBs to break away from a solely scientific worldview and adopt a broader concept of standard of care commensurate with needs in developing countries.<sup>8</sup>

We have offered moral arguments to justify a broader standard of care as opposed to a narrow standard of care that insists on worldwide uniformity.<sup>8</sup> Simply put, our position is based on the obligations to do no harm, to do good and to be fair. We should respect practices within other cultures that pose no significant risk to health and safety but reject those that infringe on universally accepted human rights. Researchers should be sensitive to the potentially adverse and invasive social impact of their intrusion into lives and cultures in countries that they do not fully understand.

We contend that an improved standard of care that progressively approaches that of rich countries would enhance, not deter, successful achievement of research goals in developing countries. Since the goal of medical research is to improve health care for research subjects and their com-

munities, as well as to advance scientific knowledge, we encourage closer links between overseas researchers, their sponsors, host country investigators, communities and health authorities. To be effective, this collaboration must be authentic, not simply pro forma, and must be done in advance of submitting research protocols to the host country IRB. These justifications and examples of how they have been applied in practice have been described in detail elsewhere.<sup>8</sup>

When a broader standard of care in research is implemented in poor countries, this will highlight the existence of different standards of care in rich and poor countries. Some view the existence of different standards in the context of research as ethically impermissible. We argue that, when an alternative, locally negotiated standard of care is applied in a poor country and the overall standard of care is ratcheted upwards through research, this represents progress towards better health care for vulnerable research participants and populations in poor countries. In research, as in health care generally, the ideal should not become the enemy of the realistically achievable. In light of the centuries of inadequate health care in poor countries, our inability to achieve immediate equity should not impede substantial research that could progressively improve health care throughout the world. Some might characterize additional and enhanced care offered to poor, vulnerable research subjects as an ethically problematic means of inducement or even coercion. However providing access to health care when this is otherwise unavailable is arguably valuable enough to outweigh what are understood to be minor risks of participation.

Inducements are justified under such circumstances, and would only be considered morally wrong if they resulted in participants taking risks with their health and lives.

In summary, we whole-heartedly agree that it is morally problematic to remain satisfied with existing low or non-existent standards of care in poor countries. We have proposed that instead of being paralyzed by a commitment to a rigid, narrow interpretation of a universal standard, a medically, ethically and contextually appropriate standard of care should be applied through a rational, deliberative and collaborative process as outlined above. This approach arguably identifies a middle ground between the two worldviews that have often clashed when researchers descend on the developing world and experiment on poor, highly vulnerable populations whose context and cultures they may not understand.

### **Policy Considerations**

We propose the following structural changes in policy to improve the ethics of clinical drug trials in developing countries:<sup>8</sup>

*Involve the community* or representatives of the participant population in the design and selection of drug trials in particular locations. Clinical drug research is usually done on cohorts of public sector clinic and hospital patients who are essentially rented to the researcher. When there is no geographically based community to consult, the researcher – with IRB oversight – should identify this participant population’s needs for additional services not already available in the public sector

and decide how research funding could help meet these needs.

*Form partnerships through consultation and collaboration* with other specialists, academic researchers, professional associations and non-governmental organizations (NGOs) that focus on the condition under research.<sup>9</sup> The goal would be to determine what practical needs could be realistically met within a modest budget, for participants in this research, the population under study and the community. It may be that all research done in the country or by regional groupings for specific conditions could be coordinated to deliver some meaningful additional services or facilities that no single researcher could provide.

*Determine locally relevant elements of standards of care* through negotiations with critical stakeholders such as community leaders, community advisory boards and health authorities.

*Ensure benefits to participants and the community.* Recent examples of how HIV research has taken on this challenge could serve as models for commercially sponsored research.<sup>8</sup> HIV vaccine researchers in South Africa will be required to allocate a portion of research funding into a trust fund to pay for anti-retroviral drugs for research subjects who become HIV positive during the trial.<sup>10</sup> After consultation with other interested researchers and organizations that focus on a particular health problem, host country researchers, supported by IRBs and health authorities, should negotiate for better care, access to drugs and support for enhanced healthcare capacity to meet the needs of participants and/or the affected population. This could take the form of specific benefits, such as post-trial access to the experimental drug

if it proves to be beneficial, to other drugs not readily available though the public sector or specific items of infrastructure, equipment or capacity that will benefit the population and/or community from which most research subjects come.<sup>11</sup> The sponsor must, in any event, either agree to provide post-trial access to the experimental drug if it proves effective and safe and the sponsor intends to market it anywhere, or failing that, must provide an alternative benefit that is approved by the IRB.

Researchers and IRBs should not be pressured into approving a protocol by a sponsor who, when pressed to offer an appropriate post-trial benefit to subjects and/or the community, responds: "Take it or leave it. If you reject, we'll go somewhere else." Finally, no developing country or IRB should have to accept less than the most favorable range of benefits granted to participants and communities in any other country, particularly those in better resourced countries.<sup>12</sup>

*Enhance IRB capacity, strengthen education of researchers and refine the above steps to meet local circumstances.* Research institutions and academic research centers should play a role in supporting researchers' and IRBs' efforts to ensure that all sponsors of research, particularly those from overseas, meet their ethical obligations when doing research in developing countries. This would ideally include setting policies that empower researchers and IRBs to impose reasonable goals on sponsors that will ensure a continuous ratcheting upwards of the benefits left behind for participants, communities and the public health sector. Sponsors' budgets should include an ethics levy that contributes a reasonable level of resourcing for IRBs to perform tasks

including monitoring, education of IRB members and the creation of educational programs for researchers.

*Clinical drug research in the private sector* in developing countries must be subject to at least the same level of ethical review and attention by health authorities and IRBs as research in the public sector. In recent years clinical drug trials have increasingly been undertaken in the private sector, where clinical research organizations can enlist private practitioners, often with no connection to a medical academic center or its IRB, in order to tap into the reservoir of private patients served by the practicing physician.<sup>13</sup> These research projects are sometimes reviewed by privately established and funded IRBs that have no link to an academic center and whose members may be appointed by organizations with commercial interests. South Africa's new Health Act of 2004 will require all IRBs, including privately organized ones, to become accredited by the National Health Research Ethics Council, which will set standards to be met for ethical review of research protocols.<sup>14</sup>

## Recommendations

Our proposals, set out above, can be summarized in these recommended steps:

- Researchers must devote more time and effort to understanding the different perceptions and views about the meaning of medicine and research held by the often poor, vulnerable populations whom they recruit as subjects. Only in this way can they avoid

exploiting or misleading them.<sup>15</sup>

- Researchers, IRBs and health authorities must not complacently justify that research is ethical by claiming “it has always been done it this way.” Ethics is a dynamic field, particularly in the context of research, and just as we expect to constantly make progress in science, so we must seek to make progress in ethics.
- Although we cannot achieve a universal standard of care overnight in the developing world, we can and should set realistic, practically achievable standards that are significantly higher than those currently accepted by the public sector in the host country and closer to that of the overseas sponsor’s own country, with progressive movement towards the ideal of a global standard of care.
- Finally, this progress should take the form of a series of improvements, so that ensuing research projects will always leave subjects, their communities and the country’s public health sector better off after the trial, not just no worse off.<sup>8</sup>


These steps are achievable but require determined efforts by all stakeholders in the research process, beginning with overseas sponsors, their host investigators and eventually involving health authorities and IRBs. Collaboration should, in appropriate cases, extend beyond these major players to involve community advisory boards, other professional organizations and NGOs. A prime example of how this

can be done effectively is the well-planned process by which researchers, collaborating with many other affected organizations, are preparing for vaccine trials in South Africa.<sup>9</sup> This serves as a model that could be adapted for use in other trials that have wide-ranging impacts on the communities in which the research is undertaken.

## **Conclusions**

International researchers should be educated about the social, economic and political context in which research is being undertaken, and they should be sensitive to the differing perceptions of research and health care that may prevail in such contexts.<sup>4,15</sup> Researchers should also understand that their scientific worldview, which allows them to see themselves as nobly advancing knowledge, is to some degree a reflection of their local values. Impoverished research subjects who have benefited little from previous research may have a different local value that views healthcare professionals primarily as providers of care. The gap between these views can be narrowed by finding a middle ground through education of researchers about perceptions of the research endeavor within specific local contexts, while simultaneously providing care that would otherwise be unavailable in the research setting. Such negotiations should be initiated by researchers and supported both by IRBs and by the development of partnerships as we have elaborated above. By meeting the local needs of researchers, participants and the local healthcare system, the most admirable universal goal could be achieved: advancing knowledge for the purpose of improving health locally

and globally.

To make such progress will require new paradigms of thinking. Firstly, we must acknowledge that research does not take place in a vacuum but rather in a world with wide disparities in which much research on vulnerable people has rarely been applied for their benefit. Secondly, researchers should increasingly view continuation of current patterns of exploitative research as ethically unacceptable. Thirdly, the need to link moral progress to scientific progress should become a high priority. Progress could be made towards such goals by coupling research with improvements in health through a broader conception of the standard of care and by linking research to development through partnerships and strategic alliances that could promote sustainability. 

## Acknowledgements

This work was supported in part by a grant from the United States National Institutes of Health's Fogarty International Center to the University of Cape Town's capacity building program in International Research Ethics in southern Africa.

## Note

This article draws extensively on two recent publications. Benatar S R. Towards progress in resolving dilemmas in international research ethics. *Journal of Law, Medicine and Ethics*. 32: (2004) (4) 574-582 Shapiro K, Benatar S R. HIV prevention research and global inequality: towards improved standards of care. *Journal*

of Medical Ethics 31: (2005) 39-47.

## References

1. S Garattini, F de Andres-Trelles, V Bertele, L Li Bassi, "Ethics of testing drugs with readily available alternatives," *Lancet* 360: (2002) 647..
2. S Garattini, V Bertele. "Adjusting Europe's drug regulation to public health needs." *Lancet* 358: (2001) 64-7
3. Lurie P, Greco D B. "US exceptionalism comes to research ethics." *Lancet* 365 (2005) 1117-19
4. Benatar S R. "Towards progress in resolving dilemmas in international research ethics." *Journal of Law, Medicine and Ethics*. 32: (2004) (4) 574-582
5. R Macklin, "After Helsinki: unresolved issues in international research," *Kennedy Institute of Ethics Journal*. 11(1): (2001) 17-36.
6. S R Benatar, P A Singer, "A new look at international research ethics," *British Medical Journal* 321 (2000) 824-26
7. Costello A, Zumla A. "Moving to research partnerships in developing countries." *British Medical Journal* 321: (2000) 827-829.
8. K Shapiro K, S R Benatar. "HIV prevention research and global inequality: towards improved standards of care." *Journal of Medical Ethics* 31: (2005) 39-47.
9. Guidelines for good practice in the conduct of clinical trials in human participants in South Africa. Department of Health Pretoria, 2000, section 7 pp 40.
10. HIV Preventive Vaccine Research. South Africa MRC Research Ethics Guidelines Book 5. 2005
11. Guidelines for good practice in the conduct of clinical trials in human participants in South Africa. Department of Health Pretoria, 2000, section. 9.3.5, pp 47
12. Guidelines for good practice in the conduct of clinical trials in human participants in South Africa. Department of Health Pretoria, 2000, section 7 pp 40
13. South Africa: an important gateway. *The Centre Watch Monthly*. March 2005 12: (3) pp 1& 6-11
14. South African National Health Act of 2004
15. Benatar S R. "Some reflections and recommendations on research ethics in developing countries." *Social Science and Medicine*, 54: (2002) 1131-41