

Viewpoint

Double ethical review of North–South collaborative clinical research: hidden paternalism or real partnership?

Raffaella Ravinetto¹, Anne Buvé², Tinto Halidou³, Pascal Lutumba³, Ambrose Talisuna⁴, Mohammad Juffrie⁵, Umberto D'Alessandro⁶ and Marleen Boelaert⁷

1 *Clinical Trials Unit, Institute of Tropical Medicine Prince Leopold, Antwerp, Belgium*

2 *Department of Microbiology, Institute of Tropical Medicine Prince Leopold, Antwerp, Belgium*

3 *Institut de Recherche en Sciences de la Santé (IRSS)-Center Muraz, Burkina Faso*

4 *Uganda Infectious Disease Research Collaboration, Kampala, Uganda*

5 *Department of Pediatrics, Faculty of Medicine, Gadjahmada University, Yogyakarta, Indonesia*

6 *Department of Parasitology, Institute of Tropical Medicine Prince Leopold, Antwerp, Belgium*

7 *Department of Public Health, Institute of Tropical Medicine Prince Leopold, Antwerp, Belgium*

Summary

Despite their universal character, the ethical principles governing clinical research need to be translated into procedures and practices, which will vary among countries and regions because of differences in local cultural norms and in the available resources. Double ethical review, by which a research protocol is submitted for ethical clearance both in the country or countries where the research takes place and in the country of the sponsor or funding agency, will then help ensure that all relevant perspectives are taken into account. In addition, a geographically and culturally close ethics committee can do a much better informed and comprehensive assessment of the respective skills of the clinical sites and of the sponsor. But the practical implementation of double ethical review can bring significant difficulties and delays, especially in multi-site and multi-country researches. Currently, most ethics committees do not proactively seek communication with others evaluating the same research protocol in different socio-economical and cultural contexts, so in practice there is no mutual learning process. Proactive communication would help to build collaborative partnership among ethical bodies, promoting common practices and resolving conflicting opinions.

keywords clinical trials, ethical review, vulnerability, developing countries, protection of study subjects

Double ethical review to ensure protection of subjects enrolled in clinical trials sponsored, coordinated or funded by foreign organizations in developing countries (Glickman *et al.* 2009) is widely recommended. 'Double ethical review' means review and ethical clearance of a research protocol both in the country or countries where the research will take place and in the country of the sponsor and/or funding agency. This procedure is proposed by many guidelines governing international clinical research, such as the CIOMS Ethical Guidelines (CIOMS, 2002) and the Nuffield Council on Bioethics (2002). Various research groups share this position (Ravinetto *et al.* 2010c); Bompert *et al.* (2008) even recommended that double ethical review of externally sponsored trials become a regulatory requirement (Bompert *et al.* 2008).

But positions in favour of the double ethical review may be inspired by more specific concerns. The US National

Bioethics Advisory Committee (2001), for instance, recommended in 2001 that any clinical research sponsored or carried out by the US government should undergo ethical review in the United States and in the host countries, so that studies conducted with US funds would comply with US regulations. However, the review in the host country would suffice if it could be proved that it achieves all the substantive ethical protections required in the United States. Likewise, the European Group on Ethics in Science and New Technologies to the European Commission stated in 2003 that scientific and ethical evaluation should be undertaken by ethical committees from all countries involved. A recent public draft reflection paper on ethical and good clinical practices aspects of trials conducted in third countries for marketing authorization to the European Medicines Agency (EMA, 2010) suggests that the sponsor of studies conducted in poorly regulated

R. Ravinetto *et al.* **Double ethical review of North–South collaborative clinical research**

countries should consider submission to an ethics committee operating within a framework with ethical standards equivalent to those of the European Union (in addition to the host country).

These North American and European positions are motivated chiefly by the legitimate concern that regulatory weaknesses in the South attract research that would not be acceptable elsewhere. The weaknesses in the host country are compensated by ethical clearance in the North, and the sponsor or donor seeks protection from potential allegations of double standard practices. This approach could be criticized as moral *imperialism*, if seen as a straightforward attempt to impose standards of a specific culture or geopolitical region onto other cultures, regions or countries (Garrafa and Lorenzo 2008). It may also be criticized as *paternalistic* by those who consider that all countries have the capacity to enforce appropriate ethical standards for protecting the rights of their population, irrespective of their level of economical development. However, the reality is different and various studies and initiatives launched to analyse, support or strengthen the ethical review system in resource-poor settings (Ezekiel *et al.* 2004; Hyder *et al.* 2004, 2009; Kirigia *et al.* 2005; Milford *et al.* 2006; Kass *et al.* 2007; Ateudijeu *et al.* 2010; Rwabihama *et al.* 2010) have shown that the ethical review is often not strong enough to fully prevent exploitative practices.

Towards a review partnership?

In our opinion, double ethical review should not be primarily seen as a compensatory mechanism for supposed weakness of ethical review in the South, but as an essential safeguard against North–South double standards. Double ethical review *de facto* strengthens the protection of the study participants and their communities, as it takes the specificities of each context into account. Despite their universal character, ethical principles governing clinical research need to be translated into rules, procedures and practices, which may significantly vary among countries and regions. This may be attributed not only to differences in local cultural norms (Macklin 2008), but also to major differences in available resources (Lang *et al.* 2010; Ravinetto *et al.* 2010a), the health system and the standard of care, health determinants, the socio-economical status of the study population, the vulnerability of the study subjects, etc. Simply applying the same ethical review procedures developed in rich countries to a poor country is *per se* not sufficient to achieve adequate protection of individuals and the community, and it may sometimes be inappropriate.

Even if the principles governing clinical research and guiding the ethical review (The Nuremberg Code 1996,

Belmont Report, 1979; Nuffield Council on Bioethics, 2002; World Medical Association 2008) do not vary, the North–South resource gap can lead to a different perception of such aspects as the pertinence of a trial for a given population, the risk/benefit ratio, the protection of confidentiality, the in-trial and post-trial benefits (Benatar *et al.* 2010) and the risk of exploitation. Similarly, the acceptability and the effectiveness of some clinical research tools and procedures, such as incentives and reimbursements to study subjects, informed consent (TDR – Special Programme for Research and Training in Tropical Diseases/World Health Organization, 2007), community involvement (Nkiya *et al.* 2010) and no-fault policy insurance, may substantially vary between affluent and poorer countries. In addition, a fair evaluation of the skills, resources and qualifications to conduct and to sponsor a clinical trial is obviously easier for an ethical review body close to the concerned institutions, as a geographically and culturally close ethics committee should be able to do a better informed and comprehensive assessment of both the clinical sites and the sponsoring organization.

If the aim of double ethical review is complementarity of opinions rather than imposing external rules, it will help to achieve the best protection of subjects and populations. Rather than just being an ‘informal quality control mechanism’ which temporarily compensates for the deficiencies of the weaker body, it will remain necessary even when both Northern and Southern ethics committee are fully functional in terms of skills, resources and independence (World Health Organization (TDR/WHO), 2000, 2002), because of the broader purpose to ensure a comprehensive and balanced review of each collaborative research.

Some open questions

The practical implementation of double ethical review can pose major challenges, especially in multi-site and multi-country studies – for instance, the case of the 4-ABC trial: an EDCTP¹-funded clinical study evaluating four artemisinin-based combinations for uncomplicated malaria in children, sponsored by the Institute of Tropical Medicine (Belgium) and conducted in seven African countries (Ravinetto *et al.* 2010b). Double ethical review was performed in two phases (first, in the country of the sponsor and then simultaneously in each of the host countries) and resulted to some extent in complementarities of comments. The ethics committee in the North stressed such aspects as patient’s indemnization in case of harm, no-fault policy

¹European and Developing Countries Clinical Trials Partnership. See: <http://www.edctp.org>

insurance and data confidentiality with electronic data transfer, while Southern ethics committees more often asked for clarification on patient's reimbursement, co-ownership of national data, details on clinical sites and on the transfer of biological samples abroad. However, delays of several months occurred, as a result of the sequential schedule and the large number of submissions (internal review boards and ethics committees in the sponsor's and in each host country, plus competent authorities in the host countries), coupled with the facts that the administrative requirements can significantly vary across ethical bodies and that the timelines of some bodies are unpredictable.

In our experience, ethics committees usually do not proactively seek communication with the other ethics committees that evaluate the same research protocol, e.g. asking information about binding and non-binding comments they raised. This is a missed opportunity for a mutual learning process among ethics committees from different contexts. Proactive communication would offer the opportunity to build collaborative partnerships among the committees, beyond partnerships between clinical researchers. Such committee partnerships could provide a space where agreement is reached on common ethical practices and standards, e.g., on informed consent, on indemnity and on harmonization of administrative requirements, where more efficient models and schedules for international ethical reviews are built and the submission schedule is optimized (e.g. parallel or consecutive submission, differentiation between detailed and expedited review etc.) and where cases of conflicting opinions in different countries are resolved. In fact, even if the local ethics committee is competent in its own country and cannot be overruled by a foreign body, in practice, a research proposal can be stopped by a negative opinion from the country of the sponsor. Opening a direct dialogue between the concerned ethics committees would be a viable and practical way to deal with such cases.

The double ethical review of internationally sponsored trials may play a major role in achieving the best protection of patients and communities. However, to be fully effective and to contribute to building an adequate shared framework of ethical practices, it should be performed in a partnership primarily built through direct, proactive communication among ethics committees involved in the review of the same research project. Currently, this is a missed opportunity.

Acknowledgements

We thank the members of the Switching the Pole Clinical Research Network and of the 4-ABC study group. This

material is based upon work funded by the Belgian Development Cooperation (DGDC) and by The European and Developing Countries Clinical Trials Partnership (EDCTP). Such support does not constitute endorsement by the funding bodies of the views expressed in this publication.

References

- Ateudijeu J, Williams J, Hirtle M *et al.* (2010) Training needs assessment in research ethics evaluation among research ethics committee members in three African countries: Cameroon, Mali and Tanzania. *Developing World Bioethics* **10**, 88–89.
- Benatar SR & Singer PA (2010) Responsibilities in international research: a new look revisited. *Journal of Medical Ethics* **36**, 194–197.
- Bompart F *et al.* (2008) Bonnes Pratiques Cliniques dans les pays en développement : recommandations en termes d'application. *Thérapie Mars-Avril* **63**, 77–82. doi: 10.2515/Therapie:2008022
- CIOMS (2002) *International Ethical Guidelines for Biomedical Research Involving Human Subjects, prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO)*. CIOMS, Geneva.
- European Medicines Agency (EMA). Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted in third countries and submitted in marketing authorisation applications to the EMA. Draft agreed by EMA Working Group on Third Countries Clinical Trials on 23 March 2010. End of consultations 30 September 2010. Available at: <http://www.ema.europa.eu/Inspections/docs/71239709en.pdf>
- Ezekiel J, Wendler D, Killen J & Grady C (2004) What makes clinical research in developing countries ethical? The Benchmarks of Ethical Research. *The Journal of Infectious Diseases* **189**, 930–937.
- Garrafa V & Lorenzo C (2008) Moral imperialism and multicentric clinical trials in peripheral countries. *Cadernos Saúde Pública. Rio de Janeiro*, **24**, 2219–2226.
- Glickman SV, Mc Hutchison GJ & Peterson ED *et al.* (2009) Ethical and scientific implications of the globalization of clinical research. *The New England Journal of Medicine* **360**, 816–823.
- Hyder AA, Wali SA, Khan AN *et al.* (2004) Ethical review of health research: a perspective from developing country researchers. *Journal of Medical Ethics* **30**, 68–72.
- Hyder AA, Dawson L, Bachani AM & Lavery JV (2009) Moving from research ethics review to research ethics systems in low-income and middle-income countries. *Lancet* **373**, 862–865.
- Kass NE, Hyder AA, Ajuwon A *et al.* (2007) The structure and function of Research Ethics Committees in Africa: a case study. *PLoS Medicine* **4**, e3. doi:10.1371/journal.pmed.0040003
- Kirigia JM, Wambebe C & Baba-Moussa A (2005) Status of national research bioethics committees in the WHO African region. *BMC Medical Ethics*, **6**, 10.

R. Ravinetto *et al.* **Double ethical review of North–South collaborative clinical research**

- Lang TA, White NJ, Hien TT, Farrar JJ, Day NPJ *et al.* (2010) Clinical Research in Resource-Limited Settings: enhancing Research Capacity and Working Together to Make Trials Less Complicated. *PLoS Neglected Tropical Diseases* 4, e619. doi:10.1371/journal.pntd.0000619.
- Macklin R. (2008) Appropriate ethical standards. *Chapter 64 of the Oxford Textbook of Clinical Research Ethics*. Oxford University Press, Oxford.
- Milford C, Wassenaar D & Slack C (2006) Resources and needs of Research Ethics Committees in Africa: preparations for HIV vaccine trials. *IRB: Ethics and Human Research* 28, 1–9.
- Nkiya A, Chilengi R & Ishengoma D *et al.* (2010) Engaging diverse communities participating in clinical trials: case examples from across Africa. *Malaria Journal* 9, 86. <http://www.malariajournal.com/content/9/1/86>
- Nuffield Council on Bioethics (2002) *The Ethics of Research Related to Healthcare in Developing Countries*. Nuffield Council on Bioethics, London.
- Ravinetto R, Mbonile L & Hite N (2010a) Ethical criteria in clinical research in developing countries: is there a global standard? *Italian Journal of Tropical Medicine* 15, 1–8.
- Ravinetto R, Talisuna A, Halidou T & D'Alessandro U on behalf of the 4-ABC study group. (2010b) Multidisciplinary approaches to north-south models of partnered research. Abstract accepted at the 59th Annual Meeting of the American Society of Tropical Medicine and Hygiene, Atlanta, November 3–7.
- Ravinetto R, Tinto H & Rouamba N *et al.* (2010c) Health research: the challenges related to ethical review and informed consent in developing countries. *The Italian Journal of Tropical Medicine* 15, 15–20.
- Rwabihama JP, Girre C & Duguet AM (2010) Ethics committees for biomedical research in some African emerging countries: which establishment for which independence? A comparison with the USA and Canada. *Journal of Medical Ethics* 36, 243e249. doi:10.1136/jme.2009.033142.
- TDR – Special Programme for Research and Training in Tropical Diseases/World Health Organization (2007). *Ethical Challenges in Study Design and Informed Consent for Health Research in Resource-Poor Settings*. TDR/SDR/SEB/ST/07.1. Special topics No 5. WHO TDR, Geneva.
- The European Group on Ethics in Science and New Technologies to the European Commission, Opinion on the Ethical Aspects of Clinical research in Developing Countries. Opinion No 17, 4th February 2003.
- The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1979) The Belmont report/ethical principles and guidelines for the protection of human subjects of research.
- The Nuremberg code (1996) Nuremberg military tribunal. *JAMA* 276, 1691.
- US National Bioethics Advisory Committee (2001) *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries. Volume I. Report and Recommendations of the National Bioethics Advisory Commission*. Bethesda, Maryland.
- World Health Organization (TDR/WHO) (2000) *Operational Guidelines for Ethics Committees That Review Biomedical Research*. WHO, Geneva. Available at: <http://apps.who.int/tdr/svc/publications/training-guideline-publications/operational-guidelines-ethics-biomedical-research>.
- World Health Organization (TDR/WHO). (2002) *Surveying and Evaluating Ethical Review Practices*. WHO, Geneva. Available at: <http://apps.who.int/tdr/svc/publications/training-guideline-publications/surveying-evaluating-ethical-practices>.
- World Medical Association (2008) Declaration of Helsinki: ethical principles for medical research involving human subjects. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and last amended by the 59th WMA General Assembly, Seoul, 2008. Available from: <http://www.wma.net/en/30publications/10policies/b3/index.html> (accessed 20 January 2011).

Corresponding Author Raffaella Maria Ravinetto, Institute of Tropical Medicine Prince Leopold Antwerp, Belgium.
E-mail: rravinetto@itg.be