Health research: the challenges related to ethical review and informed consent in developing countries

R. RAVINETTO[1], H. TINTO[2], N. ROUAMBA[2], A. TALISUNA[3], Y. ADOKE[3], A. KADIMA EBEJA[4], V. MAKETA[5], K. P. GRIETENS[1], A. BUVÉ[1], F. CRAWLEY[6]

[1]Institute of Tropical Medicine, Antwerp, Belgium
[2]Institut de Recherche en Sciences de la Santé - Centre Muraz, Bobo-Dioulasso, Burkina Faso
[3]Uganda Malaria Surveillance Project, Kampala, Uganda
[4]Human African Trypanosomiasis Platform, Kinshasa, Democratic Republic of Congo
[5]Tropical Medicine Department, Faculty of Medicine of the University of Kinshasa, Democratic Republic of Congo
[6]Good Clinical Practice Alliance – Europe. Brussels, Belgium

Summary - The globalization of clinical trials, as well as the creation of funding mechanisms for research addressing the health problems of developing countries, have led to a significant increase in the number of research projects in the South. This paper reports on a workshop held by the *Switching the Pole Network* in Antwerp in December 2008 to assess the challenges of ethical review and of the informed consent process in vulnerable populations. A systematic approach to ethical review is needed, promoting trust among research partners and improving the efficiency of international ethical review practices, while building communication strategies across traditional geographical boundaries and power structures. At the moment, the double ethical review of research sponsored or funded by Northern organizations in resource-poor settings can minimize the risk of double standard practices and enhance the protection of study participants and populations. We also need guidance to prevent the exploitation of vulnerable populations in health research; in particular those whose participation is not based on a free choice but on the necessity to access otherwise inaccessible medical care or other benefits. We hope that the issues raised can feed a debate leading to better guiding principles on health research in resource constrained settings.

Key words: research ethics, developing countries, ethical review, informed consent

INTRODUCTION

Research addressing the health problems of developing countries is of paramount importance to individual and global health. The globalization of clinical trials, mentioned by Rehnquist (2001) and by the European Group on Ethics in Science and New Technologies (2003), as well as the creation of mechanisms and partnerships aimed at funding public health oriented medical research, have led to a significant increase in the number of research programs carried out in the South, often with the participation of Northern organizations. However, as showed by the WHO (2008), Schipper and Weyzig (2008), WEMOS (2008), Lancet Editors (2007) and Lenzer (2008), carrying out health research in resource-poor settings entails potential abuse and exploitation, among other factors because of the vulnerability of the research subjects and due to the weakness of the regulatory framework in which the research takes place (Glickman *et al*., 2009).

The *Switching the Poles Network* brings together researchers from Belgium, Burkina Faso, Cambodia, Cuba, Democratic Republic of Congo, Indonesia, Nepal, Peru, Uganda and Zambia, with the objective of jointly building the capacity to conduct medical research that addresses the needs of vulnerable populations according to sound ethical principles and standards as described in applicable guidelines, including the Nuremberg code (1947), the Helsinki Declaration (World Medical Association, 2008), the Belmont Report (US National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research, 1979), the Good Clinical Practices (World Health Organization, 1995;

E-mail address for correspondence: rravinetto@itg.be

Communication presented at the 6th European Congress on Tropical Medicine and International Health. Verona, Italy 6-10 September, 2009.

International Conference of Harmonization, 1996) and the CIOMS Guidelines for Biomedical Research Involving Human Subjects (CIOMS, 2002).
During a workshop held in Antwerp, Belgium, in December 2008, the members of the Network discussed the challenges linked to the ethical review of medical research carried out in developing countries by Northern organizations, and those related to the informed consent process in vulnerable populations. The results of the workshop were presented at the 6th European Congress of Tropical Medicine (Verona, 2009), and further developed in a meeting hosted by the Forum of the European & Developing Countries Clinical Trials Partnership (Arusha, 2009).

THE ETHICAL REVIEW

The role of ethical review

Ethical review has seen considerable changes over time. Originally, the Ethics Committees (ECs) had a consultative role. However, article 15 of the current version of the Helsinki Declaration stipulates that research protocols "must be submitted for consideration, comment, guidance and approval" to the EC before the study begins. As such, the Declaration has shifted the ethical review process from being a private consultation process between researcher and institution to an essential research requirement and a factor of accountability to the public. It is the role of Governments to establish the legislative framework dictating the shared modality and rules for the ethical review of each independent EC (Crawley, 1997; TDR, 2000).

The double ethical review

"Double ethical review" refers to the procedure, applicable to North-South collaborative research, of submitting a protocol for ethical clearance in the country where the research will take place and in the country of the sponsor or funding organization. Although recommended by various authors (Bompart *et al*., 2008) and laid down in several guidelines [Nuffield Council on Bioethics (2002), European Group on Ethics in Science and New Technologies (2003), US National Bioethics Advisory Commission (2001)], to date no laws or regulations exist enforcing double ethical review. In some other instances, it has not even been substantially considered, or it has been seen as a paternalistic requirement. Within the *Switching the Poles Network*, all research protocols are subject to double ethical review, being sequentially submitted to the ITM Institutional Review Board (IRB), to the legally accredited EC of the Antwerp University Teaching Hospital (UZA) and to the competent EC in the country where the research takes place. Each protocol is examined from different perspectives.

A) The IRB of ITM and the EC of UZA

Though not legally accredited as an EC under the 2004 Belgian Law Concerning Experiments on the Human Person, the IRB of ITM provides an internal, preliminary review of all ITM-related research protocols, due to its specific expertise in tropical diseases and developing countries. In addition, it is expected to stimulate and maintain institutional expertise in research ethics and methodology.
The EC of UZA is accredited to carry out ethical review according to the Belgian Law. However, there are no specific qualification requirements for Belgian ECs that evaluate research carried out overseas.

B) The ethical review in the host countries: the example of the Democratic Republic of Congo (DRC) and Peru

Peru and the DRC represent two examples of challenges related to ethical review in developing countries.
In Peru, the number of commercial and non-commercial clinical trials has considerably increased between 1995 and 2008. Nevertheless, the number of non-commercial studies remains low as compared to industry-sponsored research. The number of ECs, located both in Lima and in the provinces, has expanded quickly which will sooner or later necessitate a review of the existing ECs for accreditation purposes. The main challenge for ECs here, as is the case for other emerging countries, is carrying out quality evaluations despite the high workload and providing public assurance that only research pertinent to the study population is carried out.
In the Democratic Republic of Congo (DRC), on the contrary, there are few research projects, they are mainly coordinated by foreign institutions, and ethical review is far from being routinely implemented (Maketa *et al*., 2009). There are only two fully functional ECs: the EC of the Public Health School in Kinshasa and the thematic EC of the National Program for the Treatment of Human African Trypanosomiasis. This scarcity of ECs and the geographical inaccessibility of many provinces represent major difficulties for ethical review, further aggravated by the lack of national legislation on health research and by the weakness of Drug Regulatory Authorities. In a country where, as a result of various humanitarian crises, the ethical review system is weak (Schopper *et al*., 2009), the main challenge is building and strengthening it.
Despite the differences, some problems are common to Belgium, Peru and DRC: for instance, the fact that many researchers still perceive ethical review as a burdensome obstacle rather than a fundamental step to protect individuals and populations, and the fact that the follow-up of the research by the EC after the initial approval is often insufficient.

The Network's recommendations on double ethical review

When Northern organizations conduct, support or sponsor collaborative research in the South, the double ethical review can contribute to ensuring the appropriate supervision of the Northern partner while limiting the consequences of the weakness of ECs in the host country's (Hyder *et al*., 2004; Hyder *et al*., 2009; Kass *et al*., 2007). The Network's members agreed that all medical research funded, sponsored, implemented or supervised by Northern organizations in developing countries should undergo a double ethical review, for three principal reasons:

- *Equity*. Given the North-South inequalities, the double review can help to avoid double-standard practices and prevent that exploitative studies are carried out by Northern organizations in the South;
- *Complementarity*. The complementarity of perspectives of Northern and Southern ECs can enhance the quality of the research and improve the protection of research subjects and populations;
- *Networking*. The double review process, if accompanied by proactive communication among ECs, can help to build trust and mutual learning. It was therefore suggested that protocols be submitted to Northern and Southern ECs simultaneously rather than sequentially: if comments are issued from one or more ECs, a single letter of reply would be sent to all ECs, making them aware of all the comments.

Further reflection is needed to establish rules dealing with disagreement: the respect of national sovereignty should be balanced with the need to ensure the strictest enforcement of ethical principles. The double ethical review should never lead to a decrease in the perceived responsibility of individual ECs: on the contrary, as indicated in 2008 during the Global Ministerial Forum on Research for Health (2008), there is a great need to work to increase the ownership of research in developing countries.

THE INFORMED CONSENT IN VULNERABLE POPULATIONS

Informed consent in health research

The requirement that individuals give voluntary consent to participate in medical research is based on the principle of respect, which originates from the belief that everybody has the right and the capacity to act voluntarily and with self-determination. Through the informed consent process, a person or his/her representative voluntarily agrees to participate in research, under the conditions of being informed of all the aspects relevant to the decision and maintaining a relationship of trust and communication with the researchers during the entire research.

The quality of the informed consent process and related ethical implications (Flory *et al*., 2004), is susceptible to several factors, including the individual characteristics of the researcher (personality, language skills, knowledge and perceptiveness to the local context, cultural and social sensibility, etc.) and of the participant (education and reading level, comprehension capacity, socio-cultural values and constraints, socio-economic status, etc.). Although most guidelines pay special attention to individuals whose free decision-making capacity is diminished or impaired because of legal or medical reasons (e.g., children, mentally disabled people, elderly, subjects in emergency situations or with incurable diseases, etc), there is a consensus in the bioethics literature that not only individuals, but also populations may have diminished autonomy and can be potentially vulnerable to exploitation: for instance, marginalized communities (Nakkash *et al*., 2009), people in hierarchical social structures, illiterate people, etc. This situation is quite frequent in resource-poor and rural contexts (Fitzgerald *et al*., 2002; TDR, 2007), due to socio-cultural and socio-economic factors, including language barriers, gender, peer and community pressure, dearth of health care and medicine, direct poverty and overall social vulnerability.

Free decision-making in particular may be impaired by the lack of access to adequate health-care. Most people in communities burdened with high disease rates and insufficient or inaccessible medical care cannot refuse to get the free, quality health-care services that are provided within the medical research projects and that are otherwise unavailable. In these populations and settings, therapeutic misconception is often greater, e.g. people expressing their gratitude to the research team for the "assistance" while being largely unaware of the research content.

Certain groups present more specific challenges: for instance, the Guidelines of the Uganda National Council for Sciences and Technology (web site) entitle minor mothers to give consent for the participation of their children in research projects. This choice is based on a delicate balance among social, cultural and legal factors, and on the notion of "adulthood" based on elements other than age, such as the person's social status.

The informed consent in health related social science research

Qualitative social science research and ethnographic studies in international health are guided by the same moral and legal principles of informed consent as health research and therefore require that partici-

pants are well and truthfully informed. The different nature of the research, the diverse characteristics of the participants and the different level of risk for respondents, however, may require a different application of the consent procedure, as described by the American Anthropological Association (2004). In ethnographic studies, the investigator uncovers the local social setting and cultural context by observing and by interacting both formally and informally with respondents in the field, making flexibility and informality key elements of research of this nature. Therefore, procedural requirements of written consent may in some cases create distrust between the researcher and respondent or lead to decreased reliability of results due to enhanced response bias.

The independent ECs are required to ensure the appropriateness of the informed consent process in social science research and any kind of health and non-health research carried out with human subjects, always taking into due account the vulnerability of the study population. Since ECs generally focus on health research, it is advisable that they get additional and specific expertise to evaluate research in borderline and non-medical fields - such as ethnographic studies.

On a different level, the social sciences can contribute to improving the quality of the informed consent procedure in medical research by providing tools to enhance the quality of the communication between the researcher and the participant and his/her community. In particular, social scientists can provide in-depth and contextualised information on how to construct context- and cultural-sensitive communication strategies with potential participants, reducing common cultural pitfalls and misunderstandings that often lead to low participation or increased drop-out rates and can seriously jeopardise health research ethics.

The Network's recommendations on informed consent process

- Individual informed consent is essential, irrespectively of the field of the research and of the characteristics of the population. Waivers granted by a competent EC should only concern the signature, never the process, and they should never be justified by the fact that the study population is poor or illiterate.
- Guidance is needed to prevent exploitation of vulnerable individuals and populations with diminished decision-making power concerning their participation in health research (including those lacking access to quality health care).
- Research institutions should try to reconcile the research of new therapeutic tools with the ethical requirement of making them accessible to everyone through quality health care systems. Even if achieving universal access to quality health care is a complex and long-term task, research institutions and sponsors could contribute to improving the quality of health care in their respective research settings on a project by project basis.
- The understanding of and sensibility for local socio-cultural values, constraints and contextual factors, always within the framework of universal ethical principles, is a prerequisite for respectful and ethical interactions between researchers and study participants in vulnerable contexts. Social scientists and anthropologists can help to design the research and consent tools accordingly, contributing to overall effectiveness, relevance and research ethics.

ACKNOWLEDGEMENT

The Switching the Poles Network is funded by the Belgian Development Cooperation.

REFERENCES

AMERICAN ANTHROPOLOGICAL ASSOCIATION (2004). Statement on Ethnography and Institutional Review Boards. Available at: http://www.aaanet.org/stmts/irb.htm.

BOMPART F. HIRSCH F., BERTOYE P.H AND VRAY M. (2008). Bonnes Pratiques Cliniques dans les pays en développement: recommandations en termes d'application. *Thérapie*, **63**(2): 77–82.

CIOMS (2002). Council for International Organizations of Medical Sciences and World Health Organization. International Ethical Guidelines for Biomedical Research Involving Human Subjects. CIOMS, Geneva.

CRAWLEY F.P. (1997). Guidelines and Recommendations for European Ethics Committees. European forum for good clinical practice (EFGCP). Revised Edition. Kessel-Lo, Belgium.

EUROPEAN GROUP ON ETHICS IN SCIENCE AND NEW TECHNOLOGIES TO THE EUROPEAN COMMISSION (2003). Opinion on the Ethical Aspects of Clinical research in Developing Countries. Opinion N° 17.

FITZGERALD D.W., MAROTTE C., VERDIER R.I, WARREN D.J., PAPE J. W. (2002). Comprehension during informed consent in a less-developed country. *The Lancet*, **360**: 1301-02.

FLORY J., EMANUEL E. (2004). Interventions to Improve Research Participants' Understanding in Informed Consent for Research: A Systematic Review. *Journal of the American Medical Association*, **292**(13): 1593-1601.

GLICKMAN S.W., McHUTCHISON J.G., PETERSON E.D., CAIRNS C.B., HARRINGTON R.A., CALIFF R.M., AND SCHULMAN K.A. (2009). Ethical and scientific implications of the globalization of clinical research. *The New England Journal of Medicine*, **360**(8): 816-823.

GLOBAL MINISTERIAL FORUM ON RESEARCH FOR HEALTH (2008). Strengthening Research for Health, Development and Equity. 17-19 November 2008, Bamako, Mali.

HYDER A.A., WALI S.A , KHAN A.N., TEOH N.B., KASS N.E., DAWSON L. (2004). Ethical review of health research: a perspective from developing country researchers. *Journal of Medical Ethics,* **30**: 68-72.

HYDER A.A, DAWSON L., BACHANI A.M., LAVERY J.V. (2009). Moving from research ethics review to research ethics systems in low-income and middle-income countries. *The Lancet*; **373**: 862-5

INTERNATIONAL CONFERENCE OF HARMONIZATION (1996). ICH Tripartite Guideline for Good Clinical Practices E6 (R1), 10th June 1996.

KASS N.E., HYDER A.A., AJUWON A., APPIAH-POKU J., BARSDORF N., ELSAYED D.E., MOKHACHANE M., MUPENDA B., NDEBELE P., NDOSSI G., SIKATEYO B., TANGWA G., TINDANA P. (2007). The structure and function of research ethics committees in Africa: A case study. *PLoS Medicine*, **4**(1): e3. doi:10.1371/journal.

LANCET EDITORS (2007). Editorial: Strengthening clinical research in India. *The Lancet*, **369**: 1233.

LENZER J. (2008). Nigerian judge orders arrests of Pfizer officials. *British Medical Journal*, **336**: 11.

MAKETA V., EBEJA A., BOELAERT M., RAVINETTO R., UTUMBA P. (2009). Ethics and clinical research in Democratic Republic of Congo (DRC). *European Journal of Tropical Medicine and International Health*, **14**(2): 48.

NAKKASH R. MAKHOUL J., AFIFI R. (2009). Obtaining informed consent: observations from community research with refugee and impoverished youth. *Journal of Medical Ethics*, **35**: 638-643.

NUFFIELD COUNCIL ON BIOETHICS (2002). The ethics of research related to healthcare in developing countries. Nuffield Council on Bioethics, London.

NUREMBERG CODE (1947). Reprinted from Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10, Vol. 2, pp. 181-182.

RENQUIST J. (2001). The globalization of Clinical Trials: a growing challenge in protecting human subjects. US Department of Health and Human Services, Office of Inspector General. OEI-01-00-00190.

SCHIPPER I., WEYZIG F. (2008). *Examples of unethical trials*. SOMO briefing paper on ethics in clinical trials. SOMO, The Netherland. Available at: www.somo.nl.

SCHOPPER D., UPSHUR R., MATTHYS F., SINGH J.A., BANDEWAR S.S., AHMAD A., VAN DONGEN E. (2009). Research Ethics Review in Humanitarian Contexts: The Experience of the Independent Ethics Review Board of Médecins Sans Frontières. *PLos Medicine*, **6** (7): 1-6.

TDR (2000). Special Programme for Research and Training in Tropical Diseases/World Health Organization. Operational Guidelines for Ethics Committees That Review Biomedical Research. TDR WHO, Geneva. Available at: www.who.int/tdr/publications/.

TDR (2007). Special Programme for Research and Training in Tropical Diseases/World Health Organization. Ethical challenges in study design and informed consent for health research in resource-poor settings. TDR/SDR/SEB/ST/07.1. Special topics N°5. WHO TDR.

UGANDA NATIONAL COUNCIL FOR SCIENCES AND TECHNOLOGY. Available at: http://www.uncst.go.ug/.

US NATIONAL BIOETHICS ADVISORY COMMISSION (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.

US NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIOURAL RESEARCH (1979). The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. Department of Health, Education and Welfare, US.

WEMOS (2008). A bitter pill: The risks of carrying out clinical drug trials in developing countries. Wemos, The Netherlands. Available at: www.wemos.nl.

WORLD HEALTH ORGANIZATION (1995). Guidelines for Good Clinical Practices for trials on pharmaceutical products. *WHO Technical Report Series* No. 850, Annex 3. WHO, Geneva.

WORLD HEALTH ORGANIZATION (2008). Clinical Trials in India: ethical concerns. Transnational drug companies are moving their clinical trials business to

India, giving a new urgency to clinical trials registry reform there. Patralekha Chatterjee reports. *Bulletin of the World Health Organization*, **86** (8): 581-582.

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, October 2008.