

Ethical criteria in clinical research in developing countries: is there a global standard?

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Summary - Clinical researchers in developing countries face multiple challenges related to contextual constraints, poor regulation and vulnerability of trials' subjects. The World Health Organization issued in 1995 its Good Clinical Practices (GCP) Guidelines, setting globally applicable standards for clinical trials. Non-compliance with GCP principles leaves room for misconduct and abuse, while a rigid interpretation of GCP processes and procedures may unnecessarily increase the research costs and even prevent research relevant to public health from being carried out.

Ethical principles and scientific standards governing research are universal and should be adopted everywhere, to ensure persons' protection and data's reliability, while avoiding any North-South ethical divide. However, principles should be translated into simple and effective processes and procedures, which ensure quality of the research and subjects' protection, without putting unnecessary obstacles to public-health oriented research. It is time to "reinvent" GCP, by updating the 1995 WHO Guidelines in light of the 15-year experience of worldwide implementation. The revision should include old and new stakeholders (including academic institutions from the South and the North, NGOs, public-private partnerships, donors, patients associations etc.) and could, by making clearer distinction between essential and procedural requirements, help researchers and sponsors to design new patient-centered tools and practices.

Key words: ethics, standards, clinical research, developing countries

INTRODUCTION

Clinical research has been a keystone in solving many public health problems faced by the world population. As reported by the Global Forum for Health Research (2004), of the estimated US\$ 56 billion spent annually on medical research by the global community, at least 90% is spent on the health needs of the richest (10% of the world's population), while only 10% addresses the needs of the remaining 90% of the world's population. The unequal distribution is linked to the poor economy in developing countries, resulting in lack of adequate financial and human resources. Nonetheless, the number of clinical trials carried out in the South has significantly increased over the last years. The increase is partly due to a trend to move the research to countries with more favourable costs, less rigorous regulations and greater availability of patients and medication-naïve patients (Rehnquist, 2001; The European Group on Ethics in Science and

New Technologies to the European Commission, 2003; Wemos and European Parliament, 2007; Schipper and Weyzig, 2008) and partly to an increase of public health-oriented studies, addressing major unanswered health problems.

Clinical researchers face many challenges in resource-limited contexts, including contextual constraints (transport, internet connection, etc.), poor regulation, and vulnerability of the trials' subjects, due to socio-economical factors, illiteracy, marginalization or exclusion.

The World Health Organization (WHO) has developed and published almost 15 years ago its Guidelines for Good Clinical Practices (GCP) (World Health Organization, 1995), for setting globally applicable standards for the conduct of trials on pharmaceutical products on human subjects. "Compliance with GCP provides public assurance that the rights, safety, and well-being of research subjects are protected and respected, consistent with

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the principles enunciated in the Declaration of Helsinki (World Medical Association, 2008) and other internationally recognized ethical guidelines, and ensures the integrity of clinical research data” (World Health Organization, 2002).

The WHO Guidelines comprises **principles, processes and procedures**.

The **principles** are summarized in chapter 1.2 of the Declaration of Helsinki: “All research involving human subjects should be conducted in accordance with the ethical principles contained in the current version of the Declaration of Helsinki. Three basic ethical principles should be respected, namely justice, respect for persons, and beneficence (maximizing benefits and minimizing harms and wrongs) and non-maleficence (doing no harm) as defined by the current revision of the International Ethical Guidelines for Biomedical Research Involving Human Subjects issued by the Council for International Organizations of Medical Sciences (CIOMS, 2002) or the laws and regulations of the country in which the research is conducted, whichever represents the greater protection for subjects. All individuals involved in the conduct of any clinical trial must be fully informed of and comply with these principles”.

The **process** and **procedures** concern the structure of the protocol, the concrete measures to be taken for the protection of trials’ subjects, the responsibilities of the Investigator, of the Sponsor and of the Monitor, the monitoring of safety, the record-keeping and handling of data, the statistics and calculations, the handling and accountability of pharmaceutical products, the role of the drug regulatory authority, the quality assurance and some additional considerations for multi-centre trials.

The WHO recommends that these principles, processes and procedures be applied to all clinical research. It has been widely demonstrated that non-compliance with GCP principles leaves room for misconduct, fraud and abuse, especially when trials are carried out in the South for convenience reasons (Schipper and Weyzig, 2008a; Wemos, 2008; Louwenberg, 2008). However, a rigid interpretation of GCP processes and procedures may unnecessarily increase the costs of the research (White, 2006; Stewart *et al.*, 2008). In developing countries, where

resources and time are limited, the emphasis on processes and procedures may create competition between medical research and patient care, and some think that it may even prevent to carry out non-commercial research relevant to public health. To analyze the tension between the two extremes of “GCP relaxation” and “GCP rigidity”, a debate took place on 8th September 2009 during the 6th European Conference of Tropical Medicine: is there a global standard for clinical research? Should standards be adapted in developing countries? How to encourage research while preventing the exploitation of vulnerable individuals or groups?

Five “debate questions” (Tab. 1) were addressed by Professor Nick White and by Dr. Lumuli Mbonile, and discussed with the moderator (Raffaella Ravinnetto) and the audience. The following chapters reflect the debate and discussion, trying to be as inclusive as possible of the different positions.

Question 1. Research standards

Clinical research is premised on two fundamental moral commitments: to improve human welfare by advancing scientific knowledge and understanding of disease, and to preserve and protect the dignity and health interests of the research participants. The potential risk of harm, as well as evidence that misconduct and fraud occurred both in the North and in the South of the world, led to agreement that sound, universal ethical standards are needed, irrespective of the geographic and economic setting where research is undertaken.

On the one hand, we were reminded that research standards, as expressed in the principles of the WHO GCP guidelines, were derived from the rule of common morality, which is applicable to all persons in all places and which, together with moral characteristics traits or virtues, is universal. Since common morality rules constitute the building blocks of research ethics and of GCP, the GCP principles should be applicable and should be adopted everywhere. GCP processes and procedures are derived from the principles, and their implementation is necessary to try and ensure *a priori* that all the patients worldwide are protected in the same way, that all the research is of sound scientific quality and that all research data are fully reliable:

Table 1 - The five debate’s questions

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1. Research standards: should WHO GCP standards be adapted for clinical research that addresses relevant health questions in developing countries?
 2. The role of funding agencies: should researchers working in externally-funded projects in developing countries advocate for an increase of research budgets to better cover GCP-requirements?
 3. Research standards in emergency settings: should exemptions to GCP requirements be considered?
 4. Ethical review of “externally sponsored trials”: should we solely focus on strengthening the ethical review in developing countries, or should we build on complementary mechanisms, based on North-South double ethical review?
 5. Standard of care: is it acceptable to use different standards concerning the choice of a placebo control, in developed versus developing countries?
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processes such as external monitoring, verification of source data and documentation of the appropriate use of investigational medicinal products are thus essential to ensure these general principles are respected.

From another perspective, however, although the principles of common morality are generalisable, the processes and procedures are not, because they are derivative and strongly influenced by cultural and contextual elements. From this perspective, it was noted that most GCP guidelines have been issued by developed countries (International Conference of Harmonization, 1996), or are based on the experience of the industry-sponsored research, so they reflect the experiences, objectives, financial capability and skills of commercial research. This applies to some extent also to the WHO GCP Guidelines, issued in 1995: the text was developed in consultation with national drug regulatory authorities within WHO Member States, and discussed during two informal consultations attended by representatives of the WHO, the International Union of Pharmacology, Universities from Indonesia, Denmark, Zambia, Brazil and China, pharmaceutical agencies from Japan, the USA, Russia and Sweden, the International Federation of Pharmaceutical Manufacturers Association and a pharmaceutical industry (Ciba-Geigy). The recommendations are very similar to those applied by industry to pre-registration clinical trials, and they require a level of human resources and management detail that is not based on a risk-approach and goes beyond the capacities of most academic and non-commercial groups.

From this perspective, several formal requirements, in addition to being complicated and expensive, are of uncertain value, because too often the focus is put on the processes rather than on the persons. For instance, external monitoring often focuses exclusively on the examination of the CRF and related documents (checklist approach), without looking at the context of the clinical sites and at the approach to the patient. The informed consent is mainly seen as a signature (verification of a formal requirement) rather than a relational process. The ethical and regulatory review themselves may focus on specific technical aspects highlighted in GCP (e.g., informed consent, investigational medicinal products etc.) rather than on a comprehensive review of the protocols, so that they often end up overlooking major scientific or methodological weaknesses in the research.

So on one hand, we face a moral requirement to ensure universal enforcement of universal research ethics principles, so as to avoid improperly designed trials, to prevent the exploitation of individuals and groups, to promote pertinent research in countries

with poor resources and to avoid any North-South ethical divide. The increase in costs linked to compliance with guidelines is, in this perspective, largely justified by the benefits.

On the other hand, we face a moral requirement to translate GCP principles into simple and effective processes and procedures: simplicity should be seen as a guiding value, for designing effective rules that ensure quality of the research and subjects' protection, without putting unnecessary obstacles to public-health oriented clinical research carried out for the benefit of the Southern populations.

A balance must be found between the two extremes of rigidity and relaxation, which both produce inequalities. There was agreement that a revision of the 1995 WHO GCP Guidelines, while leaving principles unchanged, was needed. This could act as a basis for the design of new patient-centered tools and practices.

Question 2. The role of funding agencies

The WHO GCP guidelines, published in 1995, define the sponsor as "an individual, a company, an institution or an organization which takes responsibility for the initiation, management and/or financing of a clinical trial", while it does not explicitly mention the role of the Donors, taking it for granted that each sponsor funds its own trial and manages its own budget. This is the case in industry-sponsored trials. However, a great deal of the research programs carried out by non-commercial sponsors, NGOs, academic organizations, etc., to address the health problems of populations of developing countries, are funded by external Donors.

Full compliance with GCP incurs large costs. As a result in externally-funded clinical trials it is the funding policy of the Donor/s that concretely sets the "GCP level". For instance, external monitoring is requested by GCP for ensuring subjects' protection and reliability of data: however, quality external monitoring implies additional costs, which should be covered by the Donor, which is generally from a Northern country or institution. The same applies to other tools and process which should improve the patients' protection (e.g., the no-fault policy insurance for clinical trials) or the quality and reliability of research data (e.g. validation of databases). Are the research budgets generally sufficient to cover all the "quality costs"?

On one hand, it was felt that researchers working in externally-funded projects in developing countries should advocate for an increase of research budgets, to cover GCP-requirements more comprehensively. The increase in research-related costs would be justified by important benefits: would maximize the participants' protection, ensure the quality of data, prevent misconduct, improve collaborative research

tools and increase the research awareness among participants in developing countries. From a North-South perspective, in addition, funding policies should always ensure that the same research standards are applied in the country of the donor (developed countries) and in the research countries (developing countries).

On the other hand, the implementation of GCP principles should give priority to essential requirements over formal and procedural aspects. If too much attention is given to the process and insufficient attention is given to the patient and his/her context, the increase of the “GCP budget” could mean that financial resources are diverted from essential to non-essential requirements. In this view, the donors should support what is needed to ensure optimal design, best care of the patients, ethical conduct and credible results, without diverting money to burdensome, complicated and non-essential activities.

A balance should be achieved between universal standards and contextualized practices and tools, without ever losing the focus on the patient.

Question 3. Research standards in emergency settings

Increasingly, international and nongovernmental organizations providing emergency medical care and humanitarian assistance to vulnerable populations are turning into producers of health research, which range from simple health surveys or interview studies, to complex clinical trials (The PLOs Medicine Editors, 2009; Priotto *et al.*, 2008; Priotto *et al.*, 2009). This research is of paramount importance to address the specific problems of populations living in extremely poor and unstable settings, in conflict and in disaster situations. However, there is undoubtedly a huge tension between the ideal setting for medical research, which requires stable and controlled operating environment, and emergency contexts. Situations marked by violence and insecurity, in particular, are often characterized by acute ethical dilemmas: power imbalance versus informed consent process; signed informed consent versus confidentiality and security; lack of formal ethical review structures versus need to intervene quickly (e.g. in case of epidemics); limited political and institutional recognition of ethical issues; competing interests and limitations in research skills and practice (Schopper *et al.*, 2009; Zwi *et al.*, 2006).

Full compliance with GCP formal processes and procedures may be impossible: should we then give up the possibility of carrying out research, so further neglecting the health needs of these vulnerable populations? Or should exemptions to GCP requirements (e.g., written informed consent, preliminary ethical approval, external monitoring, etc.) be

considered in emergency contexts?

On one hand, it was noted that even if the general ethical principles are universal, there are specific ethical challenges that researchers encounter in emergencies. An interesting example comes from a case study presented by Richard Black of the University of Sussex (Reed, 2002). In Liberia, two codes of conduct for humanitarian action were developed during the emergency: the Principles Humanitarian Operations (PPHO), a United Nations initiative, and the Joint Plan of Operations (JPO), initiated by the NGOs. The PPHO was focused on such issues as impartiality, neutrality, independence, informed consent and the targeting of aid, because of a concern that aid was sustaining or legitimizing armed factions. The JPO was instituted after the April 1996 looting of aid and ransacking of NGO offices by armed factions; its focus was on minimum targeted lifesaving activities. The two ethical codes tended to place limits on research and operations in Liberia, but Black argued that the very process of establishing codes was useful, because it created a dialogue between donors and agencies about ethics. Yet there was poor coordination among agencies.

Redundancy and overlap are a common problem in emergency settings, with an accumulation of similar studies without any coordination among research teams (is it ethical to approach again the same population to collect similar data if prior data remain unused?). From this experience, we can draw the lesson that establishing rules remains crucial in emergency settings, where the lack of regulation creates or aggravates specific ethical problems.

Thus, the procedures derived from research ethics principles should not be systematically waived in emergency contexts. For instance, informed consent is essentially a relational process, not a one-time signature; the “formal” requirement of signature should be maintained, unless an exemption is needed for protecting the persons and/or when the research is at very low risk (e.g., surveillance in outbreaks). Waivers should only be based on the patients’ needs and benefits. In addition, whenever possible, the study populations should be involved in designing or at least approving the alternative procedures: representatives of the community could be members of the independent review committees, and research subjects could be involved in the research process (observation, focus group, etc).

On the other hand, we were reminded that in emergency situations the distinction between essential requirements (which have an actual added value in terms of persons’ protection and research quality) and non-essential requirements (procedural requirements, without an added value), is more crucial than ever. The translation of principles into practices and

tools should have the primary objective of protecting the persons and maximizing the value of the research, without putting unnecessary obstacles to pertinent and useful research.

“Excellent studies can be very simple”: The benefits and risks should be carefully weighed on a case-by-case basis, in terms of harm reduction (for those who have already suffered harm and/or are at greater risk of harm) and of life protection. Delaying or preventing useful research may be as harmful to people as misconduct and fraud in research.

Question 4. Ethical review of “externally sponsored trials”

The term *externally sponsored research* refers to researches undertaken in a host country, but sponsored, financed or wholly or partly carried out by an external international or national organization or pharmaceutical company, with the collaboration or agreement of the appropriate authorities, institutions and personnel of the host country. Most donors are from the rich and technologically-advanced nations, while developing countries provides research sites and participants and, increasingly, medical and scientific knowledge.

The collaboration between developed and developing countries needs a balanced harmonization strategy, and this also concerns the ethical clearance process. According to the CIOMS Guidelines (Council for International Organizations of Medical Sciences, 2002), “an external sponsoring organization and individual investigators should submit the research protocol for ethical and scientific review in the country of the sponsoring organization, and the ethical standards applied should be no less stringent than they would be for research carried out in that country. The health authorities of the host country, as well as a national or local ethical review committee, should ensure that the proposed research is responsive to the health needs and priorities of the host country and meets the requisite ethical standards”. However, many developing countries lack an effective ethical review system: according recent studies, the 45% of US-funded studies conducted in developing countries in 2004 did not undergo technical, scientific or ethical review (Hyder *et al.*, 2004) and 70% of developed countries lack ethical review capacity (Milford *et al.*, 2006). Given that the overall funds for clinical research and research capacity strengthening in developing countries is still insufficient compared to global needs, which priorities should be set? Strengthening the ethical review in developing countries, or building complementary mechanisms, based on North-South double ethical review?

On one side, it was noted that research capacity building is still fragmented: the “developed” and the

“developing” blocks have created their own research priorities, review mechanisms and guidelines, rather than promoting collaboration. The North-South divide is especially evident for ethical review process and procedures: cultural diversities and standards of care have been used for many decades as an excuse for insufficient global collaboration on ethical mechanisms, raising a paradoxical question as to which to promote between culture and good health. In this perspective, the North-South collaboration on ethical review of trials is crucial and it should go well beyond the adoption of common guidelines for establishing and training Ethics Committees (ECs): a communication link should be created between ECs in the North and in the South, to benefit from the complementarity of perspectives (mutual learning), and to contribute to overcome the North-South gap in research capabilities.

On the other side, it was reminded that the relevance of North-South collaboration should not divert the focus from the “local” ethical approval, which should never be replaced by external expertise. In this view, investments should primarily be done in strengthening the review capacities in Southern countries (TDR/WHO, 2000; GCP/WHO, 2003).

From both perspectives (focus on North-South collaboration vs. focus on the quality of the local ethical approval), it appears that ethical review everywhere needs to be supported by appropriate quality assurance mechanisms encompassing the ethical, methodological and scientific points of views (bad science in clinical research is *per se* unethical). This is crucial to ensure that standards are upheld, and to avoid, as far as possible, that biased or unreasonable reviews prevent good research or endorse bad research.

Question 5. Standard of care: the use of placebo.

According to the WHO GCP, “the current revision of the Declaration of Helsinki is the accepted basis for clinical trial ethics, and must be fully followed and respected by all parties involved in the conduct of such trials”. The 2008 version of the Helsinki Declaration states that “the benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option”.

This wording leaves room for different interpretations and for translation in different practices. In addition, it does not clearly address the question of whether it is acceptable to use different standards concerning the choice of a placebo control, especially in developing countries, where the different standards of practice and care create quite specific questions (Lie *et al.*, 2004; Bhutta, 2004; Shapiro and Benatar, 2005; Wendler *et al.*, 2004; Angell, 1997; Lurie and Wolfe, 1997).

In general, exploitative studies that do not address the needs of the population of the host country are not acceptable in the frame of the Helsinki Declaration. On October 27th, 2008, however, the US FDA formally discontinued its reliance on the Declaration and substituted the ICH GCP. According to some comments, the FDA decision may have been motivated by the differences between these documents relating to the use of placebo controls in trials (Kimmelman *et al.*, 2009; Goodyear *et al.*, 2009).

Placebo controls are ethically justifiable only if they are supported by sound methodological considerations and when their use doesn't expose research participants to excessive risks of harm. In developing countries, in particular, studies which could improve health care by providing evidence of benefit compared with currently available best practice should be facilitated, and under some circumstances the use of placebo may be justified (Onder, 2005).

The risk for the participants can never be entirely eliminated: so, the risk-benefit analysis will always be complex, and should include such elements as the best available standard in the host country, the post-trial availability and affordability of the study drug, the inherent conflict between clinical research versus clinical practices, etc.

CONCLUSIONS

Ethical principles and scientific standards governing clinical research are universal, and should be adopted everywhere, to ensure protection of persons, quality of the research and reliability of data, while avoiding any North-South ethical divide.

However, the principles and standards as stated in GCP guidelines are translated in processes and procedures, which are influenced by the contexts where the guidelines are issued. In addition, they are further translated in national laws, practices and tools, which should be adapted to contextual constraints, so as to avoid exploitation and bad practices on one hand, and to encourage public health-oriented clinical research on the other hand.

It is time to "reinvent" GCP, by updating the 1995 WHO Guidelines, in light of the 15-year experience of worldwide implementation. Where possible, the updated Guidelines should be simplified and clari-

fied, by taking into account the specificities of different contexts and by building a risk-based approach which goes beyond the traditional phase I-V classification.

The revision process should include all the "old" stakeholders and "new" stakeholders (academic institutions from the South and the North, NGOs, public-private partnerships, donors, patients associations, etc.) and could, by making clearer distinction between essential and procedural requirements, help researchers and sponsors to design new patient-centered tools and practices.

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