

Guidelines for Clinical Research in Developing Countries

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Abstract – On the basis of a review of current clinical research conditions in developing countries, guidelines have been formulated to ensure scientific validity as well as adherence to universal ethical principles. The main recommendation is that projects should be reviewed by two Institutional Review Boards, one in the country where the Study Sponsor is based, and another in the country where the study is being carried out. In addition, an independent Data Safety Monitoring Board should be set up and systems established to ensure the effective reporting of Serious Adverse Events and to specify the Sponsor's obligations after the end of the Study.

1. Introduction

The Round Table set out to review how clinical research projects are currently conducted in DCs (developing countries) with a view to formulating guidelines to guarantee, on the one hand, the scientific validity of the research and, on the other hand, adherence to universal ethical principles.

Although there is no hard-and-fast definition of a DC, a broad framework has been defined based on factors that are of importance when it comes to conducting a clinical trial, notably restricted access to health care and treatment, inadequate health care infrastructure and medical training, low Gross Domestic Product, and inadequate – or ineffectively applied – regulations governing research.

It is important to start out with the idea that clinical studies conducted in DCs must benefit local people, after as well as during the research.

The term “clinical research” here is taken as covering all projects related to drugs, vaccines, therapeutic strategies and medical devices as well as post-Marketing Authorisation (MA) pharmaco-epidemiological studies.

The main reasons for wishing to conduct a clinical investigation in a DC can be divided into three broad categories:

1. Pre- or post-MA clinical studies of DC-specific diseases (*e.g.* malaria or schistosomiasis); a study in a DC is the only way to evaluate a candidate treatment.

2. A strategy that has already been evaluated in the developed world (*e.g.* the evaluation of an anti-retroviral treatment licensed in the “rich countries”) will need to be studied in DCs to take into account local particularities that may affect how it is implemented (costs, storage conditions, problems associated with stigmatisation, etc.). In the same way, a new paediatric cancer drug would have to be specifically studied in DCs to re-evaluate the benefit-to-risk ratio in a context quite distinct from that of the developed countries.

3. Studies on diseases found in both the developed and the under-developed worlds which cannot for practical reasons be conducted in the former, either because of an insufficient number of patients (*e.g.* HIV-infected women who are breast-feeding) or because the study has to be conducted in a population with a specific genetic make-up (*e.g.* some particular metabolic deficiency).

The decision to conduct a clinical research project in a DC requires good knowledge of the local epidemiology of the disease in question and of the available health care infrastructure. Training programmes may be necessary before the research can be commenced, and any project must be well integrated into the local political setting. Any research needs to take stock of a community's social organisation as well as the particularities of the local media.

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Patient support groups, if there are any, should be brought into the process. It is essential to define the patient-physician relationship clearly because clinical trials are often the only way patients can get access to an otherwise inaccessible treatment. Finally, the research must be always compatible with – and, if possible, be integrated into – national health programmes.

2. Current standards governing clinical trials

Various international texts legitimise and provide a framework for human experimentation. Some ethical texts address the scientist's social conscience: most of these originate from non-governmental organisations, learned societies or academia and such texts have inspired many of the national and European guidelines. Clinical research in the “northern hemisphere” is mainly governed by the ICH (International Conference on Harmonisation) guidelines^[1] backed up by a European Directive.^[2] However, due to issues related with some clinical trials carried out in the southern hemisphere, certain international institutions as well as national institutions in France^[3,4] and elsewhere^[5,6] proposed a specific framework. Notable among the international texts are: the World Medical Association's Helsinki Declaration^[7] which involves each physician's ethical values; the CIOMS (Council for International Organizations of Medical Sciences)/WHO (World Health Organisation) Manila Declaration^[8] which expands the principles to all biomedical research and includes a special section dealing with research in DCs; and the UNESCO (United Nations educational, scientific and cultural organization) adopted Universal Declaration on Bioethics and Human Rights which also contains a special section on DCs.^[9] An addendum to the Convention on Human Rights and Biomedicine is currently open to signature by the member states: this protocol has a special status since it is the fruit of an intergovernmental process and is bound up with international law so any state that ratifies the protocol is committing itself to adhere to the principles embodied therein, often by incorporating the text into its domestic legislation or by altering its laws to bring them into line with the Treaty to which it is a signatory. This is so in the case of France which, in the context of its ratifying of the 1997 Oviedo Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine,^[10] modified certain principles pertaining to experimentation, *e.g.* by adding a principle of minimising pain. Nevertheless, not all these texts are applicable in France since they only gain force if they are incorporated into domestic law.

In France, the only enforceable legislation – in the sense that contravention can be sanctioned – is the revised Huriet Law which was transposed from a European Directive which was itself derived from ICH “Guidelines and Good Practices”. The difficulty

comes from the fact that, in the application of this Law, research abroad is excluded. Therefore, in France as in the majority of countries, there is a legislative gap since investigators working in DCs – although morally obliged to adhere to the above-mentioned declarations – are not subject to any legal constraint and cannot be sanctioned for failure in this respect.

3. “Good Practices” standards applicable to clinical research in DCs

There are many sets of guidelines pertaining to the conduct of clinical trials (the ICH GCPs, the Helsinki Declaration, the CIOMS guidelines, etc.) but they are sometimes difficult to apply in DCs, especially if there is no local legislation concerning clinical research or if there are logistic problems. The ICH guidelines were designed for the USA, Europe and Japan, and need to be recast to cover DCs. The Round Table attempted to propose standards which are suitable for DCs, with a view to ensuring credible scientific results at the same time as guaranteeing adherence to fundamental ethical requirements. The discussion brought out that the basic ICH guidelines are ultimately “non-negotiable” and are as applicable to the southern as to the northern hemisphere, although flexibility could be introduced into certain procedural details to take stock of the realities in DCs.

4. Guidelines

The Round Table's main recommendations concern the following points.

4.1. Before the beginning of the trial

4.1.1. Informed consent

Because of cultural or environmental factors, a patient's Informed Consent may depend on other community figures (*e.g.* a local dignitary or a religious leader) or family members (*e.g.* the wife's opinion may be subordinate to that of her husband). Whatever the cultural particularities that may entail modification of procedures, the principle of Informed Consent – personal, comprehensible and fully documented – is a fundamental one and must be adhered to in all circumstances.

4.1.2. Ethics committees for projects being conducted in a DC and being sponsored by an entity based in an industrialised country

The “International Ethical Guidelines for Biomedical Research Involving Human Subjects” (CIOMS 2003) require approval by two Ethics Committees, one local (*i.e.* located in the

country where the study is being conducted) and another in the country where the sponsor is based. However, despite the recommendations of the National Consultative Ethics Committee (CCNE, Comité Consultatif National d’Ethique) for the Life Sciences, French Law does not provide for this since Institutional Review Boards (IRBs) are only currently qualified to give opinions on projects conducted in France. Nevertheless, it is the IRBs – whose composition and role are clearly established by the law as is how its members are appointed – which are the best placed to fulfil this function in a perfectly independent manner. For example, the members of the “Ile de France XI” IRB have agreed to review any files submitted to them by a variety of research institutions and non-governmental organisations although their opinion is not today formalised in the form of an IRB Ruling. In the future, this system needs to be formalised, in particular to cover the sponsor’s obligations in the matter of insurance; the question of the payment of fees to IRBs also needs to be addressed. This would make it easy to put the principles embodied in the guidelines into practice. French regulations need to be changed to encourage this. Dialogue between the two committees is highly desirable and quite indispensable in the event of disagreement. Conducting a clinical trial in a country where there is no functional Ethics Committee must be strongly discouraged but, if the trial absolutely cannot be conducted anywhere else, the opinion of an Ethics Committee in the Northern hemisphere is indispensable. Ideally, a local Ethics Committee would be established in the planning stages of the trial. Furthermore, the importance was emphasised of the Ethics Committee being appropriately composed, multidisciplinary and able to maintain its independence *vis-à-vis* both researchers and sponsors. Whether or not the political authorities or the local administration should be represented on an Ethics Committee was not seen as a stumbling block as long as the other conditions were fulfilled. All Ethics Committees must be governed by a readily accessible set of written Internal Regulations, and should be endowed with sufficient resources to guarantee that the Committee can function as it should with regular, scheduled meetings and public reporting of its deliberations.

4.1.3. Steering committees

It is strongly recommended that both a Scientific Committee and a Data and Safety Monitoring Board (DSMB) be established for major studies being conducted in DCs:

- a Scientific Committee is responsible for co-ordinating the trial and ensuring the scientific validity of the results as well as checking that it is conducted in an appropriate fashion from design through execution to analysis. At regular intervals, it should examine a series of reports which give an overview of

the study, notably concerning inclusions, drop-outs, confirmed Serious Adverse Events and deaths. This will afford a global understanding of the results, but not by treatment arm, even when the trial is not double-blinded. If the protocol needs to be amended in the light of the results of other trials, information in the literature or on the recommendations of the DSMB, this should be undertaken by the Scientific Committee;

- the role of a DSMB is to ensure that a trial is conducted appropriately and it constitutes a protective mechanism for the patients participating. Its members – experts in the field concerned and in the context of evaluation – should be independent of both the scientific team and the sponsor; they are to be nominated by the Scientific Committee and are bound by confidentiality regulations. The DSMB’s role is to preclude bias, prevent methodological distortions, protect the patients’ health, and guarantee that the study is conducted on an ethical basis. The patients’ safety depends on how well the study treatments are tolerated but also on their efficacy. The DSMB should meet regularly to review the data. Even for non-blinded studies, the existence of a DSMB means that those directly involved in the trial do not need to review all the data by treatment arm (which might result in modified behaviour patterns *vis-à-vis* “their patients”). This committee, on the basis of its regular review of the data and interim results (as planned or required in the Protocol), may advise the Scientific Committee either to continue the trial or to terminate it prematurely; it is the study’s safety wall.

It is vital that both these committees’ remit and operating modalities are governed by clear, written rules.

4.2. During the trial

4.2.1. Reporting serious adverse events (SAEs)

Simple declaration of a SAE in a clinical trial being conducted in a DC is generally inadequate. Spontaneous SAE notification for products on the market is rare in DCs, and there are various reasons for under-notification in the context of clinical trials: there are often no institutions for the recording and processing of such events; physicians tend to be more interested in a product’s efficacy than its safety; and patients may be reluctant to report an adverse event in the fear that they will be cut off from a treatment that they perceive as a lucky chance, or even as a result of their respect for the physician. The following guidelines are proposed to improve the situation in these two respects: (i) in the context of clinical research: it is necessary to make Investigators aware of the importance of monitoring for and reporting SAEs, and of encouraging patients to mention them. In some situations, it may

be worth involving a third party in the collection of SAE data, *e.g.* a representative from the medical team or of a patient support group, to whom a patient may be more open than they would be with a physician. Any reported event relayed by such a third party should be reported and evaluated by the Investigator before it is qualified as an Adverse Event; (ii) for products that came onto the market recently, a patient cohort monitoring system should be considered in order to evaluate the medium and long-term safety of the drug in real world conditions. These cohorts could be used to collect data on efficacy as well as safety, and on any practical difficulties encountered by the patients when using the product.

4.2.2. Reporting SAEs to the authorities

As a rule, sponsors notify the appropriate authorities in developed countries about any SAEs that occur in the course of trials being conducted in DCs. However, they are often unable to make such notifications locally because of the lack of an appropriate administrative institution. Before any study is undertaken, the Sponsor should actively solicit the relevant health authorities (*e.g.* the Department of the Ministry of Health responsible for drugs and pharmaceuticals) in the country where the trial is to take place to draw their attention to the trial and define the administrative body best qualified to receive and process this type of declaration.

4.2.3. Study medications

In accordance with international regulations, the Sponsor must guarantee the quality of any drugs administered during the Study. For drugs supplied by the manufacturer, satisfactory test and analytical certificates must be provided for the batches used in the Study. If the drug being evaluated was obtained locally, it is important to commission an independent laboratory to check its quality.

4.2.4. Storing and analysing biological specimens

For many research projects conducted in DCs, biological specimens are stored in laboratories in developed countries after the end of the trial. The regulations governing how such specimens are exploited and stored are complicated although two underlying principles apply: (i) how specimens may be exploited after the end of the trial must be stipulated in the Protocol and specified in the Informed Consent Form. Permission to generate new data must be unambiguously obtained, and guarantees as to how such data can be used must be included in accordance with the relevant regulations; (ii) the patients and communities involved must be informed – usually in an anonymous form – about the results of any such supplementary research.

4.3. Post-study obligations

4.3.1. Setting up sustainable systems

The Study Protocol should make explicit the Sponsor's obligations in the DC once the Study is finished. Any study conducted in a DC must bring benefit to the participating subjects and also whenever possible, to the broader community. This will involve long-term commitments, *e.g.* the donation of equipment imported to conduct the Study. Definitive terms cannot be fixed for these commitments at the outset since they will depend on the results, but they should be discussed between the Sponsor, the Principal Investigator, local health authorities and community and patient representatives throughout the duration of the Study along lines stipulated in the Protocol. Such a dialogue will lead to a general consensus as to the Sponsor's obligations after the end of the Study. The terms of the commitment will depend notably on the demonstrated benefit-to-risk ratio of the Study Treatment, whether the disease being studied is acute or chronic (*i.e.* whether the treatment is sporadic or long-term, even lifelong), and the availability of other treatments in the framework of national programmes or initiatives under the aegis of international institutions (*e.g.* the WHO).

4.3.2. Informing the patients about the results of the study

In all cases, the patients participating in a Study and their communities should be informed of the conclusions issuing from the research. The legitimacy of conducting a drug trial on a disease which currently does not benefit or will unlikely benefit from a local health care programme is, at best, questionable.

4.3.3. Local marketing authorisation (MA)

The provision of treatments which the Study has shown to be effective and safe, in circumstances that are acceptable for the people and entities concerned (health authorities, pharmaceutical companies, pharmacists, prescribing physicians, etc.), should be evaluated on a case-by-case basis. However, as a general rule, if the results are positive, local MA should be sought to so that local people can benefit from the treatment in question.

4.3.4. Compensation for study-related SAEs

Above and beyond any medical costs incurred (which should be provided for in the Study's planning stages), there is the question of compensation for any harm (including permanent total or partial disability) experienced by a participating subject, related

with their participation in a trial. Few companies insure clinical trials and policies taken out in France do not necessarily cover foreign participants. French Sponsors' insurance policies should cover all the participants in any trial, in all of the countries where the trial is being conducted.

5. Conclusion

The main recommendations made by the group concern a double review process by two Ethics Committees, one in the country where the Sponsor is based and another in the country where the Study is being conducted. In addition, an independent Data and Safety Monitoring Board should be set up and systems established to ensure the effective reporting of Serious Adverse Events and to specify the Sponsor's post-study obligations.

Other ideas, briefly touched upon by the Round Table, warrant development. Is it acceptable to conduct a trial in a DC based on methodologies or standards of care that do not meet current requirements in developed countries? *E.g.* in the developed world, a placebo cannot be used if there is an effective reference treatment for the condition in question; is it ethical to use a placebo in a DC where no other treatment is available? Must patients participating in a clinical trial always benefit from the best available standard of care or should the care provided correspond to the local conditions? The question is a complex one as emerged from the debate following revision of the Helsinki Declaration in 2000 which stipulated that the standard of care provided for participants in a clinical trial must be the best possible anywhere in the world.

Paediatrics is a special case: children are exposed to many diseases in the developing world and, in many cases, they constitute the population at highest risk. Paediatric clinical trials are particularly closely regulated in the industrialised countries. Appropriate standards should be established for paediatric clinical trials in DCs in order to guarantee scientifically valid results at the same time as ensuring ethical conduct.

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References

1. ICH International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use Mai 1996. <http://www.ich.org>
2. European Parliament and Council Directive 2001/20/EC on the approximation of the European Union the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice on medicinal products for human use 2001. http://www.clinibase.net/dossier_etudes_cliniques/etudes_cliniques_bpc/europe.pdf
3. Avis n°41 (1993) et n°78 (2003) du Comité Consultatif National d'Éthique pour les sciences du vivant CCNE. <http://www.ccne-ethique.fr>
4. Charte éthique de l'ANRS 1999. <http://www.anrs.fr>
5. Royaume-Uni, avis from Nuffield Council on Bioethics: "The ethics of research related to healthcare in developing countries" 2005. <http://www.nuffieldbioethics.org>
6. USA, Report and recommendations of the National Bioethics Advisory Commission. Ethical and policy issues in international research: clinical trials in developing countries 2001. <http://www.bioethics.gov>
7. Déclaration d'Helsinki (Edinburgh) 2000, Association Médicale Mondiale. <http://www.wma.net>
8. IOMS/WHO International ethical guidelines for biomedical research involving human subjects 1993, revise en 2001. <http://www.cioms.ch>
9. UNESCO Déclaration universelle sur la bioéthique et les droits de l'homme 2005. <http://www.unesco.org>
10. Council of Europe Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine, Oviedo 1997. <http://www.coe.int>

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