Centre for Research on Multinational Corporations

Assessment of the functioning of the clinical trials directive 2001/20/EC

Public consultation: Contribution by SOMO and Wemos

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SOMO and Wemos appreciate the opportunity given by the European Commission to express our views in this public consultation.

As end users of medicinal products that have been tested in developing countries, citizens and governments of the European Union have a responsibility towards the people on whom these drugs are tested. Therefore we commend the commitment of the European Commission to uphold fundamental ethical rules for clinical trials in third countries.

The underlying consultation paper states correctly that increasingly trials are being carried out outside Europe and North America. According to the provided statistics in footnote 53, in the period 2005-2008 18% of the trial participants were recruited in Asia and Central and South America (representing 83,466 participants in pivotal trials alone and not counting the non-pivotal trials which are more numerous). In 2007 alone this was 22%; these countries are mainly low income and developing countries (i.e. non-OECD countries). In our view this is not a limited number and these percentages have only grown since 2007.

We agree that there can be valuable benefits in conducting clinical trials in low income and developing countries. However several conditions need to be met in order for clinical trials to benefit these countries. First of all clinical research should respect ethical guidelines such as the Declaration of Helsinki. More specifically clinical research should address the public health priorities of the country where the trial takes place and trial participants should be granted post trial treatment access. Furthermore the medicinal product that results from the trial should be made affordable for the population of the country where the trial takes place. A study by a Wemos partner in India, the Centre for Studies in Ethics and Rights, described how a breast cancer drug that was tested in India was unaffordable for the majority for Indian patients. The price of the treatment was nearly 1000 euro per month.

Clinical research will not automatically lead to capacity building and sharing of know-how. On the contrary; clinical research in low income countries has been known to undermine health systems as medical staff is diverted from its regular tasks in health care delivery.

The consultation paper states correctly that international ethical guidelines, such as the Declaration of Helsinki, have been formulated to protect the rights of trial participants and that there is no shortage of agreement on the general principles. In our view, the Declaration of Helsinki provides the highest level of patient protection, especially of those in low income and developing countries and should therefore be clearly referred to as the EU standard in EU legislation. However the bodies charged with overseeing and implementing these guidelines in developing countries such as regulatory agencies and ethics committees, do not function properly. In 2007 the Latin American network Red Latinoamericana de Etica y Medicamentos (RELEM) studied the ethical framework in which clinical trials are carried out in the region. The study concluded that: 'most countries of the region are ill-equipped to protect the human subjects that participate in research.' Therefore it is essential that European regulatory authorities check whether clinical trials performed in third countries are compliant with ethical guidelines.

Comments on the suggested options to address key issue 5 : Ensuring compliance with Good Clinical Practices (GCP) in clinical trials performed in third countries.

7.3.1. Supporting regulatory framework and capacity-building where necessary

In developing countries the regulatory framework charged with overseeing and implementing ethical guidelines is often not functioning properly. Ethics committees are particularly important when it comes to protecting the rights of trial participants. However in many low income countries these ethics committees are overburdened. Members of these committees are often insufficiently trained in research ethics and lack funding to carry out their tasks in a proper manner. We would therefore strongly urge the European Commission to continue its funding of capacity-building in the South with a specific focus on strengthening of ethics committees. Furthermore we would like the Commission to consider the possibilities for the development of an international system for certification of ethics committees.

7.3.2. Self regulation by EU-based sponsors

We would advise against self-regulation of EU- based sponsors. Legally binding measures create a level playing field for all trial sponsors and reward those sponsors that take ethics seriously.

7.3.3. Strengthening international cooperation in GCP inspection and mutual recognition of GCP rules

We support this option of strengthening of international cooperation in GCP inspection. It is crucial that GCP inspectors include working with the local ethics committee responsible for the approval of the trials (and checking their structures and procedures) and to work towards alignment of GCP requirements with international standards such as the Declaration of Helsinki. It is now the practice that clinical trials in countries such as India and in Latin America are hardly monitored by local authorities after the approval of the trial. It is therefore necessary to create more CGP inspection activities in third countries especially at the time the trial takes place as it allows for more effective review of the clinical practices and timely measures can be taken in case of misconduct.

7.3.4. Optional assessment of 3rd country clinical trials by the EMEA

We are supportive of this proactive assessment of clinical trials that mandates the EMEA to assess clinical trials outside the marketing procedure as this might prevent exploitation of vulnerable trial subjects. We ask the Commission to consider that also public health oriented civil society organisations could ask for such an assessment. We would advise that this optional assessment of third country trials not only concern pivotal trials but a broader group of trials, especially selecting trials with a high risk-profile.

7.3.5. Strengthening a culture of transparency

A first essential step to protect the rights of trial subjects is increased transparency. The work of our partners in the South is severely hampered by the lack of information on clinical trials. Therefore we support the mentioned option to oblige sponsors requesting authorisation of clinical trials in the Community to make all clinical trials conducted by them available in a public register, such as the European clinical trials database EudraCT.

However, the current format of the EudraCT database does not address the requirements relevant for the protection of clinical trial participants in third countries. The database is currently only intended for information concerning clinical trials conducted within the territory of the Community and therefore does not include information about trials conducted in third countries. GCP Inspections will be more effective when performed at the time the clinical trial is running, the lack of information on running trials is a major obstacle. Sponsors of trials should make it possible for external actors to check the ethical considerations made and the precautions taken to protect vulnerable trials subjects in case they participate.

Therefore a comprehensive public database on clinical trials should:

- include third countries trials relating to medicinal products intended for use in the Community;
- have legally mandatory entry of reports, requiring the registration of the clinical trial before it actually starts as a condition for acceptance of its results for a EU marketing authorization procedure;
- Data records of the trials registries should include the locations of the trials.
- Include ethical considerations relating to the trial, for example a brief public statement from the involved ethics committee on their ethical review including ethical considerations, e.g.:
    - information about the affordability for the population of the country where the trial takes place if it concerns a poor country;
    - assessment of the public health priorities of the country where the trial takes place;
    - information about provisions for post-trial treatment;
    - the justification of placebo use;
    - justification for the inclusion of vulnerable patients if relevant and special protection measures.

We support the option to extend transparency by publishing cases of noncompliance with GCP following inspection.

More transparency is also needed in relation to the EPAR's and NPAR's; at least the ethical considerations relating to the trials as described above should be included, the locations of the trials should be mentioned, and the non-compliances with GCP following inspection should be included.

7.3.6. Strengthening scrutiny of clinical trials results of which are submitted to the EU or which are financed in the EU

Linkage 1: We support this option. We would like to point out that what is specifically needed is the strengthening of the ethical scrutiny in order to protect the rights of trial participants. Currently the information provided by trial sponsors is insufficient to establish compliance with ethical guidelines. Additional information on ethical compliance should be required from trial sponsors. To determine on which specific ethical aspects additional information is needed, it is crucial to operationalize the Declaration of Helsinki. To that end several controversial issues such as placebo controlled trials and post trial treatment access need to be discussed with all relevant stakeholders. A study by SOMO showed that placebo controlled trials for certain conditions are not accepted by ethics committees in Western Europe. Pharmaceutical industry stated it is compelled to look for locations outside Western Europe because FDA and EMEA still require placebo controlled trials for market authorisation[1]. Clarification of ethical requirements by regulatory authorities could put an end to this situation. Trial sponsors, applicants and assessors need to be provided with a checklist which ethical aspects need to be covered. We propose that strengthened ethical scrutiny will lead to rejection of trials that have not been carried out according to ethical guidelines, as is required by directive 2003/63/EC. This would be a clear signal to trial sponsors to take ethics seriously while carrying out clinical trials in third countries.

Linkage 2: We support the option to require, in a legally binding manner, additional information supporting the GCP compliance. Once again we would like to point out that what is particularly needed is information concerning ethical compliance. To establish on which ethical aspects additional information is needed, the Declaration of Helsinki should be operationalized.

Linkage 3: We are supportive of increased financing of clinical trials in third countries with funds from the European Union provided that these trials address public health priorities.

[1] Ethics for Drugs Testing in Low and Middle Income Countries, F. Weyzig and I. Schipper, SOMO February 2008