Briefing paper

Protection of Clinical Trial Participants in Countries Outside the EU

Background and purpose

Medicines intended for the European market are increasingly tested on clinical trial participants outside the EU in low and middle income countries. Over the past years, SOMO and Wemos have collected extensive evidence of violations of ethical principles and guidelines in such trials. In this briefing paper SOMO and Wemos provide the European Parliament, the European Commission and the European Medicines Agency (EMA) with policy recommendations to take their responsibility and address this problem.

About the authors

SOMO is an independent, non-profit research and network organisation that promotes sustainable and fair global economic development and the elimination of the structural causes of poverty, environmental problems, exploitation and inequality.

Wemos is an independent, non-profit organisation that advocates for the right to health of people in developing countries.

Background documents

Relevant publications are available from www.somo.nl and www.wemos.nl:

- The Globalization of Clinical Trials. Testimonies from Human Subjects (Wemos, 2010)
- Putting Contract Research Organisations on the Radar (SOMO and partners, 2011)
- Clinical Trials in Developing Countries: How to Protect People Against Unethical Practices? (SOMO, 2009)
- Ethics for Drug Testing in Low and Middle Income Countries (SOMO, 2008)
- A Bitter Pill. The risks of carrying out clinical drug trials in developing countries (Wemos, 2008)

Problem description

Clinical trials that test medicines for use in the European Union (EU) increasingly take place in low and middle income countries. Most trial participants in these countries are poor, have limited access to health care and have low medical literacy, all factors that limit their autonomy to participate in the clinical trial. Unfortunately, the bodies responsible for protecting the rights and safety of these vulnerable participants, such as national drug regulatory authorities and ethics committees, often do not function properly.

However, this is not the only concern. The ongoing fragmentation of the trial implementation process through (sub) contracting to so called contract research organisations (CROs) raises concerns over the ability of sponsors, regulatory agencies and ethics committees to supervise the implementation of clinical trials. Another point of concern is that most of the trial participants will never obtain access to the medicines they have helped to develop because of their exorbitant costs. Finally, the integrity of the data collected has been questioned: cases have been documented where participants claimed they had participated in several clinical trials at the same time to generate more income. This means the data is unreliable and may pose risks to patients in the EU.

Many cases of violations of ethical principles and guidelines have been reported (see *Background documents*). Directive 2003/63/EC states that medicines can only be considered for EU marketing authorisation if they have been tested according to ethical guidelines. In practice however the Directive is not implemented, since marketing applications are not screened with regard to their compliance with the Declaration of Helsinki, which formulates the most stringent ethical guidelines.

As medicines intended for the European market are increasingly tested on clinical trial participants outside the EU in low and middle income countries, European institutions have a moral and legal responsibility to protect their rights. Therefore, Wemos and SOMO are calling upon the European Parliament, the European Commission and the European Medicines Agency (EMA) to take measures at the following three levels:

1. Vigorously pursue the integration of ethical principles into EMA procedures,
2. Increase transparency and
3. Strengthen capacity in low and middle income countries.

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Recommendation 1: Vigorously pursue the integration of ethical principles into EMA procedures

European authorities must vigorously pursue the integration of ethical principles, such as those in the Declaration of Helsinki and those formulated by the Council of International Organisations of Medical Sciences (CIOMS), into EU market authorization procedures, including when giving scientific advice to trial sponsors at the start of clinical trials and during inspections. The following principles require specific attention as they are often violated:

- Fair compensation should be provided to trial participants in case of an adverse event. All adverse events should be regarded as related to the experimental intervention unless proven otherwise. The burden of proof that the adverse event is not related to the experimental intervention should lie with the sponsor. The sponsor's judgment in this regard should be verified by an independent authority.
- The sponsor should justify the need to conduct tests on a vulnerable population and should demonstrate in what way the population will benefit. This should be described in the protocol.
- Once a clinical trial has ended, post-trial treatment should be provided to the participants. Furthermore, clinical trials should be responsive to the health needs and priorities of the test population and community, and should only be conducted if the research results are reasonably expected to benefit this population or community.
- Ethics committees should be independent and established according to World Health Organisation Good Clinical Practice guidelines.
- The sponsor should justify placebo controlled trials according to standards laid down in the Declaration of Helsinki of 2008. Currently placebo controlled trials that are not accepted by ethics committees in the EU are performed in low and middle income countries. EMA procedures should reject applications that conduct such trials. EMA procedures must be clear about placebo controlled trials.

Recommendation 2: Increase transparency of clinical trials conducted outside the EU

- All trial sites involved in clinical trials for medicines that will be marketed in the EU, including the trial sites outside the EU should be included in the public EU Clinical Trial Register.
- The information in the Clinical Trial Register should be expanded by including information on the names of ethics committees and principle investigators at trial sites, the relevance and benefits of the study for the trial population, justification of placebo use, and post-trial treatment arrangements.
- European Public Assessment Reports of medicines should report on compliance and non-compliance with ethical guidelines during the testing phase.

Recommendation 3: Strengthen capacity in low and middle income countries

- Participants are often ill informed about their rights. Bodies should be set up to inform patients about their rights and help them gain legal redress. Currently Wemos, SOMO and partner organisations are setting up clinical trials watch organisations in several countries. They could be a source of information for EMA inspectors.
- Support should be provided to strengthen the clinical trials framework in non-EU countries. Non-EU countries should be supported in building up national bodies that monitor the quality of ethics committees.
- There should be mechanisms in place for independent monitoring of clinical trial process which includes the perspective of clinical trial participants.

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This publication is made possible with financial assistance from the Dutch Ministry of Foreign Affairs.
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