Do European registration authorities ascertain whether clinical trials in developing countries have been conducted in an ethical manner?

A study by the Wemos Foundation, Amsterdam

June 2007

Contents

1. Background

Medicines are increasingly being tested in low-income and developing countries. This allows pharmaceutical companies to reduce costs and to complete the clinical trials more quickly than would be possible in the West.
In order to receive a marketing authorization, whereupon they can be sold and used within the European Union, medicines must have been tested in an ethical manner. Commission Directive 2003/63/EC states: “To be taken into account during the assessment of an application, clinical trials, conducted outside the European Community, which relate to medicinal products intended to be used in the European Community, shall be designed, implemented and reported on what good clinical practice and ethical principles are concerned, on the basis of principles, which are equivalent to the provisions of Directive 2001/20/EC. They shall be carried out in accordance with the ethical principles that are reflected, for example, in the Declaration of Helsinki.”
Primary responsibility for assessing whether proposals for clinical trials meet the ethical requirements rests with the relevant ethical review committees in the low-income and developing countries themselves. Nevertheless, research done by, amongst others, the Indian Council of Medical Research reveals that these committees are often inadequately equipped to fulfil this task, whereupon the rights of the trial subjects may be undermined and their safety put at risk. This serves to emphasize the importance of the control function of the European registration authorities which are responsible for issuing the marketing authorization for any new medicine. The Wemos Foundation has therefore conducted a study to examine the degree to which European registration authorities ascertain whether the clinical trials for new medicines have been conducted in accordance with the ethical guidelines.

2. The form of the study

Do European registration authorities ascertain whether clinical trials in developing countries have been conducted in an ethical manner? If so, how? In late 2006, Wemos submitted these questions to all 25 European registration authorities, and to the coordinating body, the European Medicines Agency (EMEA).
Ten registration authorities responded by telephone, and answered a comprehensive questionnaire which examined the various criteria set out in the Declaration of Helsinki (see Box 1, below). Two authorities returned a completed questionnaire by e-mail. Thirteen failed to respond at all, despite repeated attempts to contact them. One agency declined to take part in the study. The twelve registration authorities which did take part represent both the established and the new European Union member states.
Wemos collated the information gathered during the study to form a report in which the authorities’ responses are presented anonymously. Copies of the report may be obtained from the Wemos office. Here, we present the main findings of the study, followed by a number of conclusions and recommendations. The word ‘respondent’ refers to a European registration authority.

3. Main findings

3.1. The form and membership of local ethical review committees is subject to little investigation by European registration authorities

Most respondents claim to ascertain whether the relevant clinical trials have been approved by a local ethical review committee. However, only two state that they also ascertain whether the form and membership of this committee meet the requirements set out in the guidelines for good clinical practice. According to these guidelines, the committee must be independent, which entails that no member can have any affiliation with the parties who finance or carry out the clinical trials themselves.

3.2. Little attention to the trials' relevance for the research population

Two of the twelve respondents state that they 'sometimes examine dossiers from developing countries more critically [than others]'. Only two respondents state that they devote specific attention to the question of whether the clinical trials concerned are of direct benefit to the research population. The Declaration of Helsinki expressly states that research of this nature can only be justified if the results are likely to benefit the research population. This would be the case if, for example, the drug being trialled is intended to treat or prevent a condition which is particularly prevalent in the country concerned. In this context, one respondent stated, "the developing countries are used to test drugs for the developed countries."

3.3. Little concern for the protection of vulnerable study populations

According to the Declaration of Helsinki, vulnerable research populations must be afforded special protection. However, only two of the respondents examine whether the clinical trials have involved (groups of) vulnerable test subjects. None of the respondents consider whether subjects have access to the best available medical treatment after the trial, which is another requirement stated by the Declaration. Respondents regard this as the responsibility of the pharmaceutical companies and the governments of the developing countries.

Four respondents attempt to ascertain whether the research subjects have been adequately informed about the form of the trial and the possible risks. They do so by a variety of means, including checking that the registration dossier contains full patient information. Only one respondent ascertains whether the subjects have indeed read and understood the information provided, and whether they have given free and informed consent. Another

respondent states that these aspects are checked during an inspection on location. However, such inspections are themselves infrequent.
When assessing the registration dossier, none of the respondents examines whether the test subjects have been paid to take part in the clinical trials.
Respondents consider that responsibility for ensuring compliance with the ethical guidelines covering the above points falls to the local ethical review committees.

3.4. Ethical shortcomings are not automatically grounds for rejection

The respondents state that, even where clinical trials have been conducted in a developing country in a manner which may be considered unethical, this is not an automatic reason for refusing the European marketing authorization. Only one respondent states that ethical shortcomings are likely to lead to postponement or withdrawal of the product approval. Another respondent states that the registration procedure would be influenced, but does not give further details.
It is common for a medicine to be tested in several countries simultaneously. “Even if the trials supporting one application were not entirely in keeping with the requirements, the others may be,” states one respondent. “If the other trials confirm the efficacy and safety of the product, we can then issue the marketing authorization,” confirms another, “but we cannot penalize the applicant.”

3.5. Registration authorities’ procedures are insufficiently transparent

Only seven of the twelve registration authorities make information concerning the assessment procedure for a new drug publicly available, either on its own website, the website of the EMEA, or on request. This means that information concerning the ethical aspects of the clinical trials’ assessment is not widely available.

4. Summary of main findings

- The European registration authorities do very little to ascertain whether clinical trials in developing countries have been conducted in an ethical manner.
- Even if a medicine has been subject to unethical testing, this will not necessarily preclude its approval for sale and use in Europe.
- The European registration authorities place much of the responsibility for ensuring compliance with the ethical guidelines at the door of the ethical review committees in the countries in which the clinical trials take place. However, they do little to check whether these committees meet the guidelines for good clinical practice in terms of form, membership and performance.
- Many European registration authorities do not publish information concerning their assessment of the registration dossier.

5. Wemos' concerns and recommendations

It is a cause for concern that, despite the existence of European Directives on this topic, the registration authorities devote so little attention to the ethical aspects of clinical trials, as set out in the Declaration of Helsinki and other documents. It is notable that these authorities often abdicate their responsibility for the ethical aspects to the local ethical review committees, even though it is known that these committees frequently fail to observe the extant rules and do not have adequate capacity.

The European registration authorities' shortcomings with regard to control have far-reaching consequences, not least in terms of the vulnerable position of the trial subjects. It is highly questionable whether the trial subjects in low-income and developing countries have indeed given full and informed consent. After all, many are illiterate, while the relationship between doctor and patient is hierarchical. Trial subjects will blindly follow the advice of their doctor, while that doctor may have a vested financial interest in recruiting as many trial subjects as possible. By virtue of their poor economic position and the lack of proper supervision and regulation, trial subjects in the developing countries are clearly more vulnerable than their counterparts in the West. Participation in a clinical trial may represent their only hope of medical treatment. After the trial is completed, they will not have access to an adequate, well functioning health system in which there is an adequate supply of drugs. It is therefore essential that effective agreements are made with regard to subjects' access to care after the trial has been completed.
The fact that the registration authorities devote so little attention to whether the trial is relevant and of benefit to the research population exacerbates the risk that trial subjects will be misused, for example to test drugs which will benefit primarily the West. This type of exploitative relationship can be avoided, at least in part, by subjecting all clinical trials conducted in developing countries to stringent review, and by withholding marketing authorization for any product which has been tested in a less than fully ethical manner.

Wemos believes that the situation in the developing countries demands greater care and responsibility on the part of the European registration authorities. It is wholly unacceptable for drugs which have been subject to unethical testing to be approved and admitted to the European market.

Box 1 Relevant sections from the Declaration of Helsinki

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

The full Declaration of Helsinki is available at www.wma.net/e/policy/b3.htm.

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Colophon

Title:	Do European registration authorities ascertain whether clinical trials in developing countries have been conducted in an ethical manner?
Document:	M3.01
Author(s):	Wemos staff
Date:	June 2007

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