Informed consent in clinical trials

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The development of a new drug is a lengthy process. Once a promising compound is identified, it must be investigated in laboratory studies and tested on laboratory animals. After years of work, the newly developed drug is ready for clinical trials, or the testing on human volunteers.

In this article I discuss the ethics of clinical trials using the example of anti-fertility vaccines. In particular I argue that the ethics of clinical testing are not confined to the recruitment stage and information provided to participants. We need a more process-oriented perspective on the ethics of trial participants' involvement.

The research and development of anti-fertility vaccines have caused much concern among the international women's health movement, involving many ethical and political problems (1, 2).

The development of anti-fertility vaccines began in the 1970s. Unlike hormonal methods, the immunological mechanism of action causes temporary infertility by provoking the production of antibodies against substances necessary to human reproduction, such as certain hormones and molecules of the sperm and the ovum. Research has been carried out in various institutions, predominantly in India and the United States.

Research on the vaccines discussed in this article, anti-human Chorionic Gonadotropin (CG) vaccines, is carried out under the auspices of the World Health Organization (WHO) in Geneva, by the National Institute of Immunology (NII) in New Delhi, and by the Population Council in New York. Clinical trials with these vaccines to test the safety and the biological effects have been carried out since the early 1970s, on small groups of of women in the United States, India, Brazil, Chile, Dominican Republic, Finland, and Sweden (3, 4, 5,6, 7). In 1986, a WHO-sponsored trial for safety was done in Australia, involving 30 women (8). A trial with 101 women was carried out in India in 1988 with the anti-hCG vaccine developed by the NII (9).

In 1991-1992 the first efficacy trial took place, and 148 women were vaccinated at the All India Institute of Medical Sciences and the Safdarjung hospital in New Delhi, and the Post Graduate Institute of Medical Education and Research in Chandigarh (10). A efficacy trial of the WHO anti-hCG vaccine started in Sweden in 1994, but was suspended a few months later because all the first seven participants experienced serious side effects.

Testing contraceptives

When a person has a disease for which no effective drug or treatment is available, participating in a trial is often the only way to get access to a potentially life-saving drug. This was the case with the testing of new treatments for AIDS. In the development of new contraceptives, the situation is quite different, because a number of more or less satisfying forms of family planning are already available and because contraceptives are meant for healthy people. Yet, biomedical researchers need the collaboration of trial participants to test the safety and efficacy of a new drug.

Successful clinical trials are a core requirement for the approval of a new drug by regulatory authorities. In order to enable researchers to recruit trial participants in an ethical manner, clinical trials generally require an informed consent procedure. Candidates receive information on the experimental drugs and on what their participation would involve. They must sign an informed consent form to express their voluntary decision to participate.

Internationally endorsed guidelines to regulate informed consent procedures were recorded for the first time in 1964 in the Declaration of Helsinki, prepared by the Council for International Organizations of Medical Sciences in collaboration with the WHO. They have been updated several times since then (11). Worldwide, ethical review committees at research centres and funding agencies scrutinise research proposals, information brochures, and final reports on the basis of these guidelines. Ethical guidelines for biomedical research involving human subjects are centred on the dual purpose of respect for a person's right to make decisions, and protection of vulnerable persons in biomedical research (12).

I have studied the trials in Australia, Sweden and India in some detail (13). In the informed consent procedures of these trials, it was believed that women actively took the decision to become research subjects on the basis of the information provided to them. For example, the introduction to the extensive information brochure accompanying the informed consent form for the 1994 efficacy trial in Sweden stated that the information was "in order for you to reach a decision". The brochure answered questions likely to be asked by "individuals who volunteer to be in the study". Participants were "free to ask questions at any time before and during the study". The decision to participate in the trial would be "of your own free will" and participants could "decide to withdraw from the study, for any reason and at any time" (14). This mode of addressing assumed that women had different options for action. Participation in the trial was envisioned as one option for women, the informed consent as a communication process, and women were seen as decision-makers.

Informed consent in India

A different picture of women's options for action emerged from the performance of the informed consent procedures in the phase II trial in India. The German documentary-maker and women's health advocate Ulrike Schaz filmed the recruitment of some women for this trial. The film showed a room in a public hospital in New Delhi where dozens of women were standing in line waiting to see a doctor. The doctor was sitting behind her desk and told a

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patient:

We have got a new injection. The effect of the injection stops children for one year. You need not be afraid about this. The injection has no side-effects. You see this injection is absolutely 100 per cent effective. We will also put in a copper-T. Continuous copper-T is not very good. If you have it three years, six years, then there is the risk of cancer. That is why we want you to change (15).

The doctor's statements diverged from the protocol. She said the anti-fertility vaccine was a new injection instead of an experimental method for which the duration and efficacy were yet to be established. And there is no evidence three or six years of copper-T use increases the risk of cancer. As a matter of fact the research protocol for this trial had been approved by the Drugs Controller of India, the institutional ethics committees, and the ethics review committee of the Canadian International Development and Research Center, one of the funders of clinical research at the NII

The film caused concern among researchers and policy makers involved in the development of anti- hCG vaccine. This representation of a trial participant differed from the one that researchers had been addressing in their information brochures. While the scene underscored the importance of proper information, the candidate's options for action seemed to depend on more than communication processes. Informed consent appeared not as a communication and decision-making process, but as a form of social intervention in a specific context, producing and reproducing power-relations.

The context of research

Moreover, the ethics of clinical trials go beyond the need for well-performed informed consent procedures. Ethics and politics are involved in the context in which clinical trials are carried out, and in organisational features as well. This becomes very clear when we compare the Indian and Swedish trials. In India, women's daily life situations facilitated their enrollment and continuation in the trial. Researchers who studied the 1991-1992 clinical trials in India point out that the most frequently mentioned advantage of participation in clinical trials was improved access to medical care. Private clinics are unaffordable and government medical treatment usually meant missing work and waiting for hours at public hospitals. As clinical trial participants, they and their families received priority treatment (16). Researchers also make participation attractive to prevent drop-outs, by providing a waiting area, cold drinks and snacks, and reimbursement for travel expenses and time lost from employments (17).

Women participating in clinical trials often use it as a means for improving their existing situation. They are in their own way getting access to an extra income, improved health care, and a sense of identity and social space outside their homes. On the other hand, one can argue that these motivations provided by the research center in some ways take undue advantage of the situation of low income, uneducated women by providing them with opportunities they would otherwise not have (17).

As Kirbat has signalled there is a tension between women as actively seeking to become research in a specific situation. Importantly, health care, reimbursement and other such provisions were effective only for poor women. The provision of a social space outside the home might not have been significant to men, and access to good-quality health care was not an issue for richer people. The researchers' arrangements suited a specific category of clinical trial participants.

Participants in the 1994 Swedish trial, too, were reimbursed for travel expenses, time lost for employment, and other trial-related expenses. However, participation provided no personal benefits, apart from the eventual anti-fertility effect during the efficacy stage of the trial and a thorough medical examination (14). The researchers encountered many problems in enrolling and keeping a sufficient number of trial participants. The original recruitment targets in the Swedish trial were 50 subjects in each of the two participating hospitals. A total of 61 women contacted the Karolinska Hospital in Stockholm in response to its initial publicity about the trial, and 17 of them remained potentially available after the interview and the screening. In the Uppsala University Hospital, a total of 16 women expressed interest and three of them passed the interview and the screening stages (18). The representative of a company involved, Mats Ehrnebo, wrote in a progress report to the WHO:

There has been a slower than expected patient recruitment. (...) It is planned then for a more extensive patient recruitment. (...) every aspect that could raise the number of patients that could be screened should be encouraged (19).

Researchers in Sweden had fewer opportunities to make participation in the trial attractive to women. Improved access to health care was not relevant for these women. For poor women in India, the clinical trials could provide a welcome opportunity to obtain better access to superior health care, an extra income and a social space outside their homes. Because of women's different spectrum of options, it was easier to recruit and keep women in the trials in India than in Sweden. This illustrates how the politics and ethics of clinical trials are not confined to obtaining women's informed consent to participate. Their participation and continuation in the trial depended not only on their understanding of the information provided to them, but also on the contexts and the power relations in which they were engaged.

How could this finding be handled in practice? First, the provision of clear and adequate information remains a key issue, and ethic committees should intensify their surveillance of clinical testing. Second, the finding that women's options for action differ according to their situation - and hence the ethicality of their participation - should play a role in the selection of trial centres. Finally, persons who can represent the users' perspectives should be involved in the planning, organisation, and evaluation of clinical trials. In the case of anti-hCG vaccines, some researchers from the WHO have proposed that women's health advocates could play a role in

monitoring the conduct of clinical trials of new contraceptive methods.

References:

1. Saheli: *Target practice. Anti-fertility vaccine research and women's health*. Saheli, New Delhi, 1998.

2. Richter J: *Vaccination against pregnancy: miracle or menace?* Zed Books, London and New Jersey, 1996.

3. Stevens VC and Crystle CD: Effects of immunization with hapten-coupled hCG on the human menstrual cycle. *Journal of Obstetrics and Gynecology* 1973; 42: 485-495.

4. Talwar GP et al: Clinical profile and toxicology studies on four women immunized with Pr-ß-hCG-TT. *Contraception* 1976; 13: 253-268.

5. Nash H et al: Observations on the antigenicity and clinical effects of a candidate anti-pregnancy vaccine: ß-subunit of human chorionic gonadotropin linked to tetanus toxoid. *Fertility and Sterility* 1980; 34: 328-335.

6. Shahani SM et al: Clinical and immunological responses with Pr-ß-hCG-TT vaccine. *Contraception* 1982; 25: 421-434.

7. Brache V et al: Whole ß-hCG: *Tetanus toxoid*. Paper presented at the scientific session on immunological aspects of reproductive health, Moscow, June 16-18 1992

8. Jones et al: 1988 Phase I clinical trial of World Health Organizations birth control vaccine. *The Lancet* 1988; 1295-1298.

9. Talwar GP et al: Phase I clinical trials with three formulations of anti-hCG vaccine. *Contraception* 1990; 41: 301-316.

10. Talwar GP et al: A vaccine that prevents pregnancy in women. *Proceedings of the National Academy of Science*, USA 1994; 91: 8532-8536.

11. Council for International Organizations of Medical Sciences: *International ethical guidelines for biomedical research involving human subjects*. Prepared by the CIOMS in collaboration with the WHO, Geneva, 1993.

12. Cook RJ and Dickens BM: Legal and ethical aspects of development and use of fertility regulating vaccines. In Ada GL and Griffin PD (eds): *Vaccines for fertility regulation: the assessment of their safety and efficacy*. Cambridge: Cambridge University Press, 1991, pp 201-232.

13. Van Kammen J: *Conceiving contraceptives, the involvement of users in anti-fertility vaccines development*. Dissertation, University of Amsterdam, 2000.

14. WHO/HRP Task Force on Vaccines for Fertility Regulation: Phase II clinical trial protocol. Prototype anti-hCG vaccine. Geneva, May 28, 1992.

15. Schaz U and Schneider I: *Antibodies against pregnancy: the dream of the perfect birth from the laboratory*. Documentary film, 1991. English copy available through USchaz, Hamburg.

16. Viswanath K. and Kirbat P: *Genealogy of a controversy: development of an anti-fertility vaccine*. Working paper number 7. Social Science and Immunisation Project, University of Delhi, 1997.

17. Kirbat P: Conducting fieldwork in clinical trial settings: anthropological and ethical remarks. *Medische Antropologie* 1998: 10: 85-93.

18. Steering committee clinical trials subcommittee: Minutes meeting. Uppsala, 29 June, 1994.

19. Ehrnebo M: *Progress report*, September 27, 1994. Unpublished paper.

Clinical trials are big business

Even *Issues in Medical Ethics* gets unsolicited email from contract research organisations. This European CRO asks: "Do you need help running your clinical trials in Europe?" It offers to handle all aspects and stages of clinical trials, to speed up the process, reduce costs and get the 'product' to the market fast. Research from trials carried out in Europe will be used to get US FDA approval. "From here we can help you conduct clinical studies more efficiently and to a lower cost than in the US. One ICH GCP compliant study run for you by us in Scandinavia may be approved by regulatory agencies covering more than 90% of the worldwide market-including the US, Europe and Far East. In Scandinavia, trials typically begin and end sooner than in the US. This means you can begin generating revenue in Europe while awaiting FDA approval."