Chapter 7
Hepatitis B Study with Gender Inequities

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Abstract This case study is about a study entitled "Comparable randomized double-blind investigation of safety and immunogenicity of vaccine against Hepatitis B in healthy adult subjects" proposed in Russia with an international sponsor. There were indications of elements of exploitation, which consisted of inadequacies in the study's design compared with its announced purpose, and the indirect inclusion of women research subjects in the clinical trial without their informed consent. On the basis of noncompliance with the applicable regulatory and ethical requirements the study was not approved by the local ethics committee (LEC).

Keywords Clinical trial · Hepatitis B · Russia · Women · Exploitation Unethical · Ethics committee

Area of Risk of Exploitation

Healthy volunteers in clinical trials contribute to medical progress without any benefits to themselves. In addition, this case is of interest with regard to gender inequities in research.

Case Description

This case study is based on an evaluation undertaken by the local ethics committee (LEC) of the research institute in Russia at the end of 2014. All documentation required for a complete ethical review of the proposed study was submitted in accordance with the national law (Russian Federation 2005), the LEC's standard operating procedure and international rules of good clinical practice. The proposed

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clinical trial was entitled: "Comparable randomized double-blind investigation of safety and immunogenicity of vaccine against Hepatitis B in healthy adult subjects".

The main purpose of the proposed clinical trial was to study the safety and immunogenicity of a vaccine against hepatitis B in comparison with a vaccine already marketed in Russia, with a view to its future registration in the country.

The study design envisaged two groups of participants made up of both men and women. The first group would be vaccinated by an investigational product (a vaccine proposed by an external sponsor), and the second (control) group would be given a well-known vaccine registered in the country. According to the protocol, the female sexual partners of male participants would be indirectly involved. For this group, the study assigned special requirements.

The requirements for these women, who were not legally and directly involved in the clinical trial, included a prohibition on and prevention of pregnancy, through the use of contraception, during the entire eight months the study lasted and for one month afterwards, even if the actual participant – their sexual partner – withdrew from the study.

Detailed information would be collected about any pregnancy and its outcome, and any adverse events (or serious adverse events) would be included in the database as part of the monitoring process.

The investigational product had been well investigated in a series of earlier clinical trials (as is clear from the protocol, investigation brochure and references), and already approved in the country of the sponsor and many other high-income countries. It was available on the open market for adults and children above ten years old. For this reason, the appropriate design of the proposed clinical trial in Russia would have been for a phase III study. However, the protocol design was equivalent to a phase I or II study.

Seventeen visits of the volunteer participants to the investigator centre were planned during the eight months of the clinical trial and for one month after its completion. Visit procedures involved a detailed physical examination and the collection of blood and urine samples for a wide spectrum of tests. The participants would come to the centre in the morning and spend a few hours there for observation. In addition, they would have to buy and use the requested products for contraception.

As a rule, healthy volunteers participating in clinical trials cannot expect any benefits. In this case, an external (i.e. non-Russian) sponsor declared that benefits were planned, because the participants (volunteers) would be vaccinated against hepatitis B, and would therefore be protected from this infection in the future.

Analysis

The case study shows ethical inadequacy at several levels.

The suggestion that the study would be beneficial to participants is controversial. Vaccination against hepatitis B is included in the national immunization calendar of

the Russian Federation. This is done with domestically and internationally produced vaccines that are registered and have been granted permission for use by approved order (Russian Federation 2014). Vaccination against hepatitis B is freely available to everybody, and obligatory for high-risk groups (newborns whose mothers are HbsAg carriers, or hepatitis B patients in the third trimester of pregnancy). Therefore there were no benefits for participants taking part in the clinical trial.

The autonomy of the women who were indirectly involved in the study was not respected. There was no information or confirmation in any part of the protocol to the effect that these women (indirect participants) should be appropriately informed about the procedures, or that their informed consent should be obtained.

In addition, their indirect involvement in the clinical trial was not covered by insurance, even in the case of pregnancy with a serious adverse event (a congenital anomaly or birth defect), because they were not included in the framework of financial contracts and insurance coverage for study participants. No other guarantee (medical, financial etc.) for these women was described in the protocol or any other study documents. This violates Russia's compulsory regulations on good clinical practice:

> In research which does not connect with treatment (without any benefits for potential participants from a medical point of view) only subjects who personally give, write and date the informed consent can be involved (Russian Federation 2005: item 4.8.13).

The situation for women indirectly involved in the clinical trial without consent would also contradict the universal ethical principles of the Declaration of Helsinki, October, 2013 regarding vulnerable groups and populations:

> Article 22: "The protocol should include information … regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study"
>
> Article 25: "Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary … no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees"
>
> Article 26: "The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal" (WMA 2013).

The requirement to carry out a pregnancy test and prevent pregnancy throughout the study also violated the women's reproductive rights and represented a direct intervention in the family's planning.

The study documentation required considerable attention to be devoted to the registering and following up of information concerning cases of pregnancy or outcomes in these women, without their informed consent. This meant that their personal information could be used without their agreement. It also contradicted the general norms guaranteeing the protection of personal data set by the Russian Federation's Federal Law on Information, Information Technologies and the Protection of Information (Russian Federation 2006a).

In addition the Federal Law on Personal Data of 27 July 2006 (Russian Federation 2006b) (updated 2015–2016), defines maintaining the confidentiality of information as an obligatory duty, and requires this information not be transferred

to third parties without the direct consent of its owner. According to article 31 of the Fundamentals Of The Legislation Of The Russian Federation On Health Protection No. 5487-1 (2007), "information contained in the person's medical documents shall make up a medical secret."

The situation is also in conflict with the rules of the Declaration of Helsinki, under the heading "Privacy and Confidentiality": "Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information" (WMA 2013: art. 24).

Two other areas of exploitation identified in this proposed clinical trial were the unreasonable exploitation of private time and the financial exploitation of participants/volunteers. The study, as noted above, was very time-consuming for participants and there was no compensation for the expenses of transport, contraceptive products or the disruption of normal daily work and activities. This violates the most recent version of the Declaration of Helsinki: "Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured" (WMA 2013: art. 15).

This case also points to gender injustice. One could argue that one can detect covert discrimination against vulnerable populations indirectly involved in the study. A fundamental understanding of the gender aspects of research should be guided by the spirit and letter of the Universal Declaration of Human Rights of 1948, which states that "the peoples of the United Nations have in the Charter reaffirmed their faith in fundamental human rights, in the dignity and worth of the human person and in the equal rights of men and women" (UN 1948: preamble).

The ethical conflicts raised by this case study suggest some general arguments that women can be discriminated against through their limited access to participation in clinical trials and the violation of their reproductive rights. The risk of exploitation is especially present when the golden rules of the protection of autonomy, confidentiality and human vulnerability are ignored. The moral force for the realisation of ethical concepts in medical research through the correct process of freely given and obtained informed consent is presented in the UNESCO Universal Declaration on Bioethics and Human Rights (UNESCO 2005) and in many other national and international documents, including the Convention on the Elimination of All Forms of Discrimination against Women, adopted by the United Nations in 1979 (UN 1979).

In summary, the following are the ethical issues raised by this case study:

- gender inequity
- violation of reproductive rights
- inappropriate promises of benefit
- lack of insurance
- confidentiality not preserved
- unreasonable use of private time

Outcome of the Application for Ethics Approval

All properly submitted application documents were reviewed according to the established review procedure (the LEC's standard operating procedure). On the basis of detailed review, discussion took place at a meeting of the LEC with a quorum of its members present. An independent consultant (a specialist in bioethics) was invited to join the meeting after signing an agreement on confidentiality and conflict of interest. Decision-making took place after sufficient time had been allowed for discussion, and was reached by consensus in accordance with the LEC's standard operating procedure. On the basis of disapproving or unfavourable opinions from all members of the LEC, the decision was made in the negative, with detailed and clearly stated reasons provided to the applicant. The clinical trial was not approved.

Lessons Learned and Recommendations

- The system of ethical review worked well in this case, as an unethical study was not approved.
- The possibility of indirectly masking/silencing and blindly exploiting women (pregnant or otherwise) in a study requires attention.
- Gender variety and an assessment of its influence on risk-benefit ratios should be an integral part of clinical trial planning.
- Clinical trials should exclude any opportunity for non-informed or non-agreed interventions that will impact on the privacy of participants' lives, especially in the context of women's reproductive rights.
- Unreasonable risks and burdens, including inadequate compensation and an excessive time burden, must be avoided.

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