Ethical Issues to Consider Before Starting Research: Example of a Study on Preventing Mother-to-Child Transmission of the Hepatitis B Virus

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Distinction between treatment and research

Clinical research investigates interventions that may affect human health. This may be observational, limited to a description, or interventional, evaluating the consequences of an intervention on the wellbeing of a population or group; but no matter the form, it always involves interactions with the participants. The possible immediate or future consequences of these interactions must be taken into consideration, especially because the patient is not the one seeking the research. Usually it is a physician who designs the research study and proposes participation in it to a person who contacts him or her for treatment, not to be a research subject. In a way, this changes the tacit contract between doctor and patient. In order to not mislead the patient, the doctor must clearly explain the objectives of the research, thus assuming two roles: first as a physician trying to provide the best possible care to improve a specific patient's health condition (using current medical knowledge), and second as a researcher trying to answer an unresolved scientific question with the ultimate goal of adding to the body of knowledge about human health as a whole.

In the early twenty-first century, biomedicine is increasingly based on the results of clinical studies, i.e., experiments on patients that have demonstrated the efficacy and effectiveness[1] of diagnostic tests, prophylactic or therapeutic interventions, or explorations. This scientific foundation gives credibility to public health systems and justifies their funding. The most convincing recommendations from health authorities must be based on data generated when evaluating interventions. In the

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1. Efficacy: exhibits some health benefit, as predefined and evaluated in a clinical study; effectiveness: provides benefits to patients in real-life conditions.

absence of such data, the analysis of data collected from groups over a period of time (called cohorts) may be used.

Yet in many situations such data are either unavailable or of uncertain quality. Thus, some recommendations are only based on expert opinions formed through personal experience and/or a thorough review of the scientific literature and pathogenesis rationale. Due to subjectivity and uncertainty, the best course of action may remain unclear. Should we—can we—question a practice recommended by experts when it seems useful despite a lack of decisive evidence?

Is it ethical to conduct a clinical study comparing a recommended intervention versus no intervention, to determine its efficacy? For example, randomized "controlled" clinical trials can be conducted to compare the effects of a drug against a comparator. In such trials, patients are randomly assigned to one of two groups, one group receiving the drug and the other receiving something that looks similar but does not contain the active ingredient (a placebo).

This question is not specific to a place or a period of time, but arises in a specific context that may influence how we think about it. We will illustrate this issue of research ethics by describing our approach in a specific example: the use of antivirals to prevent mother-to-child transmission (MTCT) of hepatitis B virus in Southeast Asia.

Preventing mother-to-child transmission of the hepatitis B virus

Chronic hepatitis B virus (HBV) affects 257 million people in the world.[2] Hepatitis C affects 71 million people, and viral hepatides B and C together were the seventh leading cause of death worldwide in 2013.[3] These diseases led to 1.34 million deaths in 2015 (more than HIV-related deaths), a number that has increased by 22% since 2000.[4] Asia is disproportionately affected by this pandemic, where MTCT is the primary source of new HBV infections.[5] WHO recommends universal HBV immunization, i.e., vaccinating all children regardless of maternal infection, beginning with a first dose of the vaccine administered shortly after birth. This strategy has considerably reduced the

2. World Health Organization. (2017). *Global hepatitis report 2017*. World Health Organization. Available at: http://apps.who.int/iris/bitstream/10665/255016/1/9789241565455-eng.pdf?ua=1.
3. Stanaway, J. D., Abraham D., Flaxman, A. D., Naghavi, M., Fitzmaurice, C., Vos, T., Abubakar, I. (2016). The global burden of viral hepatitis from 1990 to 2013: findings from the global burden of disease study 2013. *Lancet*, 388, 1081–1088. http://dx.doi.org/10.1016/S0140-6736(16)30579-7
4. World Health Organization. (2017). *Global hepatitis report 2017*. World Health Organization. Available at: http://apps.who.int/iris/bitstream/10665/255016/1/9789241565455-eng.pdf?ua=1
5. WHO. (2015) *Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B Infection*. WHO: Geneva, Switzerland, p 136.

prevalence of HBV everywhere it has been implemented. When infants are born to infected mothers, the additional administration of a vaccine composed of specific antibodies (anti-HB immunoglobulins) taken from immunized, uninfected individuals is considered to be effective, even though it is based on old studies that were not conducted in accordance with today's quality standards. The efficacy of this practice is not known with great certainty, especially if the mother's viral load is not high. Because of this uncertainty, and the fact that this additional intervention increases program costs and logistics (cold chain), this strategy is not universally recommended and is not always covered by a country's health insurance systems.

Furthermore, despite this dual intervention (vaccine plus immunoglobulins), HBV may still be transmitted when the mother has a very high viral load. Therefore, it has been proposed that anti-HBV antiviral treatment be prescribed to these mothers during the end of pregnancy and first weeks following birth.

In 2015, no studies meeting international clinical research quality criteria had clearly demonstrated the efficacy or safety (absence of adverse effects) of this approach for the mother and child. An antiviral prescribed during the end of pregnancy does reduce the maternal viral load. Therefore, the approach seems logical and similar to the approach used to prevent MTCT of HIV. More and more physicians have been prescribing antivirals to pregnant women infected with HBV, even though this practice is not formally approved by the health authorities that regulate and monitor the use of medicines because of the lack of well-established evidence. Exposure to antivirals, even for a few months, may actually cause adverse effects of varying severity to both mother and child. These risks should be compared against the uncertain benefits of the intervention. Neither the U.S. Food and Drug Administration (FDA) nor the European Medicines Agency (EMA) have approved this indication for an antiviral because of the lack of data. And yet the three main associations for the study of liver diseases (APASL, EASL, and AASLD[6]) recommend the use of this prophylactic treatment, though the strength of recommendation varies. The American Association for the Study of Liver Diseases, for example, bases its recommendation on a retrospective meta-analysis, yet recognizes its limitations and does not give specific guidelines on treatment administration. In its most recent (2015) recommendations for hepatitis B treatment, WHO decided not to formulate guidelines on the use of antivirals for this indication, preferring to wait for conclusive evidence of their efficacy and safety.[7]

6. Asian Pacific Association for the Study of the Liver Diseases, European Association for the Study of the Liver, and American Association for the Study of the Liver.
7. WHO. (2015). *Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B Infection*. WHO: Geneva, Switzerland, p 136.

Given the wide range of expert opinions on this issue, the question doctors ask themselves—or should—is how to know whether or not it is legitimate to expose women and children to an antiviral treatment when the efficacy and tolerance of the treatment by individuals is unknown. This is a question best answered by a clinical study, which could tell us if such prophylactic treatment actually helps prevent the transmission of HBV without causing any major adverse effects. If such a study were submitted to an ethics committee, what type of questions would need to be addressed?

Ethical review of an experimental clinical study project

First and foremost, for research to be ethical it must (i) be based in science, (ii) address an actual issue, and (iii) be likely to reach a conclusion, whether expected or unexpected. Researchers must convince patients—potential participants—that the research is useful and that there are good reasons for conducting it. They must also explain the benefits patients might expect both for themselves and for others with the same condition in the future. In our example, the investigator is personally convinced that a clinical study can provide unique information that will definitely support recommendations for the use of this prophylaxis or provide a rationale for not using it. Pending the results of the study, it is unknown whether patients will benefit from receiving the treatment.

Investigators also need to explain any risks the research might pose for the patients, their families, or others close to them. In our example, the knowledge gained from systematically recording the pregnancy outcomes among women who took the drug during pregnancy was reassuring, but we could not rule out the possibility that this type of treatment during pregnancy might affect the fetus or the child.

One of the methods used by people who review the ethical aspects of research like clinical research is to “put yourself in the place” of the participant, and ask if you yourself would agree to participate in it. In our example, without any treatment a mother may transmit the virus to her child. However, due to the lack of evidence from clinical trials, we cannot be sure that treating the mother will in fact decrease this risk.

Another key aspect of ethical research is summarizing and explaining the scientific questions being investigated so that patients can make what is called an informed choice. An informed decision can only be made after a patient has understood the issue, which requires explanation at an appropriate level (see the chapter on informed consent). One way of devising a simple explanation is to talk about the study with, and explain its important details to, someone who is not a health professional. When an institution has a community advisory board in place, such exchanges occur naturally. When research involves people from several cultures, this

becomes an essential step towards clearing up any of the ambiguities or misunderstandings that abound in intercultural relations, especially because ideas can have culturally based meanings that may cause confusion, even when the words are translated into the appropriate language.

Researchers must examine their own conscience

While investigators are rationale beings, they are also human beings. As such, they must question their own motivations for conducting the research. Is there a personal interest involved (financial or otherwise, such as academic or professional advancement) that would steer the research to be performed in a certain way, to obtain a particular result? An investigator's organization could also influence how a scientific question is asked and studied. These aspects may be discussed with the ethics committee for the research organization where the investigator works.

Another issue is that the research may be largely funded by a foreign organization. Are there any reasons for the participants to believe that they are taking risks that would not be taken in the country providing the funding? Patients and investigators both may question the motivations of those behind the research program. Who will benefit financially from the scientific results? The country where the funds come from, or the country where the research is being conducted? In the case given here, it makes sense to conduct research in a country in the Mekong region because over 100 million people are infected with HBV in Asia, so the primary expected benefit will mainly be for populations in the countries on that continent. Any treatment, once its hoped-for efficacy and tolerance have been proven, must be available and accessible to the population from which patients were selected.

Special case of pregnant women

Some texts on ethics as well as regulations in many countries consider pregnant women, fetuses, and children to be "vulnerable" populations that are fragile and unable to defend themselves, thus requiring additional protections when involved in research (e.g., the committee chairperson cannot approve the research on his or her own, there is no exemption for written consent). An additional question in our case was whether or not it was acceptable to expose the mother to any treatment-related risks when the treatment was for the exclusive benefit of the child.

Conclusion

This summary does not presume to cover all ethical questions that should be asked when designing a study involving an intervention in human health. There are manuals that provide thorough coverage of these questions. We hope that the real-life example given here can help readers in their own journey of introspective enquiry when designing a clinical trial.

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