

The National Advisory Board on
Social Welfare and Health Care Ethics ETENE

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LEGAL EFFECTS OF WITHDRAWING CONSENT

The Ministry of Social Affairs and Health invited a representative of ETENE to take part in a hearing related to the legal effects of withdrawal of consent in medical research. As ETENE's General Secretary will be attending a conference abroad at the time of the hearing and an invitation to attend the hearing had not been extended to the chairpersons of the board, the advisory board submits its views to the Ministry in writing.

In its most typical form, medical research is an activity where the interests of the various parties may either coincide or conflict. As a rule, the objective of a trial benefits all parties: the health and well-being of the subjects and those affected by the same group of illnesses improves as a result of the trial, the researchers can make progress in their work, and the party financing the trial may be able to place their product in the market. This does not always work out, however, as the trial may have adverse effects on some subjects, a drug may prove ineffective, or the research method turns out to be impracticable.

Before the entry into force of the Medical Research Act, research was guided by international regulations, the most significant of which are the World Medical Association's Declaration of Helsinki, and the Council of Europe Convention on Human Rights and Biomedicine ETS 164 (Biomedicine Convention) and its Additional Protocol Concerning Biomedical Research (ETS 195), of which the Convention entered into force internationally in 1999 and the Additional Protocol in 2007. As a result of the Declaration of Helsinki, the first advisory bodies on ethics were established in Finland as early as in the 1960 to evaluate medical research projects in Finland. As the Medical Research Act entered into force, hospital districts were given the authority to appoint ethics committees, and the Act contains provisions on the composition, size and tasks of the ethics committees. The international agreement on good clinical practice, ICH-GCP, has been applied to clinical trial practices in pharmaceutical research. Since the Medical Research Act entered into force, a Directive on the conduct of clinical trials on medicinal products for human use (2001/20/EC) was adopted in the European Union and implemented in Finland through amendments to the Medical Research Act and the Act on medicines (lääkelaki 395/1987). The processing of personal data in Finland is regulated by the Personal Data Act passed to implement the EU Directive on the protection of individuals with regard to the processing of personal data (1995/46/EC). The Clinical Trial Directive is to be repealed as the Clinical Trial Regulation enters into force in about two years. A new personal data regulation that would repeal the Personal Data Directive is also being drafted in the EU. The regulation will put an individual's right to self-determination in even stronger terms than the Personal Data Directive.

Against the backdrop of abuses that cast a shadow over medical research, consent was enshrined as an absolute condition for trials in the Nuremberg Code of 1949. Later in the Declaration of Helsinki, the issue of consent was clarified regarding subjects who are incapable of giving their consent and situations where urgent intervention is required, and also situations where a person withdraws their earlier consent. The point of departure in these cases, too, always is informed consent whenever possible, both regarding participation in a trial and the use of personal data.



Conflict between ethical principles and interests

Ethics refers to the examination and consideration of different viewpoints, where emphasising these viewpoints differently, often at varying points in time, may lead into different solutions. In medical research, the truthfulness and integrity of data plays a role in the quality and reliability of the results. A subject's right to refuse to take part in a trial or to withdraw from a trial results in incomplete and uncertain data in this subject's case. In principle the problem is the same, regardless of whether the subject originally consented to taking part in the trial, or whether the consent was withdrawn in an early stage of the trial or at the very end. The subject does not have to give a reason when refusing to take part or withdrawing their consent. In this respect, there is a conflict of interests between the subject and the researcher. In a conflict of interests of this type, international conventions and rules unambiguously put the interests of the subject before the interests of science and society.

The purpose of medical research is to produce information that can be generalised to apply to the entire patient group. The data collected in trials has increased in volume, expanded and become differentiated many times over since 1996, the year in which the ICH-GCP principles were laid down. Many clinical trials involve genome analysis, increasingly covering entire genomes. Research data is mainly processed, stored and transmitted electronically.

Using genome data, a person can today already be identified by a hundred different genetic markers. By combining the data in anonymized genome data registers, it has been possible to identify dozens of people (e.g. Gymrek et al. *Science* 2013; 339, 321–324). Consequently, the coding of conventional identifiers does not necessarily protect the subject's privacy to the same extent as previously. The electronic processing, storage and transmission of data has made questions of a completely new type relevant to the protection of a subject's privacy.

When assessing the legal effects of withdrawing consent, an individual's right to privacy and control of their personal data is at odds with the right of society and also of the party financing the trial to obtain as much data as possible from the trial, and to own and control the data they have obtained. The data is needed to assess the effect, safety and potential risks of a drug; society has a duty to protect its citizens against drugs that either are not sufficiently effective or may have negative effects from being approved for general use. Are we, in other words, talking about the interests of society, other persons affected by the same illness, or a private company, and do these interests overrule the wishes and interests of an individual subject?

This question is less emphatic in situations where the collected trial data is less significant for evaluating the effectiveness, safety or other effects of the drug to be studied. For example, data on the subject's other chronic illnesses, which are unrelated to the trial, may be of great significance to the subject and cause him or her to withdraw from the trial. The genome data may reveal some other risk that affects the subject's willingness to continue the trial. Societal reasons, including the discovery of abuses related to the trial, may also persuade subjects to withdraw.

The purpose of scientific research is to produce new information. In medical research, the subject has to give their consent to both the trial procedures and the processing of their data. The website of the National Committee on Medical Research Ethics (TUKIJA) notes: "Informed consent of the subjects is an elemental condition for carrying out medical research. This is a fundamental ethical norm which must not be treated as a formality. Participating in medical research must be voluntary in all cases and in all circumstances. Research where human integrity is compromised can only be carried out with the consent of the subject or a representative of the same (close relative, another person closely connected with the subject, or a legal representative). Volunteer research subjects must also be allowed to withdraw their consent at any time without justifying their decision to anyone."



Is consent to the processing of data a different issue - and also of secondary importance - compared to consent to a medical procedure? Even if the processing of personal data does not physically compromise the individual's integrity, the processing of sensitive health information touches the very core of a subject's humanity, vulnerability and mental integrity.

In Western research ethics and medical ethics, an individual's right to self-determination has been given rather a prominent position. An individual's right to self-determination cannot be overlooked without weighty reasons. Consent, which also includes the right to withdraw consent, is at the core of self-determination. The European Data Protection Ombudsmen defined the significance of consent in their publication "Opinion 15/2011 on the definition of consent". The publication states that if the activities can continue once consent is withdrawn, the individual has in some ways been misled. In other words, if consent to processing the data is not needed, neither should it be requested. If consent is requested, the withdrawal of consent must have clear effects; after withdrawal, the processing cannot continue.

In terms of the trial, withdrawal of consent to data processing may of course mean additional problems. After the data have been analysed, removing the data of individual subjects may be impossible or cause unreasonable additional problems. The removal of data changes the end results of the study if the subjects having withdrawn their consent are part of the same intervention group, and the outcome of the trial was particularly poor for them due to adverse effects or low response. In this case, too, recording the poor outcome as the end result of the trial would coincide with the interests of the subjects, rather than removing it from the data. The smaller the group of subjects, the more important their data are. In trials to test treatments for rare illnesses, for example, the withdrawal of a subject may be more significant than in trials on large groups of patients.

It is impossible to assess in advance what type of data will be important for the end results of the trial and what will not. Uncertainty and unpredictability of the end result are some of the basic characteristics of scientific research. When analysing the data, new and sometimes significant information may be revealed. Significant information will accumulate in the database in any case, once adequate numbers of research results have been obtained in the trial. If the collection of research data of an individual subject is interrupted before the trial has been completed, it will in any case be necessary to assess the end result of the trial for him or her. In fact, removing this subject's data may even make the trial data more truthful; if the trial is less convincing than expected because of withdrawals, it may be necessary to recruit more subjects, who will potentially go through the entire trial protocol.

These actions are also part of the nature of research for other reasons. For example, the effects of a drug being studied may turn out to be less powerful than expected compared to a reference drug or a placebo. In order to bring out significant differences between the groups, it may sometimes be necessary to recruit more subjects. Additional recruitments naturally mean more work and sometimes additional costs for the researchers. Subjects who withdraw from the trial also add to its uncertainty, which may be controlled by using more default information on the progress of the study. The EMA has published instructions for using a calculation method that strives to reduce the impacts of withdrawals on the research results. However, these instructions note that even if the given values in the calculation strive to simulate the actual research, they cannot eliminate the uncertainty of trial results.

The requirements, methodology and also data used in clinical trials of drugs have undergone crucial changes since the ICH-GCP was adopted in 1996. Our society, and such aspects of it as the human rights principles and their interpretations, have changed significantly over the last few decades. It would be naive to claim that research is still conducted following the same rules, even if striving for accuracy, integrity and repeatability by all possible means naturally remains relevant. Rather than reverting to 1990s methodologies and data transmission environments, it is more appropriate to adjust the existing rules, conventions and principles to the modern-day setting.



Other options also exist for counteracting the effects of consent withdrawals. All withdrawals and interruptions of trials should be recorded and reported to the pharmacovigilance authorities. The number of subjects who drop out is significant for the trial results, and the withdrawals of consent have a particular impact on how the research data are evaluated and interpreted. Keeping track of subjects who drop out or withdraw their consent is also significant in branches of science other than medical research, and it should be one of the endpoints of the research. Finnish subjects are highly positive towards research, and withdrawals of consent are rare. Dropping out of a trial is more common, in which case the consent to processing the data is still valid.

Key role is played by estimating the number of subjects both dropping out and withdrawing their consent in advance and indicating how these will be accounted for when evaluating the study. If these figures deviate from the estimates, the situation should be assessed by ethical committees and, in case of medical research, by the pharmacovigilance authority. As part of its initial assessment, the ethical committee should also evaluate which data are essential for the safety, effects and risks of the drug. The authorities will then have right of access to this data.

Proposed amendments to the Medical Research Act

From the ethical point of view both alternatives, either including the provisions in the section on clinical trials on medicinal products or in Section 6, will have the same effect: the act would restrict the subjects' right to exercise self-determination by forbidding the use of their data in a trial. Does this case represent a sufficiently significant societal interest, and do alternatives exist? The integrity of the study alone is not a sufficient justification for not granting an individual the right to forbid the use of their results in a trial by withdrawing their consent, as when a subject drops out of a trial, part of the so-called research results on him or her are guesswork in any case. If the data of a subject having withdrawn their consent are removed completely from the research data (in a trial for a medicinal product, they are however kept for the authorities), the end result of the trial may be more truthful than in cases where the data already collected would continue to be used in the trial.

Viewpoints related to the subject's safety are likely to only be in a key role in clinical trials of medicines and equipment, and in terms of ethics, only including the addition in Chapter 2a should thus be adequate.

On behalf of the Advisory Board

Chairman

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General Secretary

Ritva Halila

