

Codex of Bioethics

On the concepts and practice of biomedical research

<https://ett.aek.hu/en/codex-of-bioethics/>

Recommendation

A quarter of a century ago the emergence of ethics committees giving expert opinion on clinical biomedical research was one of the major events of the change of regime in Hungary.

Given the fact that ethics committees are composed of not only physicians but of specialists of other fields, as well, that is – among others clergymen and lawyers representing the “laic”, non-medical society –, a system of ethics in compliance with European legislation, also evolved in Hungary.

These ethics committees represent the dual value system, which assess partly in terms of the profession and partly in terms of society, that is in terms of patients’ rights, the professional-ethical aspects of the possibility of initiating a biomedical research.

Within the frames of the Codex of Bioethics, the Medical Research Council operating as a board of the Ministry of Human Capacities combines the experiences of the past 25 years with the widely known international declarations and directives on ethics, the European and Hungarian legislative environment regulating biomedical, clinical research is based on

The Codex addresses both the professionals and the whole society as not only the profession but laymen as well – thus others than physicians – are also concerned by these issues.

The Codex based on the Codex of Ethics of Scientific Knowledge of the Hungarian Academy of Sciences systematizes the ethical aspects not always codifiable by law of a highly important field of science and it provides useful starting points to everybody who wishes to deal with these issues.

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Preamble

The legal environment for human, biomedical, clinical research is constituted by the following legislative measures: the Helsinki declaration, the Act 2002/VI ratifying the joining of Hungary to the Oviedo Convention, the documents of the European Union, as well as the documents of the WHO, and additional international directives based on the ethos thereof, and naturally Hungarian legislation. Development in science brought a range of new professional and ethical challenges and problems to the surface, and questions are often arisen, the specific legal regulation of which is unsolvable, and the ethical assessment thereof is also complex. Therefore it is necessary to summarize for both the researchers performing trials and to lay society all those ethical aspects, which might be regularly faced in the everyday practice of research.

The Codex on the Ethics of Science of the Hungarian Academy of Science is valid for all research activities performed in any field of science. In the case of human, biomedical clinical research activities, there may arise numerous special standpoints to be taken into account besides general principles, which anticipate the need for a codex of bioethics resuming the peculiarities of the field.

In our country, the committees of research ethics with a national authority are operated by **the Medical Research Council (MRC=ETT)**. Clinical trials with test preparations fall within the competence of the **Ethics Committee for Clinical Pharmacology of MRC**, trials on genetics or human reproduction and trials performed with certain, advanced therapeutic methods are the competence of the **Committee of Human Reproduction of MRC**, and any additional trials fall within the competence of the **Scientific and Research Committee of MRC**. **The approval of these national committees of research ethics on the basis of professional-ethical considerations is required to all biomedical trials, which involve human participants.** Besides the MRC ethical committees the system of regional committees (SRC=RKEB) of research ethics has also been established. In cases authorized by law, SRCs may also grant professional-ethical authorization as to the starting and continuation of trials belonging to a specified field. The uniform operation of ethical committees and that of the SRCs are coordinated by the Presidency of the MRC=ETT. Professional-ethical opinions are issued by ethical committees. In these fields profession and ethics are very hard to be divided as the validation of professional criteria has an ethical side as well, to the assessment of which outstanding professionalism is needed. Therefore, the appropriate personal composition of ethical committees and the proportionate representation of professional and ethical considerations are of special importance.

Scientific research activities always constitute the subject of social interest. Society is particularly interested in the results of this field of science once they are also related to healthcare, therefore these researches are constantly under spotlight. Thus transparency is a criterion of extreme importance. In turn ensuring transparency may be conflicting with a great number of other aspects as from the protection of industrial and intellectual property to the interests of individual patients. It is important that ethical aspects and contradictions of this

special field should be cognizable to professional circles and to society, as well. It is therefore that the MRC considered the creation of the codex of bioethics of clinical research justified for the benefit of both the researchers and the public.

1. The Conduct of a Biomedical Researcher

General criteria set for the conduct of a researcher dealing with biomedical research related to human subjects, samples taken from human beings and data on humans do not differ from those set for other researchers. There are however such “extra” behavioural considerations and requirements of a special research ethical kind – partly ensuing from related specialities – which exceed generally applicable concepts and rules, and that are to be known, or to be thought of by those acting on this field. The “extra ethical expectations” in biomedical research derive primarily from dealing with people. That is why the knowledge and continuous monitoring of this issue and further training form part of a researcher’s righteous behaviour. The patients’ interest and protection are essential in medicine, and this is the foundation of bioethics too. However traditional medical behaviour and ethics do not prove to be enough. A researcher’s behaviour ensuing from traditional medical ethics is naturally in connection with criteria set for a biomedical researcher’s correct behaviour. Nevertheless an expert dealing with biomedical research might be faced by a lot of questions not dealt with by medical ethics. First of all there is a fundamental aspect that the researchers dealing with biomedical research are restricted in their freedom as researchers independently from their qualification and position. They can only act according to a previously established and approved research project. Assessment of whether the research project is vocationally and ethically correct does not depend on them or on their superiors. They can solely conduct research activities in accordance with projects previously approved by the relevant ethical committee. The professional-ethical judgement of biomedical, clinical research activities have in turn some fundamental aspects that do not arise in other research activities.

2. Protection of the Research Subjects of the Study

The rights, safety and welfare of the people involved in a study have priority over the interests of science and society; therefore the risks faced by the subjects of a research should be minimised as much as possible.

Carrying out a clinical examination or using an investigational medicinal product on a human being may only be performed in possession of an ethical approval and an official authorization. The examination may solely be conducted according to the conditions specified in the authorization, as well as the provisions of the authorized study project. The approved protocol is considered to be a rule for the profession, therefore failure to comply with it has or may have legal consequences. A deviation from the approved research project is ethically unacceptable unless it has been previously permitted. Hence only those acute cases may be considered to be exceptions, where the physician is forced to abruptly change the protocol by the interest of the patient. Any deviation from the protocol must be documented and reported to the sponsor immediately.

In the course of the planning and implementation of biomedical research the protection of the safety and rights of persons – either healthy volunteers or patients – involved in the trial is of a top priority. In case of people of increased vulnerability and limited ability to assert their own rights, ensuring the adherence to the requirement is particularly to be taken care of.

2.1. Ethics of Trials Pursued on Healthy Volunteers

Research of any kind may solely be conducted on healthy volunteers if potential risks affecting the subjects of the study do not exceed the potential benefits of the research. In the case of early (Phase I. and II. – see later on) examinations, the basis for the benefit/risk assessment may be primarily formed by the critical judgment of the results of preclinical examinations.

Previous proper notification of the volunteers and obtaining their written consent are required. In lack of these, a study is ethically not to be allowed.

2.1.1. Dealing with Random Findings

In case of an involvement in an examination or in the course of conducting a trial, a health risk previously not known or a potentially existing disease of the volunteer that clinically has not been manifested yet, might be detected by the principal investigator of the study. In such cases, the volunteer must be excluded from the trial. While providing information to persons to be involved (patients or healthy volunteers) particular care is required to be taken to clarify, whether the volunteer wishes to be informed about the content of a potential random finding, which may be not indifferent to him.

2.1.2. Aspects of Minimal Risk

Clinical trials on healthy volunteers may be conducted by complying with extremely stringent, multidisciplinary scientific and technical requirements. In case of research conducted with investigational medicinal products, determination of the dose that can be safely administered is of top priority. In research activities of this type, the exploratory examination should be started by the lowest possible dose calculated on the basis of preclinical data as a dose still not exerting any pharmacological effect, so that the healthy volunteer should not be exposed to the harms of an unknown compound having potentially unfavourable pharmacokinetic attributions. At the same time, the designation of the upper limit of the dose that can be safely administered is of extreme importance as in later stages of development this dose limit may not be exceeded at any time.

In Phase I studies, the number and the volume of blood samples to be taken need to be kept on a minimal level in the interest of the volunteer.

2.2. Patients in Biomedical Trials

Clinical examinations – including those of bioavailability and bioequivalence – have to be planned, implemented and reported according to the concepts of good clinical practice (GCP) in line with the Helsinki declaration on the ethical principles of medical research. Conditions to be met:

(i) from a professional point of view, the examination should be adequately based on preclinical and clinical results in accordance with the phase of the planned clinical examination, as well as the number and health status of research subjects to be included;

(ii) potential risks threatening individual patients must not exceed the potential benefits (at the same time, the notification provided to patients must contain the fact, that it is not sure that the examination would be of any benefit to the involved person).

In the study plan, adequate criteria of inclusion and exclusion are to be determined, that is appropriate parameters are to be defined to make clear, who may take part in the study, and the participation of which patients is contraindicated. It is in the same way that „*stopping rule*” must be specified that is the rule which is related to the stopping of the whole trial or the exclusion thereof of a patient. An independent committee constantly monitoring data and endowed with powers guaranteeing the above mentioned has to be set up.

2.2.1. Placebo

The advantages, risks, burdens and effectiveness of the new intervention must be tested against those of the best proven drug/intervention except for the following cases:

- if there is no proven intervention, the use of the placebo or that of a group without treatment is acceptable;
- if the application of a group left untreated is absolutely necessary for the determination of effectiveness or safety of an intervention;

- if the patients receiving a less efficient treatment than the best possible one, treated with a placebo, or left untreated are not going to be exposed to the risk of any severe or irreversible harm.

The fulfilling of the above conditions should be monitored carefully, and any abuse of this possibility must be avoided.

2.3. Participation of People with Limited Ability to Assert their Rights (Vulnerable People) in Biomedical Trials

Particular care should be taken in order to ensure that the interests of patients belonging to the following groups should prevail, and their privacy should not be hurt: vulnerable persons, pregnant women, their embryos, foetuses, lactating women, infants and young children, persons performing their military service, persons living in care homes, as well as in residential homes. The participation of persons deprived of liberty in clinical trials is ethically unacceptable.

Children may be involved in clinical trials only if the following conditions are met:

- it is justified by the occurrence of the pathology to be treated at underage persons and by the positive risk-benefit ratio expected;
- if the disease to be treated is not restricted to children, the examination carried out on children was preceded by a successful trial on adults with the same indication and with the same investigational medicinal product;
- the examination requiring the involvement of younger children was preceded by a successful trial on older children with the same indication and with the same investigational medicinal product (but the involvement of different age-groups might potentially take place within the frames of the same examination);
- The children to be involved in the examination are informed by means according to their age and mental capacities, and the children give their consent to the examination. The patient information for various age groups is in its substantial part naturally the same, but it ought to be different in terms of its manner.
- The parents are provided with comprehensive information, and thereafter their written consent is obtained.

In case of vulnerable patients with limited ability of asserting their rights, patient information is substituted by the information of the person entitled to give consent, and the consent form is also to be signed by the person entitled to give consent. It is not allowed to involve the vulnerable patient in a trial or in a part of the trial (e.g. genetic test) in the participation of which he refused to get involved in a previous statement. If later on the patient regains his ability to act, he must be informed about the examination without delay, and his further participation should depend on his consent.

2.4. Financial Compensation Granted to the Subjects of Trials

Persons – healthy or ill – participating in the phase I trial may be granted a uniformly defined financial compensation for inconveniences incurred in the course of the examination, as well as for the loss of time and revenue. Those involved in a study on pharmacokinetics and pharmacodynamics of a non-therapeutic purpose may similarly be granted financial allowance.

The amount of compensation is also essential ethically: it should not be disproportionately low or high considering strain. In the latter case it may be feared that the participant gives his consent to take a health risk in return to a financial compensation

At later phase trials, the expenses of the patient supported by invoices (travel, accommodation, catering) may be reimbursed. Donation of smaller objects, medical devices may also occur – it is again the extent of donation that is essential from the point of view of ethics. Financial compensation for the participation in a study must not be offered to minors or incapacitated persons.

2.5. Ethical Aspects of Informing the Subjects of Trials and the Ethics of their Consent

Informed consent is a generally accepted legal, ethical and regulatory requirement at every intervention related to health – in everyday health care routine just as in medical research. It is clearly stated by the latest version (2013, Fortaleza, Brasilia) of the Helsinki Declaration, as well as by the Belmont Report universally accepted in the United States that a health intervention may only be carried out by fully respecting the autonomy of the concerned persons (should they be patients or healthy volunteers). **The information should include the method, purpose, potential benefits and risks of the intervention. The person involved should be given the opportunity to have a free choice between the acceptance and the refusal of interventions.**

In leaflets informing patients and healthy volunteers, cultural diversity of participants should be paid regard to. These may exert an influence on moral values, which determine the consenting to the intervention. The information provided to patients must be clear, and no intervention should be started, except for those occurring in special circumstances (emergency, lifesaving), until the patient concerned is not in a state to give a valid consent. **Within the provided information it should be clearly stated whether a directly therapeutical intervention or a scientific research is being referred to.** It should be made clear too if the current research is targeted primarily to the testing of a new pharmaceutical, which later on could serve the benefit of other patients, and possibly also of the patient involved in the study. In case the involvement of minors is justified in the trial, it is also necessary to supply information adequate for the age and for the supposed mental maturity level of those to be involved, and to supply special information to the parents too.

Health literacy of diseased persons or those of the volunteers are often limited, and it should by any means be taken into account when preparing the information leaflet. Increasing the extent of the text is only justified if it makes the information leaflet more clear and comprehensible, otherwise it would only put the reading and understanding skills of the average non-expert population to the test. It should be kept in view that it is not the main purpose and aim of patient information to disclaim the responsibility of the institution carrying out the trial.

The patient information leaflet should be prepared for every trial according to a precisely defined pattern. This is the documentation that is signed by the patient or the volunteer (either ill or healthy) taking part in the examination. **The physician leading the examination must have appropriate skills to meet the challenge of clearly explaining the point of participation to the volunteer.** To provide information needs skills to acquire, and their teaching needs to be incorporated in the material of the GCP or in the courses for medical specialists. In today's health care, directly therapeutic interventions and scientific research aiming to improve the effectiveness of therapies keep converging, and they cannot always be easily distinguished. This difference must be made obvious in the information leaflet given to patients or to healthy volunteers. If the purpose of a particular study is the introduction of a new pharmaceutical, and the examination is initiated and financed by the producing pharmaceutical company, this should be clearly put in writing for the volunteer. Information must also be given about the potentially non-commercial nature of the trial.

As long as the test material (e.g. blood or tissue sample) is intended to be used later on in a previously not determined trial, the consent to this may only be requested from the participant of the trial in case it is definitely guaranteed that the test material originating from him is anonymized, and thus the origin thereof cannot be revealed. If the need for an additional re-examination rises, it is possible to contact the subjects concerned and to obtain their specific permission through the original examination centre where the code of the specimen is confidentially stored according to legal requirements.

The autonomous decision of those taking part in the trial might be influenced by the socio-demographic situation originating from the increase in the average age span of the population. Members of the population aged 65 and over need generally more medical interventions, and it is just because of demographic changes that their participation in certain researches proves to be necessary. As a condition it must be appreciated that some difficulties might come up in the understanding of the essence of trials by the volunteers.

3. Ethical Evaluation of the Trial

3.1. Purpose of the Trial

The ethical and scientific assessment of clinical trials is inseparable. The purpose of a trial may be that of clinical pharmacology (studies on pharmacokinetics, pharmacodynamics, bioequivalence, biosimilarity and tolerability), or the examination of the effectiveness of the preparation. The examination of the effectiveness of the preparation may also be explorative („proof of concept”), that is an efficacy study confirming previous expectations. The professional logical and chronological order of the phases of clinical development is determined, so the phase classification of the examination is objective.

Examination of the pharmacodynamic or pharmacokinetic properties or of the tolerability of the experimental drug to be tested, and studies on special population kinetics and interactions should be carried out in the early phase (Phase I), too, i.e. when the active substance is used “first in man”. The ethical condition for the starting of such examinations is that the trial on humans, or its purposes should be duly justified and convincingly supported by the results of the non-clinical *in vitro* and *in vivo* pharmacological and toxicological researches previously performed with the substance under development.

In this phase, examinations are performed on a limited number (6-10) of research subjects, most often healthy volunteers. In such trials, people unable to cooperate – e.g. drug-addicts, soldiers under dependency, convicts, etc.) are not allowed to participate either from a professional, or from an ethical point of view. Study subjects should generally be persons aged between 18-40 years, selected from both genders if possible. In case of women’s participation, reproductive activity should particularly be taken into consideration. Health status surveys should be performed by careful screening tests. The phase I trial may only be carried out as laid down in regulation, and only in institutions designated as suitable by the drug regulatory authority. It may occur, that the pharmacological, toxicological properties of the substance contraindicate the testing on healthy volunteers, or its efficiency and pharmacokinetic conditions are to be tested but in a specified disease. In such cases the clinical examination may be performed only on a defined group of diseased persons.

The purpose of phase II (explorative) trials is to verify results gained by that time in phase I studies in a patient group selected according to the effect and mechanism of action of the active substance. Such a trial is ethically acceptable in case the results being already at disposal provide sufficient reasons and grounds to the testing of investigational medicinal product in those suffering of a selected disease, and the target is realizable by the examination performed in the given indication with the methods planned. In addition to this, it is set as a professional-ethical condition that the projected dose-range should be considered safe on the basis of the results of the completed phase I trials.

The purpose of phase III (confirmative) trials is to verify the therapeutic effect perceived in phase II trials by involving a higher number of patients, furthermore to test the

investigational medicinal product on particular patient groups (e.g. elderly patients, children, patients with impaired kidney and liver function, patients with the coexistence of various diseases). Examination of the possibility and risks of drug-interactions also belongs here. It can be assessed on the basis of the previously obtained results whether the proposed aim (or further examination of the product in general) is ethically acceptable.

Phase IV trials may be conducted in order to verify the safe usage of an already registered pharmaceutical or to confirm its efficiency in everyday practice. The clarification of the purpose is a particularly important issue in the case of these examinations. It is unethical to conduct such studies for promotional purposes primarily or exclusively in the interest of the producers.

The prohibition of discrimination is a fundamental ethical principle in the involvement of participants in the trials.

3.2. Personal and material conditions of the examination

Trials having an acceptable purpose and being reasonably planned may also be professionally and ethically objectionable, if the protection of study subjects or that of their interests, as well as the safety of the obtained results are not guaranteed. The examination must be carried out by persons possessing the required qualifications and professional experience. The projected measurements should be directed at parameters, which are relevant according to current scientific knowledge and suitable to determine actual professional issues. Both interventions and measurements should be carried out with up-to-date and valid methods and tools, and the data are to be subjected to generally recognized statistical analyses. In addition, the preparedness to adequate management of potential risks or complications of the examination is also a key requirement. The professionals prepared to act in such cases, the tools needed and the institutions suitable for providing specialist care in the particular situation should be available, and financial resources for incurring costs must be ensured.

3.3. Ethical Aspects of the Adverse Reactions in the Trial

In case of adverse reactions perceived in the course of the examinations, one should proceed according to professional and administrative rules. In certain cases it may become necessary to stop the study. It is ethically unacceptable to conceal the causes.

3.4. Communication of the Trial and that of the Results

Biomedical research conducted on humans must be made public, and this applies also to the results obtained. Therefore clinical examinations before their starting (launching of the recruitment or performing the first intervention) should be registered in a publicly accessible, searchable database, and the most important data should be made public. In turn, while carrying out the examination the actualization and up-dating of these data must be ensured.

It is ethically unacceptable to take into consideration only a part of the results obtained at the assessment of an examination on humans. In order to avoid this, disclosure of the examination results (not that of the primary data) must also be ensured, regardless whether they are favourable or unfavourable observations from the point of view of parties carrying out, supporting or sponsoring the trial. Main outcome parameters are to be recorded by any means in the open database registering the study, or – if the former is not possible – on an internet platform developed for purpose by the study coordinator or sponsor of the examination. In addition – unless it is prohibited by special circumstances – the publishing of the results in scientific journals is to be sought for even if the findings do not support the expected effects.

3.5. Ethics of Reporting a Trial

The closure of examinations is followed by the compilation of a report. It is unethical to report the results in an incorrect, distorted way (*misinterpretation*), and to provide an erroneous deduction of consequences. This is particularly dangerous in connection with the assessment of efficacy, or that of indication area. It is unethical if the examination report does not include the data, which do not support the original hypothesis, or are even contrary to the aims specified in the examination plan. It is unethical if the adverse reactions observed during the examination are withheld or blunted. The findings not confirming the original hypothesis should also be made public to the profession.

4. Research Ethics Committees

4.1. Composition of a Research Ethics Committee

Committees contributing to the authorization of biomedical studies conducted on humans, as well as to the monitoring of the implementation of the protocol, give independent professional-ethical board opinion. Besides the representatives of the profession (researchers and physicians), non-professional “laic” members must also participate in the opinion making. As a layman, anybody can participate in the work of an ethical committee, but it is expedient that committee members be primarily involved in health care, thus professionals other than physicians, nurses, bioethicists, or representatives of patient organizations, theologians, as well as health law specialists and jurists dealing with patient rights.

The composition of the ethics committees must be of multidisciplinary and multi sectorial nature. In addition to ensuring of adequate scientific expertise, the well-balanced composition of the committee as to age and gender is a key ethical requirement. In case of examinations directed to rare diseases, wherein the assessment presupposes the existence of a specific knowledge, it may be necessary to request an *ad hoc* external expert opinion.

Members of the ethics committee receive regular training, and further training courses. The research ethics committee itself has also its own role in the teaching of ethical considerations.

The committee members form independent opinions as the total independence of the committee is a fundamental ethical principle

4.2. Tasks of the Research Ethics Committee

The primary professional-ethical mission of the research ethics committee is **to assess the appropriateness of the measures taken for ensuring the protection of people involved in the study**. Research activities serve to increase scientific or practical knowledge. However fundamental contradictions may occur between the scientific considerations of researches and the interests of the study subjects.

The ethics committee assesses the benefit-risk ratio of trials conducted with a scientific purpose from the aspect of the protection of participants, and it pays special attention to this viewpoint while judging the inclusion of participants and criticizing the way and quality of the acquisition of their informed consent.

The professional-ethical evaluation is also extended to the questions whether the trial is medically justified, and its execution can give an authentic answer/solution to a relevant issue. These considerations form in fact a part of the protection of study subjects (as well as that of the whole society).

4.2.1. Evaluation of Projected Trials

4.2.1.1. The Research Plan Documentation

While studying the research plan documentation the committee must assess the professional-ethical appropriateness of the trial. One of the cornerstones of the protection of research subjects is to guarantee that the projected examination is professionally well grounded, and that it serves a meaningful and rational purpose. Furthermore, it is a professional-ethical issue of high importance how much the risk of participating in the trial is proportionate to its benefit, and what measures are taken by the applicant for the sake of the participants' safety.

So the ethical assessment of research plan cannot be set apart from the professional-scientific evaluation of the soundness of the projected examination and its purposes, of its risk/benefit ratio, and of the conditions to be met.

4.2.1.2. Aspects of the Ethical Endorsement of the Financial Project

While assessing the financial plan of the research, potential, not declared conflicts of interest should be examined. Such an ethical problem rises if the remuneration of researchers is substantially higher than usual, or if the remuneration of the institution hosting the trial is unacceptably low, if the sponsor of the research pays the researcher in a differentiated way according to the number of recruited subjects (above a certain number of subjects, a larger sum is due for the inclusion than under this threshold), if researchers get special incentives for an exceptionally fast recruitment of the subjects. This condition requires a particularly careful consideration in cases, wherein the recruitment for international, multicentre examination is of a "competitive type", and recruitment is centrally stopped at reaching a previously specified number of recruited subjects.

4.2.1.3. Ethical Assessment of the Recruitment of Study Subjects

The group (age, gender, literacy skills, cultural characteristics, economic status and ethnical characteristics) the study subjects are recruited from, may be influenced by the professional content of the trial. The committee must evaluate the justification of the inclusion and exclusion criteria, and it is by taking into account the characteristics of the target group that it must be considered, whether the way of recruitment and the tools are appropriate for contacting the members of the groups and their representatives, as well as for providing them with comprehensive information.

4.2.1.4. Ethical Evaluation of the Procedure of „Informed Consent“

The consent of study subjects should be based on appropriate information (2.5. point). Information to be provided orally and in writing must be complete and comprehensible from the point of view of study subjects or their legal representatives.

It should be clearly justified, if persons not able of consenting are intended to be involved in the research. In such cases the planned way of acquiring consent or that of the authorization for involvement should be considered particularly carefully.

It should be guaranteed that the subjects of the study be able to obtain new information, which become accessible in the course of the research process if they are relevant for the conduction of the research. If in the course of the research there emerge new pieces of information, which influence the benefit/risk ratio of the research, then a new patient information leaflet and a declaration of consent must be prepared and signed by the participants of the examination. In the course of the research, the receipt and appropriate handling of complaints arriving from study subjects or their representatives is also an ethical requirement.

4.2.2. Control of Ongoing Trials by the Ethics Committee

After having authorized the plan of research, the research ethics committee verifies the process of the research, as well. Besides regular inspections, unscheduled ones might also be necessary, and events may occur that are to be reported to the ethics committee having issued the authorization, and the committee may decide to even suspend the ethical authorization of the ongoing study. The committee receives an account report of the completed or suspended examination and evaluates it.

4.2.2.1. Regular Inspections

The local, regional research ethics committees must control – at least once a year according to ethical viewpoints – the examinations in process falling under their competence. The controlling must cover the process of the informed consent and whether all research activities are performed according to the research plan. It is unethical to deviate from the research plan while conducting a research.

4.2.2.2. Unscheduled Inspections

Unscheduled inspection is ethically justified if:

- some addition or modification of the research plan influences the rights, safety, welfare of the study subjects or the process of the research. In accordance with the provisions issued by the European Medicines Agency (EMA), the approval of the planned changes by the competent Hungarian committee should precede this inspection.
- serious, unexpected side-effects are revealed, with regard to the research or to the product being tested;
- such an event occurs, or such a new piece of information becomes available, which exerts an influence on the assessment of the benefit/risk ratio of the research.

4.2.2.3. Notification of the Approving Ethics Committee

The ethics committee must be immediately notified if:

- an adverse event occurs, which was not indicated in the information form, or in the declaration of consent;
- the appearance of an “anticipated” adverse events is so serious, that it requires additional medical treatment or the prolongation of potential in-patient care;
- an event occurs, which threatens the research subjects’ privacy (e.g. the loss of research documents).

4.2.3. Public Reporting on the Work of the Committee

Ethics committees must inform the public of their activity. Therefore each research ethics committee should report on its work at least once a year, and should make his report available to the public. However the report of the committee must not contain personal information, which refers to the subjects of the trials.

It is considered unethical if the report infringes copyright or violates industrial rights, interests, or it provides undue research advantages. Therefore the report may not contain information connected with these issues.

4.3. *Obligation of Confidentiality*

In the course of their work, the members of the committee get possession of confidential information. Therefore, the members, i.e. all those who become acquainted with the research documentation must sign – even before concluding a contract – a declaration of confidentiality and must assume an obligation that they will not misuse this knowledge. The obligation of confidentiality is related to the contacting not only with a third party, but also with the leader and the participants of the trials, as well as with the sponsors. Only the regulatory authority is entitled to contact with the sponsor. The violation of the obligation of confidentiality is an ethical and potentially legal offence to be investigated and sanctioned.

4.4. *Ethical Aspects of the Conflicts of Interest*

Decisions concerning the affairs submitted to the committee should be made by those members who are independent from the given research plan and from persons and institutions involved in its implementation. Committee members should announce the fact of any conflict of interest arising – their involvement directly or indirectly – in advance, and in this case, they cannot take part in the evaluation of the particular research plan.

Members of the ethics committee cannot participate in the evaluation of a given research plan if they or anyone in their close contact are professionally and/or financially interested in the implementation – or even in the cancellation – of the research, take part in the research in any way, have interests at the company submitting the research plan or work at the same department of the host institution.

The adherence to these guidelines is only seemingly simple. Pharmaceutical companies also sponsor – occasionally by way of foundations – numerous, indirect researches

that are in connection with their own pharmaceutical products. Research may entail not only financial interest, but it may also mean gain in prestige both for the researcher and the institution. Therefore, interests may almost be confluent, so they do not necessarily clash. The Committee should take this fact also into consideration.

5. Specific Ethical Aspects of Special Areas

5.1. Human Reproduction

5.1.1. Assisted Reproduction and Genetic Risks

As a result of the development achieved in the field of biology, cytology and medical technology, reproduction with medical assistance may be realized since the end of the 20th century.

Assisted reproduction techniques (ART) are primarily applied to the medical treatment of infertility, but the continuous development of reproduction medicine and genetic technology opens a wide range of options for having a child. This is at the same time the application of a “positive right” to reproduction for people unable to beget their own offspring because of an illness. It has numerous scientific and ethical aspects.

The coordinated application of ART and that of genetic laboratory technology (“reprogenetics”) may be realized in various situations. Such a situation may occur, e.g. if in the course of the **treatment of infertility** genetic issues emerge, or if the medical examination of the couple that wishes to have a child reveals a genetic trait, which may be transmissible to the offspring, and therefore genetic counselling, genetic risk assessment will be needed in the course of the treatment. In both cases, depending on the outcome of the examination (if carrying genetic alterations leading to a high-risk, serious disease are detected) the application of ART, namely pre-implantation genetic diagnosis (PGDP), gametes donation and adaptation may be professionally substantiated. From an ethical point of view, the designation “serious illness” may cause difficulties; the possibility of healing and that of autonomy, as well as age at the appearance of symptoms must be taken into consideration.

The death of embryos implanted may be caused not only by a genetic defect being present in one of the members of the couple, but also by a random deviation emerging in the course of *in vitro* fertilization (IVF), mainly aneuploidy.

The idea of carrying out pre-implantation genetic screening (PGS) in order to assess the suitability of pre-embryos to be implanted arises rightly, as it justifies the application of more and more methods and ethical considerations in line with the development of science. In this case there is no need for genetic counselling, as it is not the prevention of any genetic disease appearing with high risk in the foetus that is set as a target, but the increased success of the IVF treatment. However based on past experience, the success of PGS is contested, as it is considered by influential professional organizations to be a procedure in the research phase. However it falls ethically under special assessment that the genetic technics applied in the course of the procedure may enable apart from the screening for aneuploidy, the screening for any other genetic characteristics („*sex selection*”, „*designer baby*”, see below), that is from the point of view of ethics, the method applied to carry out the examination, has also got a relevance. Therefore a special organization – the International Committee for Monitoring

Assisted Reproductive Technology (ICMART) – was established for monitoring the new technics and evaluating the results.

Given the genetic disease of one of the members of the couple that wishes to have a child, the risk may be increased that the child to be born will inherit the disorder. In this case, it is from the beginning of the procedure that the involvement of a genetics specialist and a genetic counselling are needed.

In case the termination of pregnancy is not acceptable for the pregnant woman from conscientious or any other reason, the joint application of ART and PGD and thorough information related to parental decision-making are justified. In the offspring to be born the manifestation of the genetic deviation may be prevented by gamete donation. Special ethical considerations (man or woman, age, kinship, etc.) are justified by the procedure (see later on). Mitochondrial transplantation is a specified case for the avoidance of genetic anomaly by ART.

5.1.2. Professional-Ethical Aspects of the Storage of Gametes

The storage of gametes is justified in numerous cases, e.g. in various illnesses. Due to their physiological properties, the extraction of sperms and their storage in a frozen state (cryopreservation) is relatively easily accomplished. As it is only following a lengthy pre-treatment that oocytes may be obtained, and their freezing and long-term storage in a deep-frozen state (vitrification) became possible only recently, the ethical evaluation of the procedures dealing with the gametes of the two genders differs in several respects.

While storing gametes, a special care should be taken to safety including identification, ruling out the exchange of samples as well as ensuring adequate technical conditions.

Male gametes

1. Parenting by the use of gametes stored in a sperm bank is ethically acceptable – in case of fruitless relationships of couples being sterile because of the infertility of the husband/male life partner – for single women and lesbian couples.
2. Ethical aspects are to be considered in professional procedural guidelines, which determine the medical, genetic screening of the donors before obtaining the sperms.

Female gametes

1. The heterologous donation of the oocyte is to be individually organized by the coordination of the processes of the extraction and that of the acute implantation, which renders the anonymity more difficult. It is expedient to carry it out the procedure within the family, in the frame of an agreement, recorded in writing, as well. Consideration should be given to the age of the donor and that of the recipient and to the risks due to diseases of the individuals born from the oocyte.

2. Freezing of an oocyte (or ovarian incision and freezing) may be carried out for the purpose of an autologous use, when a woman of a reproductive age faces a treatment bearing a risk of mutation because of a malignant tumour.

5.1.3. General Ethical Considerations of the Evaluation of Human Reproduction

Being motivated to reproduction, which stems from the intrinsic feature of the living world, is determined by biological processes, but assuming the tasks of childbearing depends on **autonomous decisions**. In the decision regarding reproduction beside the natural instinct resulting from the fact that humans are biological beings, social, economic, traditional and short-term, fashion-generated factors also play a role. Responsibility for childbearing is equally shared by both genders in the **natural form of reproduction**. In their decision related to reproduction, a man and a woman cannot ignore the interests of the child. However the continuous development of technologies related to reproduction and genetics justifies the consideration of **special ethical aspects, which occur when assisted reproduction procedures are applied**. While applying ART procedures, the participation of men and women in the processes differs, but efforts should be made that the two genders equally take part in assuming responsibility for childbearing. As it is the case of the natural way of accepting tasks with childbearing, one of the basic aspects of the application of ART is that the interests of the child to be born should be taken into special consideration. In order to promote this, the long term follow up of children who have already been given birth to, should also be rendered possible. It is an important guiding principle, that a treatment of assisted reproduction should only take place, if the conditions guaranteeing the coming fore of the interests of the child to be born are given („*reasonable welfare standard*”).

The process of the assisted reproduction is carried out with the participation of physicians, so the protection and follow up of the health of the child to be born needs increased medical care. As a consequence, in the ART applications, wherein genetic interventions also occur, the individual right to autonomous (non-directive) decision – which is of utmost importance in genetics otherwise – appears in a different way: professional guidance resulting from the professional responsibility and duty of the physician may come into conflict with the autonomous decision right of the individual. The physician should seek a way to inform the individual as thoroughly as possible. In the course of a reproduction treatment, patients are entitled to detailed, individualized information, especially on the nature, sequence, short and long term risks, benefits, as well as the health impacts of the intervention.

Besides promoting the assuming of responsibility for childbearing, the attending physician should take care of health, dignity and privacy rights of patients, especially of women particularly exposed to the procedure.

Respecting the patients' human dignity is a top priority aspect of care. A clinic providing reproduction treatments should give emotional, mental and professional assistance – even in cases of failure – to couples, as well as to single women requesting reproduction interventions.

It is ethically not acceptable to manipulate gametes or the genetic pool of embryos for the creation of any health, physical-mental traits deemed beneficial („*designer baby*”). It is ethically not acceptable either to choose the gender of the off-spring by the application of ART and/or PGD („*sex selection*”), unless the aim is to prevent the occurrence of sex-linked, serious, untreatable diseases. In this case, the legal order ruling genetic procedures shall prevail.

Though the procedure is by all means artificial, the impacts of “medicalization” should be minimized as far as possible. In the course of the treatment, it is not only the success of the reproduction procedure that is the target, but care should also be taken of the reproductive and general health status of the participants in the intervention.

It is subject to specific assessment, when an *in vitro* intervention takes place on a non-infertile couple in order to provide help to an already born sick child with the utilization of the umbilical cord blood of a new born baby with compatible properties (a lifesaving sibling). Organ procurement from an underage living individual is ethically impermissible.

In the field of the donation of gametes, as well as that of embryos, the prohibition of profit making should be strictly observed.

5.2. Genetic Examinations and Research

The application of genetic examination methods continuously growing in number – including the human genome analysis – raises a large number of new ethical-professional questions affecting or addressing not only individuals but communities too and regarding even the informed consent. This is why the specific aspects of this field are discussed separately. It is a special ethical problem to decide in what conditions may the results of such an examination, which are in principle anonymized, be brought to the attention of participants. The issue is further complicated by the fact that the volunteers, once interested, can reveal genetic features even by using conventional methods.

5.2.1. Special Status of Genetic Data

Human genetic data are to be treated as sensitive personal data of the individuals, as they are connate, do not change through the life span, and the information obtained from the sample taken from the individual is projected to several persons, i.e. the family members.

The special status of human genetic data is due to the fact that they can predict the genetic predispositions of individuals, they can exert a significant impact on the family, the off-springs included, on the following generations, and in certain cases on the whole group the concerned individual belongs to.

Genetic data are peculiar as they may include information, the relevance of which was unknown at taking the biological sample, but which have medical and cultural significance for the individual and his family in the future.

Each individual possesses specific genetic features. Nevertheless the individual's identity cannot be merely reduced to his genetic characteristics, as it includes complex educational, environmental and personal factors, emotional, social, mental and cultural ties to others, as well as the dimension of freedom.

5.2.2. Prohibition of Discrimination and Stigmatization

When it is justified to compare genetic samples originating from different populations or to study genetic characteristics of individuals in certain patient groups, it must be done so that it should not incur any stigmatization disadvantage either for the individuals, or for the groups, as it is ethically unacceptable. All efforts should be made to avoid the use of human genetic data for purposes that are discriminative or that lead to stigmatization of either the individual, or the family or the group in any way.

5.2.3. Individualization of the Provision of Information and that of Treatment; Genetic Counselling

Before genetic sample taking, the individual should be given detailed information on the purpose of the procedure (of the research), and the result of the examination should be communicated in an individualized way, including the explanation of the consequences. In case the examination regards predictive or inclining factors, a genetic counselling must be ensured to the patient in a way detailed by law. The provision of information must specify the purpose for which human genetic data are generated from the biological sample, and communicate the fact, that these data will be utilized and stored. The provision of information must notify – if needed – the risks and consequences.

With regard to the specific personal status of genetic information, the provision of information before the sample taking for genetic examination should be ensured in the frame of genetic counselling in a form imposed by a special legislating rule. It is an ethical imperative that when human genetic data are collected for research, serving diagnostics, health care, or medical and scientific purposes, genetic counselling of an adequate way should be ensured in every phase of genetic testing and screening. Genetic testing should not be enforced; it should be culturally adapted and consistent with the best interests of the person concerned.

5.2.4. Consenting to Genetic Examinations

As to the collection of human genetic and biological data, as to their subsequent processing, utilization and storage, a free, informed, unambiguous and uninfluenced previous consenting of the participants should be requested, irrespectively to whether the procedure takes place in a public or in a private institution. The consent should also regard the way the sample will be stored. When the participants are being informed, the attention of the individual should be drawn on the peculiarity of the genetic sample, namely that it might reveal important information for the future of the individual and his family, which is yet unknown at the time of sample taking, and that the individual can only access these

information, if the link between the sample and the individual has not been destroyed irretrievably (coded vs. anonymised storage).

When human genetic data and biological samples are collected for medical and research purposes, the person concerned may withdraw his consent, except for the case, when these data may not be linked irretrievably to an identifiable person. The withdrawal of the consent may not entail either disadvantage, or retribution as to the person concerned.

Once the consent has been withdrawn, genetic data or biological samples of the individual may only be used further if their linking with the person concerned is irretrievably impossible. If data can still be associated with the person concerned, then the procedure is up to him/her. When the decision of the given person is not available, not realizable or not safe, then the data and the biological samples must be either made irretrievably unconnectable with the person concerned or destroyed.

5.2.5. Privacy Policy in Effect in Genetic Examinations

Through getting to know genetic data, insight may be gained to personal information, which could have been concealed by the individual, or which have been unknown even to him (e.g. a predisposition to diseases occurring later in life). In case of genetic data, the disposal of human rights and personal data are rendered even more difficult by the fact that the interpretation of genetic data is the task of specialists, therefore the interpretation of the result of a predictive genetic test takes place in the frame of the genetic counselling. Personal genetic data should be treated by ensuring adequate informatics and data protection expertise and by taking current legislation into consideration. The persons and competent people responsible for the processing of human genetic data and biological samples must take the necessary measures to ensure the accuracy, reliability, quality and safety of these data and biological samples. In the course of the planning of research protocols, the practical implementation of data protection should also be envisaged.

5.2.6. Access to Genetic Data

Not a single person may be denied the possibility of accessing their own genetic data, except if these data are irretrievably not linked with the person in question as an identifiable source, or if the access is restricted by the legislation of the given country because of interests related to public health, public safety or national security. Human genetic data and biological samples that can be linked to an identifiable person are not allowed to be disclosed or to be made available to third party, especially to employers, insurance companies, educational institutions and to the family, unless it is authorized by law. Human genetic data and biological samples collected for medical and scientific research purposes may remain linkable to an identifiable person only in case it is required by the research, assuming that the right of the individual to secrecy and the confidentiality and also the secrecy of the data and that of the biological samples are ensured according to the provisions of the national legislation.

When human genetic data are collected for medical purposes or for those of scientific research, it is to be notified that as a part of information procedure at the time of consent the

person concerned has the right to decide whether or not they wish to be informed on the results. It may not be applied in the case of data irretrievably disconnected from the identifiable person, as well as data, which do not lead to results individually related to the person taking part in the research. The right of not being informed may be extended, where necessary, to the relatives who may be concerned by the results.

5.3. Psychiatric Examinations

The peculiarities of psychiatric diseases urge the consideration of special aspects in the ethical assessment of biomedical research activities conducted in this field. The issue of legal capacity directly affecting informed consent, as well as the possibilities and risks of the application of placebo are to be highlighted in particular.

5.3.1. Person under Guardianship as a Subject of Psychiatric Clinical Trials

Guardianship partially limiting legal capacity is not an absolute excluding factor in terms of participation in psychiatric clinical trials, i.e. it does not deprive the person under guardianship from his right of taking part in a clinical study and of making independently a statement thereof. Nevertheless, an individual with limited legal capacity can only take a decision without the consent of the guardian appointed for him, in issues of such consequences that do not considerably affect his lifestyle and living conditions. Thus it is essential to consider how his participation in a given examination can be specifically evaluated. Those who have previously, in the possession of their legal capacity, excluded or refused to participate, cannot be included in the trial.

Clinical research conducted on an incapacitated person or on a person with limited legal capacity may solely be carried on in case it does not exceed significantly a minimum level of risk, i.e. if

- a) the trial may be directly beneficial to the health of the research subjects,
- b) the scientific knowledge to be acquired may be useful for the person in question or for those suffering of similar diseases,
- c) the research cannot be carried out with similar efficiency on persons who are in possession of their legal capacity,
- d) the patients gave their consent according to respective rules.

5.3.2. Loss of Legal Capacity in the Course of the Clinical Trial

In case of certain psychiatric diseases, one must reckon with the fact that the patients involved in the trial might lose their ability to act in the course of the trial. The loss of the ability to act does not give grounds in itself for the exclusion of the patient from the study.

5.3.3. Placebo Controlled Clinical Trials on Psychiatric Patients

General considerations as to the application of placebo (see chapter 2.2.1) in psychiatric examinations are completed by the following professional-ethical rules:

- It is ethically unacceptable to provide placebo only treatment to patients with high risk for auto- and/or hetero-aggressive acts.
- It is forbidden to replace the sustaining treatment of patients suffering from certain psychiatric diseases in a steadily compensated state with placebo.

As to the application of placebo, a continuous revision is justified from a professional-ethical standpoint on the following areas:

- in the prevention of the relapse of schizophrenia,
- in acute maniac episode and in the serious form of major depression,
- in case of obsessive-compulsive disorder and in serious forms of social phobia.

Continuous hospitalization and intense observation are needed for the application of placebo in certain psychiatric diseases, which should be regarded separately in the protocol.

6. Period of Validity for the Codex

The scope of certain parts of the Codex may undergo rapid changes. The permanent renewal of methods and technologies, the occurrence of new diseases, as well as the showing up of new social claims may also entail a constant change in the trends and problems of biomedical research. Therefore, systematic rethinking and review will be predictably required in certain parts of the Codex.

GLOSSARY – TECHNICAL TERMS EXPLAINED

aneuploidy	Deviation of the number of chromosomes from the normal value (46 in humans) – heredity resulting in an inadequate set of chromosomes.
bioequivalence studies	Clinical trials with the aim to assess the expected <i>in vivo</i> biological equivalence of various preparations of an active substance.
biosimilarity studies	Clinical trials carried out with biologically produced active pharmaceutical substances, with the aim to prove, that the clinical effects of pharmaceuticals obtained through different manufacturing processes do not significantly differ from each other.
bioavailability	The proportion of a dose of the substance, which appears in an unaltered form in the circulation (generally expressed in percent).
pharmacodynamics	Biochemical and physiological/clinical effects of pharmaceutical substances exerted on the organism, the mechanism of the effect and that of the concentration dependence included – the time course of changes in the pharmacological effects.
pharmacokinetics	Characterization of the absorption, distribution, metabolism and elimination (ADME) of a substance
advanced therapeutical methods	Gene therapy (genes having therapeutic effects), somatic cell therapy (somatic cell preparations, the biological characteristics of which were changed in a way of genetic engineering), „tissue engineering” (genetically altered tissue preparations), and the clinical application of the combination thereof.
good clinical practice	Good Clinical Practice (GCP) is an internationally accepted procedural order in medical interventions of any kind.
interaction studies	<p>Studies on how the concurrent use of pharmaceuticals influence each other’s pharmacodynamic impacts or pharmacokinetic characteristics.</p> <p>In a broader context, herein is included the studying of how the impact or kinetic characteristics of a pharmaceutical are influenced by concurrently consumed food.</p>

placebo	Preparation containing no active substance (which is identical in its external appearance with the preparation containing active substance).
preclinical studies	Trials conducted on biological preparations, then on animals (preferably on several species) before the testing on human in order to learn about the nature of a compound, the totality of <i>in vitro</i> and <i>in vivo</i> (animal) experimentation underlying clinical examinations. Chemical-analytical and technological analyses of the pharmaceutical substance and that of the formed product are also included.
tolerability studies	Determination of how high doses of an investigational medicinal product can be tolerated by the patients in order to achieve the desired effect.
toxicology	The branch of pharmacology dealing with the adverse effects of pharmaceutical substances or of chemicals in general.

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