Ethical aspects of scientific research

Professor A.Kh.Alenova,
NTBC MoH RK

Ethics is a goodwill philosophy but not ONLY good action

I. Kant

In respect to scientific research:

Ethics is a philosophy of good ACTION but not only goodwill

Medical ethics evolution

Medical ethics evolved from Hippocratic Oath principles: "Do not do harm" and "Do good" to "Nurnberg Code of medical ethics" and modern International Conference on Harmonization (ICH), Declaration of Helsinki and International Convention on Human Rights and Bio-medicine.

Ethical aspects of clinical research

Violation of patients' rights

- ✓ Second World War – experiments of German doctors on concentration camps' prisoners
- ✓ 1933-1973 – USA, research on untreated syphilis course in Afro-Americans
- ✓ 1956-1972 – USA, Willowbrook study

Declaration of Helsinki
of the World Medical Association

Ethical principles of medical research with participation of people as human subjects

- ✓ Adopted at XVIII General Assembly of the World Medical Association in 1964 Helsinki
- ✓ Last edition - 2008, Seoul

What is the main idea of the Declaration of Helsinki?

Wellbeing of those under test prevails over the interests of science and society

Main principles of the Declaration of Helsinki

- ✓ Researcher's responsibility – protection of life, health, inviolability of private life and dignity of a respondent
- ✓ Research plan and implementation method should be clearly formulated in the protocol

Main principles of the Declaration of Helsinki

- ✓ Protocol should be approved by an independent Ethical Committee
- ✓ Researcher should report to the Ethical Committee about all current information and especially about any serious adverse events

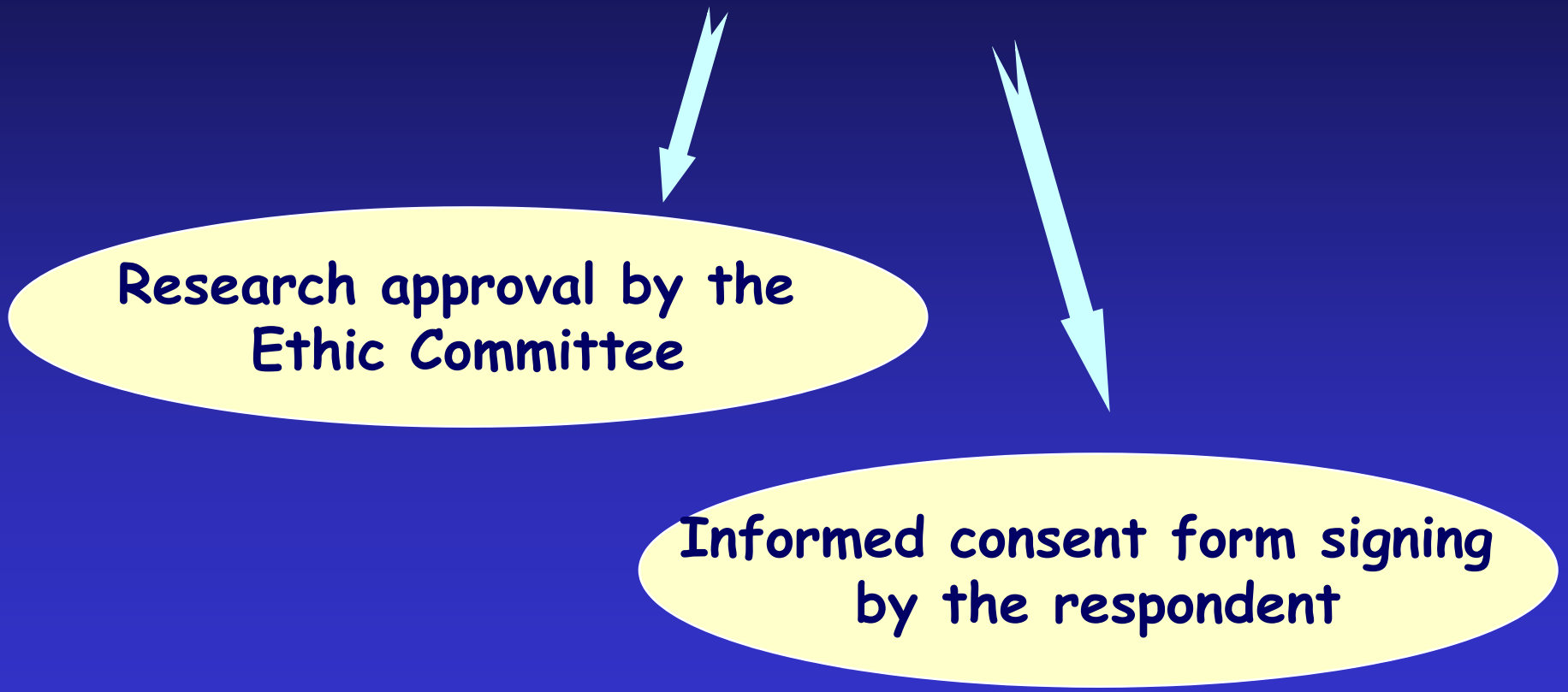
Main principles of the Declaration of Helsinki

- ✓ Research should be carried out by the qualified specialists
- ✓ Evaluation of possible risks and expected benefits
- ✓ Expected benefit should prevail over risks

Main principles of the Declaration of Helsinki

- ✓ Respondents should provide their voluntary and informed consent for their participation in the research
- ✓ Confidentiality of the respondent's participation in the research
- ✓ If the respondents are incapable, consent for their participation in the research should be provided by their authorized representatives

Surety of the ethic norms observance



Ethical Committee

An independent organization created by doctors and researchers, as well as other professionals, which is responsible for protecting the rights and health of the subjects, and provides public assurance of such protection by reviewing and giving a positive opinion on the study protocols and amendments thereto, as well as on the procedure of obtaining and documenting the informed consent of the subjects
ICH GCP Rules

Ethical Committee

- Researcher in France who started the clinical research without EC approval, could be sentenced to imprisonment for the period of 2 to 12 months, and penalty in the amount of € 900 to
- € 15,000.

Ethical expertize mechanism in the RK

Ethical Committee composition

- ✓ Minimal composition – 5 people (usually 7-12 people)
- ✓ At least one EC staff member should not be a researcher
- ✓ At least one EC staff member should not be a worker of this medical facility
- ✓ External advisors and consultants may be enlisted for the EC activity, and they have a deliberative vote

EC standard operational procedures (1)

- ✓ Committee's composition and membership
- ✓ Order of Committee's meeting
- ✓ Procedure of the application submission for ethical assessment
- ✓ Order of research documentation review

EC standard operational procedures (2)

- ✓ Procedure of the EC decision making
- ✓ Procedure of the expedited document review
- ✓ Order of the amendments review
- ✓ Order of the documents storage and archiving

The following are the subjects to the ethical expertise

- All ЛС clinical research
- All pre-clinical research
- All thesis works
- All scientific projects on the new medical technologies development and introduction

Some kinds of ethical expertize popular in the west and uncommon here

- Expertize of scientific bad faith (плagiarism, forgery)
- Expertize of deontology violation by the medical staff
- Expertize of the educational process violation

Ethical Committee tasks

In the clinical research:

- Design does not expose to danger the patients' rights and wellness
- Risks for the subjects do not exceed the scientific importance
- Participants' selection is honest and fair
- IC's content and accessibility meet the fixed requirements

EC's tasks (2)

- Process of obtaining IC does not violate the participants' rights
- Patient's confidentiality and medical secrecy will be kept
- Researchers have adequate resources and qualification
- Research will be carried out in accordance with the established standards
- Vulnerable groups patients' rights are protected

Patients' vulnerable categories

- Children
- Woman of childbearing age
- Pregnant women
- People with mental diseases
- Unconscious patients
- Incurable patients
- Ethnic minority representatives
- Students of medical institutes and colleges
- Servicemen and prisoners (prohibited)

4 principles of the ethic expertize

Independence

Competence

Pluralism

Transparency

Main documents for the ethic expertize

- ✓ Research protocol
- ✓ Researcher's brochure
- ✓ Individual registration card
- ✓ Respondent's informed consent form
- ✓ Information on the researcher's qualification (CV)
- ✓ Copy of the respondent's medical insurance policy

Additional documents for the ethic expertize (if specified)

- ✓ Patients' diaries
- ✓ Questionnaires and forms
- ✓ Samples of advertising materials for respondents' recruitment
- ✓ Information about incentives to be paid to respondents, if provided for

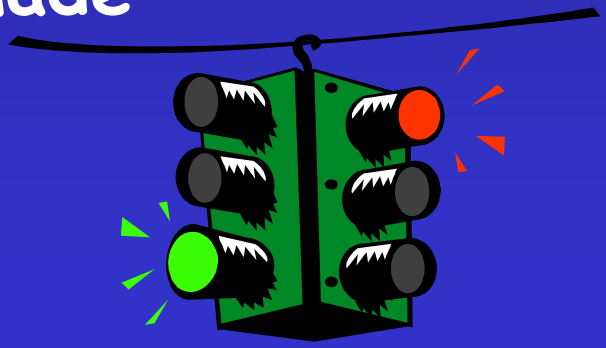
Types of EC's decisions

Approval

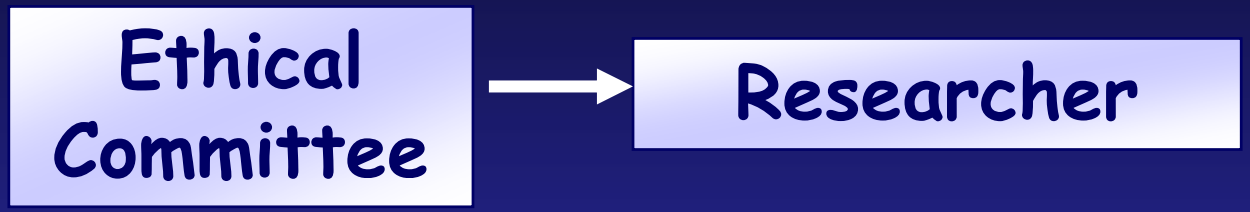
Suspension of the previous approval

Disapproval

Conditional approval provided that certain amendments are made



EC's decision execution



- ✓Extraction from EC meeting protocol:
  - List of documents reviewed
  - EC's adopted decision
- ✓ List of EC members
- ✓ EC's SOPs (24 SOPs)

Documents to be submitted to EC in *the course* of the research

- ✓ Amendments to the approved research documents
- ✓ Information about serious adverse events arisen in the course of the research; and safety reports
- ✓ Any information that substantially influence upon conducting of research
- ✓ Interim report on research implementation (at least annually)

Document to be submitted to the EC *after* completion of the research

- Final report on clinical research

Storage of documents in EC

In accordance with ICH GCP Rules all documents and correspondence shall be kept with the EC

no less than 3 years

after completion of clinical research

Informed consent

Voluntary confirmation by a respondent of his/her wish to participate in the research upon informing him/her about all details that could influence upon his/her decision

ICH GCP Rules

Regulatory system

1. **Constitution of the Republic of Kazakhstan**
   dated 30 August 1995 (Articles 12; 14;18;)
2. **Normative-legal acts in healthcare sector:**
   - *"Code of the RK on Health of Nation and Health System" 2009 (where the EC status and functions are stipulated) :*
     - **Clause 74. Clinical research and (or) trial of pharmacological and medicinal drugs, medical goods and equipment**

       1. Clinical research and (or) trial of pharmacological and medicinal drugs, medical goods and equipment is carried out with people as subjects of research to reveal or confirmation of any clinical, pharmacological and (or) pharmaco-dynamic effects among drugs under trial and (or) to study suction, bio-transformation and excretion to ensure safety and effectiveness.
       2. Clinical research and (or) trial of pharmacological and medicinal drugs, medical goods and equipment is carried out in the order established by the authorized body.

Clause 180. Medical and biological experiments, pre-clinical (non-clinical) and clinical research, use of the new diagnostic methods, treatment and medical rehabilitation

1. The purpose of medical and biological experiments, pre-clinical and clinical research is to obtain assessment and proof of their safety and effectiveness using scientific methods.

2. Pre-clinical (non-clinical) research is carried out on animals.

3. Clinical research (CR) with participation of people, subject to obtaining positive pre-clinical results, can be conducted only with their written informed consent.

4. CR with participation of minors can be conducted in parallel with the research among adults in order to get the following data:
   1) medical technologies or drugs intended for treatment of children;
   2) best dosage of medication intended for treatment of minors.

Clinical research with participation of minors is conducted only with their written informed consent of their authorized representatives.

Clause 180. Medical and biological experiments, pre-clinical (non-clinical) and clinical research, use of the new diagnostic methods, treatment and medical rehabilitation

5. In obtaining the consent for minor's participation in the clinical research his/her authorized representative should be informed about the following :

1) medical technology, pharmacological or medical drug, essence and duration of the clinical research;

2) safety and effectiveness of this medical technology, pharmacological or medical drug, as well as about health risk level;

3) actions in case of unforeseen circumstances while using of the medical technology, pharmacological or medical drugs;

4) health insurance conditions.

Clause 180. Medical and biological experiments, pre-clinical (non-clinical) and clinical research, use of the new diagnostic methods, treatment and medical rehabilitation

6. Clinical research may be stopped at any stage:
   1) at the request of the research participants (minors), their authorized representatives, patients or volunteers;
   2) in case of occurrence of threat to the lives and health of minors, patients or volunteers.

7. Mandatory conditions of clinical research are the execution of life and health insurance for the research participants, patients and volunteers, as well as ethical assessment of the research materials.

8. Use of the new diagnostic, treatment and medical rehabilitation methods is possible only under condition of obtaining positive clinical research results.

Clause 180. Medical and biological experiments, pre-clinical (non-clinical) and clinical research, use of the new diagnostic methods, treatment and medical rehabilitation

9. It is prohibited to conduct clinical research of medical technologies, pharmacological and medical drugs among:

1) minors having no authorized representatives,;

2) pregnant women, except cases of medical technologies and drugs clinical research intended for pregnant, when the required information can be obtained only in clinical research among them and the risks of harm to them and their fetuses are excluded;

3) Servicemen;

4) People in detention and, in temporary detention facilities and research-trial detention centers;

Clause 180. Medical and biological experiments, pre-clinical (non-clinical) and clinical research, use of the new diagnostic methods, treatment and medical rehabilitation

5) people recognized by the court as incapable, except cases of medical technologies and drugs clinical research intended for psychic disorders (diseases) treatment in patients with psychic disorders (diseases).

10. Clinical research standards (due clinical and scientific practice) are approved by the authorized bodies and governmental organs within their competence.

11. Order of medical and biological experiments, pre-clinical (non-clinical) and clinical research and the order of use of the new methods of diagnostics, treatment and medical rehabilitation are approved by the authorized body.

Clause 180. Medical and biological experiments, pre-clinical (non-clinical) and clinical research, use of the new diagnostic methods, treatment and medical rehabilitation

12. Issuing of permissions for pre-clinical (non-clinical) and clinical research of pharmacological and medical means, and clinical research of medical technologies is carried out by the authorized body.

13 Issuing of permissions for use of the new methods of diagnostics, treatment and medical rehabilitation is carried out by the authorized body subject that the clinical research meets the standards based on evidence medicine and approved by the authorized and governmental bodies.

Normative base (2) (regulatory acts)

- Order of the MoH RK **№ 442** dated 25.07.2007 "On approval of the Rules for pre-clinical research, medical and biological experiments and clinical research in the RK";

- Order of the MoH RK **№ 744** dated 19 .11. 2009 "On approval of the Rules for clinical research and (or) trials of pharmacological and medical means, medical goods and equipment.

Normative base (3)

Order of the MoH RK № 744

Clinical trial phases (CT);

- *Ethical Committee (EC);*
- *CT order:*
  - *Protocol,*
  - *Researcher's brochure,*
  - *Informed consent (IC);*
  - *Researcher's CV,*
  - *Respondents' insurance,*
  - *Agreement between the customer and CT basis*
  - *Patient's obligations are specified in the IC,*
  - *Discomfort and risks;*
  - *Objectively expected benefit.*
  - *Incentives, amount of payment.*
  - *Data identifying a person is confidential.*

Normative base (4)

3. *State standards of the RK "Due laboratory practice" , "Due clinical practice" approved by Order № 575, dated 29 December, 2006, of the Chairman of the Committee for technical regulation and metrology of the Ministry of Industry and Trade of the RK;*

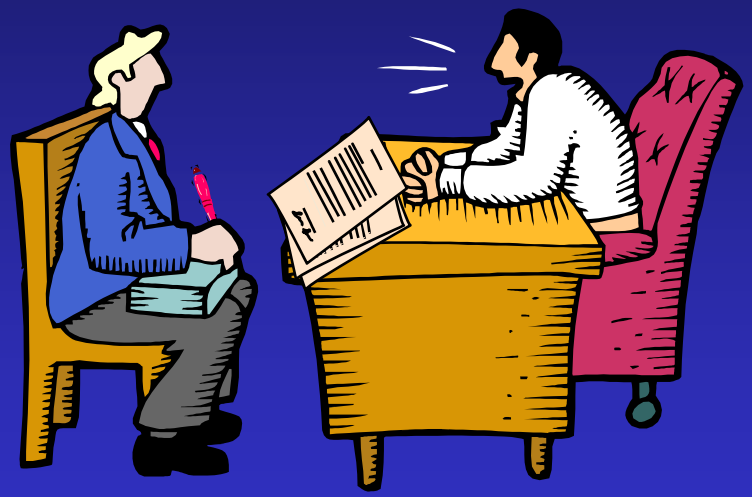
- *Other normative and legislative acts of the Republic of Kazakhstan;*
- *Regulations on the Central Commission on Ethics under the Ministry of Health of the Republic of Kazakhstan, dated 30 July 2008;*

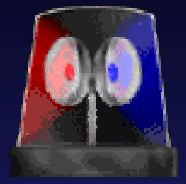
International normative base

- *Declaration of Helsinki of the World Medical Association (1964);*
- *Convention on human rights and bio-medicine (1997);*
- *ICN and GCP Regulations (Good Clinical Practice),*
- *WHO recommendations for ECs carrying out an expertize of biomedical research (2000);*
- *European Convention on protection of rights of vertebrate animals used for experimental and other scientific purposes (1986);*

Consent main components

- ✓Voluntary
- ✓Informed
- ✓Written





Attention!

Any errors or malusage related to the informed consent signing are considered to be severe and dramatic to the future researcher's career.

Informed consent form

1. Information for a patient about research:
   - In the native language
   - Clear
   - Unbiased
2. Printed form for obtaining a respondent's signature

Correct understanding of the words' meanings:

"Protocol" - 41 %

"Randomization" - 22 %

"Double blind trial" - 17 %

"Ethical Committee" - 12 %

"Concomitant treatment" - 7 % of patients

Content of the Informed Consent Form (1)

- ✓ Regulations on conducting the research
- ✓ Research goal
- ✓ Types of treatment (including placebo) and probability of random distribution into treatment groups
- ✓ Research procedures description
- ✓ Respondent's obligations

Content of the Informed Consent Form (2)

- ✓ Expected benefit and possible risk
- ✓ Availability and assessment of alternative treatment methods
- ✓ Indemnity in case of harm to the respondent's health
- ✓ Voluntary participation in the research
- ✓ Confidentiality guarantee

Content of the Informed Consent Form (3)

- ✓ Carrying out of monitoring, audit, and inspection of the research
- ✓ Expected duration of the research
- ✓ Approximate number of the respondents included into research
- ✓ Contact names and telephone numbers

Process of the informed consent obtaining

- ✓ Necessary for inclusion of a patient into research
- ✓ Important for the whole research implementation – ensures accurate observance of the research procedures by a patient

GLP

- Good Laboratory Practice – international standard of planning and carrying out research in animals.
- GLP OECD 41 pages. Many clarifying documents
- Laboratory practice rules in RK are approved by Order № 442 of the MoH RK

Pre-clinical research principles introduces by Russel and Burch

1. Reduction – maximally possible reduction of the number of animals used for necessary educational and scientific purposes

Pre-clinical research principles introduces by Russel and Burch

2. Refinement – improvement, perfection of the experimental methods for reduction or exclusion of negative effects on animals

Pre-clinical research principles introduces by Russel and Burch

3. Replacement – removal of animals from experimental or educational work, if there is a possibility to get similar results using alternative methods.

Ethical expertize of pre-clinical research

- Carried out by the local Ethical Committee.
- Ethical Committee should be sure that:

1. The research is necessary.
2. Research is well-planned.
3. Animals are kept in the adequate conditions.

Ethical expertize of pre-clinical research

4. Researcher are qualified enough to conduct the research.
5. Adequate anesthesia is provided for in the course of research.
6. Painless euthanasia method is available.

Ethical expertise of faith scientific practice

- Detection of data forgery, plagiarism and falsification.

In the USA: Office research integrity

http://ori.dhhs.gov

In Great Britain: The UK Research Integrity Office (UKRIO)

http://www.ukrio.org/home/index.cfm

In Germany: Committee of Inquiry on Allegation of Scientific Misconduct

http://www.dfg.de/en/

There is no such expertize in the RK

Federal rules in the area of ethical norm violation in scientific research (USA)

- Violation of the ethical norms in scientific research are the following:
  - Forgery,
  - Falsification or
  - Plagiarism

  in writing the application for conducting the research, carrying out or reviewing the study, and developing the final report on their outcomes.

- Forgery means substitution of data or results of scientific research, and registration of substituted data or results, or submission of information about them.

Federal rules in the area of ethical norm violation in scientific research (USA)

- Falsification means manipulating of research materials, equipment or processes; change or hiding of data or results in such a manner that research appear to be inaccurately represented.
- Plagiarism means borrowing of others' ideas, methods, results or words without proper references to their source.
- Different scientific points of view do not relate to violation of ethic norms in scientific research.

http://www.imbp.ru/BioEtika/Info/SS26193.doc