

Human Research Ethics

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Key points

- The history of research with human subjects has a dark side.
- Ethical regulations and codes of ethics exist to protect research participants.
- They are grounded in a number of principles which must be understood in order to protect human subjects in research.
- These principles have solid grounding. Nevertheless, there are areas of controversy and debate, which must also be understood

Case 1

- Mr. Jean-Baptiste Denis, a doctor in Paris, repeats English experiments of transfusion on animals.
- Then he tries it on a 'madman' and attempts a transfusion of calf blood.
- The patient dies.
- His wife accuses him of murder.
- He appeals to the court, which acquits him, but the verdict specifies that in the future it will be necessary to obtain the agreement of the Faculty of Medicine in Paris.
- The risk is too high.

(433)

An Extract

*Of a Letter of M. Denis Prof. of Philosophy and Mathematicks to M. * * * touching the Transfusion of Blood, of April 2. 1667.*

This we English out of the 8th Journal des Scavans of 1667.
viz.

Since the Experiments, of which I wrote to you the 9th of March, we have transfused the blood of three Calves into three Dogs, to assure our selves, what the mixture of two such differing sorts of blood might produce. I shall hereafter acquaint you at large with the particulars; at present I shall onely inform you, that the Animals, into whom the blood hath been transmitted, do all of them eat as well as before, and that one of these three Dogs, from whom the day before so much blood had been drawn, that he could hardly stir any more, having been supplied the next morning with the blood of a Calf, recover'd instantly his strength, and shew'd a surprizing vigor.

We have found new wayes of making this Transfusion with so much facility, that M. Emmerez undertakes to perform it *without any Ligature*, onely by pricking, like that, which is used in *Letting of blood*.

Observations

Concerning the Uniting of Barks of Trees cut, to the Tree it self; made by Christopher Merret M. D. and read before the Royal Society January 9. 1666.

IN the midt of March An. 1664. I made a Section of the Rinds of *Alb*, and of the Tree, fally called *Sycamore*. The first Section of each of the Rinds was square, whereof three sides were cut,



Case 2

- Albert Neisser, a famous Prussian dermatologist, inoculated 15 prostitutes with syphilis, hoping to vaccinate them.
- All of them contract the disease. The youngest was ten years old.
- None of them knew about the experiment
- A scandal erupts, followed by an intense debate on human experimentation.
- The resulting Prussian Code of 1900 is the first state code of research ethics.
- Neisser is fined.



Case 3

- 1932-1973
- 1932, Alabama: start of the « Tuskegee Study of Untreated Syphilis in the Negro Male »
- 600 People are participating:
 - 399 - syphilis
 - 201 - control group



(Courtesy National Archives)

Case 3

- As a benefit from participating, subjects receive free health examinations, meals and funeral insurance
- They were never informed of the aim of the study
- They were never treated
- They were not informed of alternatives



The study lasted nearly 40 years
(Courtesy National Archives)

Case 3

- July 1972: The study is on the front page of the New York Times.
- Given the scandal, a committee is charged to evaluate the case: the study is deemed « ethically unjustified » and stopped.
- A joint complaint is filed in 1973.
- The negotiated agreement includes free healthcare services for participants, as well as for their infected wives and children
- Part of the mistrust of African-Americans towards the healthcare system is still considered to be due this study

Cases in psychology

Also problematic research studies outside of medicine:

- The Robbers Cave Experiment (mid 1950)
- Milgram's studies (1961)
- Prison simulation experiment at Stanford (1971)

Risks of human research

- Harming the participants: risks of the study, breach of confidentiality, ...
- Failure to respect the participants: lack of consent, exploitation, ...

Two pillars of ethical experimental research

Do good

- Avoid harms
- Benefit participants
- Favorable risk-benefit

Do right

- Avoid wrongs
- Fairness
- Respect for dignity...

Codes

Nuremberg Code (1947)

https://en.wikipedia.org/wiki/Nuremberg_Code

Helsinki Declaration (1964, revised)

<https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>

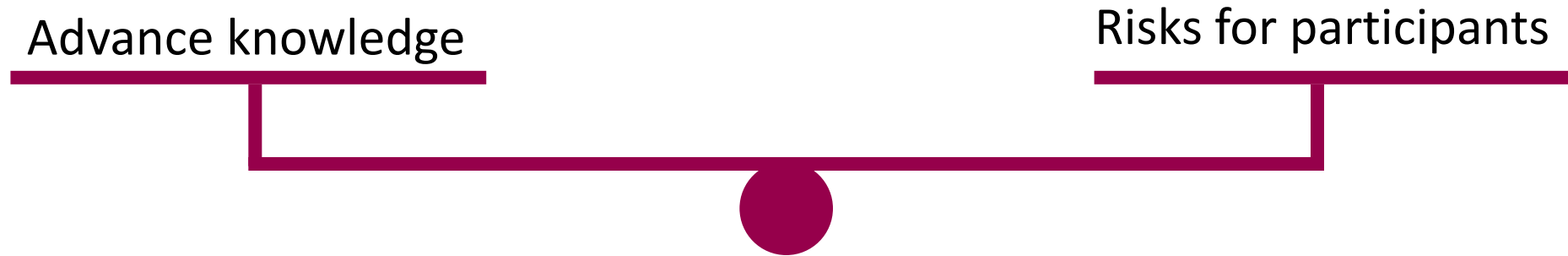
Belmont Report (1976)

<http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html>

Council for International Organizations of Medical Sciences (CIOMS)

<https://www.google.com/url?q=https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf&sa=D&source=docs&ust=1693400546594219&usg=AOvVaw37jRRwQTCH6hJ2Cif8331>

Permissibility of human research



**Human subjects research can be justified
But it is never trivial.**

Risks despite good intentions

- Having good intentions and ensuring informed consent does not eliminate all the risks
- The researchers' and participants' judgement can be biased
 - Role conflicts and misunderstanding
 - Pursuit of a good cause
 - Conformity
 - Obedience
 - Conflict of interest



Permissibility of human research

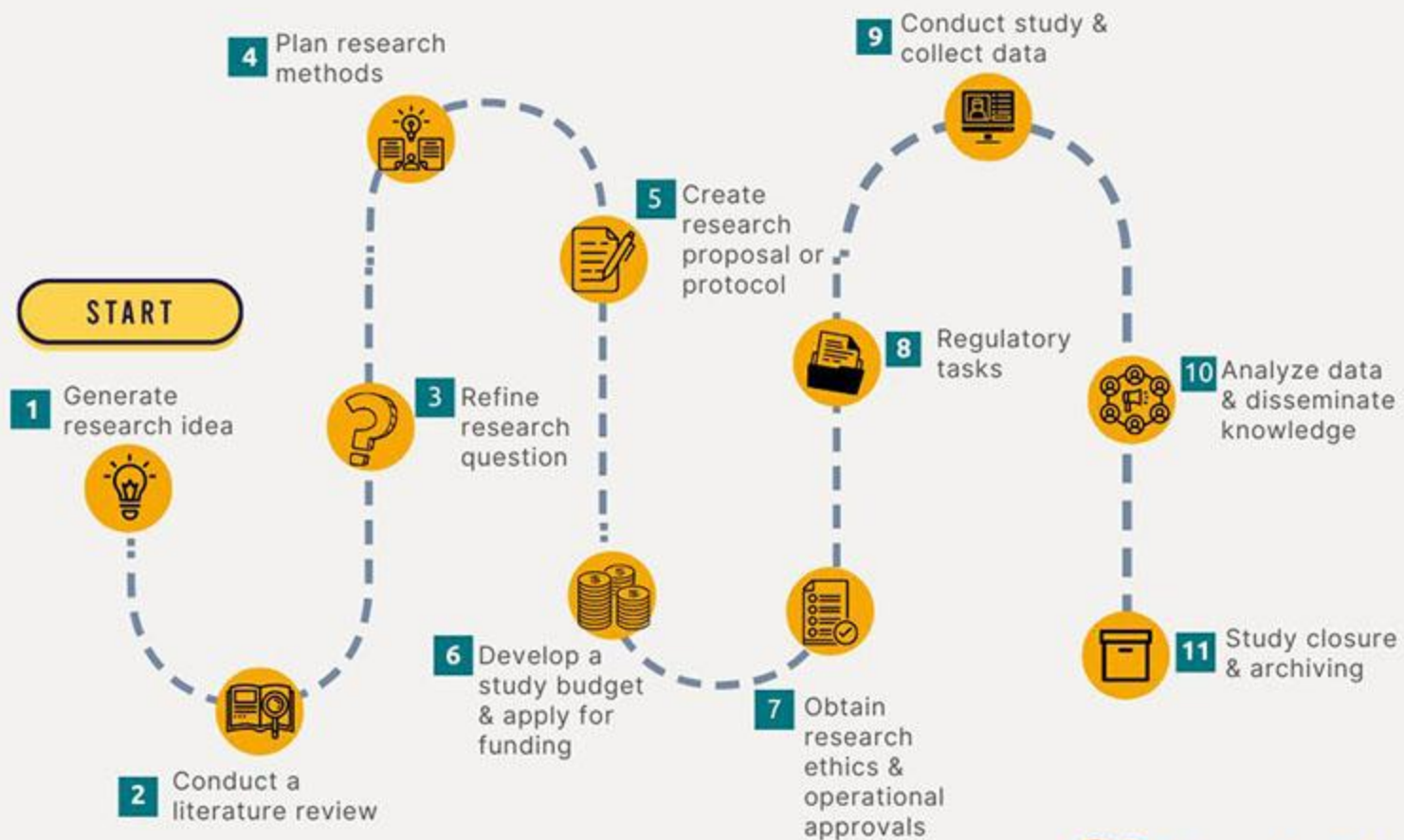
- Research places persons at risk for the benefit of others.
- Some implications:
 - some chance of this benefit must exist
 - some risks are unacceptable
 - much of research ethics is about weighing what is acceptable or unacceptable in the face of competing interests.
 - conflicts of interest and asymmetric relations of power can affect these assessments.
 - much of the work of an IEC/IRB is about making these assessments as if conflicts of interests and asymmetric relations of power did not exist.

Benchmark for ethical research

- Collaborative partnership
- Social value
- Scientific validity
- Fair selection of subjects
- Favorable risk-benefit ratio
- Independent review
- Informed consent
- Respect for recruited participants and study community

Emanuel, Wendler, Killen, Grady, 2004

Research Roadmap



Research question

- The research must potentially yield some benefit to justify the risks for participants
- For that we need a good research question (i.e. with social value)
 - **Social value**
 - Scientifically relevant (or)
 - Potential benefit for society
- Collaborative partnership: involve the target community in the decision on the research question
- Examples: no repeating well-established results, interventions which will not be implementable, financially but not clinically relevant question, etc

Research methods

- The research have good methods to justify the risks for participants
- Otherwise, the experiment cannot answer the question
- **Scientific validity**
- Examples: insufficient sample, non representative sample, no null hypothesis, issues with staff qualifications, issues with measurement methods, etc.



Choice of research population

Fair selection of research participants

- Scientific relevance is necessary but not sufficient
- No exploitation
- No favoritism
- Depends on the risks and benefits of the study
- No selection based on commodity
- Recruitment methods matter too (ads only at uni, Amazon Mturk, etc.)



Risk Benefit Ratio

- **Favorable risk-benefit ratio**
- Minimize risks
 - Choice of method
 - Choice of research population
 - Precautions
- Maximize direct benefits
 - Choice of question
 - Choice of method
 - Choice of research population
- This concerns **direct** risks and benefits: those which are inherent to the scientific requirements of the study.



Risk Benefit Ratio

- The benefits of research for individuals and communities must outweigh the risks
 - This is a difficult assessment!
 - There is no ideal way of doing this, especially as regards weighing individual risks against social or community benefits.

Informed consent

- Respect for the right of persons to make decisions for their lives and sovereignty over their body and personal information
- Recognize the right of persons to decide for themselves whether or not they will participate in research.
- Choice regarding participation in a specific research project (consent needs to be informed!)
- By consenting, participants authorize researchers to expose them to risks for the benefit of others.
- Consent can be withdrawn anytime



Elements of informed consent

- Potential subjects must:
 - Receive all relevant information
 - Understand this information
 - Be capable of decision-making regarding the choice put to them
 - Make a free and voluntary choice whether or not to participate.

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MÉDIATION 12H15 - 12H45

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MÉDIATION / THURSDAY

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Respect for participants and communities

- Protecting confidentiality
- Providing new relevant information
- Ensure careful monitoring, treatment, and/or withdrawal from the protocol in case of problems.
- Share research results.

Respect for participants and communities

- Protect confidentiality
- Make new relevant information available
- Provide careful follow-up, treatment and/or withdrawal from protocol in case of a problem
- Share results of the research.

Vulnerability

- An identifiably higher risk of wrong.
 - Any wrong
 - For any reason

Hurst, 2008

- In research, a higher risk of being included in a study that does not respect:
 - Social value
 - Scientific validity
 - Fair selection of participants
 - Favorable risk-benefit ratio
 - Independent review
 - Free and informed consent
 - Respect for participants

Emanuel, Wendler, Grady, 2000

Vulnerability - protection

Vulnerability	Protection
Language comprehension	Translation-interpretation
Reading difficulties	Oral explanations
Comprehension ability	Adjustment of acceptable risk level without participant consent

Vulnerable groups and individuals

- Extra steps need to be taken to make sure vulnerable groups and individuals are as protected as other participants
- Make sure that
 - There is no coercion/exploitation
 - No added risks
 - No unfair exclusion/inclusion
 - Informed consent is achieved



Research with indigenous communities

- Research with indigenous communities
 - Power differential
 - Potential impact on the culture and values of the community
- Researchers need to:
 - Obtain the community's approval for conducting research.
 - Avoid participating in the wrong of postcolonialism and racism.
 - Avoid missionary and political activism.
 - Avoid intimate relationships with research participants.
 - Reach an agreement with the community regarding intellectual property rights in advance.
 - Avoid genetic testing of a community that could lead to discrimination within or of the community.
(see CIOMS p.13 and cf. section 7 risk of harm and benefits)

Placebo

- Using a placebo for an arm of a study is ethically problematic if there is an effective intervention for the condition under study
- It can nevertheless be used if:
 - There is no effective intervention
 - In addition to an effective intervention
 - Or if there are compelling scientific reasons to use a placebo AND the risk for participants is minimal
- Participants need to be informed of the randomized use of placebo



Double use of data

- Research data should be used only according to the research protocol
- If you want to reuse data, you need to ask for consent
- Or have obtained a broad consent

Confidentiality

- Participants' data protection is both an important aspect of research ethics and a fundamental human right.
- Measures need to be taken to protect the privacy of participants and ensure the confidentiality of their information.
 - Only anonymized data should be shared.
 - Personal data should be deleted when no longer needed.
 - Measures might need to be taken so that the specific community or population cannot be identified
 - When non-anonymized data is to be used for another purpose than the one researchers obtained consent for, further consent should be obtained.
 - Think about how you intend to use participants' data while developing the research protocol and consider asking participants their consent for reusing their data in the future during enrollment.

Independent Review

- Makes assessment on all the aspects discussed above
- Protects human subjects of research, and constitutes a promise to them that principles of research ethics have been respected.
- Contributes to avoiding that conflicts of interest could decrease protection to human subjects (including the 'enthusiastic bias')
- Helps researchers to develop and conduct ethically justifiable research.
- Provides guarantees to citizens that the research from which they benefit is conducted in a justifiable manner.
- Cantonal and Institutional Ethics committees

Human Research Act (HRA)

- See law course

Institutional Ethics Committee

- <https://actu.epfl.ch/news/epfl-human-research-ethics-committee-hrec/>

The mission of the EPFL Human Research Ethics Committee's (HREC) is to ensure that non-invasive human research projects conducted at EPFL are designed in compliance with the fundamental ethical principles of respect for persons, beneficence and justice and the principles deriving therefrom, such as consideration of benefits and risks, informed consent of participants, privacy and data protection.

All projects involving human participants must be designed and carried out in compliance with ethical principles. In general, these projects are subject to review by the Commission cantonale (VD) d'éthique de la recherche sur l'être humain (CER). In some cases, non-invasive human research projects do not require an authorisation from the CER but need an ethical clearance in order to receive third-party funding (for example, upcoming Horizon 2020 projects); such projects can be reviewed by the EPFL Human Research Ethics Committee.

Conclusion

- Participating to research involves risks
- It is important to take the time to assess risks carefully and thoroughly in order to minimize them
- IRB can help with this and provide helpful recommendation
- Watch out for your own biases and conflicts of interest

Case study 4

- Henrietta Lacks (1920–1951): HeLa
- A particularly aggressive cancer, treated at Johns Hopkins Hospital (Baltimore, USA)
- Sampling and culturing of her cells
- The discovery of "immortal" cells. HeLa: the first human cell line
- HeLa cells are cultured, sold, and shipped by the billions to laboratories around the world
- Henrietta's family was not informed of the sampling, the existence of a HeLa factory, or the use made of these cells...



Case study 4

- Use: Cell lines for most cancers, polio vaccine, chemotherapy, cloning, in vitro fertilization, genome sequencing, various drugs (influenza, herpes, hemophilia)
- 1973: Her husband and children only learn about the cell sampling and its use much later, quite by chance
- 1980s -: The family publicly expresses its disapproval that Henrietta's contribution to science has not been recognized and accuses the scientists of violating her privacy and failing to provide explanations
- 2013: Agreement between the NIH and the Lacks family
- See: <https://www.youtube.com/watch?v=pgB1IqGp8BE>

Case study 4

- What are the ethical issues?
- What harm was done to Henrietta Lacks and her family?
- Was this normal practice in the 1950s?

Case study 5

Hepatitis studies were conducted at the Willowbrook State School for children with mental retardation from 1956-1971. Hepatitis was a major problem at Willowbrook. Given the unsanitary conditions that the children lived in, it was virtually inevitable that children would contract Hepatitis. This further added to stigmatization of the children, a good number of who became carriers (and later were reintegrated into public schools). Dr. Saul Krugman, the principal investigator, proposed research that appeared promising in distinguishing between strains of Hepatitis and in developing a vaccine. However, his study design involved feeding children local strains of live Hepatitis, i.e., deliberately infecting them.

Case Study 5

Krugman argued that the development of a vaccine would outweigh the anticipated minor harms to these children. He also argued that they were bound to be exposed to the same strains under the natural conditions; they would be admitted to a special well-staffed unit where they would be isolated from exposure to other infectious diseases; they were likely to have only a sub-clinical infection followed by immunity to the particular hepatitis virus; and only children with parents who gave informed consent would be included.

However, critics of the study thought the parental permission letter downplayed the fact that the children would be intentionally infected with Hepatitis. Moreover, due to crowding and long wait lists for admission to the school, at times the only available rooms for children were on the experimental wing, thus influencing the decision of some parents who did not have the resources to care for their children.

Case study 5

- Would you have approved this study? Why?
- What changes would you have suggested? Or would you have demanded that it be abandoned?