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TRAINING DATA STEWARDS

FOR LIFE SCIENCES

Informed Consent Procedures

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07.03.22

HUMAN SUBJECTS RESEARCH

Which ethical issues related to informed consent would you choose as most relevant?

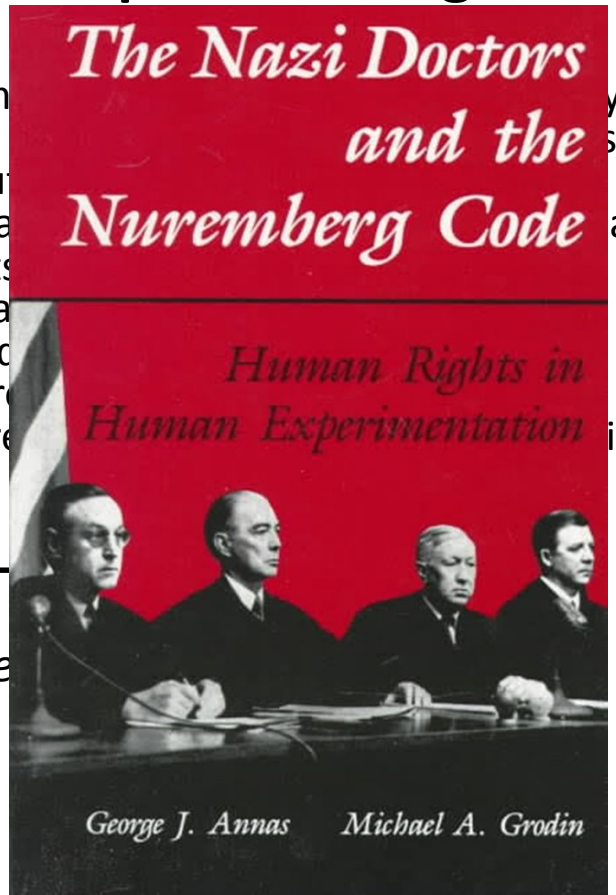
Most commonly identified in regulatory contexts as involving the interaction with individuals and the use and archive of personally identifiable data (Frankel and Siang 1999; Moreno et al. 2013)

Historical Background | Nuremberg Code (1947)

The results of the research m y other means.
The study must be rationally se or condition to be studied.
It must avoid unnecessary su
The study cannot include dea able consequence.
Its benefits must outweigh its
The study must use proper fa
The study must be conducted
Participants may withdraw fr
Investigators must be prepare ipants die or become disabled as a result of participation.

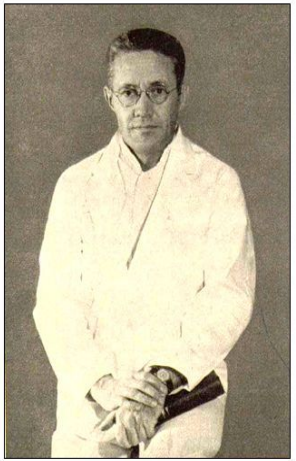
Universal Declaration of H

Freedom and Dignity unde



Historical Background

Henry Knowles Beecher 1904-1976



- Prominent researcher and anesthesiologist
- Chronicled 22 unethical studies
- *"Ethics in Clinical Research"*, published in the *New England Journal of Medicine*, June 1966.
- Beecher's revelations led to IRBs and informed consent

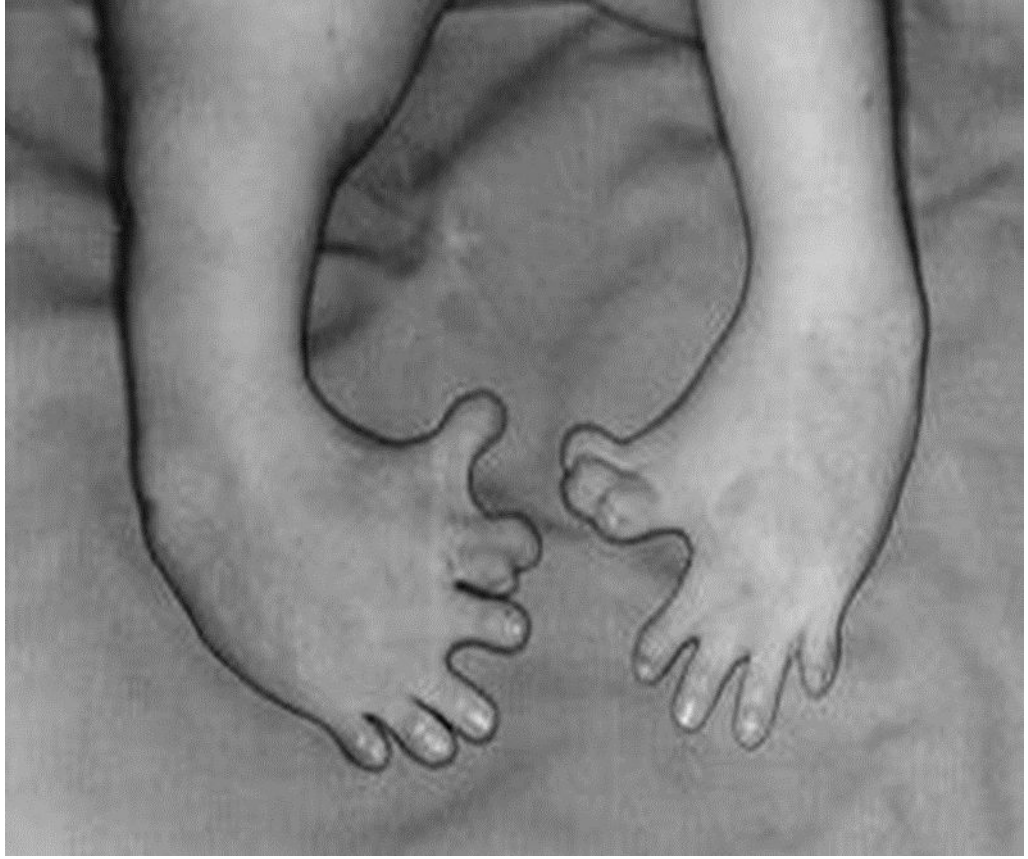
"In short order, federal regulations mandated the creation of institutional review boards to review all protocols submitted for federal funding to make certain that subjects had given informed consent and that the risks did not outweigh the benefits. For the first time, decisions that were traditionally left to the consciences of individual physicians came under collective surveillance.... The memory of the postwar record precludes a return to a hands-off policy, and institutional review boards are now regarded as symbolically and actually valuable. At least, researchers today would not consider submitting protocols like those in Beecher's list of 22. At most, more subjects are giving truly informed consent."
(Rothman DJ: Ethics and human experimentation: Henry Beecher revisited. N Engl J Med 1987; 317:1195-9)

Unethical experiments with Human Beings

New England Journal of Medicine special article entitled “Ethics and Clinical Research” by Henry Beecher (1966)

3 of the 22 unethical experiments:

- Brooklyn case : Old people with dementia were injected with cancer cells to study the immunological response.
- Willowbrook Case: Institutionalised children with mental illness were injected with hepatitis virus.
- Tuskegee Case (1972): 400 black men who had syphilis were left untreated when penicillin was already being used for this disease.



Thalidomide / 1962 / Federal Drug and Cosmetic Act (1964)

Helsinki Declaration/ 1964 / World Medical Association (updated version 2013)

Belmont Report (1979)

- National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research
- Informed Consent; subjects recruitment; risk/ benefit analysis
- Selection, representation, and the burden of participation must be fair and equitable

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

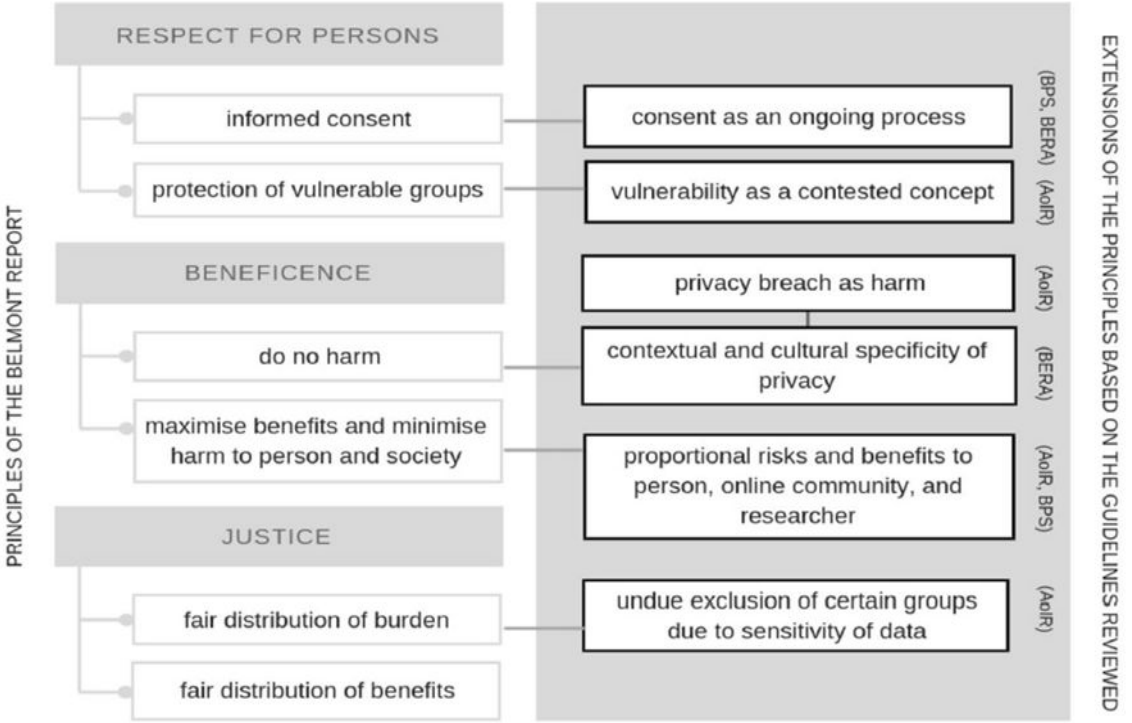
Beneficence

Respect for the Person

Justice

Revisiting the Belmont Report's ethical principles in internet-mediated research: perspectives from disciplinary associations in the social

Fig. 1 Extensions of the Belmont Report's principles based on the guidelines reviewed



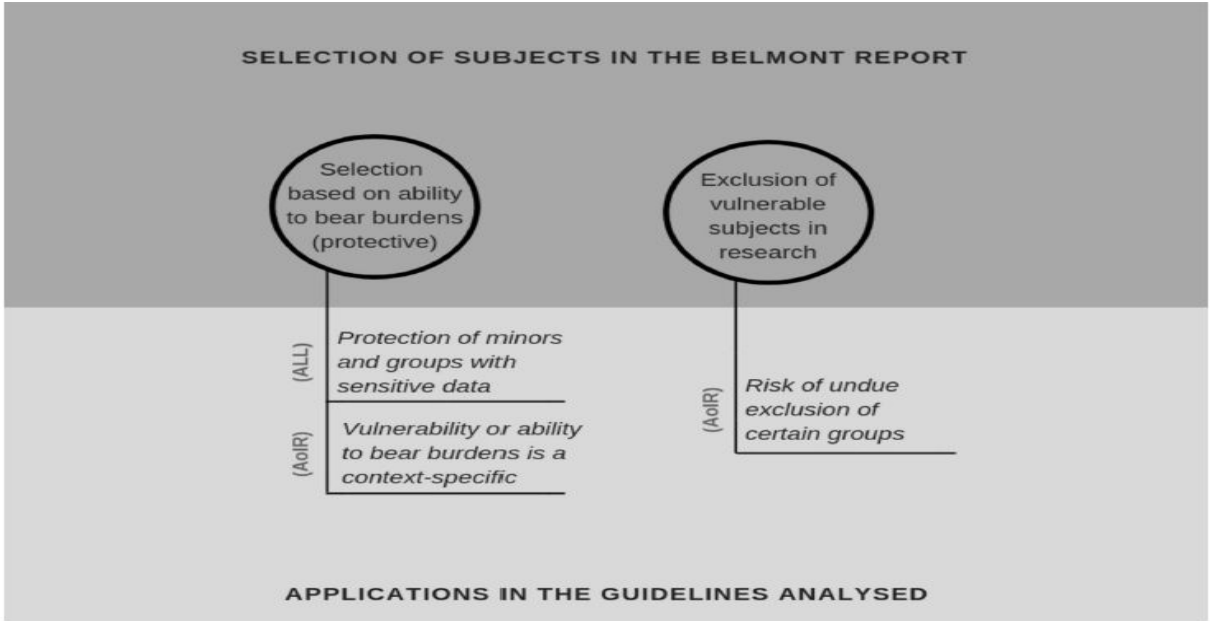


Fig. 4 Comparison of the application of the justice principle as a function of subject selection between the Belmont Report and the guidelines analysed

The justice principle | Subject selection (the Belmont Report and internet mediated research guidelines)

Informed Consent in the Helsinki Declaration (1964)

- During course of research, every precaution must be taken to protect the **privacy of research subjects** and the **confidentiality of their personal information.** No information of the research subject should be divulged to a third party without written permission of the participant.
- During the consenting process, a detailed **discussion about the methodology, potential risks and anticipated benefits, conflicts of interest, source of funding, institutional affiliation** must be done. The person has **right to refuse from participation or withdraw from the study at any time without reprisal.**

DECISION MAKING AND THE CHALLENGES OF Vulnerability

Decision-making capacity (DMC) is an indispensable prerequisite, including consent, refusal to participate, and thus, the basis of the principle of autonomy

Two moral requirements are entailed in DMC evaluations:

RESPECT FOR THE AUTONOMY OF THOSE WHO ARE ABLE TO MAKE THEIR OWN DECISIONS and

PROVISION OF PROTECTION FOR THOSE WITH DIMINISHED DECISIONAL CAPACITY

ASSESSMENT OF DMC IS ESSENTIAL

VULNERABILITIES

Kenneth Kipnis, VULNERABILITY IN RESEARCH SUBJECTS:A BIOETHICAL TAXONOMY, 2004

"... in the minds of many investigators the paradigmatic research subject remains more or less a mature, respectable, moderately well-educated, clear thinking, literate, self-supporting US citizen in good standing – that is, a man who could understand a 12- page consent form and act intelligently on the basis of its contents."

Kipnis K. Vulnerability in Research Subjects: A Bioethical Taxonomy. Commissioned Paper. In Ethical and Policy Issues in Research Involving Human Research Participants. Bethesda, MD: National Bioethics Advisory Commission. 2001

“Having ascertained that a candidate-subject (C-S) is vulnerable in one or more of those discrete ways, researchers would then be required 1) to conduct further inquiries and, if necessary 2) to implement compensating measures in the design of the protocol as a condition for proceeding”

KIPNIS, “VULNERABILITY IN RESEARCH SUBJECTS:A BIOETHICAL TAXONOMY “

RESEARCH WITH HUMANS

Section 2: HUMANS		YES/ NO		Page	Information to be provided	Documents to be provided/kept on file
Does your research involve human participants?		☐	☐		Confirm that informed consent has been obtained. **plus:**	Informed Consent Forms + Information Sheets. **plus:**
If **YES:**	- Are they volunteers for social or human sciences research?	☐	☐		Details of recruitment, inclusion and exclusion criteria and informed consent procedures.	Copies of ethics approvals (if required).
	- Are they persons unable to give informed consent (including children/minors)?	☐	☐		Details of your procedures for obtaining approval from the guardian/ legal representative and the agreement of the children or other minors. What steps will you take to ensure that participants are not subjected to any form of coercion?	Copies of ethics approvals.

RESEARCH WITH HUMANS

Section 2: HUMANS		YES/ NO		Page	Information to be provided	Documents to be provided/kept on file
	- Are they vulnerable individuals or groups?	☐	☐		Details of the type of vulnerability. Details of recruitment, inclusion and exclusion criteria and informed consent procedures. These must demonstrate appropriate efforts to ensure fully informed understanding of the implications of participation.	Copies of ethics approvals.
	- Are they children/minors?	☐	☐		Details of the age range. What are your assent procedures and parental consent for children and other minors? What steps will you take to ensure the welfare of the child or other minor? What justification is there for involving minors?	Copies of ethics approvals.

RESEARCH WITH HUMANS

Section 2: HUMANS		YES/ NO		Page	Information to be provided	Documents to be provided/kept on file
	- Are they patients?	☐	☐		What disease/condition /disability do they have? Details of recruitment, inclusion and exclusion criteria and informed consent procedures What is your policy on incidental findings?	Copies of ethics approvals.
	- Are they healthy volunteers for medical studies?	☐	☐			Copies of ethics approvals.

RESEARCH WITH HUMANS

Section 2: HUMANS		YES/ NO		Page	Information to be provided	Documents to be provided/kept on file
Does your research involve physical interventions on the study participants?		☐	☐			
If **YES:**	- Does it involve invasive techniques *(e.g. collection of human cells or tissues, surgical or medical interventions, invasive studies on the brain, TMS etc.)*?	☐	☐		Risk assessment for each technique and overall.	Copies of ethics approvals.
	- Does it involve collection of biological samples?	☐	☐		What type of samples will be collected? What are your procedures for collecting biological samples?	Copies of ethics approvals.

In which cases do researchers need to make use and provide an informed consent form?

(https://ec.europa.eu/research/participants/data/ref/fp7/89807/informed-consent_en.pdf)

When the research involves:

Patients
Children
Incompetent/Incapacitated persons
Healthy volunteers
Immigrants
Others (i.e.prisoners)

When the research uses/collects:

Human Genetic Material
Biological samples
Personal data

What type of information should be provided to the research subject?

- A statement that the study involves research subjects and an **explanation of the purposes** of the research.
- The **expected duration** of the subject's participation.
- A **description of the procedures** to be followed/ of the **medicine** that is going to be
- tested, and an identification of any procedures which are experimental.
- A statement that participation is **voluntary**.
- Information about who is organising and funding the research.
- A description of any reasonably **foreseeable risk, discomfort or disadvantages**.
- A description of any **benefits to the subject or to others** which may reasonably be
- expected from the research avoiding inappropriate expectations.
- A disclosure of appropriate **alternative procedures for treatment/diagnosis** if any,
- that might be advantageous to the subject.

What type of information should be provided to the research subject?

- A statement describing the procedures adopted for ensuring **data protection/confidentiality/privacy** including duration of storage of personal data.
- A description of how **incidental findings are handled**.
- A description of any planned **genetic tests**.
- For research involving more than minimal risk, an explanation as to whether there are any **treatments or compensation if injury occurs** and, if so, what they consist of, or where further information may be obtained. Insurance coverage should be mentioned.
- A reference to **whom to contact for answers** to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.
- A statement offering the subject the **opportunity to ask questions and to withdraw at any time** from the research without consequences.
- An explanation of what will happen with the **data or samples at the end of the research** period and if the data/ samples are retained or sent/sold to a third party for further research.
- Information about what will happen to the **results** of the research.

Projects involving children

- Informed consent of parents/legal representative* must be obtained, but also, when the child is able to give assent, the investigator must also obtain that assent.
- In long-term studies, where the child reaches the age of majority, the research team should obtain his/her consent to continue the study and/or for the use of samples already obtained.
- A child's refusal to participate or continue participating in the research should always be respected.
- Researchers should avoid exerting any pressure against the child/his-her parents that will lead to the participation of the child to the research

Informed Consent and Information sheets are comprehensive and separate for parents/legal representative and for children

- Information for children five years and under should be predominantly pictorial.
- For pre-adolescent (aged up to 16) information sheets should explain briefly and in simple terms the background and aim of the study, so the child can consider assent. It also should contain an explanation that their parents will be asked for consent.
- If an adolescent aged 16 to 18 is no longer a minor as defined in national law, or is an “emancipated minor”, then written informed consent is required from these individuals.
- **Assent** of the child who is able to give must be required.
- Information sheets should **indicate how the study will affect the child** at home, school or other activities.

Projects involving incapacitated adults not able to give informed consent

The informed consent must be obtained from the legal representative* if:

- Consent represents the **subject's presumed will**.
- The person not able to give informed legal consent has received **information according to his/her capacit**y of understanding.
- The research is **essential** to validate data obtained in clinical trials on persons able to give informed consent or by other research methods.
- The research **relates directly to a life-threatening or debilitating clinical condition** from which the incapacitated adult concerned suffers.
- There are grounds for expecting that administering the medicinal product to be tested will produce **a benefit to the patient** outweighing the risks or produce no risk at all.

Projects involving illiterate populations

Free and informed consent always has to be given by each individual involved in a trial/research.

- Where formal written informed consent from the participant is not possible, the following strategies should be used:
- - Presence of a community representative trained by the scientific team.
- - Witnessing the oral approval by a trained and independent community representative. He/She will verify that the purpose of the research has been explained to the participant and he/she has understood what is proposed.

Clinical Trials Regulation

(https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-regulation

CTIS went live on 31 January 2022 together with the public Clinical Trials website. For more information, see:
Clinical Trials Information System
Development of the Clinical Trials Information System
Clinical Trials website

Article 29 **Informed consent**

Informed consent shall be **written, dated and signed** by the person performing the interview and by the subject or, where the subject is not able to give informed consent, his or her legally designated representative after having been duly informed.

Where the subject is **unable to write, consent may be given and recorded through appropriate alternative means in the presence of at least one impartial witness. In that case, the witness shall sign and date the informed consent document.**
The subject or, where the subject is not able to give informed consent, his or her legally designated representative shall be provided with a copy of the document (or the record) by which informed consent has been given.

The informed consent shall be documented.

Adequate time shall be given for the subject or his or her legally designated representative to consider his or her decision to participate in the clinical trial.

Vulnerabilities and Informed Consent

In order to certify that informed consent is given freely, the investigator should take into account all relevant circumstances which might influence the decision of a potential subject to participate in a clinical trial, in particular whether the potential subject belongs to an economically or socially disadvantaged group or is in a situation of institutional or hierarchical dependency that could inappropriately influence her or his decision to participate.

Emergency situations and informed consent

Cases where for example a patient has suffered a sudden life-threatening medical condition due to multiple traumas, strokes or heart attacks, necessitating immediate medical intervention. For such cases, intervention within an ongoing clinical trial, which has already been approved, may be pertinent.
However, in certain emergency situations, it is not possible to obtain informed consent prior to the intervention. The clinical trial should relate directly to the medical condition because of which it is not possible within the therapeutic window to obtain prior informed consent from the subject or from his or her legally designated representative.
Any previously expressed objection by the patient should be respected, and informed consent from the subject or from his or her legally designated representative should be sought as soon as possible.

Personal data processing and withdrawal of informed consent

With a view to respecting personal data protection rights, encompassing the right to access, rectification and withdrawal, as well as specify the situations when restriction on those rights may be imposed,
while safeguarding the robustness and reliability of data from clinical trials used for scientific purposes and the safety of subjects participating in clinical trials,
it is appropriate to provide that, without prejudice to Directive 95/46/EC, the withdrawal of informed consent should not affect the results of activities already carried out, such as the storage and use of data obtained on the basis of informed consent before withdrawal.

SPECIFIC CASES

Cells or tissues from clinical practice (secondary use) | For human cells or tissues which you or others have derived from clinical practice (e.g. waste material from surgery or other operations) provide evidence (e.g. copies of examples of informed consent documentation) that the donors have given informed consent for the use of their waste cells or tissues (either specifically for the research or generally, for any secondary use).

If, for the purposes of your research, you intend to collect more additional material than would normally be collected during the standard clinical procedure (e.g. a larger than normal tissue sample or a sample that includes some additional adjacent material), you must ensure that informed consent has also been given for collecting additional material. You must also explain the need for such material in your grant proposal and show that you have obtained appropriate ethics approvals.

Secondary use for future research

If you intend to store the material for future use in other projects, you must:

- confirm that you have obtained the donor’s consent for such secondary use
- state the legislation under which the material will be stored
- state how long it will be stored and what you will do with it at the end of the research.

SPECIFIC CASES

Biobanking | Biobanks raise significant ethical issues concerning informed consent and data privacy. ‘Biobanks’ are repositories for the storage of biological samples (usually human) and play a significant role in biomedical research. These ‘libraries’ provide researchers with access to large numbers of tissue samples, genetic material and associated data. If your project has the aim or effect of setting up a biobank, you must ensure that there is strict compliance with appropriate European and national ethical standards.

You must confirm that informed consent has been obtained and show that you have obtained all necessary ethics approvals (or that you are exempted under national law).

No samples/data may be placed in the biobank before all appropriate consents and ethics approvals have been obtained

Informed Consent Genetic testing

Genetic testing | For using or storing human cells or tissues for genetic testing, you must obtain the donor's informed consent for the genetic testing, and show that you have obtained approval from the relevant ethics and data protection bodies; and any licence required under national legislation.

PERSONAL DATA

Section 4: PROTECTION OF PERSONAL DATA	YES/NO		Page	Information to be provided	Documents to be provided/kept on file
Does your research involve further processing of previously collected personal data ('secondary use') *(including use of pre-existing data sets or sources, merging existing data sets, sharing data with non-EU member states)?*	☐	☐		Details on the database used or of the source of the data. Details of your procedures for data processing. Details of your data safety procedures (protective measures to avoid unforeseen, usage or disclosure, including mosaic effect, i.e. obtaining identification by merging multiple sources). Confirm that data is openly and publicly accessible or that consent for secondary use has been obtained (and details of how this consent was obtained (automatic opt-in, etc.)). Confirm permissions by the owner/manager of the data sets.	Evidence of open public access *(e.g. print screen from website)*. Informed Consent Forms + Information Sheets + other consent documents (opt in processes, etc.). Copies of permissions (if required).

Personal data' are defined extremely broadly and include 'any information relating to an identified or identifiable natural person'. An 'identifiable natural person', or 'data subject', is 'one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person' (Article 4(1) GDPR).

Personal data include data such as internet protocol (IP) addresses (unique identifiers that can be used to identify the owner of devices connected to the internet) and data from 'smart meters' monitoring energy usage by addresses linked to identifiable persons.

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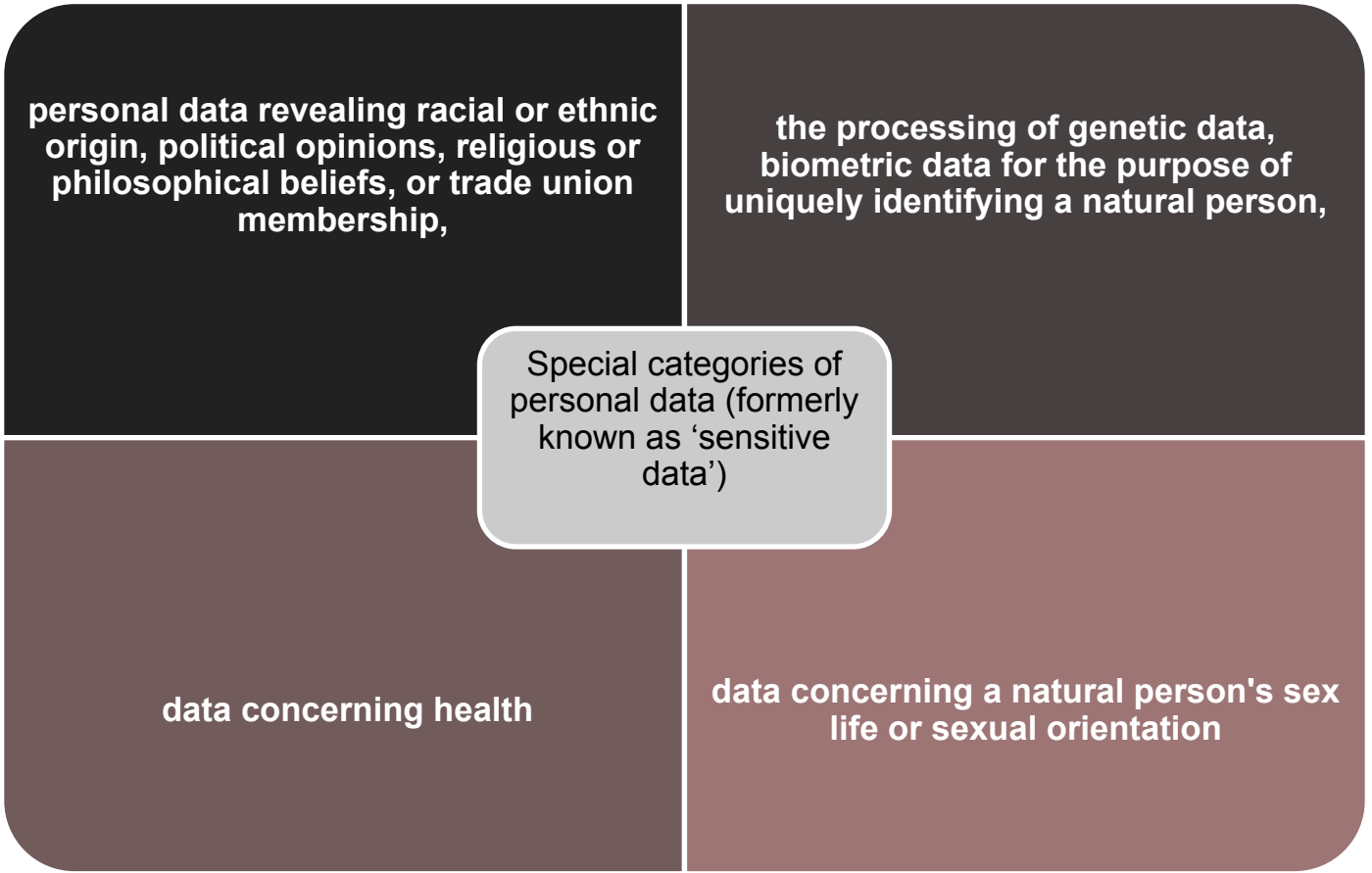
personal data revealing racial or ethnic origin, political opinions, religious or philosophical beliefs, or trade union membership,
the processing of genetic data, biometric data for the purpose of uniquely identifying a natural person,
Special categories of personal data (formerly known as ‘sensitive data’)
data concerning health
data concerning a natural person's sex life or sexual orientation

- Only data that sed are exempt from these requ tion can provide individual data and anonymity, pseudonymised ata because it is possible to re-id
- Even if your proj gin or acquisition of the data may

TRAINING DATA STEWARDS
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Pseudonymisation and anonymisation: understanding the difference

- Pseudony… as an individua… d identity, using te… tify the individua… ction obligatio… versibly anonym…
- Anonym… nto anonym… ential for re-identi…
- Re-iden… ack into persona…

You are collecting 'anonymised' data only if the anonymisation happens at the point and time at which the data are collected from the research subject, so that no personal data are actually processed. If anonymisation takes place at a later stage, e.g. you intend to remove personally identifiable information during the transcription of audio recordings or at the point at which survey data are fed into a database, **the raw data are still personal data and your proposal must include provisions for their protection up until the point at which they are deleted or rendered anonymous.**

The Changing Face of Informed Consent

https://louisville.edu/mobileelsi/our-research-project/background-articles/the-changing-face-of-informed-consent/view

E-consent includes a display of the official document, but the document can be enhanced with **pop-up definitions** of **unfamiliar terms** and **links to additional information or an audio version**.

Built-in quizzes assess comprehension and correct misunderstandings of key trial features; an example of an e-consent knowledge review questionnaire is shown at www.youtube.com/watch ?v=HtLuqJdYuoQ.54

A participant must be given the opportunity to have questions answered during the informed consent process through a **telephone call, real-time video, or electronic messaging**, and the discussion may be guided by review of a participant's errors.

Most studies have shown that participants' recall of key facts about a study is better with the use of e-consent with these interactive features than with paper

When e-consent is performed remotely, the identity of the person who is giving the consent can be confirmed in one of several ways, such as **digital signature, username and password, or biometrics.**

Participants receive a copy of the completed e-consent form, which can be provided electronically.

Signed e-consent records are stored securely (e.g., encrypted to protect privacy, with audit trails to track any changes).

IC for Genomic Medicine Era

Completeness

:: Is IC content "complete" – addressing all relevant dimensions of the trial protocol and trial site context, or clinical use, with substantive treatment of genetic processes /techniques/ implications? Are long-term follow-up implications addressed? Are commitments to knowledge-sharing of results clear?

Comprehension

:: Is IC content reading level and cultural references/allusions/ metaphors appropriate to trial participants/ patients/ parents? Are IC drafts tested, with post-transaction assessment mechanisms? Are lifelong genetic implications well understood?

Quantification

:: Are representations of risk, benefit, potential harms, and other known/unknown aspects of the trial/clinical use presented with adequate precision, accuracy?

Capacity/Constraints

:: Are cognitive function and other decision capacity factors addressed? Are there robust processes to protect the independent consideration and election to consent or decline? Are power relationships managed/ mitigated? Are assent and consent options fully engaged/insulated?

Colour

:: Does IC content include and integrate graphics/ visualizations/video/interactives to enrich key messages and present complex genetic concepts?

Competence

:: Who conducted the IC transaction? Who else was involved and what roles did they play [before and during]? What training and experience did they bring to the IC transaction? How is their performance evaluated?

Coherence/Concision

:: Is there continuity and consistency across IC transaction content and formats? Does the IC content avoid unnecessary text, legalese and process?

Community

:: How has the patient community relevant to the disease area/gene therapy been engaged to help fashion the IC content and otherwise guide how IC was conducted and assessed? Who was responsible for that engagement? How was is documented?

https://ge2p2global-centerforinformedconsentintegrity.org/informed-consent-in-the-genomic-medicine-era/

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