



Ethics in Horizon Europe

'How-to' identify and assess ethics issues – Part 1

7-8 July 2022

Ethics & Research Integrity Sector (DG RTD 03.001)

The Ethics Issues

1. Human embryonic stem cells & human embryos
2. Humans
3. Human cells/tissues
4. Personal data
5. Animals
6. Non-EU countries
7. Environment, health & safety
8. Artificial Intelligence
9. Other ethics issues
10. *Crosscutting issue: Misuse*

Self-Assessment

(Pre-)Screening

Assessment

Check/Review

The Ethics Issues

3 questions to **identify** the Ethics Issues:

1. What are the **research objectives**? (e.g., study of vulnerable populations)
2. What is the **research methodology**? (e.g., interventional clinical trial, laboratory experiment, genetic modification of animals, intervention in natural environment, analysis of personal data, etc.)
! What **materials / sources** are used and **how** are these obtained? (e.g., iPSC, video recordings, radioactive isotopes, etc.)
3. What is the **potential impact** of the research? (e.g., environmental damage, animal welfare, population stigmatization, etc.).

Next step: Does the application adequately describe **how the applicable ethical (and legal) standards and principles will be met?**



2. Humans

Why is it an ethics issue?

- History of research ethics: response to **cases of severe exploitation and harm to research participants**
 - E.g., The Nuremberg Code (1947), formulated in response to torturous and murderous experiments on humans during Nazi-regime, the Tuskegee Syphilis study (1932-1972), Havasupai Case (2004)
- Research involves **risks of harm & exploitation** – in **medical research** as well as **social sciences and humanities**
 - **Impact on health, wellbeing**
 - **Social, relational, economic & legal risks**
 - **Privacy-related risks**
 - E.g., research involving political dissidents, research on personal or sensitive topics (e.g., on gender, identity, sexual preferences, infertility, other topics inducing stress, anxiety, humiliation, social exclusion), research involving social media, web crawling, behavioural analysis and predictions, political opinion research, criminological research, ...

When is it an ethics issue?

Humans must be considered as **'research participants'** whenever they are **recruited, observed, actively engaged, or in any other way may be influenced, manipulated, or directed** by the research.

→ Check **methodology**: surveys, questionnaires, interviews, clinical interventions, donations, recordings, behavioral observations, online observation, radiological examinations, etc.

! Participants are not always aware of the research

- Group observation (Are people influenced? How are observations recorded? Is there a risk of harm?)
- Deception and covert research (e.g., ethnography, psychological experiments, criminological research)

! Participants may not consider themselves as participants

- E.g., employees used to develop and test biometric identification system



How must it be addressed?

Fundamental principles:

- **Respect for human dignity and autonomy**
- **Full protection of safety, wellbeing, privacy**
- **Fair distribution of benefits and burdens**

Free and informed consent
Confidentiality
Proportionality / Minimizing risks
Independent ethics review

How must it be addressed?

For medical research:

- Declaration of Helsinki (1964, WMA)
- Oviedo Convention on Human Rights and Biomedicine (1997, CoE) & Additional Protocols
- EU Regulation No 536/2014 on clinical trials on medicinal products for human use
- ... national and regional law and regulations !

For social sciences and humanities:

- Challenge: Less of ethics awareness, guidance, and 'ethics infrastructure'

Informed consent

- Sometimes **legally** required (e.g., *Clinical Trial Regulation 536/2014*), **always** ethically required!
 - **Limited exceptions:** E.g., research in public interest (mostly re-use of information for research purposes), covert research
- Not just a form, but **an entire procedure:**
 - Informing the (potential) participants (via information sheet and/or other methods)
 - Verifying (potential) participants' understanding of the research, the risks and the benefits
 - Clear and unambiguous expression of willingness to participate, clearly documented
 - Ensuring participation is entirely voluntary throughout the entire research (right to withdraw)
- Informed consent **≠** consent as a legal basis for personal data processing (*Art. 6(1)(a) GDPR*)

Informed consent

The process must guarantee that:

- The information must be given in lay terms
- Without pressure of any kind
- The information means used for obtaining consent should be adjusted to the particularities of situation/research participant
- Informed consent must be written, dated and signed by the person performing the research and by the research participant
- Adequate time needs to be given to the research participant/legally designated representative to consider the decision to participate

The information sheet must:

- describe the aims, methods, duration and implications of the research, the nature of the participation and any benefits, risks or discomfort that might ensue
- disclose appropriate alternative procedures for treatment/diagnosis (if applicable)
- describe any planned genetic tests
- information on whether there are any treatments or compensation if injury occurs, including description of insurance policies
- explicitly state that participation is voluntary and that anyone has the right to refuse to participate and to withdraw their participation, samples or data at any time — without any consequences
- provide information about the organisation and funding of the research + a contact person
- provide information about what will happen to the results of the research

Incidental findings

- In medical research, genetic research, but may also be relevant in other fields!
 - E.g., psychological research leading to brain tumor diagnoses
- Important that research participants are **aware of potential incidental findings** and of possible **limits of confidentiality**:
 - E.g., in cases of genetic information important for relatives (especially when genetic findings are 'actionable')
 - E.g., in case of 'unexpected findings' such as illegal activities and legal disclosure obligations of the researcher

Vulnerable participants

- **Children, patients, members of minority communities, refugees, person illiterate, persons at risk of coercion** (e.g., employees, students, prisoners), etc.
- Risk-benefit balance must be carefully assessed in light of specific context, needs and interest.
 - ! Risks of **misuse** of research results, e.g., through discrimination and stigmatization
- Risks of coercion and undue inducement must be effectively mitigated.
- Informed consent procedures must be adapted to their needs and interest.
- Children and other persons unable to give informed consent should only be involved in research, but only if:
 - The research results can only be obtained by involving those groups
 - Participation only involves minimal risks
 - The research directly benefits the participant and/or the group

Informed consent: exceptional cases

- Informed consent by legal representative (parents, guardian, ...)
 - Whenever possible, assent by participant should be sought. **Dissent** should always be respected.
- Consent based on advance directives
 - E.g., collection of biological materials for research after death. ! Be aware of legal limitations !
- Retrospective consent
 - E.g., in cases of research involving deception (only when risks are minimal)
- Oral consent:
 - Exceptional cases where signing consent forms (or other records of consent) may jeopardise the anonymity and expose research participants to risks. E.g., research involving political dissidents, communities at risk of persecution, ...

Key information

- Inclusion / exclusion criteria
 - E.g., for patients, what disease/condition/disability do they have?
 - E.g., in social medial research: can it be ensured that children are not involved?
- Justification for including children or other person unable to give informed consent
- Recruitment procedures (including compensations offered)
- Risk-assessment for the techniques used, e.g., for the use of invasive techniques, procedures to mitigate pain & discomfort
- Informed consent procedures & templates
- Incidental findings policies

2 HUMANS		In Ethics Self-Assessment or description of methodology		Information to be provided in the proposal	Documents to be kept on file and provided on request
Does your activity involve human participants?		<input type="checkbox"/>	<input type="checkbox"/>	Please provide information in one of the subcategories below	
If YES:	Are they volunteers?	<input type="checkbox"/>	<input type="checkbox"/>	1) Details on recruitment, inclusion and exclusion criteria and informed consent procedures. 2) Details on unexpected findings policy.	1) Copies of ethics approvals (if required by law or practice). 2) Informed consent forms and information sheets.
	Are they healthy volunteers for medical studies?	<input type="checkbox"/>	<input type="checkbox"/>	1) Details of the recruitment, inclusion and exclusion criteria and informed consent procedures. 2) Details on incidental findings policy.	1) Copies of ethics approvals. 2) Informed consent forms and information sheets.
	Are they patients for	<input type="checkbox"/>	<input type="checkbox"/>	1) Details on the	1) Copies of ethics

Ethics 'supporting' documents in Annex
! Not for all calls.
Submission of ethics supporting documents requested for serious/complex cases during project monitoring.

Not a 'tick-box' exercise!
Quality of provided information must be assessed in light of ethical principles.

Does your activity involve interventions (physical also including imaging technology, behavioural treatments, tracking and tracing, etc.) on the study participants?	<input type="checkbox"/>	<input type="checkbox"/>		
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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.)?	<input type="checkbox"/>	<input type="checkbox"/>	1) Risk assessment for each technique and overall.	1) Copies of ethics approvals.
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	Does it involve collection of biological samples?	<input type="checkbox"/>	<input type="checkbox"/>	1) Details on the type of samples to be collected. 2) Procedure for the collection of biological samples.	1) Copies of ethics approvals.
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Does your activity involve conducting a clinical study as defined by the Clinical Trial Regulation 536/2014 (using pharmaceuticals, biologicals, radiopharmaceuticals, or advanced therapy medicinal products)? (n/a for DEP)	<input type="checkbox"/>	<input type="checkbox"/>		
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→ Separate annex 'Essential information involving clinical studies'

2. Humans

- New developments in research:
 - Human enhancement
 - AI-enabled medical devices, diagnostic tools & precision medicine
 - Neurotechnology
 - ‘Rapid research’ context: the Covid pandemic and beyond...

2. Humans

- Additional guidance notes:
 - Functional Magnetic Resonance Imaging Social science and humanities
 - Research Ethics in Ethnography/Anthropology
 - Research on refugees, asylum seekers and migrants
 - Ethics in Social Science and Humanities
 - Ethical Guidance for Research With a Potential for Human Enhancement
 - Ethics for Clinical Trials on Medicinal Products Conducted with Paediatric Population
 - Ethical considerations for clinical trials on medicinal products conducted with minors — Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use



1. Human embryonic stem cells & human embryos

Why is it an ethics issue?

- **High sensitivity:**

- Divergence in Member State legal and ethical frameworks
- Ethical tensions (e.g., debate on the moral status of the embryo)
- ! Non-eligible activities, e.g., destruction of human embryos



Actions NOT eligible for funding

Article 18 (1)

- a) activities aimed at human cloning for reproductive purposes;
- b) activities intended to modify the genetic heritage of human beings which could make such changes heritable;
- c) activities intended to create human embryos solely for the purpose of research or for the purpose of stem cell procurement, including by means of somatic cell nuclear transfer.'

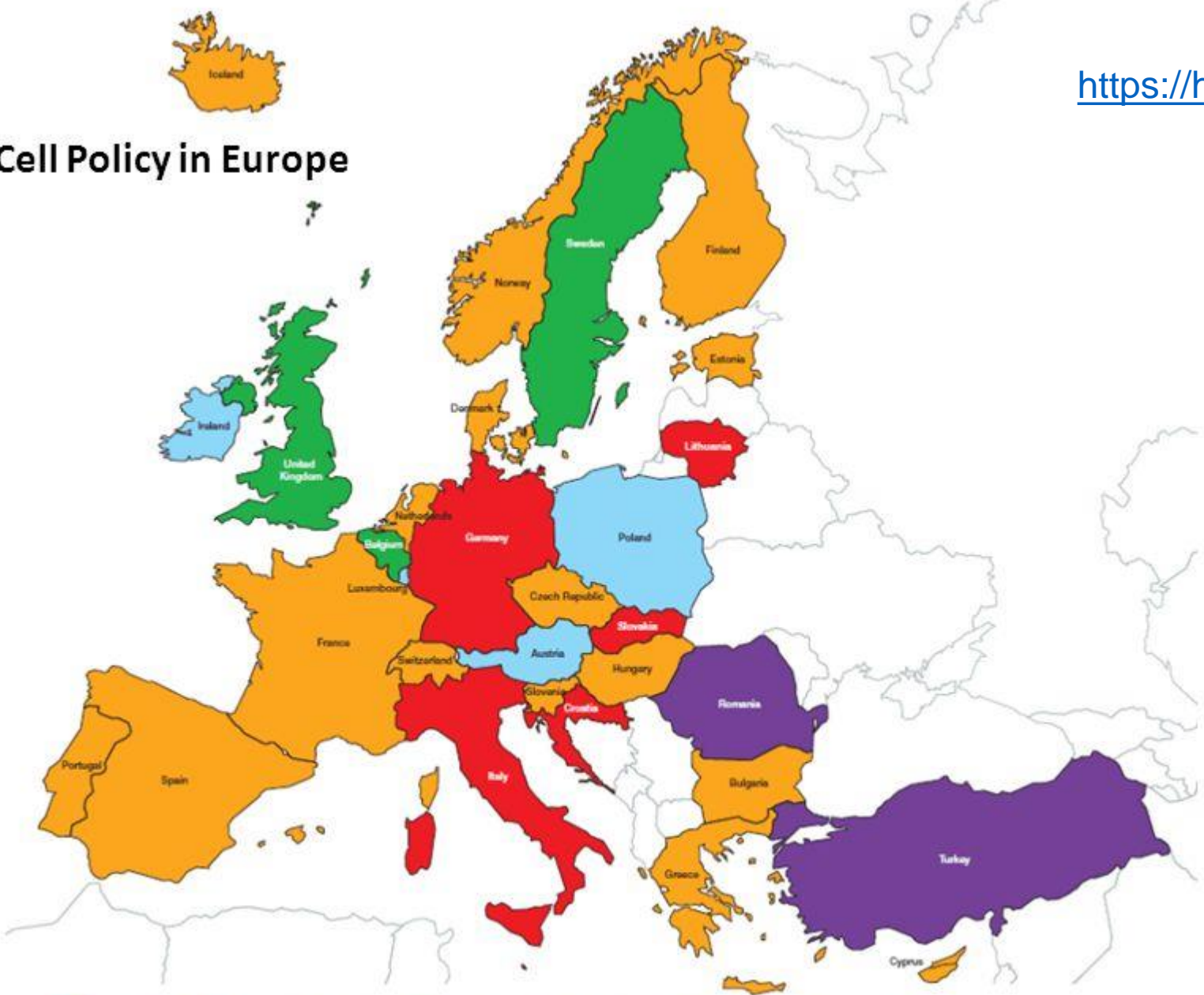
! Research on human embryonic stem cells may be financed **depending on the contents of the scientific proposal and the legal framework of the Member State involved.**

- d) activities that 'lead to the destruction of human embryos (for example, for obtaining stem cells).'
(*Joint Declaration of the EP, Council and EC 2021/C 185/01*)

hESC and hE research - Regulation across Europe

- **Broad spectrum of laws & regulations across Europe:**
 - **Complete ban** (e.g., Malta, Lithuania, Poland)
 - Ban on derivation of hESC but research on **imported cell lines** allowed (e.g., Germany, Austria and Italy)
 - Research on hESC derived from **surplus IVF embryos** allowed (e.g., the Netherlands, Finland)
 - **Research on surplus embryos** allowed (e.g., France, Spain)
 - **Creation of embryos for research purposes** and **research on surplus embryos allowed** (e.g., Belgium, UK, Sweden)

Stem Cell Policy in Europe



- Very permissive (hESC often can derive from different sources, including surplus IVF embryos and embryos created for research).
- Permissive with restrictions (hESC research only on surplus IVF embryos).
- Restrictive by default. Legislation implicitly prohibits hESC research.
- Very restrictive. Legislation clearly prohibits hESC research.
- Unlegislated. There is no specific legislation concerning hESC research.

When is it an ethics issue?

- NOT: Induced pluripotent stem cells (iPSC) or adult stem cells (for example from haematopoietic stem cells from cord blood or bone marrow)
- NOT: Secondary use of embryonic and foetal tissue (e.g., extraembryonic cells and primitive endoderm (PE) cells, donations after pregnancy terminations, etc.)
- NOT: organoids derived from stem cells *in vitro*
 - ! Embryoids, blastoids, and gastruloids (generated from hESC)

When is it an ethics issue?

- Human embryo = not defined, broadly interpreted
- Question of viability
- From fertilization until ... 14-day limit (before the primitive streak (day 14 or 15) as the precursor to the spinal cord)



How must it be addressed? (hESC)

1. **Compliance with Member States legal framework**
2. **Project-specific ethics approval**
3. **Compliance with agreed EU principles:**
 1. The project uses **existing cultured cell lines** only
 2. That are **NOT derived from embryos specially created for research** or by **somatic cell nuclear transfer**
 3. That were derived from **supernumerary non-implanted embryos** resulting from in vitro fertilisation
 4. **Informed consent** has been obtained
 5. **Personal data and privacy** of donors are **protected**
 6. **NO financial inducements** were provided for the donation of embryos
4. **Confirmation of scientific necessity**
5. **Mandatory Ethics Assessment** (*Article 19(3) Horizon Europe Regulation*)
6. **Additional approval procedure** by Member States (*Joint Declaration of the EP, Council and EC 2021/C 185/01 + Council DECISION (EU) 2021/764*)

How must it be addressed? (hESC)

- Applicants must :
 - Provide information on the origins of the cell line
 - Provide details on the licensing and control measures of the member state in which the research will take place
 - Register the cell line, the project, and subclones, in the hPSCReg
 - Obtain ethical approval and other authorizations required by national law
 - Confirm compliance with the **6 principles**

How must it be addressed? (hE)

- Applicants must provide:
 - Information on the origins of the embryos
 - Details on recruitment, inclusion and exclusion criteria, and informed consent procedures
 - Informed consent forms & information sheets
 - Ethics approval copies
 - Confirmation that the embryos will not be destroyed.

- Use of human embryonic stem cells (hESC)

Current status:

Does this proposal involve the use of hESC? *

No Yes

If YES, please state whether the use of hESC is, or is not, in your opinion, necessary to achieve the scientific objectives of the proposal and the reasons why. Alternatively, please state if it cannot be assessed whether the use of hESC is necessary or not, because of a lack of information.

0 / 4000 characters

- Use of human embryos

Current status:

Does this proposal involve the use of human embryos? *

No Yes

If YES, please explain how the human embryos will be used in the project.

0 / 4000 characters

- Activities excluded from funding

Current status:

Activities that :

- aim at human cloning for reproductive purposes, or
- intend to modify the genetic heritage of human beings which could make such changes heritable (with the exception of research relating to cancer treatment of the gonads, which may be financed), or
- intend to create human embryos solely for the purpose of research or for the purpose of stem cell procurement, including by means of somatic cell nuclear transfer, or
- lead to the destruction of human embryos (for example, for obtaining stem cells)

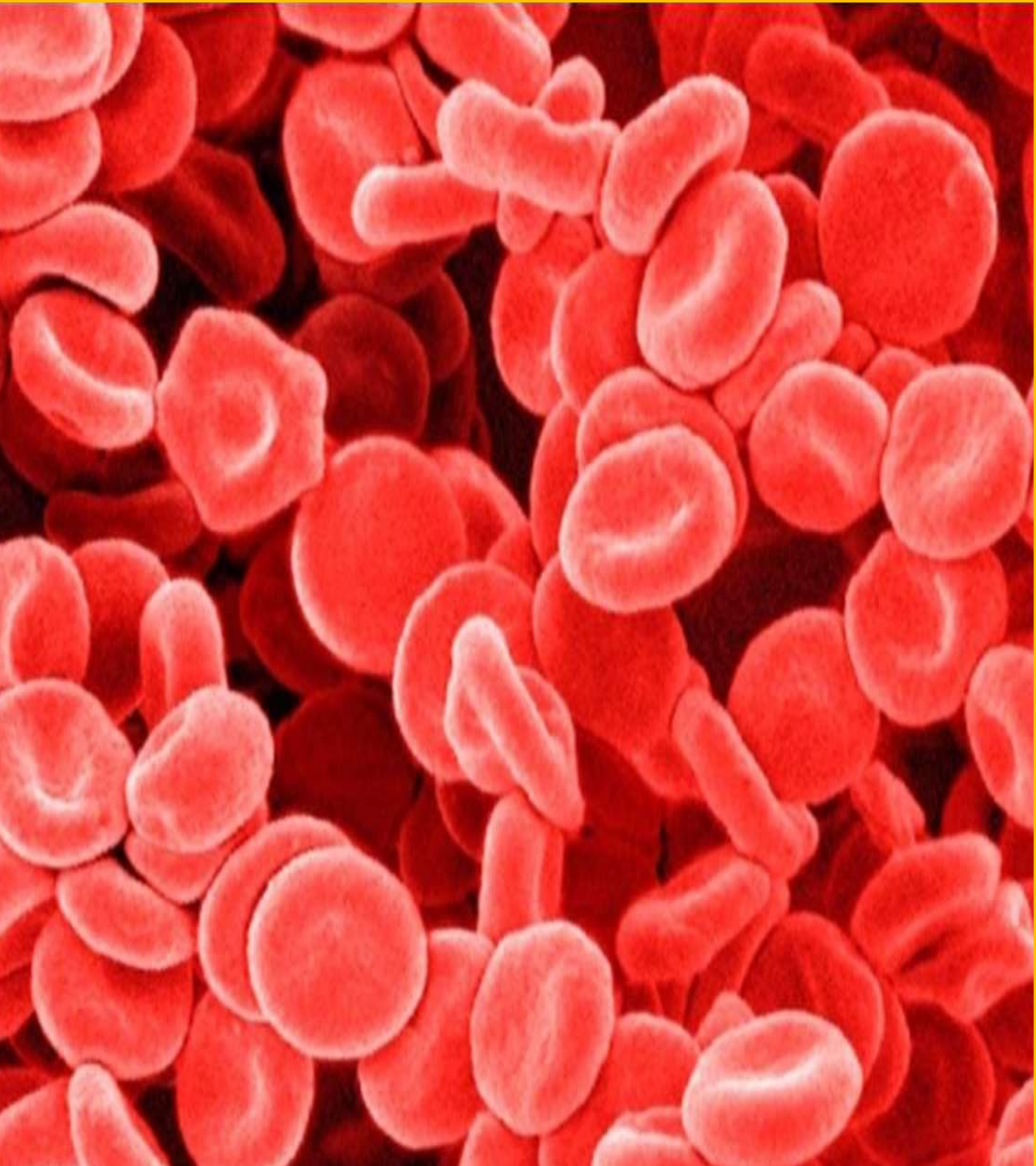
are excluded from funding. Does the proposal include any of these activities? *

No Yes

Does your activity involve Human Embryonic Stem Cells (hESCs)?		<input type="checkbox"/>	<input type="checkbox"/>		
If YES:	Will they be directly derived from embryos within this project?	<input type="checkbox"/>	<input type="checkbox"/>	<i>Activity not eligible for funding</i>	<i>Activity not eligible for funding</i>
	Are they previously established cells lines? Are the cell lines registered in the European registry for human embryonic stem cell lines?	<input type="checkbox"/>	<input type="checkbox"/>	1) Origin and line of cells. 2) Details on licensing and control measures by the competent authorities of the Member States involved 3) Declaration confirming that the 6 specific conditions (<i>see below</i>) for activities involving human embryonic stem cells are met.	1) Copies of ethics approval. 2) Declaration that the human embryonic stem cell lines used in the project are registered in the European hESC registry (www.hpscereg.eu).
Does your activity involve the use of human embryos?		<input type="checkbox"/>	<input type="checkbox"/>	1) Origin of embryos. 2) Details of the recruitment, inclusion and exclusion criteria and informed consent procedures. 3) Confirmation that informed consent has been obtained.	1) Copies of ethics approval. 2) Informed consent forms and information sheets.

New developments and challenges

- Debate about the 14-day limit for embryo research
- Embryo-models, derived from hESC or iPSCs: referred to as embryoids, artificial embryos, blastids, gastruloids, ‘synthetic entities with embryo-like features’, ...
 - Not derived via fertilization!
 - Conceptual confusion, mimic aspects of early embryos, but are not embryos and unable to become fully functional human embryos.
 - Permit the study of early development without having to create or destroy human embryos
 - ! Nonetheless: prohibited in some countries, legal uncertainty on others



3. Human cells and tissues

Why is it an ethics issue?

- Enormous amounts of human cells & tissues collected and '**banked**' for research
- Critical for gaining insight in diseases and promote development of new therapeutics & techniques
- Ethical issues:
 - Sense of identity
 - Confidentiality (of related health and genetic information)
 - Ownership & compensation



Henrietta Lacks, whose cancer cells were the source of the HeLa cell line

When is it an ethics issues?

- Includes **all types of biological samples of human origin**
 - Gametes, blood, bone marrow, urine, stool, organs, plasma, skin, serum, cancer cells, hair, sweat, ...
- Includes **foetal/embryonic cells/tissue** other than hESC
 - extraembryonic cells and primitive endoderm (PE) cells, donations after pregnancy terminations
- Includes **induced pluripotent stem cells** (iPSC) from somatic cells, **hematopoietic stem cells, Umbilical Cord Stem Cells**
- Includes **organoids** derived from iPSC or hESC

How must it be addressed?

Human cells and tissues may be obtained:

- From commercial sources
- From another project, laboratory or institution
- From a biobank
- As part of the research project

Free and informed consent

Protection of privacy

! When cells/tissues/samples are collected within or directly for the purpose of the project
→ Principles for human involvement apply

How must it be addressed?

1. **Informed consent** of the donors

- As research participants, e.g. in earlier study
- As patients, consenting to the use for research of cells/tissues/samples from clinical practice

! Specific consent for the collection of additional material must be given

Information to be included: how long it will be stored, where, for what research it will be used, whether samples will be pseudonymized or anonymized, genetic sequencing will be used, incidental findings, and when/how it will be destroyed, discarded.

2. Protect **privacy & confidentiality** of the donors

! Genetic information

How must it be addressed?

3. Ensure **legal compliance** for using/producing/storing of human biological materials
 - Compliance with **EU Directive 2004/23/EC** on tissues and cells
 - Relevant **national law and regulations: licenses, authorization, material transfer agreement, import/export licenses**, may be required
4. For PSC: registration of cell line and the project in the **hPSCReg: <https://hpscereg.eu/>**

Consent for secondary use

- **For identifiable samples:** always verify whether the initial consent covers the proposed research – in particular genetic sequencing !
 - **‘Broad consent’?**
 - Only acceptable if the risks for the donor are minimal to non-existent
 - More & more difficult to guarantee due to the increase of genetic sequencing of samples
- High risks → **‘specific’** consent

Key information



- Details on the source of the material (details of provider/laboratory/institution/biobank)
- Details on what will happen to the material at the end of the research
- Confirmation that material is fully anonymised or that consent (for secondary use) has been obtained
- If the material is **collected for the project**:
 - Details on the informed consent procedures, the amount to be collected and the procedure for collection
 - Ethics approval
- If the material is intended to be **stored for future use** in other projects, the applicant must:
 - confirm that the donor's **consent for such secondary use** has been obtained
 - state the **legislation** under which the material will be stored
 - state **how long it will be stored** and what he/she will do with it at the end of the research

3.3 Ethics issues checklist

3 HUMAN CELLS / TISSUES		YES/ NO		Information to be provided in the proposal	Documents to be provided on request
Does your activity involve the use of human cells or tissues (other than those covered by section 1)?		<input type="checkbox"/>	<input type="checkbox"/>	Please provide information in one of the subcategories below.	
If YES:	Are they human embryonic or foetal cells or tissues?	<input type="checkbox"/>	<input type="checkbox"/>	1) Origin of human foetal tissues/cells. 2) Details on informed consent procedures. 3) Confirmation that the informed consent has been obtained. 4) If applicable, details on the induced human pluripotent cell lines.	1) Copies of ethics approvals. 2) Informed consent forms and information Sheets. 3) If applicable, registration certificates of the cell lines and project from the hPSCreg.
	Are they available commercially?	<input type="checkbox"/>	<input type="checkbox"/>	1) Details on cell types and provider (company or other).	1) Copies of import licences (if relevant).

3. Human cells and tissues

- New developments:
 - Organoids
 - Brain organoids
 - Gonadal organoids from iPSC
 - Creation of human-animal chimeras
 - Whole genome sequencing

Thank you for your attention!

Questions?