Fact sheet for Ethics Committees

Every publicly funded research project that involves human participants is subject to ethical and scientific evaluation. The ethical evaluation of a project is carried out by a body called an independent ethics committee (IEC) or institutional review board (IRB). Members of the ethics committee may include representatives of patient advocacy groups, laypeople, theologians or legal representatives, as well as medical personnel. The following factsheet gives an introduction to pluripotent stem cells and the roles and tasks of the ethics committees in human pluripotent stem cell research.

What are pluripotent stem cells used for in human medical research?

Human pluripotent stem cells (hPSCs), whether human embryonic stem cells (hESCs) or induced pluripotent stem cells (iPSCs), play an important role in human biological research. They are not only excellent tools to model human development and disease, but are also widely used in other areas of research, such as the testing and development of new drugs and treatment methods. Current efforts also focus on the use of hPSC-derived cells for therapy, with the first clinical trials in humans already underway. The use of pluripotent stem cells is expected to further increase steadily worldwide as seen by the growing number of publications and patents related to stem cells.

What does "pluripotency" mean and how is this ability used in research?

Pluripotency describes the ability of stem cells to differentiate into any type of body cell, including germ cells.. Because of this high differentiation potential, novel areas of application arise: organoids, germ cells, human / animal chimeras, or even combinations of cells to make synthetic lifeforms such as xenobots are conceivable on the basis of stem cell lines and are already being researched and developed.

How do researchers obtain pluripotent stem cells for their research?

All of these research areas rely on the initial donation of a human cellular sample material by volunteers. Researchers need biological donor material in order to generate hPSC - lines. While hESC can only be derived from embryos, iPSC can be produced from somatic cells, i.e. any living cell of the human body, e.g from skin, hair follicles, blood or urinary cells. The value of such source material for the generation of pluripotent stem cell lines should not be underestimated for research, and the ethical and social framework conditions for these voluntary donations must be observed and considered.

Why does research with human pluripotent stem cells require ethical guidance?

Research with human pluripotent stem cell lines must be ethically monitored, because the research material, the pluripotent stem cells, is immortal in the lab and contains sensitive personal data of the donor in the form of the genetic material that can for instance reveal disease risk, family relationships, as well as personal features of the donor. The research participant's wishes and rights must be ensured during the entire timeline of the conducted research involving any specific restrictions and limitations mentioned in the donor consent form.

Research with human stem cells is subject to diverse national legislations and international guidelines and recommendations which, in addition to quality and good scientific practice specifications, also outline the ethically desirable handling of this biological material (see e.g. https://www.eurostemcell.org/regulation-stem-cell-research-europe).

What aspects need to be considered in the ethical assessment of stem cell research projects?

On the one hand, the ethical evaluation concerns the research projects themselves - what are the research objectives and methods, what purposes are being pursued with the project, what results can be expected. On the other hand, it also concerns the ethical background of the cells to be used in the projects: where do they come from, how and under what conditions were they obtained, what restrictions on use are they subject to?

As science in this field is constantly advancing into new realms of possibility, this development is sometimes very quick and not all routes that can be conducted with stem cells can be foreseen. For example genome editing technologies such as CRISPR/Cas9 allow to edit the genomic code with unprecedented speed and

precision to allow modulation of the personalized donor cells. Recent advances in tissue engineering and cell biology allow the formation of organoids, organ-on-chip devices, germ cells, new embryos and even the creation of human-animal chimeric cells. Such engineered biological systems formed from stem cells in the laboratory open up new fields of application but also ethical and social challenges.

What different ethical values need to be balanced in the field of human stem cell research?

Freedom of research is a high ethical and societal good, not only because of the human desire to seek the truth and accumulate knowledge, but also because it can form the basis for greater social prosperity and an increase in the health of society as a whole through scientific progress. With a continuously aging society and higher life expectancy in the countries with public access to a modern and continuously developing medical system, the need for new technologies and scientific developments is even increasing with the elderly population. Regenerative medicine, which uses also the power of stem cells may improve healthy ageing. However, other ethical values must not be underestimated: the value of human autonomy and the right to self-determination, the value of protecting personal data and privacy, i.e. the rights of the donor of biological material for research.

How is it ensured that cell donations are voluntary and informed?

Cell donations from volunteers are to be understood as sensitive, personal entities that should only be used as research objects under very specific ethical conditions. Every single human cell donated for research has its origin in the autonomous decision of a person who not only cedes ownership of parts of their body to the public/research community, but also provides sensitive personal data (e.g. relating to their individual genome). This autonomous decision requires a clear ethical framework in order to treat the donors in question with respect, fulfil their wishes on an equal footing.

Cell donations must be voluntary and without pressure, it must be informed, respectful and include a description of all the risks, opportunities and consequences associated with the donation for the donor. The fact that the cell donation took place in this way is recorded and made transparent and comprehensible in a document: the declaration of consent (often combined with a patient/donor information sheet describing the ongoing study in detail), which the donor signs. This documentation should be the benchmark and the minimal quality criteria applied to the ethically sound derivation of human cell material donated for stem cell research. In addition to research, many cell donations can also be made available for commercial purposes or for cell therapies - these aspects are also part of the declaration of consent.

Stem cell researchers are obliged to respect the donor's autonomy. If, for example, the declaration of consent contains restrictions on the use of the donated material, these must be respected and controlled, ideally by an independent quality control mechanisms/ third party qualified and eligible to conduct this check.

In which cases can the donor be represented by others in the consent process?

For the production of hESC lines, surplus embryos created during artificial fertilisation that have to be discarded are usually used. In this case, parental consent is required if the embryo is to be used and destroyed for research purposes. Particular care should be taken with regard to cell donation by children/minors: Children are also capable of donating cells for research and should also be given an information and consent process appropriate to their understanding, but the consent of the custodian (parents) is also required here. This may also be the case for people with limited cognitive abilities (guardians).

What role can ethics committees play in the assessment of project plans?

Ethics committees can be used to assess whether a project fulfils social and ethical values as well as purely scientific ones and if the conducted research follows the local laws, guidelines and good scientific practices. Particularly the law regarding stem cell use may be subject to nation specific regulation. This includes assessing the project objective, the project method and the human material to be used in this project. National legal frameworks of participating project partners must be carefully analysed and balanced, as the legal situation in the field of stem cell research can vary greatly from country to country (see e.g. https://www.eurostemcell.org/regulation-stem-cell-research-europe).

What role can ethics committees play in assessing the ethical background of human pluripotent stem cells?

Ethics committees can be tasked with assessing the ethical background of the cell material to be used in new projects. Here, the declaration of consent signed by the donor at the time of cell donation (of the starting material for the stem cell lines to be produced or already produced and used in the project) will be considered in particular.

The tasks of an ethics committee are summarized:

1) a researcher must obtain an ethics approval to obtain biosamples and/or clinical data from participants of a research study. All PIS and ICF required to get samples/data must be reviewed by the ethics committee. In the case of generation of new pluripotent stem cells, the ethics committee must ensure that the PIS and ICF meet ethics standards for derivation of e.g. hESC or hiPSC;

2) if a researcher wants to use an existing PSC line, but cannot obtain information on the ethical provenance of the line (ie. Sources of hPSC are historical, cell lines are commercially available, but no information on the consent is provided), an ethics committee can review these cases individually, and decide on the basis of the evidence at hand whether there is an ethical basis for using these cell lines in publicly funded research.

How can ethics committees be consulted if there are no consent forms for available cell lines?

If such consent is not available, which may be the case for various reasons (e.g. because the drafting and signing of a consent document was not mandatory at the time of cell donation, or because the declaration of consent was lost, or because the consent did not cover/could not anticipate the scope of the application in question), an ethics committee may also be called upon to make a decision on the handling/use of the cells in question. In this case, the ethics committee must represent the interests of the donor and the ethical values of a society in equal measure.

How can hPSCreg® support the work of ethics committees?

For members of ethics committees, the hPSCreg® registry (www.hpscreg.eu) can be used as a tool to become more informed about all available data and documents relating to a stem cell line and it covers further valuable functions for ethical assessments:

Firstly, hPSCreg provides an overview of human stem cell lines developed worldwide. hPSCreg also includes a database of stem cell-related projects (https://hpscreg.eu/browse/projects) and links them with data on the stem cell lines used and a database of global clinical trials (https://hpscreg.eu/browse/trials). The database allows a clear assignment of the generator institution, the owner and the distributor of a stem cell line and all published research associated, providing a transparent provenance to a specific stem cell line beyond a number of specific and very detailed biological characterization data that report on the biological properties of the stem cell.

In addition to these purely scientific tasks, hPSCreg also offers support and guidance from an ethical perspective: the donation of cells and use of human biological material in research is subject to international guidelines, e.g. co-developed in cooperation with the international society for stem cell research (ISSCR) aiming for the establishment of harmonized standards and guidelines in the stem cell field. hPSCreg also implements recommendations and national legislation, which can vary greatly internationally, particularly in the area of research with human embryos and hESCs. To help categorise national differences and legislation, hPSCreg offers a legislation world map (https://hpscreg.eu/map).

To assess the ethical background of stem cell lines, hPSCreg collects the declarations of consent regarding the biological source material in a confidential manner, the consent forms are not public and reviewed manually by experts in the field of bioethics which often requires their translation and screening for specific use restrictions and related.

In a careful process of checking the ethical background of stem cell lines, these are validated with regard to their origin and their proof of pluripotency. Two major biological quality criteria are checked by hPSCreg team along the ethical aspects 1: the biological markers that proof that the stem cell is a stem cell (pluripotency) and 2: the ability of the stem cell to form the three major germ layers of the human body, also by data that report on markers for this differentiation

(differentiated cell markers) besides other biological characteristics that report on the identity, quality and origin of the stem cell. If necessary, cell lines can be even certified if they fulfil the ethical and scientific requirements specified by the European Commission (see: https://ec.europa.eu/info/funding-tenders/opportunities/docs/2021-2027/common/guidance/how-to-complete-your-ethics-self-assessment_en.pdf). hPSCreg® certificates attest to the ethical provenance of cell lines for European Commission funding.

If declarations of consent are missing for the donors of the material used to generate the pluripotent stem cell lines, then the researcher must obtain an approval from the ethics committee of their home institution. The approval issued by the local ethics committee can then be saved as an alternative to consent in the Ethics Section of the cell line concerned. hPSCreg archives the ethics approval document as part of a "paper trail" documenting the ethical provenance of the cell line, and the approval is not publicly visible. Should questions about the ethical background of these cell lines arise at a later date, the stored ethics committee approvals remain available for future clarification. In this way, the approvals are not only stored locally (i.e. where they were issued or by the person who requested them), but also in an internationally networked database that manages this information confidentially.

Where can I find further information?

https://hpscreg.eu/about/documents-and-governance

https://www.isscr.org/guidelines

https://ec.europa.eu/info/funding-tenders/opportunities/docs/2021-2027/common/guidance/how-to-complete-your-ethics-self-assessment_en.pdf

https://www.eurogct.org/theme/factsheets