

Code of Practice for the Operation of the European Human Pluripotent Stem Cell Registry – hESCreg*

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1. Background and Mission

1.1. Background

Human pluripotent stem cell (hPSC) research holds unprecedented promise for the development of cellular therapies for degenerative pathologies and trauma. It may also provide new tools for drug discovery and toxicity testing, as well as for the study of human development, disease physiology and gene control. The number of hPSC lines that are available and that are subsequently being used in numerous fields of research is increasing steadily. Yet, there remains a lack of effective coordination to enable direct comparison of the known characteristics of such hPSC lines. The European Commission decided to set up a European registry of embryonic stem cells in 2007 to resolve this situation. Currently the hESCreg database (now the human pluripotent stem cell registry) has recorded more than 700 human embryonic stem cell (hESC) lines. Moreover, it is likely that 1000s of human induced pluripotent stem cell (hiPSC) lines will also be established but it is improbable that all of these lines will achieve the scientific scrutiny of peer review in the scientific literature. The hESCreg project provides coordination of comparative information on the derivation, characteristics and quality of hPSC lines (hESCs and hiPSCs), increasing transparency of data and enabling researchers to select cell lines with appropriate ethical provenance and suitable characteristics for research purposes. In its new form, the hESCreg project will enhance the information available on hESC lines and will also provide a resource to extend these benefits to researchers wishing to use well characterised and ethically sourced hiPSC lines. This is intended to

contribute to an optimal access to and use of human pluripotent stem cells, ensuring that the results of research ultimately become more quickly available to all patients across Europe.

1.2. Mission

The primary objectives of hESCreg are to provide information on existing hPSC lines, their derivation, molecular characteristics, use and quality, and to act as a platform for coordination and cooperation. The hESCreg makes this information freely accessible to the research community, funding agencies, governmental bodies, regulators and the public at large in order to further open-up the field and promote the validation of research findings and the efficient use of existing hPSC lines. Accordingly, hESCreg will bring a focus to hPSC lines which have been validated according to scientific consensus opinion and fundamental ethical requirements. It will also contribute to avoiding redundancy and ensuring comparable quality standards.

To achieve the primary objectives, specific goals have been identified. hESCreg will:

1. Define and implement eligibility criteria for listing of hPSC in the registry.
2. Establish and disseminate registry criteria as well as the registration, access and quality control mechanisms to hPSC providers and users.
3. Build a mechanism for monitoring registry performance, whereby input from existing registries, banks, networks and research initiatives will be incorporated.
4. Develop the technical backbone of the registry by designing and implementing an Internet-based access mode for cell lines listed in the hESCreg. This includes the development of tools, conditions and logistics for technical information about the cell lines, ethical provenance, availability for research, scientific contact person and any restrictions regarding their use.
5. Develop the registry into a knowledge-service tool of registered hPSCs for research and clinical applications. This will include the annotation of listed hPSC lines with information on their performance under given culture conditions, specific characteristics, experimental results and legal status. This includes interlinking with other registries.
6. Maintain regular dissemination, communication and updating mechanisms of the contents of the registry.
7. Promote use of existing international standards and standardised nomenclature.

2. Policies

The project management group will respond to its remit under the applicable Directives and laws of the European Union. It will also acknowledge and notify users of the specific laws and regulations associated with particular European states via an expert panel of national experts that form the hESCreg Committee of National Representatives (CNR).

In its interactions with physical biorepositories of hPSC lines, the hESCreg expects that they will comply with the standards identified through international consensus on stem cell banking (ISCBI, 2009) and cell line nomenclature and reporting (Luong et al., 2011).

Ethics: The hESCreg project management group will ensure that a robust process is implemented to gather key documentation and statements from providers of hESCreg-data as evidence of ethical provenance, including documenting the informed consent process and any donor restrictions relating to the cell lines referenced on the hESCreg. Key EU regulation and guidance that will be used in hESCreg include:

- [Opinion 16- 07/05/2002 Ethical aspects of patenting inventions involving human stem cells](#)
- [Opinion n°22- 13/07/2007 - The ethics review of hESC FP7 research projects](#)

- Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells.
- Directives 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data

Donor Privacy: With regards to donor privacy: the hESCreg will make all reasonable efforts within its available resources to protect the privacy and the confidentiality of donors who provided biological samples for the derivation of stem cell lines presented on the hESCreg database. More specifically, hESCreg will ensure that it does not publish or release into the public domain any data or other information that could reasonably be expected to lead to the re-identification of donors.

Data Access: The hESCreg project management group acknowledges and supports the widely accepted ethical and scientific imperative of data sharing. It is the opinion of the group that dissemination of scientific data from human genetics research is desirable to coordinate and enhance research into human biology and health. The hESCreg will therefore actively facilitate the dissemination of such data and has a responsibility to the scientific community to make scientific data available on the data provided to it. Nevertheless the hESCreg also has fiduciary commitments to the donor population associated with the data it holds under the [Directive 95/46/EC \(Article 19 Working Party\)](#) and the appropriate working party documents. In this regard, certain genomic, epigenomic, phenotypic and demographic data and identity profiles likely to create a risk of direct or indirect re-identification of donors through a combination of public data sources, will only be available from hESCreg to *bona fide* researchers through a controlled data access mechanism (Isasi et al., 2014). A requestor of controlled data must have obtained approval by an independent oversight ethics committee, and should commit to:

- 1) Use the data in conformity with widely recognized good research practice and with applicable legal and ethical requirements,
- 2) Use the data solely for the purposes of the hESCreg- approved research protocol,
- 3) Not to share or release hESCreg supplied data with unauthorized third parties (who can apply independently to gain data access); and
- 4) Not to use the data alone or in combination with other data sets to either attempt or create the conditions for the re-identification of an individual donors or their families (see Isasi et al., 2008 and 2014).

Data Security: The hESCreg maintains a high level of security for the hESCreg system (see 2.3) and provides suitable protection and back up within the resources available, in case of accidental or deliberate breach of hESCreg security or damage to the integrity of its data. Data security guidance and regulation that will be used by hESCreg includes:

- [Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data](#)
- [Directive 95/46/EC Article 29 data protection working party](#)

2.1 General Governance

The Project Management group of the hESCreg has overall responsibility for the governance of the project. The group will be accountable through its Committee of National Representatives, stakeholder engagement (see below) and its reporting to the European Commission. The hESCreg is subject to the scrutiny of the EU formal project review process.

2.2 Data Quality and Standardisation

The registry will ensure high standards for the validity and quality of data that is entered onto the registry. It will use its Committee of National Representatives experts for independent review. In addition, it will adopt international scientific and regulatory standards where relevant. In particular, hESCreg management with privacy ([Directive 95/46/EC Article 29 working party](#)) will seek to ensure that data used on hESCreg does not facilitate donor re-identification and of donors.

2.3 Data Security

A high degree of security will be provided by the Project Management group through the provision of appropriate electronic systems and staff procedures and through compliance with the respective European Directives ([Dir95/46/EC](#)). (see section 4). The hESCreg is operated under a best practice agreement with the Charité's IT department (Universitätsmedizin Berlin). hESCreg management aims to ensure security through a controlled access mechanisms and other measures to prevent unwanted attempts to access hESCreg protected data.

2.4 Ethics and Regulation

A primary function of hESCreg is to assure that appropriate donor consent is in place for each registered stem cell line. The registry management will ensure the implementation of EU regulations and ethical positions/opinions and their application. This will be facilitated by the network of the hPSCreg Committee of National Representatives (CNR) with one representative for each state (see Appendix 1 for the Terms of Reference). Particular attention will be paid to address the plurality of European positions on the moral status of the human embryo and the resulting variation in national guidance and regulation. The hESCreg will take responsibility to assure that each cell line has been subjected to a rigorous provenance evaluation which includes evidence that each line was established from tissue or cells donated under informed consent process appropriate for the derivation and use of stem cell lines. The key criteria for such an evaluation are that for each cell line to be registered at least one of the following must be provided:

1. Consent form (blank or original with signatures redacted) and copy of the information provided to donor/s;
2. Approval /waiver (or equivalent) by the principal investigator's local oversight ethics body for the project application to derive the cell line;
3. A signed and dated Ethics Evaluation form.

In addition, the issues relating to the availability of personalized genetic data from cell lines and donor privacy will also be a focus of hESCreg activity. The policy of the hESCreg relating to release of genetic data on stem cell line is as follows:

- It is broadly recognised that there are great benefits to be had from the sharing of genetic data amongst the scientific and clinical communities. However, hESCreg will establish procedures aimed to limit the risk for data misuse and mission creep. A genetics data policy document is under development.

To address these and other ethical issues appropriately, the registry will utilise the expertise of its partners, an Ethics Advisor (Appendix 2), the Committee of National Representatives and also has access to the expertise of the International Stem Cell Forum Ethics Working Party, which draws on international expertise in this area.

When collating data the requirements of the regulations on genetic manipulation will also be considered. A Data Access Committee (DACO) will decide on the specific measures with respect to data accessibility (Appendix 3).

3. Quality Assurance and Traceability

3.1 Quality

The quality of data entered into the registry is ensured by the use of appropriate accepted standards and a robust data entry processing system with an evaluation process based on criteria agreed by a high level international team of independent advisors (Committee of National Representatives). This is designed to be a transparent process which allows for presentation of alternative scientific views. The overall process is outlined in Figure 1 and at each stage data entry is evaluated against a set of specific and measurable criteria as described in Table 1.

Table 1: Data Evaluation Criteria for Cell Registry

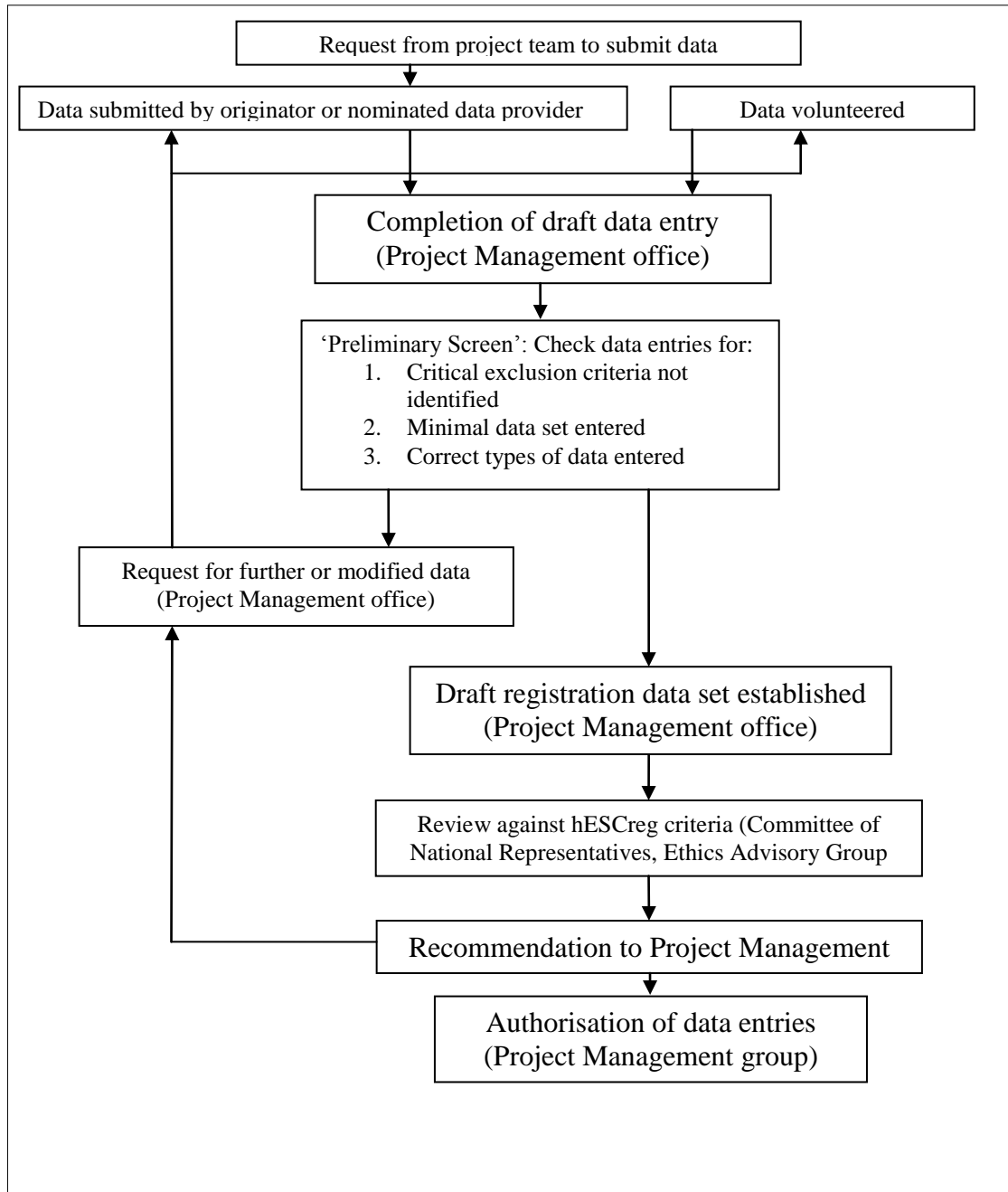
Evaluation Stage	Responsible Party	Criteria
Preliminary screen	Project Management	<ul style="list-style-type: none"> • Minimum eligibility data presented in an unambiguous and appropriate form. • Cell/tissue donor has provided evidence of informed consent for donation and use in research in response to (i) an ethics evaluation form and (ii) by provision of the informed consent information used for a specific cell line. • No explicit exclusions for cell line use (ethical, legal).
Scientific and regulatory evaluation	Overseen by Data Access Committee (DACO) (i.e. Project Management group and Ethics Advisor) with advise from the Committee of National representatives (CNR) and Ethics Advisory Group	<ul style="list-style-type: none"> • Confirmation that providers of data are <i>bona fide</i> researchers, and validation of adherence to relevant <i>data protection</i> regulations • Decide on access categories for data in hESCreg.
Ethical review	Ethics Advisory Group (ISCF Ethics Working Party Secretariat and hESCreg Ethics Advisor)	<ul style="list-style-type: none"> • Evidence of appropriate informed consent. • Adherence to national laws and regulations. • Appropriate traceability for provenance.
Final evaluation	Project Management	<ul style="list-style-type: none"> • All minimum eligibility criteria complete and validated. • Evidence provided of traceability to informed consent. • Suitable recommendation for inclusion from CNR and Ethics Advisory Group and CNR. • Any necessary annotations have been completed • Compliance with any other hESCreg criteria.

It is normal for there to be different scientific viewpoints and opinions and these may well arise within the Committee of National Representatives regarding the data available for a particular cell line. In the event of conflicting views amongst the Committee of National Representatives, the project management recommendation will be made by the Scientific Advisory Board chair based on the majority decision and a commentary will be agreed by the chair with the Committee of National Representatives, which addresses the issues arising and recognises alternative views. Full details of this and other evaluation procedures are given in the accompanying hESCreg protocols.

Following evaluation and acceptance of a cell line entry for the registry, it could be discovered that data provided was erroneous, misreported or even falsified. If such information is brought to light, it

will be the responsibility of the project management to evaluate the new information and prepare a plan of action to deal with the issue promptly in an open and accountable way. This would normally be through an extraordinary meeting of the Committee of National Representatives (CNR) to propose options and recommendations to the project management. Refusal of registration or removal of registered lines from the hESCreg will be notified to the relevant EC project officer.

Figure 1: Evaluation process of for the data provided to the registry



3.2 Traceability

The project management ensure that all data entered on the registry is traceable to a specific provider through a system which records and logs any changes. Procedures for the registry operation are given version numbers when updated or corrected and earlier versions are archived.

Providers of information on fully informed consent for cell lines are required to identify that they are the primary source (i.e. were involved in the original derivation process) and confirm that ethical approvals and consent procedures are consistent with requirements of the European Human Tissues and Cells Directive by providing, i.e. uploading copies of the relevant documents.

4. Data Security

The hESCreg data security is managed by the Information Technology department at Charité hospital IT department, which handles the patient data-base for Europe's largest university hospital. Accordingly, hESCreg data security adheres to relevant EU guidelines (see policy section above), German law and the state of Berlin regulation on electronic data processing systems and personal data protection.

The hESCreg Internet front end, the database back end as well as all future complementary extensions are provided by the Charité hospital IT department. They are currently hosted on a virtual server system within the Data Management Center (DMC) of the Charité hospital. Consequently, the platform benefits from the rigorous safety precautions in place to avoid interference from outside intruders (hackers) as well as internal accidental or deliberate corruption. With increasing complexity of the database, it is envisaged to move the platform onto a dedicated server within the Charité DMC domain.

5. Stakeholder Engagement

The hESCreg is committed to establish interactions with a wide range of stakeholders from the scientific, regulatory and other communities, by engaging with numerous organisations, projects and workshops, amongst other activities. . The registry website will also be developed to provide information of interest to the general public on stem cells, links to other sources of information and an on-line forum and feedback system. Contacts made by stakeholders with the registry will be managed by the project management team through the Berlin office. These will be reviewed at regular project management meetings.

6. Risk Management

This is a challenging project handling controversial issues with a high level of web-based interaction. Management of risks that could impact on the successful operation of the project is therefore vital to enable the project to move forward smoothly and to optimise project achievements. A risk management system will therefore be established, in liaison with the Committee of National Representatives and the Ethics Advisor, which will be responsible for identifying and evaluating risks in the form of a risk register. It will also develop action plans to reduce significant risks to an acceptable level. Risk management will be the responsibility of the project management team. The risk register will be reviewed annually by the management group using advice from the Committee of National Representatives to identify any new or changing risks.

7. Sustainability

Key measures of the success of the project will be its sustainability and its longer term value to the European Commission hPSC governance and other stakeholders. This is a topic of ongoing discussion with the European Commission and the management group will work to develop a plan for long term sustainability.

8 References

Andrews, P.W., Arias-Diaz, J., Auerbach, J., Alvarez, M., Ahrlund-Richter, L., Baker, D., Benvenisty, N., Ben-Josef, D., Blin, G., Borghese, L., Borstlap, J., Bruce, K., Brüstle, O., Buckle, R., Camby, C., Choo, A.B., Chen, W., Collins, D., Colman, A., Crombie, C., Crook, J.M., Cypess, R., De Sousa, P., Dhawan, J., Douay, L., Dvorak, P., Dyke, T., Eriksson, L., Firpo, M., Fitzgerald, C., Glover, C., Gokhale, P., Greene, M., Ha, H-Y., Hampl, A., Healy, L., Hei, D., Holm, F., Hovatta, O., Hunt, C., Hwang, S-M., Inamdar, M., Isasi, R., Itskovitz-Eldor, J., Jessie, N., Kim, D-W, Kirzner, R., Kiatpongsan, S., Knowles, B.B., Kuo, H-C., Laughlin, M., Lavon, N., Ludwig, T., Lakov, M., Lee, D-R., Macauley, J., McKay, R., Menasche, P., Menendez, P-M., Michalska, A., Mileikovskaia, M., Minger, S., Mishra, G., Moody, J., Montgomery, K., Morris, C., Mummery, C., Nagy, A., Nakamura, Y., Nakatsuji, N., Nishikawa, S-I, Oh, S., Oh, S-K, Olson, P., Otonkoski, T., M., Patole, M., Park, H-S., Pei, X., Pera, M., Rajala, K., Reubinoff, B., Robins, A., Rooke, H., Rumayor, V., Scotmann, H., Sherlock, J., Simon, C., Sipp, D., Skinner, R., Smith, D., Stacey, G.N., Stefanovic, S., Strehl, R., Taft, R., Takahashi, T., Talib, S., Terstegge, S., Turner, R., Tuuri, T., Yu, J., Zandstra, P., Zapata, A., Zng, F., Zhou Q., Tannenbaum, S. (2009). Consensus guidance for banking and supply of human embryonic stem cell lines for research purposes. *Stem Cell Reviews and Reports* 5, pp301-314.

Opinion 16- 07/05/2002 Ethical aspects of patenting inventions involving human stem cells

http://ec.europa.eu/bepa/european-group-ethics/docs/publications/opinion_22_final_follow_up_en.pdf

Opinion n°22- 13/07/2007 - The ethics review of hESC FP7 research projects

http://ec.europa.eu/bepa/european-group-ethics/docs/publications/opinion_22_final_follow_up_en.pdf

Directives 95/46/EC of the European Parliament and of the Council of Europe of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data

(<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31995L0046:en:HTML>)

Article 29 data protection working party on the protection of individuals with regard to the processing of personal data

(<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31995L0046:en:HTML>)

Directive 2004/23/EC of the European Parliament and of the Council of Europe of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells.

(http://eurex.europa.eu/smartapi/cgi/sga_doc?smartapi!celexapi!prod!CELEXnumdoc&lg=en&numdoc=32004L0023&model=guichett)

Directive 2006/17/EC implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells

(<http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:038:0040:0052:EN:PDF>)

Directive 2006/86/EC implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells

(http://eur-lex.europa.eu/LexUriServ/site/en/oj/2006/l_294/l_29420061025en00320050.pdf)

Isasi RM, Knoppers BM. Governing stem cell banks and registries: emerging issues. *Stem Cell Res.* 2009 Sep-Nov;3(2-3):96-105.

Isasi R, Andrews PW, Baltz JM, Bredenoord AL, Burton P, Chiu I-M, Hull SC, Jung J-W, Kurtz A, Lomax G, Ludwig T, McDonald M, Morris C, Ng Alka Sharma HH, Stacey G, Williams C, Zeng F Knoppers MM. Identifiability and Privacy in Pluripotent Stem Cell Research. *Cell Stem Cells.* 2014 (in press).

Luong MX, Auerbach J, Crook JM, Daheron L, Hei D, Lomax G, Loring JF, Ludwig T, Schlaeger TM, Smith KP, Stacey G, Xu RH, Zeng F.(2011)A call for standardized naming and reporting of human ESC and iPSC lines. *Cell Stem Cell.* 8(4):357-359.

Appendix 1: Terms of Reference for the Committee of National Representatives (CNR).

- Provide input on national stem cell lines
- Advise on national and international regulation
- Support and advise on development of hPSCreg policies and strategy
- To raise with the project management team, any new developments that impact on the database and its scientific quality, and make recommendations for updating and improving the database and website
- To work with the hPSCreg management to assist development of the registry and provide ad hoc advice on specific scientific or other issues as required.

Appendix 2: Terms of Reference for the Ethics Advisor (EA) and Ethics Advisory Group (EAG).

- Provide input and guidance on ethical and regulatory / legal conduct of the registry
- Prepare relevant policy statements in cooperation with the SAB and the CNR
- To work with the hESCreg management to assist development of the registry and provide ad hoc advice on specific ethical or legal issues as required.
- Assist the hESCreg-management in conducting ethical provenance assessment and data access decisions
- The EWP Academic Secretariat serves as the Ethics Advisor and forms one member of the Ethics Advisory Group
- The Ethics Advisory Group is comprised of the members of the ISCF Ethics Working Party and the Ethics Working Party secretariat.
- The EAG advises the hESCreg management, which together with the Ethics Advisor make the final decision on ethical issues in the hESCreg project

Appendix 3: Terms of Reference of the Data Access Committee (DACO)

- The Data Access Group is comprised of the hESCreg Ethics Advisor and members of the Project Management group
- Confirmation that providers of data are *bona fide* researchers
- Validation of adherence to relevant data protection regulations
- Decide on access categories for data in hESCreg
- DACO is advised by the Committee for National Representatives (CNR) and Ethics Advisory Group

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