

Code of Practice for the Operation of the European Human Embryonic Stem Cell Registry

Contents:

Code of Practice for the Operation of the European Human Embryonic Stem Cell Registry	1
1. Background and Mission.....	1
1.1. Background.....	1
1.2. Mission.....	2
2. Policy Statements: Overlying Standards and Principles.....	2
2.1 General Governance.....	2
2.2 Data Quality and Standardisation	2
2.3 Data Security.....	2
2.4 Ethics and Regulation	3
3. Quality Assurance and Traceability of Scientific and Ethical Data.....	3
3.1 Quality.....	3
3.2 Traceability	4
4. Provisions for Data Security	5
5. Stakeholder Engagement.....	5
6. Risk Management	5
7. Sustainability	5
8. Cell Line Data Evaluation	5
Appendix: Terms of Reference for the Scientific Advisory Board and Steering Committee.....	7

1. Background and Mission

1.1. Background

Human embryonic stem cell (hESC) 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 studying human development, disease physiology and gene control. The number of hESC lines that are available and that are subsequently being used in numerous lines of research is increasing steadily. Yet there is little coordination of hESC line derivation and the provision of comparative information on the characteristics and quality of these cells. This has severely hindered reproducibility of findings and obscured transparency in the field. Obtaining consistent information on hESC is hampered further by legislative fragmentation, particularly in Europe. This reflects the continent’s historic pluralism and the different ethical, philosophical and political positions in the different countries. It is also a result of the absence of a single commonly accepted definition for the moral status of an embryo. To resolve this situation, the European Commission has decided to set up a European registry of stem cells to contribute to an optimal access to and use of 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 hESC lines, their derivation, molecular characteristics, use and quality, and to act as a platform for coordination and cooperation. hESCreg makes this information freely accessible to the research community, 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 hESC lines. Accordingly, hESCreg will 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 hESC in the registry.
2. Establish a working mechanism for registry performance whereby input from existing registries, banks, networks and research initiatives will be incorporated.
3. Establish and disseminate registry criteria as well as the registration, access and quality control mechanisms to hESC providers and users.
4. Develop the technical backbone of the registry and to design and implement an Internet-based access mode for cell lines listed in the European hESC-registry. This includes the development of tools, conditions and logistics for technical information about the cell lines, their access, contact person and restrictions about their use.
5. Develop the registry into a knowledge-service tool of registered hESCs for research and application. This will include the annotation of listed hESC lines with information on their performance in culture, specific characteristics, experimental results and legal status. This includes the interlinking with other registries.
6. Provide regular dissemination, communication and updating mechanisms of the registry content.

2. Policy Statements: Overlying Standards and Principles

The project management will aim to deliver its remit under the applicable Directives and laws of the European Union and will acknowledge the specific laws and regulations associated with particular European states.

2.1 General Governance

The project management group has overall responsibility for the governance of the project. The projects seek to be accountable through stakeholder engagement (see below). All work of the registry is subject to the scrutiny of the EU formal project review process and the EU ethics review body.

2.2 Data Quality and Standardisation

The registry will strive to ensure high standards for the quality of data that is entered onto the registry and will adopt international scientific and regulatory standards wherever relevant.

2.3 Data Security

The project management will assure a high degree of security through the provision of appropriate electronic systems and staff procedures. hESCreg is operated under a best practice agreement with the Charité's IT department. For more details see section 4.

2.4 Ethics and Regulation

The registry management will ensure the implementation of EU regulations and ethical positions and the application of these standards. This will be facilitated by the network of hESCREG national contacts for each state (Steering Committee), the international Scientific Advisory Board and an independent Ethics Advisory Board. Terms of reference for the Steering Committee and the Scientific Advisory Board are given in the Appendix. The registry also has access the expertise of the International Stem Cell Forum Ethics Working Party which draws on international expertise in this area.

3. Quality Assurance and Traceability of Scientific and Ethical Data

3.1 Quality

Quality of data entered into the registry is assured by 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 SAB. This is designed to be a transparent process which allows for scientific debate and presentation of alternative scientific views. The overall process is outlined in Figure 1 and at each stage each data entry is evaluated against a set of specific and measurable criteria as described in Table 1.

Table 1: Data Evaluation Criteria

Evaluation Stage	Responsible Party	Criteria
Preliminary screen	Project Management	<ul style="list-style-type: none"> • Minimum eligibility data provided in unambiguous and appropriate form • Cell/tissue donor has provided evidence of fully informed consent for use in research consistent with European law • No evidence of any critical issues that would exclude cell line e.g. ethical, legal
Scientific evaluation	Scientific Advisory Board	<ul style="list-style-type: none"> • Correctly reported scientific data • Cell line data reveals characteristics of a <i>bona fide</i> stem cell line
Scientific and regulatory evaluation	Steering Committee	<ul style="list-style-type: none"> • Identify use of correct national regulation
Ethical review	Ethics Advisory Board	<ul style="list-style-type: none"> • Evidence of appropriate informed consent under national laws • Appropriate traceability for ethical provenance • Compliance with any other hESCreg criteria
Final evaluation	Project Management	<ul style="list-style-type: none"> • All minimum eligibility criteria complete and correct • Evidence provided of traceable fully informed consent • SAB recommendation for inclusion

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

It is possible that following evaluation and acceptance of a cell line entry for the registry that it may be discovered that data provided was erroneous or even falsified. If such information is brought to light it will be the duty 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 and this would normally be through an emergency communication with the SAB.

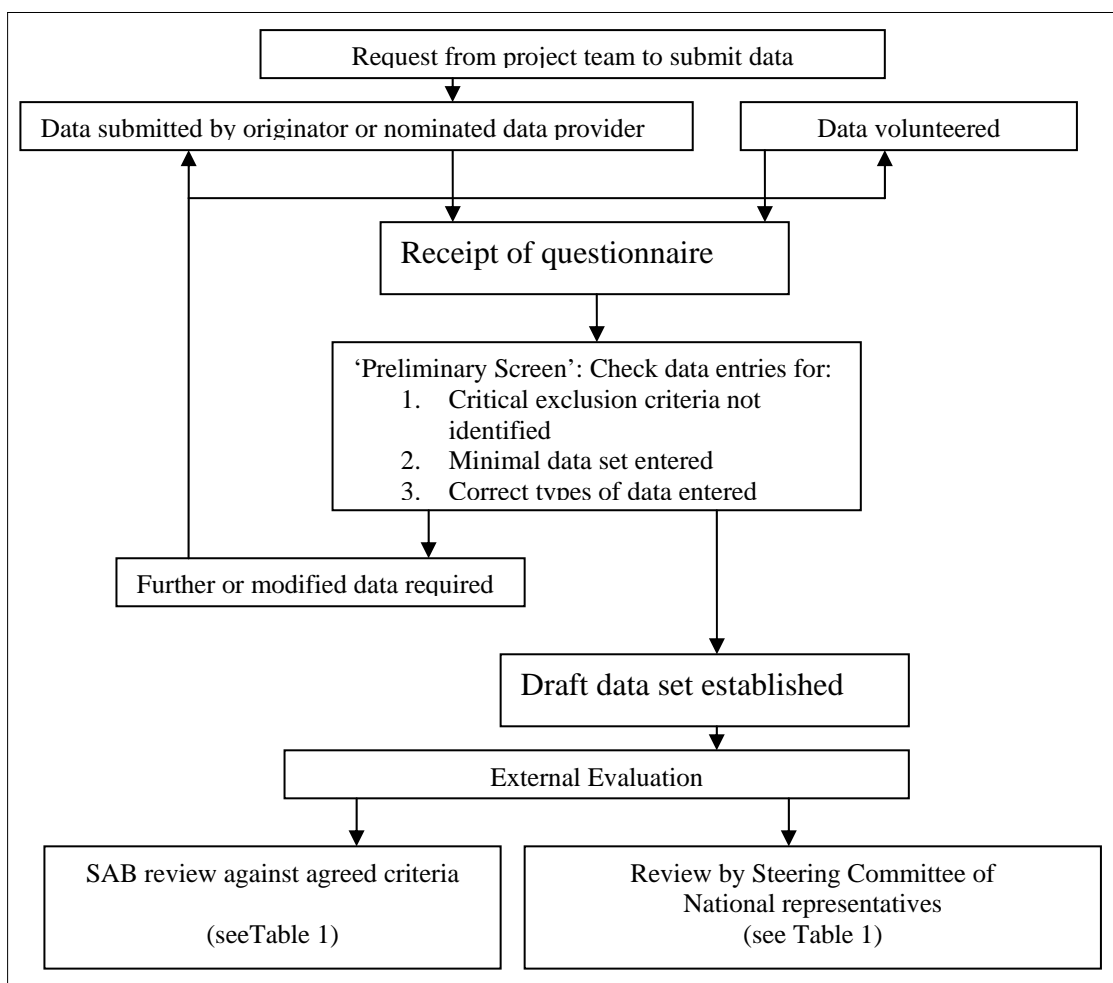


Figure 1: Evaluation process of for the data provided to the registry

3.2 Traceability

The project management can ensure that all data entered on the registry is traceable to the providing agent through a logging system with replacement information allocated a new document version number on a real-time basis.

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

4. Provisions for Data Security

The Charité's IT department, which also handles the patient's data for Europe's largest university hospital, adheres to the strictest EU guidelines, German law and 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's IT department. They are currently hosted on a virtual server system within the DMZ of the Charité. Consequently the platform benefits from the rigorous safety precautions in place to avoid interference from outside (hackers) and internal accidental and even internal deliberate corruption. As the project evolves, and with increasing complexity of the database, it is envisaged to move the platform onto a dedicated server within the Charité domain.

5. Stakeholder Engagement

The registry is committed in the project programme to a series of public symposia and workshops that will seek to engage stakeholders from the scientific, regulatory and other communities. Areas of the registry website will be developed to provide information of interest to the general public who wish to obtain information on stem cells. This will be in the shape of the non-database content of the website itself, a simple online-contact form or a regular newsletter that is open to the interested general public at large. 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 dealing with an area which is controversial for some members of European society and which has established high standards for its aims and operation. Management of risks that could damage the project is therefore vital to enable the project to move forward smoothly and to enhance the project achievements. A risk management system will therefore be established and maintained which identifies and evaluates risks in the form of a risk register, and also delivers action plans to reduce significant risks to an acceptable level. The risk register will be reviewed annually by the management group and the SAB to identify new risks and those which may have changed.

7. Sustainability

Key measures of the success of the project will be its sustainability and its longer term value to 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. Cell Line Data Evaluation

Evaluation of registry data must be an open, fair and scientifically rigorous process and remain neutral on the science and ethics. Good governance of this process, including the

involvement of a scientific advisory board (SAB) will be vital to ensure that the natural debates on science and ethics are enabled that record different scientific views and acknowledge national differences. There will also be strong focus on standardisation to enable comparison of data on lines from different sources. Through these activities it is intended that the registry will command the highest level of respect as an international model for resolution of international data on stem cells in a way that is scientifically robust and accommodates cultural diversity.

Appendix: Terms of Reference for the Scientific Advisory Board and Steering Committee.

Steering Committee Terms of Reference

- Meet formally on a regular basis (for details see hESCreg protocols)
- Provide input on national stem cell lines
- Receive commentary from SAB
- Authorise overall data entries subject to formal reports from SAB chair on scientific stem cell content
- Advise on national and international regulation
- Support and advise on development of hESCreg policies and strategy
- Advise hESCreg management team on remedial actions and resolution of issues

Scientific Advisory Board Terms of Reference

- To review cell line entries submitted for the database
- Provide a commentary on the quality of scientific data sets and make recommendations on their inclusion in the database
- Provide qualifying statements where differences of opinion arise in the SAB or where data submitted does not match the view of the SAB
- **Provide a formal report through the chair for each SAB meeting to the hESCreg Steering Committee**
- To raise with hESCreg project management, 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 hESCreg management to assist development of the registry and provide *ad hoc* advice on specific scientific issues.

This Code of Practice has been approved by the hESCreg Steering Committee and the hESCreg Scientific Advisory Board



Joeri Borstlap
Technical Coordinator



Anna Veiga
Scientific Coordinator



Chairman elect
hESCreg Scientific Advisory Board