

D3.2: Report of database for inclusion into European human Pluripotent Stem Cell Registry (hPSCreg).

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1. Executive Summary

The Report outlines the procedures and content needed to register induced pluripotent stem cell (iPSC) – Lines Intended For Clinical Use (LIFCU) into the centralized registry hPSCreg. The inclusion of iPSC lines derived from homologous haplotyped source cells from cord blood banks and bone marrow donors is a key requirement for the data scheme and Registry integration. The integration must implement FAIR principles – the cells and associated metadata must be Findable, Accessible, Interoperable and Reusable. The report was drafted using input from WG3 and other interested WGs in the Haplo-iPS action.

2. Introduction

Although clinical grade (LIFCU) iPSC – lines have been established in multiple centers and companies, information of the lines is scattered, not easily findable and associated data often hidden behind paywalls or not available. Although the Registry hPSCreg allows in principle to register such lines, these are not specifically filtered and characterization information is minimal. This lack of information triggers the use of only very few commercially available allogenic cell lines. Furthermore, associated costs and intellectual property restrictions trigger many companies to establish their own cell lines, which are often not made public.

Haplotyped HLA homozygous iPSC - lines are a suitable source material to develop cell therapies of organ replacement products as they allow transplantation into suitable hosts avoiding immune reaction. It has been calculated that a small number of such lines is sufficient to immunologically cover most of the European population.

This report outlines pathways and data schemes to make the potential source material findable and accessible through a registry. Ideally, such a Registry not only identifies the haplotyped iPSC – lines, but also primary cell resources suitable for reprogramming. These are cells in cord blood banks and cells from registered bone marrow donors.

A few lines HLA homozygous iPSC – lines already exist, for example in Japan, South Korea and Spain. The characterization features of these lines served as basis to develop a scientific data scheme. Furthermore, ethical provenance features are based on the model developed in WG of Haplo-iPS. A model to link the Registry of iPSC – LIFCU with resources of HLA – typed primary cells is also provided.

3. Database Content

3.1 Database content for ethical provenance

Ethical provenance must transparently and traceably allow to determine donor consent for scope of use, means of data protection, preserving autonomy and participation, and ethics committee approval for the donation of cells and their reprogramming, as applicable. The hPSCreg already evaluates donor consent

information and ethics approval (**Annex 1**). It does not, however, register information on reconsenting, disposal of banked cells, recontacting and other ethical issues relevant for cell banks storing cells for other purposes than the establishment of iPSC. WG5 of the Haplo-iPS project established relevant ethical principles to be used in such a context. This needs to be implemented into a registry format to be transparently accessible for each cell line.

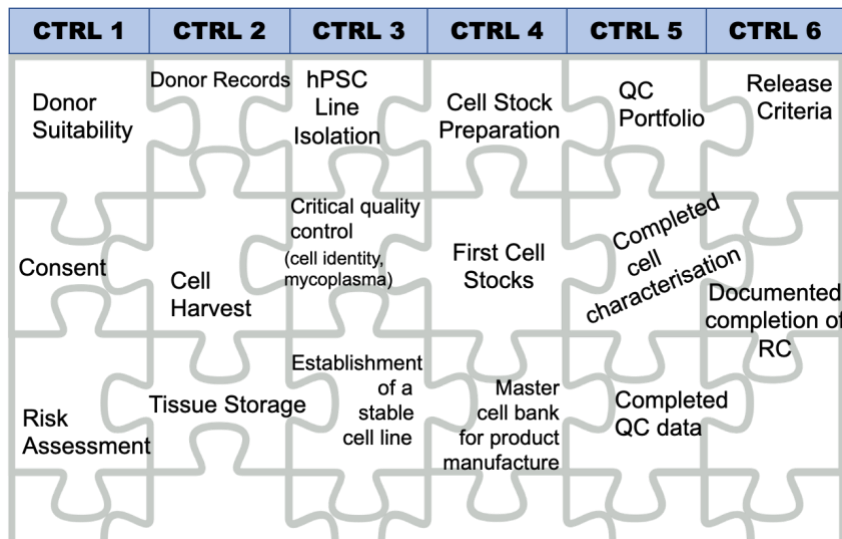
The main points to be added to hPSCreg for this end are:

- That the material stored in pseudonymized to allow for re-contacting of donors to explicitly allow for iPSC generation and scope of application in clinical contexts on a global scale.
- The results obtained using the cells can be published
- That genetic information can be obtained from the donated material and processed for research, quality assessment and clinical use
- That health issues and incidental findings can be communicated to the donor, including the parents/guardians of children
- That the material can be used commercially and financial interests are waived
- Whether the donors wish to be informed about the use of the cells and results obtained.

3.2 Database content for scientific characterization

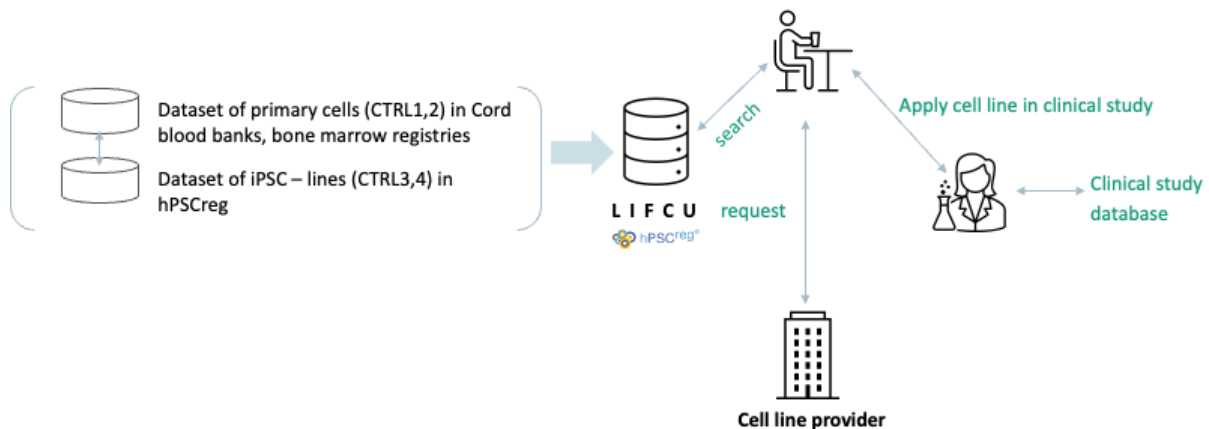
The existing database content and data scheme of the established Registry hPSCreg was used and adapted to accommodate information relevant for lines intended for clinical use (LIFCU, Figure 1). The data scheme is shown in **Annex 2**. Requirements for source material as stipulated in the new EU regulation 2024/1938 (SoHO) was not yet considered for drafting the data scheme. It is relevant mainly for collection of primary material from which iPSC. Will be derived.

Figure 1. Clinical translation readiness level (CTRL) along the development chain. The Data scheme covers CTRL1-4. CTRL1 and -2 are mostly performed in cord blood banks or other cell banks collecting primary material.



As the LIFCU process starts with donor derived data and collection, characterization and deposition of primary cells (CTRL1,2), these data must be accessible even after iPSC are derived and data deposited in a central registry. A unique identifier (established in hPSCreg) allows for the findability of data in the connected resources from donation to application.

Figure 2. Data flow starts with data from holders of primary cells intended for clinical use (e.g. cord blood banks). Once LIFCU iPSC were derived, these will be registered using the data scheme in Annex1. A link is maintained between the primary bank and the Registry to access and exchange data. Researchers search the Registry for suitable LIFCU lines through a central resource, which also allows access to primary sources.



3.3 Integration into hPSCreg

The Registry hPSCreg is an EU-funded project. The current funding period is ending in April 2027 and the next funding cycle will be an interim funding for 2027 pending European Commission budget finalization. The Registry is currently managed by the Fraunhofer Institute for Biomedical Engineering in Germany. Because of the current funding situation, and required updates for the hPSCreg backend and frontend software, an active integration of the data scheme developed in Haplo-iPS is not possible.

Based on this assessment, Haplo-iPS focused on coordinating with hPSCreg the development of the data scheme (Annex 2), which design for integration into hPSCreg at any time with sufficient funding. It can be separated into two main resources:

- A) iPSC data directly integrated into hPSCreg
- B) Primary cell and donor data accessible via hPSCreg in third parties

The data scheme for (A) has been discussed in 3.2 and is described in Annex 2.

The data access and data scheme for (B) requires the connection of data in hPSCreg with data in primary cell resources (e.g. cord blood banks, bone marrow registries) via a common identifier. The hPSCreg issues unique persistent identifiers, which can fulfil this findability function. It requires that type (B) resources must register their iPSC – lines in the central registry. This allows users to access relevant annotated data within type A and B resources.

The hPSCreg also implements interoperability features, which allow for the comparison of data for example by using semantically annotated ontologies and standard nomenclatures (e.g. HLA, STR). To make all data interoperable in the CTRL development pipeline, the use of searchable and interoperable data annotations/metadata is required. Harmonization of standards already used by multiple federated resources were not investigated and was not part of the Haplo-iPS project.

3.4 Outlook

A data scheme for integration of LIFCU lines and a model for data exchange between primary source material resources and a central registry was developed. The next step is the integration of the data scheme into hPSCreg, which is conditional of sufficient continuing funding for hPSCreg. Furthermore, to connect the central Registry (hPSCreg) with data from key primary resources such as cord blood banks and make these data fully FAIR, all resources must implement the use of a common identifier issued by the central Registry. In addition, the harmonization of data standards to make all data interoperable and clear information on accessibility of data must be developed and implemented. In addition, to add the application of SoHO regulation and relevant approvals and authorizations in the central registry will help to assess suitability of LIFCU cells for use.

ANNEX 1. Ethical provenance data in hPSCreg

Donor Consent Form & Donor Information Sheet		
Item	Statement	Response
3	Has informed consent been obtained from the donor of the tissue from which the pluripotent stem cells have been derived?	yes/no
4	Was the consent voluntarily given?	yes/no
5	Has the donor been informed that participation will not directly influence their personal treatment?	yes/no
6	Can you provide us with a copy of the Donor Information Sheet provided to the donor?	yes/no
	If “yes”	upload blank/redacted file
	If “no”, * Please provide contact information of the holder of the original Donor Information Sheet.	freetext
7	Please upload the blank/redacted donor consent form: Please only upload the blank form, without any identifying donor information or signature. If you don't have the form, see below for information who does or alternative consent.	file should be uploaded
10	Is there other documentation provided to the donor for consenting purposes?	yes/no
	If “yes”	upload file
11	Confirm that consent was obtained by a qualified professional	yes/no
12	Has the donor agreed to be re-contacted?	yes/no/unknown
13	Has the donor been informed about how her/his data will be protected?	yes/no
Permitted Uses: Research		
14	Does consent explicitly allow the derivation of pluripotent stem cells?	yes/no
15	Does consent expressly prevent the derivation of pluripotent stem cells?	yes/no
16	Does consent pertain to a specific research project?	yes/no
	If “yes”, Please provide details	freetext
17	Does consent permit unforeseen future research, without further consent?	yes/no
18	Does the consent permit uses of donated embryo/tissue or derived cell line intended for clinical treatment or human applications?	yes/no
Permitted Uses: Commercial Exploitation		
19	Does consent expressly prevent development of commercial products?	yes/no
20	Does consent expressly prevent financial gain from any use of the donated embryo/tissue, including any product made from it?	yes/no
Storage of and Access to Material		

21	Does consent expressly permit storage of donated tissue for an unlimited time?	yes/no
22	Does consent expressly permit storage of cells derived from the donated tissue for an unlimited time?	yes/no
23	Does consent prevent the DONATED BIOSAMPLE from being made available to researchers anywhere in the world?	yes/no
24	Does consent prevent CELLS DERIVED FROM THE DONATED BIOSAMPLE from being made available to researchers anywhere in the world?	yes/no
25	Does consent permit research by: an academic institution?	yes/no
26	Does consent permit research by: a public organisation?	yes/no
27	Does consent permit research by: a non-profit company?	yes/no
28	Does consent permit research by: a for-profit corporation?	yes/no
Data and Information		
29	Does consent expressly permit collection of genetic information?	yes/no
30	Does consent expressly permit storage of genetic information?	yes/no
31	Does consent prevent dissemination of genetic information?	yes/no
32	Has the donor been informed that their donated biosample or derived cells may be tested for the presence of microbiological agents / pathogens?	yes/no
33	Has the donor consented to receive information discovered during use of donated embryo/tissue that has significant health implications for the donor?	yes/no
34	How may genetic information associated with the cell line be accessed?	Open Access / Controlled Access / No Information
Benefits		
35	Will the donor expect to receive financial benefit, beyond reasonable expenses, in return for donating the biosample?	yes/no
36	Does the consent anticipate that the donor will be notified of results or outcomes of any research involving the donated samples or derived cells?	yes/no
Withdrawal		
37	Does the consent permit the donor, upon withdrawal of consent, to stop the use of the derived cell line(s) that have already been created from donated samples?	yes/no
38	Does the consent permit the donor, upon withdrawal of consent, to stop delivery or use of information and data about the donor?	yes/no
Medical Records		
39	Does consent permit access to medical records of the donor?	yes/no
40	Does consent permit access to any other source of information about the clinical treatment or health of the donor?	yes/no
Ethics Committee / Institutional Review Board opinion		

41	Has a favourable opinion been obtained from a research ethics committee, or other ethics review panel, in relation to the Research Protocol including the consent provisions? (yes/no)	yes/no
	If “no”: clarification needed.	
	- If “yes”: a) Name of accrediting authority involved? (freetext) b) Approval number (freetext)	Freetext for both answers
42	Has a favourable opinion been obtained from a research ethics committee, or other ethics review panel, in relation to the PROPOSED PROJECT, involving use of donated embryo/tissue or derived cells?	yes/no
	- If “yes”: a) Name of accrediting authority involved? (freetext) b) Approval number (freetext)	Freetext for both answers

ANNEX 2. Data schema iPSC intended for clinical use (LIFCU)

The main focus of this data scheme should be the integration in the existing Registry hPSCreg. Instead of developing a new data scheme, lines registered in hPSCreg could also be an iPSC - based LIFCU - line, if the relevant information is given.

Registration of a LIFCU is selected upfront and the data scheme below will then be opened to registration using the hPSCreg backend.

In general, the data scheme is divided into 8 sections:

- General
- Donor
- Ethics
- Derivation
- Culture Conditions
- Characterisation
- Genotyping
- Genetic Modification

LIFCU registration in hPSCreg

General Information

- Generator institution
 - Name
 - Address
 - Contact details
- Owner
 - Name
 - Address
 - Contact details
- Distributor
 - Name
 - Address
 - Contact details
- Clinical Grade line?
 - yes/no
 - Mandatory for all cell lines
- If yes
 - Has the line been declared "safe" by registered/licensed retrieval establishment, according to local standards?

- yes/no
- Mandatory for clinical grade lines
- If yes:
 - Please provide detailsName of accrediting authority involved?
 - Freetext field
 - Mandatory for clinical grade lines
 - Approval number
 - Freetext field
 - Mandatory for clinical grade lines
- Derivation Country
 - mandatory for clinical grade lines

Donor Information

- Blood Type
 - A, B, AB, 0
 - Mandatory for clinical grade lines
- Rhesus factor
 - positive/negative
 - Mandatory for clinical grade lines
- Sex
 - mandatory for all cell lines
 - Female, Male, Unknown
- Disease Status
 - mandatory for all cell lines
 - yes/no
 - If yes
 - Has the disease been tested by lab/device meeting local standards?
 - yes/no
 - Mandatory for clinical grade lines
 - If yes:
 - Please provide details
 - Freetext field
 - Mandatory for clinical grade lines
- Travel history
 - List of countries and year?
- family history of prion disease
 - yes/no
 - Mandatory for clinical grade lines
 - If yes
 - Please provide details
 - Freetext
- High risk behaviour for HIV, HBV, HCV
 - yes/no
 - Mandatory for clinical grade lines
 - If yes
 - Please provide details

- Freetext
- unexplained lymphadenopathy mass or mucocutaneous lesions
 - yes/no
- needle tracks or other signs of injection drug abuse
 - yes/no
- active infections of clinical significance
 - yes/no

Derivation

- Source cell (line)
 - Select a source cell line previously used in hPSCreg (if existing)
 - Name of source cell line (if existing)
 - freetext field
 - Url for source cell line (if existing)
 - freetext field
 - Cell type of the source cell (fibroblast, erythroblast, ...)
 - ontology term
 - Origin of the source cell (arm, blood, bone marrow, ...)
 - ontology term
 - Derived under GMP?
 - yes/no
 - should be mandatory for clinical grade lines
 - Additional source cell type information (free text)
- Source cell lot
 - Select a lot previously used in hPSCreg (if existing)
 - source cell line lot number (if existing)
 - freetext
 - Year when the source cell was collected
 - year
 - would year be enough or do we need an exact date for clinical grade lines?
 - Should be mandatory for clinical grade lines
 - Age of donor at time of collection
 - age range
 - should be mandatory for clinical grade lines
- Source cell line vendor
 - Select already registered vendor OR
 - Vendor name and Vendor URL
 - freetext fields
 - GMP manufacturing license
 - yes/no
 - if yes:
 - licensing authority name
 - name
 - freetext
 - link
 - freetext
- Passage number reprogrammed

☐ freetext

Reprogramming

- Vector type for reprogramming
 - ☐ integrating, Non-integrating, None
 - if integrating:
 - Vector
 - ☐ Virus, Plasmid, Transposon, Other
 - If Virus:
 - Specify virus type
 - ☐ Adenovirus, Retrovirus, Lentivirus, Other
 - if Other: Specify 'other' (freetext)
 - If Transposon:
 - Specify transposon type
 - ☐ PiggyBack Transposon, Sleeping Beauty, Other
 - if Other: Specify 'other' (freetext)
 - If Other:
 - Specify 'other' (freetext)
 - Vector Vendor
 - ☐ freetext
 - Has the Vector been GMP-certified?
 - ☐ Yes/no
 - Gene List
 - ☐ POU5F1
 - ☐ SOX2
 - ☐ KLF4
 - ☐ MYC
 - Is the used vector excisable
 - ☐ yes/no
 - Absence of reprogramming vector(s)
 - ☐ yes/no
 - Have the reprogramming vectors been silenced?
 - ☐ Yes/no/unknown
 - Methods used?
 - ☐ Immune marker staining
 - ☐ PCR
 - ☐ rtPCR
 - ☐ Sequencing
 - Notes on reprogramming vector silencing
 - ☐ freetext
 - Files and images showing reprogramming vector expressed or silenced

- Upload
- if Non-Integrating
 - Vector
 - Episomal, Sendai virus, AAV, Other
 - Vector Vendor
 - freetext
 - Has the Vector been GMP-certified?
 - Yes/no
 - Gene List
 - POU5F1
 - SOX2
 - KLF4
 - MYC
 - Is the used vector excisable
 - yes/no
 - Absence of reprogramming vector(s)
 - yes/no
 - Have the reprogramming vectors been silenced?
 - Yes/no/unknown
 - Methods used?
 - Immune marker staining
 - PCR
 - rtPCR
 - Sequencing
 - Notes on reprogramming vector silencing
 - freetext
 - Files and images showing reprogramming vector expressed or silenced
 - Upload
- AS above should simply be asked to state
 - Type of used vector free reprogramming factor(s)
 - mRNA, Protein, Small molecules, miRNA, None
 - name + link
 - Selection criteria for clones
 - freetext
 - Derived under xeno-free conditions
 - yes/no
 - Derived under GMP?
 - Yes/no

Genotyping

- Are the HLA genes deleted?
 - Yes/no
 - if yes:
 - Which HLA genes are deleted?
- HLA typing
 - yes/no

- ☐ should be mandatory for clinical grade lines
- ☐ If yes:
 - Has the Immunotyping been done by a lab/device meeting local standards?
 - yes/no
 - mandatory for clinical grade lines
 - If yes:
 - ☐ Name of lab/device that did the Immunotyping
 - freetext field
 - ☐ lab license
 - yes/no
 - if yes:
 - license number
 - ☐ freetext
 - Type I
 - should be mandatory for clinical grade lines
 - Type II
 - should be mandatory for clinical grade lines
 - Non-HLA Genes
 - should be mandatory for clinical grade lines
- STR/Fingerprinting
 - ☐ yes/no
 - ☐ mandatory for all cell lines
- Has the cell line karyotype been analysed?
 - ☐ yes/no/unknown
 - ☐ mandatory for all cell lines
 - ☐ If yes:
 - Passage number
 - Number
 - Cell Line Karyotype
 - Freetext or upload

Characterisation

- Microbiology/Virology Screening?
 - ☐ should be mandatory for clinical grade lines
 - ☐ If yes
 - HIV 1
 - positive/negative/not done
 - should be mandatory for clinical grade lines
 - if positive or negative:
 - ☐ method
 - freetext
 - ☐ name of lab
 - freetext
 - ☐ lab license
 - yes/no
 - if yes:
 - license number

☐ freetext

■ HIV 2

- positive/negative/not done
- should be mandatory for clinical grade lines
- if positive or negative:
 - ☐ method
 - freetext
 - ☐ name of lab
 - freetext
 - ☐ lab license
 - yes/no
 - if yes:
 - license number
 - ☐ freetext

■ Hepatitis B

- positive/negative/not done
- should be mandatory for clinical grade lines
- if positive or negative:
 - ☐ method
 - freetext
 - ☐ name of lab
 - freetext
 - ☐ lab license
 - yes/no
 - if yes:
 - license number
 - ☐ freetext

■ Hepatitis C

- positive/negative/not done
- should be mandatory for clinical grade lines
- if positive or negative:
 - ☐ method
 - freetext
 - ☐ name of lab
 - freetext
 - ☐ lab license
 - yes/no
 - if yes:
 - license number
 - ☐ freetext

■ Mycoplasma

- positive/negative/not done
- should be mandatory for clinical grade lines
- if positive or negative:
 - ☐ method
 - freetext
 - ☐ name of lab
 - freetext
 - ☐ lab license

- yes/no
 - if yes:
 - license number
 - freetext
- TSE infectivity
 - positive/negative/not done
 - should be mandatory for clinical grade lines
 - if positive or negative:
 - method
 - freetext
 - name of lab
 - freetext
 - lab license
 - yes/no
 - if yes:
 - license number
 - freetext
- HTLV I
 - positive/negative/not done
 - should be mandatory for clinical grade lines
 - if positive or negative:
 - method
 - freetext
 - name of lab
 - freetext
 - lab license
 - yes/no
 - if yes:
 - license number
 - freetext
- HTLV II
 - positive/negative/not done
 - should be mandatory for clinical grade lines
 - if positive or negative:
 - method
 - freetext
 - name of lab
 - freetext
 - lab license
 - yes/no
 - if yes:
 - license number
 - freetext
- WNV
 - positive/negative/not done
 - should be mandatory for clinical grade lines
 - if positive or negative:
 - method
 - freetext

- name of lab
 - freetext
- lab license
 - yes/no
 - if yes:
 - license number
 - freetext
- Tuberculosis
 - positive/negative/not done
 - should be mandatory for clinical grade lines
 - if positive or negative:
 - method
 - freetext
 - name of lab
 - freetext
 - lab license
 - yes/no
 - if yes:
 - license number
 - freetext
- CJD
 - positive/negative/not done
 - should be mandatory for clinical grade lines
 - if positive or negative:
 - method
 - freetext
 - name of lab
 - freetext
 - lab license
 - yes/no
 - if yes:
 - license number
 - freetext
- EBV
 - positive/negative/not done
 - should be mandatory for clinical grade lines
 - if positive or negative:
 - method
 - freetext
 - name of lab
 - freetext
 - lab license
 - yes/no
 - if yes:
 - license number
 - freetext
- CMV
 - positive/negative/not done
 - should be mandatory for clinical grade lines

- if positive or negative:
 - method
 - freetext
 - name of lab
 - freetext
 - lab license
 - yes/no
 - if yes:
 - license number
 - freetext
- Syphilis
 - positive/negative/not done
 - should be mandatory for clinical grade lines
 - if positive or negative:
 - method
 - freetext
 - name of lab
 - freetext
 - lab license
 - yes/no
 - if yes:
 - license number
 - freetext
- Herpes
 - positive/negative/not done
 - should be mandatory for clinical grade lines
 - if positive or negative:
 - method
 - freetext
 - name of lab
 - freetext
 - lab license
 - yes/no
 - if yes:
 - license number
 - freetext
- Toxoplasmosis
 - positive/negative/not done
 - should be mandatory for clinical grade lines
 - if positive or negative:
 - method
 - freetext
 - name of lab
 - freetext
 - lab license
 - yes/no
 - if yes:
 - license number
 - freetext

- Malignancy
 - positive/negative/not done
 - should be mandatory for clinical grade lines
 - if positive or negative:
 - method
 - freetext
 - name of lab
 - freetext
 - lab license
 - yes/no
 - if yes:
 - license number
 - freetext
- Other
 - Freetext field
 - positive/negative/not done
 - if positive or negative:
 - method
 - freetext
 - name of lab
 - freetext
 - lab license
 - yes/no
 - if yes:
 - license number
 - freetext
- Analysis of Undifferentiated Cells
 - Marker Expression
 - EpiPluriScore
 - PluriTest
 - Morphology
 - hPSC Scorecard
 - Other pluripotency tests
- Transcriptome Characterisation
 - RNA Sequencing
 - Gene Expression Array
- Differentiation Potency
 - Endoderm
 - Mesoderm
 - Ectoderm

Ethics

- Does consent permit research by:
 - an academic institution?
 - yes/no
 - A public institution?
 - yes/no
 - A non-profit company?

- yes/no
 - ☐ A for-profit corporation?
 - yes/no
- Does consent expressly permit collection of genetic information?
 - ☐ yes/no
- Does consent expressly permit storage of genetic information?
 - ☐ yes/no
- Does consent prevent dissemination of genetic information?
 - ☐ yes/no
- Does consent expressly prevent development of commercial products?
 - ☐ yes/no
- Licence/Registration status
 - ☐ 2004/23/EC compliant? (EU)
 - yes/no
 - ☐ 2002/98/EC compliant? (EU)
 - yes/no
 - ☐ Part 1271 compliant? (US)
 - yes/no
 - ☐ CTO Regulation? (Canada)
 - yes/no
 - ☐ CSA compliant? (Canada)
 - yes/no
 - ☐ Category 1 Outsourcing Inst? (Japan)
 - yes/no
 - ☐ Category 2 Outsourcing Inst? (Japan)
 - yes/no
 - ☐ Category 3 Outsourcing Inst? (Japan)
 - yes/no
- Accreditation
 - ☐ AABB
 - yes/no
 - ☐ AATB
 - yes/no
 - ☐ FACT
 - yes/no
 - ☐ Other
 - freetext field

Culture Conditions

- Culture conditions: Medium
 - ☐ GMP status?
 - Freetext?
- Passage method
 - ☐ Checkbox Enzymatically, Enzyme-free cell dissociation, mechanically, Other
 - Already in hPSCreg, should be mandatory for clinical grade lines