Site visit inspection report on compliance with HTA licensing standards
Inspection date: 15 January 2020

North West Embryonic Stem Cell Centre (NWESCC)

HTA licensing number 22627

Licensed under the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended)

and

Licensed under the Human Tissue Act 2004

Licensable activities carried out by the establishment

Licensed activities – Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended)

'E' = Establishment is licensed to carry out this activity and is currently carrying it out.

'E*' = Establishment is licensed to carry out this activity but is not currently carrying it out.

Site	Procurement	Processing	Testing	Storage	Distribution	Import	Export
NWESCC		E*		E	E*		

Tissue types authorised for licensed activities – Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended)

'Authorised' = Establishment is authorised to carry out this activity and is currently carrying it out.

'Authorised*' = Establishment is authorised to carry out this activity but is not currently carrying it out.

Tissue Category; Tissue Type	Procurement	Processing	Testing	Storage	Distribution	Import	Export
Other; human Embryonic Stem Cells (hESCs)		Authorised*		Authorised	Authorised*		

Licensed activities – Human Tissue Act 2004

'Licensed' = Establishment is licensed to carry out this activity and is currently carrying it out.

'Licensed*' = Establishment is licensed to carry out this activity but is not currently carrying it out.

Area	Storage of relevant material which has come from a human body for use for a scheduled purpose
NWESCC	Licensed*

Summary of inspection findings

The HTA found the Designated Individual (DI) and the Licence Holder (LH) to be suitable in accordance with the requirements of the legislation.

Although the HTA found that NWESCC (the establishment) had met the majority of the HTA's standards, five minor shortfalls were found against standards for Governance and Quality, and Premises, Facilities and Equipment. The shortfalls were related to the validation of the incubation times for the environmental monitoring plates, the procedures for retention of raw and traceability data, labelling with the Single European Code (SEC), the procedures for reporting serious adverse events to the HTA, and the procedures for temperature monitoring.

The HTA has assessed the establishment as suitable to be licensed for the activities specified, subject to corrective and preventative actions being implemented to meet the shortfalls identified during the inspection.

Compliance with HTA standards

Minor Shortfalls

Human Tissue (Quality and Safety for Human Application) Regulations 2007 Standards

Standard	Inspection findings	Level of shortfall
GQ2 There is a documented system of quality management and audit.		
d) Processes affecting the quality and safety of tissues and / or cells are validated and undergo regular evaluation to ensure they continue to achieve the intended results.	The establishment's procedures require environmental monitoring plates to be incubated at 30-35ºC for 3-5 days, and 20-25ºC for 5-7 days for Tryptone Soya Agar (TSA) and Sabouraud Dextrose Agar (SDA) plates, respectively. The procedures also allow these incubation periods to be extended by one day if required. The establishment was unable to provide validation data to support these practices. ***The establishment took action to address this shortfall before the issue of the final report. The HTA now assess this standard as fully met.***	**Minor**
GQ4 There is a systematic and planned approach to the management of records.		
h) Raw data which are critical to the safety and quality of tissues and cells are kept for 10 years after the use, expiry date or disposal of tissues and / or cells.	The establishment does not have procedures in place to ensure raw data and traceability records are kept for 10 and 30 years respectively after the use, expiry or disposal of tissues and/or cells.	**Minor**

i) The minimum data to ensure traceability from donor to recipient as required by Directions 002/2018 are kept for 30 years after the use, expiry or disposal of tissues and / or cells.	***The establishment took action to address this shortfall before the issue of the final report. The HTA now assess this standard as fully met.***	
GQ6 A coding and records system facilitates traceability of bodies, body parts, tissues and cells, ensuring a robust audit trail.		
d) The requirements of the Single European Code are adhered to as set out in Directions 002/2018.	The establishment's procedure for the implementation of the SEC does not meet the requirements as set out in paragraph 175b of the "Guide to Quality and Safety Assurance for Human Tissues and Cells for Patient Treatment", which stipulates that the code must be preceded by the letters "SEC". ***The establishment took action to address this shortfall before the issue of the final report. The HTA now assess this standard as fully met.***	**Minor**
GQ7 There are systems to ensure that all adverse events are investigated promptly.		
a) There are procedures for the identification, reporting, investigation and recording of adverse events and reactions, including documentation of any corrective or preventative actions.	The establishment's procedures do not specify the requirement for the DI to report adverse events to the HTA within 24 hours of discovery or determination. ***The establishment took action to address this shortfall before the issue of the final report. The HTA now assess this standard as fully met.***	**Minor**

PFE3 There are appropriate facilities for the storage of bodies, body parts, tissues, cells, consumables and records.		
a) Tissues, cells, consumables and records are stored in secure environments and precautions are taken to minimise risk of damage, theft or contamination.	The establishment uses manual temperature loggers to monitor storage areas and equipment that are not linked to their electronic monitoring system. The loggers' display shows the current temperature, and a visual indicator which is used to inform the operator of whether an excursion from the required temperature range has occurred since the last visual check. The establishment's procedures do not set out the requirement to manually reset the visual indicator following a temperature excursion. Therefore, any subsequent temperature excursions would not be detected and assessed until the next monthly download of logged temperature data. ***The establishment took action to address this shortfall before the issue of the final report. The HTA now assess this standard as fully met.***	**Minor**

The HTA requires the DI to submit a completed corrective and preventative action (CAPA) plan setting out how the shortfalls will be addressed, within 14 days of receipt of the final report (refer to Appendix 2 for recommended timeframes within which to complete actions). The HTA will then inform the establishment of the evidence required to demonstrate that the actions agreed in the plan have been completed.

Advice

The HTA advises the DI to consider the following to further improve practice:

Number	Standard	Advice
1.	GQ2b, GQ7a	The DI is advised to update procedures relating to the documentation of incidents and audits. The procedures should ensure that initial events, and the evidence demonstrating that CAPAs were completed within the required timeframe, are clearly recorded. The DI is also advised to regularly review if CAPAs are sufficiently robust to mitigate the risk of reoccurrence.
2.	GQ7a PFE2b	Standard operating procedure (SOP) QC-UOM-006 V08 for 'The Handling, Recording and Testing of Environmental Monitoring Samples and Data' includes a section to follow when environmental monitoring results have exceeded the establishment's predefined action or alert levels. The DI is advised to update this section to provide additional guidance to staff. For example, the procedure should clearly direct staff to instructions set out in other SOPs regarding the cleaning to be undertaken following such an excursion. This will help to ensure that the required corrective action is promptly undertaken.
3.	GQ8a	The DI is advised to expand on the establishment's current risk assessments to include the risks associated with the receipt and storage of consumables and/or reagents.
4.	GQ8d	The establishment is planning to test new methods of cell culturing and freezing to see if these improve the quality of stored cells. The DI is reminded of the requirement to inform the HTA prior to implementing any significant changes to the processing procedures for tissues and/or cells that could subsequently be used for human application.
5.	PFE2b	The DI is advised to consider updating the establishment's environmental monitoring procedures to include the monitoring of:

		• hard to reach areas such as the edges and corners of the transfer hatches which cannot be sampled using contact plates; and • high-frequency contact areas used by multiple operators during processing, such as equipment buttons and transfer hatch latches.
6.	PFE2d	The DI is advised to install a mirror at the entrance of the newly repurposed unclassified primary change room, to allow operators to check that all hair is completely covered prior to entering the clean rooms.
7.	PFE5d	The DI is advised to implement a documented review and release process for equipment which has undergone maintenance, calibration or repair. This will help to ensure that the potential impact of any equipment found to be out of the specified range prior to calibration has been assessed, and that the establishment is assured that equipment is fit-for-purpose before it is returned to use.

Background

NWESCC has been licensed by the HTA since September 2011. This was the fifth site visit inspection of the establishment; the most recent previous inspection took place in December 2017. Since the previous inspection, there have been no significant changes to the licence arrangements or the activities carried out under the licence. The establishment continues to store hESCs for research and human application. Since the last inspection, the establishment has not carried out any licensable activities other than storage.

Description of inspection activities undertaken

The HTA's regulatory requirements are set out in Appendix 1. The inspection team covered the following areas during the inspection:

Standards assessed against during inspection

During the inspection, compliance with 72 of the 121 standards under the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended) was assessed. The following standards were not assessed: GQ1k, GQ1o, GQ3d, GQ7e, GQ7f, PFE5f and

D2b. The remaining 42 standards were not applicable. The establishment does not currently store relevant material for a scheduled purpose, therefore compliance with the standards under the Human Tissue Act 2004 (HT Act) was not assessed.

Review of governance documentation
The inspection included a review of documentation relevant to the establishment's licensable activities. This included policies and procedural documents, risk assessments, internal and independent audits, staff training records, equipment maintenance records, reported incidents and adverse events, governance meeting minutes and temperature monitoring records for storage areas.

Visual inspection
The visual inspection included the storage areas for the consumables, cells, and the room where the -80ºC freezer is located. The Quality Control (QC) laboratory was also inspected and this provided a view into the clean rooms used for processing. As processing is not currently taking place, the HTA did not enter the clean room suite.

Audit of records
An audit of traceability was performed for samples which were previously in storage. The associated records relating to three vials of cells that had been removed from the liquid nitrogen tanks for research were reviewed. In addition to this, the records for one vial which had been disposed of due to damage to the label, and one vial which had been sent for karyotype testing were also reviewed. No discrepancies were identified.

Meetings with establishment staff
Discussions were held with the DI, who is a Professor of Stem Cells and Development, the Production Manager, the Cleanroom Technicians, the Cleanroom Manufacturing and Validation Technician, the Quality Coordinator and the Research Governance, Ethics and Integrity Officer.

Report sent to DI for factual accuracy: 12 February 2020

Report returned from DI: No factual accuracy or request for redaction comments were made by the DI

Final report issued: 20 February 2020

Appendix 1: The HTA's regulatory requirements

The HTA must assure itself that the DI, Licence Holder, premises and practices are suitable.

The statutory duties of the DI are set down in Section 18 of the HT Act. They are to secure that:

- the other persons to whom the licence applies are suitable persons to participate in the carrying-on of the licensed activity;
- suitable practices are used in the course of carrying on that activity; and
- the conditions of the licence are complied with.

The HTA developed its licensing standards with input from its stakeholders. They are designed to ensure the safe and ethical use of human tissue and the dignified and respectful treatment of the deceased. The HTA inspects the establishments it licences against four groups of standards:

- consent
- governance and quality systems
- premises facilities and equipment
- disposal.

This is an exception-based report: only those standards that have been assessed as not met are included. Where the HTA determines that a standard is not met, the level of the shortfall is classified as 'Critical', 'Major' or 'Minor' (see Appendix 2: Classification of the level of shortfall). Where HTA standards are fully met, but the HTA has identified an area of practice that could be further improved, advice is given to the DI.
Reports of HTA inspections carried out from 1 November 2010 are published on the HTA's website.

Appendix 2: Classification of the level of shortfall (HA)

Where the HTA determines that a licensing standard is not met, the improvements required will be stated and the level of the shortfall will be classified as 'Critical', 'Major' or 'Minor'. Where the HTA is not presented with evidence that an establishment meets the requirements of an expected standard, it works on the premise that a lack of evidence indicates a shortfall.

The action an establishment will be required to make following the identification of a shortfall is based on the HTA's assessment of risk of harm and/or a breach of the HT Act, Human Tissue (Quality and Safety for Human Application) Regulations 2007, or associated Directions.

1. **Critical shortfall:**

   A shortfall which poses a significant direct risk of causing harm to a recipient patient or to a living donor,

   Or

   A shortfall which poses a significant risk to human safety and/or dignity or is a breach of the HT Act or associated Directions,

   Or

   A number of 'major' shortfalls, none of which are critical on its own, but viewed cumulatively represent a systemic failure and therefore are considered 'critical'.

   A critical shortfall may result in one or more of the following:

   - A notice of proposal being issued to revoke the licence
   - Some or all of the licensable activity at the establishment ceasing with immediate effect until a corrective action plan is developed, agreed by the HTA and implemented.
   - A notice of suspension of licensable activities
   - Additional conditions being proposed
   - Directions being issued requiring specific action to be taken straightaway

2. **Major shortfall:**

A non-critical shortfall.

A shortfall in the carrying out of licensable activities which poses an indirect risk to the safety of a donor or a recipient

or

A shortfall in the establishment's quality and safety procedures which poses an indirect risk to the safety of a donor or a recipient;

or

A shortfall which indicates a major deviation from the Human Tissue (Quality and Safety for Human Application) Regulations 2007 or the HTA Directions;

or

A shortfall which indicates a breach in the relevant Codes of Practice, the HT Act and other relevant professional and statutory guidelines;

or

A shortfall which indicates a failure to carry out satisfactory procedures or a failure on the part of the designated individual to fulfil his or her legal duties;

or

A combination of several 'minor' shortfalls, none of which is major on its own, but which, viewed cumulatively, could constitute a major shortfall.

In response to a major shortfall, an establishment is expected to implement corrective and preventative actions within 1-2 months of the issue of the final inspection report. Major shortfalls pose a higher level of risk and therefore a shorter deadline is given, compared to minor shortfalls, to ensure the level of risk is reduced in an appropriate timeframe.

3. Minor shortfall:

A shortfall which cannot be classified as either critical or major and, which can be addressed by further development by the establishment.

This category of shortfall requires the development of a corrective action plan, the results of which will usually be assessed by the HTA either by desk based review or at the time of the next inspection.

In response to a minor shortfall, an establishment is expected to implement corrective and preventative actions within 3-4 months of the issue of the final inspection report.

Follow up actions

A template corrective and preventative action plan will be sent as a separate Word document with the final inspection report. Establishments must complete this template and return it to the HTA within 14 days of the issue of the final report.

Based on the level of the shortfall, the HTA will consider the most suitable type of follow-up of the completion of the corrective and preventative action plan. This may include a combination of

- a follow-up site-visit inspection
- a request for information that shows completion of actions
- monitoring of the action plan completion
- follow up at next routine site-visit inspection.

After an assessment of the proposed action plan establishments will be notified of the follow-up approach the HTA will take.

Appendix 3: HTA standards
The HTA standards applicable to this establishment are shown below; those not assessed during the inspection are shown in grey text. Individual standards which are not applicable to this establishment have been excluded. The establishment does not store relevant material for a scheduled purpose therefore compliance with the standards under the HT Act was not assessed.

Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended)

Governance and Quality
GQ1 All aspects of the establishment's work are supported by ratified documented policies and procedures as part of the overall governance process.
a) There is an organisational chart clearly defining the lines of accountability and reporting relationships.
b) There are procedures for all licensable activities that ensure integrity of tissue and / or cells and minimise the risk of contamination.
c) There are regular governance meetings, for example health and safety, risk management and clinical governance committees, which are recorded by agendas and minutes.
d) There is a document control system to ensure that changes to documents are reviewed, approved, dated and documented by an authorised person and only current documents are in use.
g) There are procedures to ensure that an authorised person verifies that tissues and / or cells received by the establishment meet required specifications.
h) There are procedures for the management and quarantine of non-conforming consignments or those with incomplete test results, to ensure no risk of cross contamination.
i) There are procedures to ensure tissues and / or cells are not released from quarantine until verification has been completed and recorded.
j) There are procedures detailing the critical materials and reagents used and where applicable, materials and reagents meet the

standards laid down by the European directives on medical devices and in vitro diagnostic medical devices.
k) There is a procedure for handling returned products.
l) There are procedures to ensure that in the event of termination of activities for whatever reason, stored tissues and / or cells are transferred to another licensed establishment or establishments.
o) There is a complaints system in place.
t) There are procedures for the re-provision of service in an emergency.
GQ2 There is a documented system of quality management and audit.
a) There is a quality management system which ensures continuous and systematic improvement.
b) There is an internal audit system for all licensable activities.
c) An audit is conducted in an independent manner at least every two years to verify compliance with protocols and HTA standards, and any findings and corrective actions are documented.
d) Processes affecting the quality and safety of tissues and / or cells are validated and undergo regular evaluation to ensure they continue to achieve the intended results.
GQ3 Staff are appropriately qualified and trained in techniques relevant to their work and are continuously updating their skills.
a) There are clearly documented job descriptions for all staff.
b) There are orientation and induction programmes for new staff.
c) There are continuous professional development (CPD) plans for staff and attendance at training is recorded.
d) There is annual documented mandatory training (e.g. health and safety and fire).

e) Personnel are trained in all tasks relevant to their work and their competence is recorded.
f) There is a documented training programme that ensures that staff have adequate knowledge of the scientific and ethical principles relevant to their work, and the regulatory context.
g) There is a documented training programme that ensures that staff understand the organisational structure and the quality systems used within the establishment.
h) There is a system of staff appraisal.
i) Where appropriate, staff are registered with a professional or statutory body.
j) There are training and reference manuals available.
k) The establishment is sufficiently staffed to carry out its activities.
GQ4 There is a systematic and planned approach to the management of records.
a) There are procedures for the creation, identification, maintenance, access, amendment, retention and destruction of records.
b) There is a system for the regular audit of records and their content to check for completeness, legibility and accuracy and to resolve any discrepancies found.
c) Written records are legible and indelible. Records kept in other formats such as computerised records are stored on a validated system.
d) There is a system for back-up / recovery in the event of loss of computerised records.
e) The establishment keeps a register of the types and quantities of tissues and / or cells that are procured, tested, preserved, processed, stored and distributed or otherwise disposed of, and on the origin and destination of tissues and cells intended for human application.
g) There is a system to ensure records are secure and that donor confidentiality is maintained in accordance with Directions 002/2018.

h) Raw data which are critical to the safety and quality of tissues and cells are kept for 10 years after the use, expiry date or disposal of tissues and / or cells.
i) The minimum data to ensure traceability from donor to recipient as required by Directions 002/2018 are kept for 30 years after the use, expiry or disposal of tissues and / or cells.
j) Records are kept of products and material coming into contact with the tissues and / or cells.
l) The establishment records the acceptance or rejection of tissue and / or cells that it receives and in the case of rejection why this rejection occurred.
m) In the event of termination of activities of the establishment a contingency plan to ensure records of traceability are maintained for 10 or 30 years as required.
GQ6 A coding and records system facilitates traceability of tissues and / or cells, ensuring a robust audit trail.
a) There is a donor identification system which assigns a unique code to each donation and to each of the products associated with it.
b) An audit trail is maintained, which includes details of when the tissues and / or cells were acquired and from where, the uses to which the tissues and / or cells were put, when the tissues and / or cells were transferred elsewhere and to whom.
c) The establishment has procedures to ensure that tissues and / or cells imported, procured, processed, stored, distributed and exported are traceable from donor to recipient and vice versa.
d) The requirements of the Single European Code are adhered to as set out in Directions 002/2018.
GQ7 There are systems to ensure that all adverse events, reactions and/or incidents are investigated promptly.
a) There are procedures for the identification, reporting, investigation and recording of adverse events and reactions, including documentation of any corrective or preventative actions.
b) There is a system to receive and distribute national and local information (e.g. HTA regulatory alerts) and notify the HTA and

other establishments as necessary of serious adverse events or reactions.
c) The responsibilities of personnel investigating adverse events and reactions are clearly defined.
d) There are procedures to identify and decide the fate of tissues and / or cells affected by an adverse event, reaction or deviation from the required quality and safety standards.
e) In the event of a recall, there are personnel authorised within the establishment to assess the need for a recall and if appropriate initiate and coordinate a recall.
f) There is an effective, documented recall procedure which includes a description of responsibilities and actions to be taken in the event of a recall including notification of the HTA and pre-defined times in which actions must be taken.
GQ8 Risk assessments of the establishment's practices and processes are completed regularly and are recorded and monitored appropriately.
a) There are documented risk assessments for all practices and processes.
b) Risk assessments are reviewed regularly, as a minimum annually or when any changes are made that may affect the quality and safety of tissues and cells.
c) Staff can access risk assessments and are made aware of local hazards at training.

Premises, Facilities and Equipment
PFE1 The premises are fit for purpose.
a) A risk assessment has been carried out of the premises to ensure that they are fit for purpose.
b) There are procedures to review and maintain the safety of staff, visitors and patients.
c) The premises have sufficient space for procedures to be carried out safely and efficiently.

e) There are procedures to ensure that the premises are secure and confidentiality is maintained.
f) There is access to a nominated, registered medical practitioner and / or a scientific advisor to provide advice and oversee the establishment's medical and scientific activities.
PFE2 Environmental controls are in place to avoid potential contamination.
a) Tissues and / or cells stored in quarantine are stored separately from tissue and / or cells that have been released from quarantine.
b) Where processing of tissues and / or cells involves exposure to the environment, it occurs in an appropriate, monitored environment as required by Directions 002/2018.
c) There are procedures for cleaning and decontamination.
d) Staff are provided with appropriate protective clothing and equipment that minimise the risk of contamination of tissue and / or cells and the risk of infection to themselves.
PFE3 There are appropriate facilities for the storage of tissues and / or cells, consumables and records.
a) Tissues, cells, consumables and records are stored in secure environments and precautions are taken to minimise risk of damage, theft or contamination.
b) There are systems to deal with emergencies on a 24 hour basis.
c) Tissues and / or cells are stored in controlled, monitored and recorded conditions that maintain tissue and / or cell integrity.
d) There is a documented, specified maximum storage period for tissues and / or cells.
PFE5 Equipment is appropriate for use, maintained, quality assured, validated and where appropriate monitored.
a) Critical equipment and technical devices are identified, validated, regularly inspected and records are maintained.
b) Critical equipment is maintained and serviced in accordance with the manufacturer's instructions.

c) Equipment affecting critical processes and storage parameters is identified and monitored to detect malfunctions and defects and procedures are in place to take any corrective actions.
d) New and repaired equipment is validated before use and this is documented.
e) There are documented agreements with maintenance companies.
f) Cleaning, disinfection and sanitation of critical equipment is performed regularly and this is recorded.
h) Users have access to instructions for equipment and receive training in the use of equipment and maintenance where appropriate.
i) Staff are aware of how to report an equipment problem.
j) For each critical process, the materials, equipment and personnel are identified and documented.
k) There are contingency plans for equipment failure.

Disposal
D1 There is a clear and sensitive policy for disposing of tissues and / or cells.
a) The disposal policy complies with HTA's Codes of Practice.
b) The disposal procedure complies with Health and Safety recommendations.
c) There is a documented procedure on disposal which ensures that there is no cross contamination.
D2 The reasons for disposal and the methods used are carefully documented.
a) There is a procedure for tracking the disposal of tissue and / or cells that details the method and reason for disposal.
b) Disposal arrangements reflect (where applicable) the consent given for disposal.