Master Thesis

A REVIEW OF ESTABLISHMENTS WORKING WITH HUMAN TISSUE OF THE RESEARCH SECTOR IN THE UNITED KINGDOM

An analysis of Human Tissue Authority published compliance reports

Submitted by

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Statutory Declaration

I declare on my honour that I have written this dissertation independently and without assistance, that no sources other than those cited were used and that the sources used verbatim or in substance have been marked as such.

Cambridge, 28th of June 2020

Foreword

This thesis reviews the work of the Human Tissue Authority in the United Kingdom after almost ten years of publicly available inspection reports.

It is intended to further the understanding of the regulatory requirements of the Authority in those establishments that use and store human tissue for research purposes.

I have taken pleasure in finding out more about the Authority's expectations and portraying this information in this piece of work.

If readers extract from this work information that helps to improve practice at their places of work or study, I will feel an enormous sense of achievement and satisfaction.

Acknowledgement

I would like to thank my thesis supervisor Prof. Berthold Huppertz for his support and guidance and the whole team in Graz. Also, thank you to my class fellows for all the thought provoking conversations, friendliness, good humour and sense of comradery. I have truly enjoyed this course.

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Abstract in German

EINE ÜBERPRÜFUNG VON FORSCHUNGSEINRICHTUNGEN, DIE MIT MENSCHLICHEM GEWEBE IM VEREINIGTEN KÖNIGREICH ARBEITEN

Eine Analyse der von der "Human Tissue Authority" publizierten Compliance-Berichte

Mit dem "Human Tissue Act" des Vereinigten Königreichs von 2004 wurde die „Human Tissue Authority" als Aufsichtsbehörde für Einrichtungen etabliert, die menschliches Gewebe entnehmen, lagern, verwenden und entsorgen. Die Behörde regelt durch Lizenzierung und Überprüfung diejenigen Organisationen, die mit menschlichem Gewebe arbeiten. Diese Arbeit hat 158 veröffentlichte Überprüfungsberichte der „Human Tissue Authority" analysiert und hat die gemeinsamen Non-Compliance-Trends im gesamten Forschungssektor zwischen 2010 und 2020 erfasst. Die meisten Mängel und Empfehlungen wurden in den Governance – und Qualitätssicherungssystem-Standards verzeichnet, gefolgt von Rückverfolgbarkeitsnormen, den Räumlichkeiten, den Einrichtungs- und Ausrüstungsstandards und schließlich den Einwilligungsstandards. Diese Arbeit hat gezeigt, dass der Privatsektor mehr Konformität aufweist als der öffentliche Sektor, während kein Unterschied zwischen „Multisite" und „Singlesite" Lizenzen, unabhängig von deren Finanzierungsquellen, zu beobachten war. Abschließend wurde die internationale Regulierungslandschaft und die Rolle der „Human Tissue Authority" im Forschungsbereich diskutiert.

Abstract in English

A REVIEW OF ESTABLISHMENTS WORKING WITH HUMAN TISSUE OF THE RESEARCH SECTOR IN THE UNITED KINGDOM

An analysis of Human Tissue Authority published compliance reports

The United Kingdom's Human Tissue Act of 2004 established the Human Tissue Authority as the regulatory body of institutions removing, storing, using, and disposing human tissue. The Authority regulates by means of licensing and inspections those organisations working with human tissue. This work has analysed 158 Human Tissue Authority's published inspection reports and has captured common non-compliance trends across the research sector between the years 2010 and 2020. The largest number of shortfalls and advice was recorded in the governance and quality system standard, followed by the traceability standard, premises, facilities and equipment standard, and finally the consent standard. This work has also shown that the private sector is more compliant than the public sector, while a difference could not be observed between multisite and single site licences regardless of their source of funding. Finally, the international regulatory landscape and the role of the Human Tissue Authority in the research sector were discussed.

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Abbreviations

AATB – American Association of Tissue Banks
C – Consent standard
CAP - College of American Pathologists
CAPA – Corrective Action Preventative Action
CEN – European Committee for Standardization
CLH – Contact Licence Holder
CLIA - Clinical Laboratory Improvement Amendments
CMS - Centers for Medicare & Medicaid Services
D – Disposal standard
DI – Designated Individual
EC – European Council
EU – European Union
FDA – Food and Drug Administration
FFPE – Formalin Fixed Paraffin Embedded
GCP – Good Clinical Practice
GLP – Good Laboratory Practice
GQS – Governance and Quality System standard
H0 – Null hypothesis
H1 – Alternative hypothesis
HCTERS - Human Cell and Tissue Establishment Registration
HRA – Health Research Authority
HT Act – Human Tissue Act
HTA – Human Tissue Authority
ID – Identification
ISO - International Organization for Standardization
LAAV - Licence Application Assessment Visit
LH – Licence Holder
LIMS – Laboratory Information Management System
MTA – Material Transfer Agreement
MRC – Medical Research Council
NA – Non-applicable
OIDP - Office of Infectious Disease and HIV/AIDS Policy
ORA – Office of Regulatory Affairs
PD – Persons Designated
PFE – Premises, Facilities and Equipment standard
PPE – Personal Protective Equipment
QMS – Quality Management System
REC – Research Ethics Committee
SOP – Standard Operating Procedure
T – Traceability standard
UK –United Kingdom
UKECA - United Kingdom Ethics Committee Authority
U.S. – United States

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1 Introduction

1.1 Human Tissue Act 2004 and the Human Tissue Authority

The Human Tissue Act 2004 came into force in the United Kingdom after several tissue retention scandals were identified in two major UK hospitals (1-4). Two inquiries led by the government (5,6) concluded that human tissue storage and use without appropriate patient consent was widespread practice in the United Kingdom, and that previous legislation was in need of updating. The Human Tissue Act 2004 (7) annulled and replaced the Human Tissue Act 1961 (8), the Anatomy Act 1984 (9), and the Human Organ Transplants Act 1989 (10). The new Act became a key piece of legislation for all professionals working with human material (11,12). The main principles of the Act revolve around consent, dignity, quality and openness when dealing with human tissue.

The Act established the Human Tissue Authority (HTA) as the watchdog of the law to protect public confidence (13) which was diminished by the organ retention scandals of the years 1999-2000 (14). The Authority regulates UK establishments by means of licensing and inspecting all professional sectors that deal with human tissue namely: Anatomy, Research, Post-Mortem, Bone marrow donations, Public exhibitions and the Teaching sector. All inspection reports from the 1st November 2010 are available from the Human Tissue Authority website (13).

1.2 Human Tissue Authority licence

A licence is required under the UK Human Tissue Act 2004 for the storage of cellular material, which has come directly from a human body, what the law defines as 'relevant material', for its use for a 'scheduled purpose'. The Act outlines the use of relevant material for the purpose of research in connection with disorders, or the functioning of the human body as a scheduled purpose (7). Establishments in the UK storing human tissue for research need to be licensed unless the research is being carried out with appropriate ethical approval.

The responsible body for overseeing and issuing licences is the Human Tissue Authority (HTA). The HTA is a non-departmental public body of the Department of Health and Social Care, which is overseen by lay and professional members appointed by the UK government. They act as the regulator of organisations that remove, store and use human tissue for research. They also oversee the removal, storage and use of human tissue for medical treatment, post-mortem examination, education and training, and public display. They also grant approval for organ and bone marrow donations from the living (13).

There are conditions for when a licence is issued by the HTA, which need to be fulfilled by the licensed establishment. A licence requires to have certain roles in place so that all activities carried out under the licence are monitored by responsible and appropriately trained individuals. The authority of an HTA licence is exerted by a Designated Individual (DI). The DI in turn can designate other individuals to help in the overseeing of the activities under the licence. These assistants are called Persons Designated (PD). There must also exist a Licence Holder (LH), which is typically a corporate body. Each corporate body will have a representative known as the Contact Licence Holder (CLH) who, in the organisation, has a position of more seniority than the DI. The CLH is able to apply for a change in the licence, nominate a new DI and substitute him or her when necessary (13).

It is important to note that by inspecting establishments and publishing the post inspection reports on its website, the HTA is protecting public confidence. By having a governmental body that oversees the use of human tissue and organs, and has an open public disclosure policy, patients and families are reassured that their wishes are respected and that the tissue and organs donated for research or transplantation, for instance, are used safely and ethically. One of the HTA goals is to nurture a trust worthy culture where people are more willing to donate their tissues and organs for the advancement of medical science and also to help people in need of transplants (13).

There are a few technicalities (13) that need to be explained in order to understand the results in this thesis. These are:

- Consent for research is not required under the Human Tissue Act 2004 for imported material, but it must be stored in a licensed establishment. The HTA provides guidance and advice on how to source this material in a safe and ethical way, and it

considers good practice to have mechanisms in place to check that appropriate and valid consent has been sought in the source country.

- Human tissue collections that are being used under a research project that has valid ethical approval granted by a recognised research ethics committee (REC) in the UK do not need to be stored in licensed premises. However, when the ethic approval expires, the samples must be moved to a licensed establishment, as failing to do so, would result in a breach of the Human Tissue Act 2004.
- Institutions carrying out research ethically approved by internal ethics committees such as university ethics committees must have a licence to store the material as these committees are not recognized by the HTA. Only RECs established under the UK Health Departments or part of the United Kingdom Ethics Committee Authority (UKECA) are recognised by the HTA.

1.3 Human Tissue Authority inspections

HTA inspectors focus on a set of very well defined standards in each of their visits to all licensed establishments in the research sector (15). These standards include consent, governance and quality system, traceability, and premises, facilities and equipment. Inspection reports are exception based which means only shortfalls against all standards are reported. If standards are not met, the HTA will state the shortfall in a final report and classify it as critical, major or minor. Critical shortfalls are those which pose a risk to human safety/dignity or are a breach of the Human Tissue Act 2004 or associated directives. Major shortfalls are non-critical but can also be associated to breach of human dignity. They also indicate unsatisfactory practices and breach of the Codes of Practice. Minor shortfalls are defined as ‘a departure from expected standards’ which would require a corrective action plan being put in place and addressed within a specific time frame by the licensed institution. The Authority also provides advice to the different establishments to address shortfalls and to clarify expectations (15).

1.4 The aim of this thesis

The purpose of this thesis is to analyse the results of HTA inspection findings in the research sector and to see whether common trends exist. The aim is to draw conclusions

and learned lessons that can be applied to other institutions including the author's, which is also licensed by the Human Tissue Authority. The overall goal is to improve practice and awareness of the requirements. At the time of writing this thesis, there were 158 published reports of the research sector on the HTA website.

Before analysing the published reports from the research sector, the author hypothesised the following:

- Greater shortfalls would be observed in the governance and quality system standard, premises, facilities and equipment standard compared to the consent and traceability standards. The logic behind it being funding in a research environment would typically be diverted to the science itself rather than to maintain a quality system or state of the art facilities needed for optimal tissue storage.
- The author also anticipated greater shortfalls in bigger organizations, which are funded publicly compared to smaller organisations funded privately.

2 Methods

2.1 Overview

The methodology used for this thesis consisted of the analysis of 158 published reports available from the United Kingdom Human Tissue Authority's website (13). Results for all reports were tabulated in a form that facilitated statistical analysis and graphical representation of the outcomes by using both RStudio and Excel.

As previously described, the HTA inspectors divide the final report and categorise all findings into four standards: consent standard, governance and quality system standard, traceability standard and premises, facilities and equipment standard. Each of these four standards are divided into 13 categories, which are further divided into 47 subcategories.

Inspectors classify the establishment's shortfalls as 'critical', 'major' and 'minor' against each of the subcategory standards. A final classification called 'advice' is also included in

the reports and has also been tabulated in this thesis. Advice is given by the Authority as recommendations for improving practices.

2.2 Human Tissue Authority report

The reports analysed in this thesis, which are published in the HTA website after an establishment has been inspected, follow a pre-defined format depicted in Table 1.

Title	*Site visit inspection report on compliance with the HTA licensing standards.*
Name of establishment under inspection	
HTA licensing number i.e. a unique identifier consisting of 5 digits.	
Licence type	*Licensed under the Human Tissue Act 2004 for the * storage of relevant material which has come from a human body for use for a scheduled purpose.*
Date of the inspection	
Summary of inspection findings	*Statement from the HTA regarding the suitability of the Designated Individual (DI), the licence Holder (LH) the premises and practices and a short summary of all findings and the standards they relate to, and a sentence explaining that the DI has been given advice after the inspection.*
The HTA's regulatory requirements	*Statement about how the Authority satisfies itself that the DI is a suitable person to supervise the activities and practices carried out at the licensed establishment, followed by a quote from Section 18 of the Human Tissue Act 2004 describing the statutory duties of the DI. According to the Act, the DI must ensure:* • *The people working under the licence are suitable to carry out the activities* • *There are suitable practices in the establishment* • *The conditions of the licence are being met* *A description of the licensing standards which are grouped under four categories:* • *Consent* • *Governance and quality systems* • *Traceability which substituted 'Disposal' after April 2017 in all HTA reports* • *Premises facilities and equipment* *An explanation about the type of report is given to the establishment. Here, it is explained that*

	only unmet standards are presented. This is defined as an exception-based report. Findings or shortfalls are classified as 'Critical', 'Major' or 'Minor'. The HTA also offers advice on how to further improve practice, not only to correct the shortfalls identified, but also when the standards are met and improvements could still be made.
Background to the establishment	*In this section, a typical report would detail what type of licence the establishment holds, when it was granted, and the number of past inspections the establishment has been subjected to. This is followed by a description of the human tissue types the establishment stores such as number of samples and their provenance, and whether they are being used with research ethics committee approval. A description of storage premises, laboratories and activities carried out at the establishment are also included in this section.*
and description of inspection activities undertaken	*Here, the HTA describes how the inspection timetable was developed. Typically, before an inspection, the Authority would consider the activities conducted under the licence, the annual reports sent by the establishment in what is called compliance update information, discussions with the DI ahead of the inspection, any previous communications with the HTA, and all previous inspection compliance report's findings. Subsequently, the HTA describes how the inspection took place. Generally, there is a review of procedures, interviews with different staff and a visual inspection of storage areas. To conclude, there is a brief description of the amount of randomly selected samples inspected and how traceability was assessed. The HTA would follow existing samples from consent records to storage location and vice versa; also picking a selection of samples that have been catalogued as disposed of.*
Inspection findings and compliance with the HTA standards	*The HTA presents the shortfalls in a tabulated manner where each unmet standard is described in detail. HTA standards relate to consent, governance and quality systems, traceability, and premises, facilities and equipment. Below is an extract from the compliance report from the London School of Hygiene and Tropical Medicine showing two inspection shortfalls. HTA licence number 12066. Final report issued 28 August 2018.*

Standard	Inspection findings	Level of shortfall
C2 Staff involved in seeking consent receive training and support in the essential requirements of taking consent		
b) Records demonstrate up-to-date staff training.	Consent training is available and addresses the requirements of the HT Act and HTA's Codes of Practice; however, this is not distributed to all relevant staff. The establishment could not provide evidence that staff members who seek consent had received up-to-date training. *See Advice, item 2.*	**Minor**
c) Competency is assessed and maintained.	Competency is not assessed and there are no arrangements to ensure consent-seeking proficiency is maintained.	**Minor**

Advice

In this section, the HTA provides advice to the DI for further improvement of practices. Below is an extract from a compliance report from the London School of Hygiene and Tropical Medicine showing two items of advice given by the Authority. HTA licence number 12066. Final report issued 28 August 2018.

No.	Standard	Advice
1.	C1(a)	The consent SOP (LSHTM-SOP-005-03) references the old HTA Code of Practice 1. The DI is advised to update this reference to the Code of Practice A: Guiding principles and the fundamental principle of consent.
2.	C2(a)	To address the shortfalls against C2(b) and C2(c), the DI has a consent training presentation which should be given to all consent seekers. The DI is also advised to make relevant staff aware of the HTA Codes of Practice A (Guiding Principles and the fundamental principle of consent) and E (Research). The Codes provide anyone undertaking activities with a reference source which gives practical advice on the minimum steps necessary to comply with the relevant legislation and HTA guidance and standards.

Concluding comments

This section provides a summary of all shortfalls identified in the inspection i.e. number of shortfalls in relation to which standards with a final assessment from the Authority in regards to the suitability of the establishment to maintain the licence. If shortfalls are identified, the HTA will request the submission of a completed corrective and preventative action (CAPA) plan detailing how the shortfalls will be addressed by the establishment. This has to be received by the HTA within 14 days of issuing the final report. The HTA will subsequently communicate to the establishment which evidence should be submitted to demonstrate all agreed actions have been achieved.

Report sent to DI for factual accuracy - date

Report returned from DI - date

Final report issue - date

Completion of corrective and preventative actions (CAPA) plan and date	*If all actions detailed in the CAPA plan have been satisfactorily achieved, the HTA will update the report to include this information together with a date of completion.*
Appendix 1	*HTA standards either pre or post-April 2017.*
Appendix 2	*Classification of the level of shortfall: critical shortfall, major shortfall, minor shortfall and follow up actions.*

Table 1**:** HTA compliance report format post April 2017. Report format taken from compliance report London School of Hygiene and Tropical Medicine. HTA licensing number 12066. Final report issued 28 August 2018. Taken from HTA website (13).

2.3 HTA report shortfalls tabulation

158 reports were downloaded from the HTA website on three different occasions between September 2019 and January 2020 covering almost 9 years of inspections – from December 2010 to January 2020. See Annex 1 for the list of inspected licences. 138 reports were inspection reports for organisations already granted with a licence, while 20 were Licence Application Assessment Visit (LAAV) reports. All reports were read and all shortfalls were captured in an Excel spreadsheet. Each row in the spreadsheet represented a different establishment while the columns captured the following information:

A. Licence number (unique ID for the establishment)
B. Final report issued date
C. Name of establishment
D. Number of staff if known
E. Number of sites
F. Multisite (yes/no)
G. Private (yes/no)
H. Consent standard subcategories (nine different codes)
I. Governance and quality system subcategories (19 different codes)
J. Traceability subcategories (nine different codes)

K. Premises, facilities and equipment subcategories (ten different codes)
L. Major shortfalls description
M. Minor shortfalls description
N. Advice description

A numerical rank of the shortfalls was assigned against each of the standard subcategories in the following manner:

- Critical shortfalls with a number '1'
- Major shortfalls with a number '2'
- Minor shortfalls with a number '3'
- Advice with a number '4'
- No findings with a number '5' – these were assigned by the author after recording all shortfalls and advice from all reports
- In very few occasions, the Authority was not able to assess some standards, so these were marked as non-applicable ('NA')

Typically, the Authority provided advice after a reported shortfall in the same standard subcategory. For example, if a minor shortfall was reported in standard subcategory C1a, the Authority would have also advised to address the finding. For these cases and to ensure consistency in the analysis, the author only recorded the numerical rank of the shortfall and not the advice. Referring to the previous example, the author assigned only a '3' under standard subcategory C1a while the value '4' was omitted. A description of each shortfall was also noted in the last columns of the spreadsheet to increase the understanding of the results. See Figure 1 for a snapshot of the Excel spreadsheet.

	A	B	C	D	E	F	G	H	I	J
1	License number	Final report issued date	Institute name	Number of Staff	Number of Sites	Multisite (YES/NO	Private (YES/NO	C1a	C1b	C1c
2	12650	09-Apr-19	The Francis Crick institute	1800	1	No	No	5	5	5
3	12217	26-Jul-19	John Radcliffe Hospital	Unknown	5	Yes	No	5	5	5
4	12202	01-Apr-19	GlaxoSmithKline	Unknown	3	Yes	Yes	5	5	5
5	12182	30-Apr-19	University of Sheffield	Unknown	1	No	No	5	5	5
6	12643	13-May-19	Immunocore Ltd	Unkwnon	3	Yes	Yes	5	5	5
7	30004	02-Jul-19	The Christie	Unknown	3	Yes	No	5	5	5
8	12015	23-Jul-19	University of Westminster	Unknown	1	No	No	3	5	3
9	12384	05-Aug-19	Leicester Royal Infirmary	Unknown	3	Yes	No	4	2	3
10	12074	20-Jun-19	Unilever Research and Development Port Sunlight	Unknown	2	Yes	Yes	2	5	2
11	12664	25-Apr-19	ADC Therapeutics (UK) Ltd	Unknown	1	No	Yes	5	5	5
12	12291	13-Mar-19	Salford Royal NHS Foundation Trust	Unknown	1	No	No	5	4	5
13	12548	15-Jan-19	Liverpool School of Tropical Medicine	Unknown	2	Yes	No	5	5	5
14	12635	12-Dec-18	Adaptimmune Ltd	Unknown	1	No	Yes	5	5	5
15	12682	19-Dec-18	Teeside University (licence application)	Unknown	2	Yes	No	5	5	5
16	12196	15-Jan-19	University of Cambridge - Downing Site	Unknown	4	Yes	No	5	5	5

Figure 1: A snapshot of the Excel spreadsheet used to tabulate the observations and variables for this thesis.

2.4 Change of reporting system by the HTA

In April 2017, the Authority revised their Codes of Practice in line with inspection findings data collected after several years of inspections (13). At this point, the Authority took the opportunity to update some of the standards used to inspect the different establishments (15). Even though the majority of standards remained the same, the Authority made some changes. To capture these changes and to ensure a unique way of analysing the results was used to display the data on this thesis, a comparison between the standards used by the Authority pre and post April 2017 was performed by the author. It was concluded that the analysis could still be performed using one system for all reports. The chosen system for analysing all reports was based on the revised and current method used by the Authority on their inspections post April 2017. Refer to Annex 2 for standards after April 2017, Annex 3 for standards pre-April 2017 and Annex 4 for the author's comparison made between the two. The main differences between the two sets of standards are summarised in Table 2 below.

HTA Standards Pre-April 2017	**HTA Standards Post-April 2017**
The HTA reported on the following standards: • Consent • Governance and quality systems • Premises, facilities and equipment • **Disposal**	The HTA reports on the following standards: • Consent • Governance and quality systems • **Traceability** • Premises, facilities and equipment
The Authority divided the standards in categories further divided into **non coded** subcategories: • Consent - categories C1, C2 and C3, all further divided into non coded subcategories • Governance and quality system - categories GQ1 to GQ8 all further divided into non coded	The Authority divided the standards in categories further divided into **coded** subcategories: • Consent - categories C1 and C2 further divided into coded subcategories i.e. C1 (a-f) and C2 (a-c) • Governance and quality system – categories and subcategories GQ1

subcategories • Premises, facilities and equipment - categories PFE1 to PFE5 all further divided into non coded subcategories • Disposal standards D1 to D2 all further divided into non coded subcategories	(a-e), GQ2 (a-b), GQ3 (a-d), GQ4 (a-c), GQ5 (a-b), GQ6 (a-c) • Traceability - categories T1 (a-g) and T2 (a-b) • Premises, facilities and equipment – categories PFE1 (a-c), PFE2 (a-d) and PFE3 (a-c)
Reports are presented with a table of shortfalls against each of the 18 categories i.e. C1, C2, C3, etc.	Reports are presented with a table of shortfalls against each of the coded 47 subcategories i.e. C1a, C1b, C1c, etc.

Table 2**:** Differences between HTA standards pre and post April 2017.

3 Results

3.1 HTA standards, categories and subcategories

The results are based on the four HTA standards published after April 2017: consent (C), governance and quality systems (GQS), traceability (T), and premises, facilities and equipment (PFE). Each of these four are further divided into 13 categories and subsequent 47 subcategories. Below are the standards as extracted from the published HTA guidelines for the research sector (15).

Consent Standards

C1 Consent is obtained in accordance with the requirements of the Human Tissue Act 2004 (HT Act) and as set out in the code of practice.

C1a - Consent procedures are documented and these, along with any associated documents, comply with the HT Act and the HTA's Codes of Practice.

C1b - Consent forms are available to those using or releasing relevant material for a scheduled purpose.

C1c - Where applicable, there are agreements with other parties to ensure that consent is obtained in accordance with the requirements of the HT Act and the HTA's Codes of Practice.

C1d - Written information is provided to those from whom consent is sought, which reflects the requirements of the HT Act and the HTA's Codes of Practice.

C1e - Language translations are available when appropriate.

C1f - Information is available in formats appropriate to the situation.

C2 Staff involved in seeking consent receive training and support in the essential requirements of taking consent.

C2a - There is suitable training and support of staff involved in seeking consent, which addresses the requirements of the HT Act and the HTA's Codes of Practice.

C2b - Records demonstrate up-to-date staff training.

C2c - Competency is assessed and maintained.

Governance and quality system standards

GQ1 All aspects of the establishments work are governed by documented policies and procedures as part of the overall governance process.

GQ1a - Ratified, documented and up-to-date policies and procedures are in place, covering all licensable activities.

GQ1b - There is a document control system.

GQ1c - There are change control mechanisms for the implementation of new operational procedures.

GQ1d - Matters relating to HTA-licensed activities are discussed at regular governance meetings, involving establishment staff.

GQ1e - There is a system for managing complaints.

GQ2 There is a documented system of audit.

GQ2a - There is a documented schedule of audits covering licensable activities.

GQ2b - Audit findings include who is responsible for follow-up actions and the timeframes for completing these.

GQ3 Staff are appropriately qualified and trained in techniques relevant to their work and are continuously updating their skills.

GQ3a - Qualifications of staff and all training are recorded, records showing attendance at training.

GQ3b - There are documented induction training programmes for new staff.

GQ3c - Training provisions include those for visiting staff.

GQ3d - Staff have appraisals and personal development plans.

GQ4 There is a systematic and planned approach to the management of records.

GQ4a - There are suitable systems for the creation, review, amendment, retention and destruction of records.

GQ4b - There are provisions for back-up / recovery in the event of loss of records.

GQ4c - Systems ensure data protection, confidentiality and public disclosure (whistleblowing).

GQ5 There are systems to ensure that all adverse events are investigated promptly.

GQ5a - Staff are instructed in how to use incident reporting systems.

GQ5b - Effective corrective and preventive actions are taken where necessary and improvements in practice are made.

GQ6 Risk assessments of the establishment's practices and processes are completed regularly, recorded and monitored.

GQ6a - There are documented risk assessments for all practices and processes requiring compliance with the HT Act and the HTA's Codes of Practice.

GQ6b - Risk assessments are reviewed regularly.

GQ6c - Staff can access risk assessments and are made aware of risks during training.

Traceability standards

T1 A coding and records system facilitates the traceability of bodies and human tissue, ensuring a robust audit trail.

T1a - There is an identification system which assigns a unique code to each donation and to each of the products associated with it.

T1b - A register of donated material, and the associated products where relevant, is maintained.

T1c - An audit trail is maintained, which includes details of: when and where the bodies or tissue were acquired and received; the consent obtained; all sample storage locations; the uses to which any material was put; when and where the material was transferred, and to whom.

T1d - A system is in place to ensure that traceability of relevant material is maintained during transport.

T1e - Records of transportation and delivery are kept.

T1f - Records of any agreements with courier or transport companies are kept.

T1g - Records of any agreements with recipients of relevant material are kept.

T2 Bodies and human tissue are disposed of in an appropriate manner.

T2a - Disposal is carried out in accordance with the HTA's Codes of Practice.

T2b - The date, reason for disposal and the method used are documented.

Premises, facilities and equipment standards

PFE1 The premises are secure and fit for purpose.

PFE1a - An assessment of the premises has been carried out to ensure that they are appropriate for the purpose.

PFE1b - Arrangements are in place to ensure that the premises are secure and confidentiality is maintained.

PFE1c - There are documented cleaning and decontamination procedures.

PFE2 There are appropriate facilities for the storage of bodies and human tissue.

PFE2a - There is sufficient storage capacity.

PFE2b - Where relevant, storage arrangements ensure the dignity of the deceased.

PFE2c - Storage conditions are monitored, recorded and acted on when required.

PFE2d - There are documented contingency plans in place in case of failure in storage area.

PFE3 Equipment is appropriate for use, maintained, validated and where appropriate monitored.

PFE3a - Equipment is subject to recommended calibration, validation, maintenance, monitoring, and records are kept.

PFE3b - Users have access to instructions for equipment and are aware of how to report an equipment problem.

PFE3c - Staff are provided with suitable personal protective equipment.

3.2 Overview of the results

The percentage and number of major and minor shortfalls, advice, and non-shortfalls ('all good') for all four standards are summarised in Figure 2 and Table 3. Over almost 10 years of inspections, there were no critical shortfalls identified by the Authority in the research sector, nor a licence was revoked.

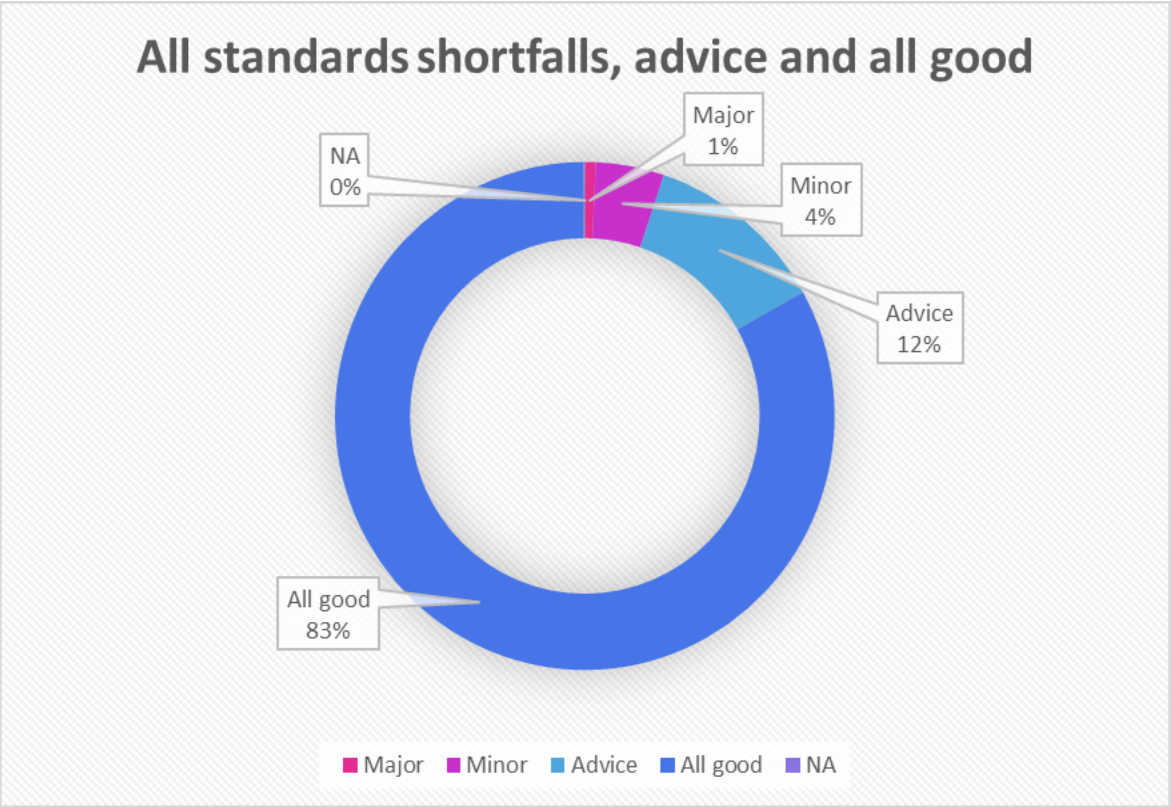

Figure 2**:** Percentage distribution of all shortfalls, non-shortfalls (‘all good’) and advice in all standards reported by the Human Tissue Authority from December 2010 to January 2020 after 158 establishment inspections.

Standard / Shortfall	Consent (C)	Governance and quality systems (GQS)	Traceability (T)	Premises, facilities and equipment (PFE)	Total
Major	13	13	16	10	**52**
Minor	40	169	67	53	**329**
Advice	122	387	173	192	**874**
All good	1245	2429	1166	1325	**6165**
NA	2	4			**6**

Table 3**:** Total number of major shortfalls, minor shortfalls, advice and ‘all good’ reported by the Human Tissue Authority in each of the four standards after 158 establishment inspections carried out from December 2010 to January 2020.

The 52 major shortfalls were reported in 23 different establishments. These establishments were also reported to have 160 minor shortfalls and 128 items of advice. There were 70 establishments where 169 minor shortfalls were reported along with 419 pieces of advice. There were 64 establishments that had no shortfalls reported only 327 items of advice

given. One establishment was reported to have no shortfalls or advice given. This was a licence application assessment visit.

Results from this compilation also showed that:

- There was only one establishment (same licence number) inspected twice in the 9-year period.
- There were 20 Licence Application Assessment Visit (LAAV) reports.
- 58% (91) of the establishments inspected were publicly funded while 42% (67) were private.
- 109 establishments had one site licence registration while 49 establishments were multisite. Of the 49 multisite establishments, 25 had two sites, 11 had three sites, six had four sites, five had five sites, one had six sites, and one had 11 sites.
- Of the 109 single site licences, 54 were establishments publicly funded while 55 were private.
- Of the 49 multisite establishments, 37 were establishments publicly funded while 12 were private.
- On six occasions, the Authority could not assess a standard subcategory during the inspection for which the author reported a non-applicable ('NA') value.

3.3 Greater number of shortfalls and advice

The total count of major, minor shortfalls and advice reported in each standard was divided by the total number of subcategories in each of the standards. See Figure 3.

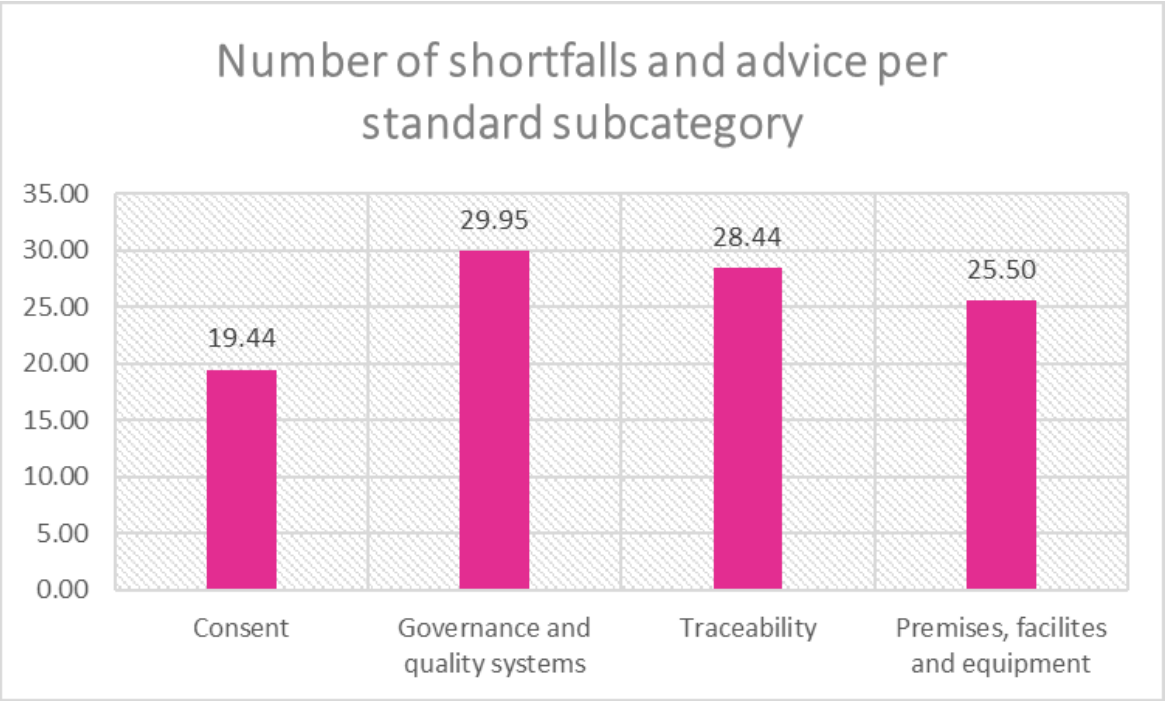

Figure 3: Total count of major, minor shortfalls and advice divided by the total number of subcategories in each standard reported by the Human Tissue Authority after 158 establishment inspections carried out from December 2010 to January 2020.

It was identified that the largest number of shortfalls and advice per standard subcategory reported by the HTA was in the governance and quality system standard ((13+169+387)/19=29.95). This was followed by the traceability standard ((16+67+173)/9=28.44), premises, facilities and equipment standard ((10+53+192)/10=25.50) and finally consent standard ((13+40+122)/9=19.44).

A Spearman correlation analysis was used to examine the relationship between all four standards. Figure 4 shows the matrix-scatter plot of mean scores per standard.

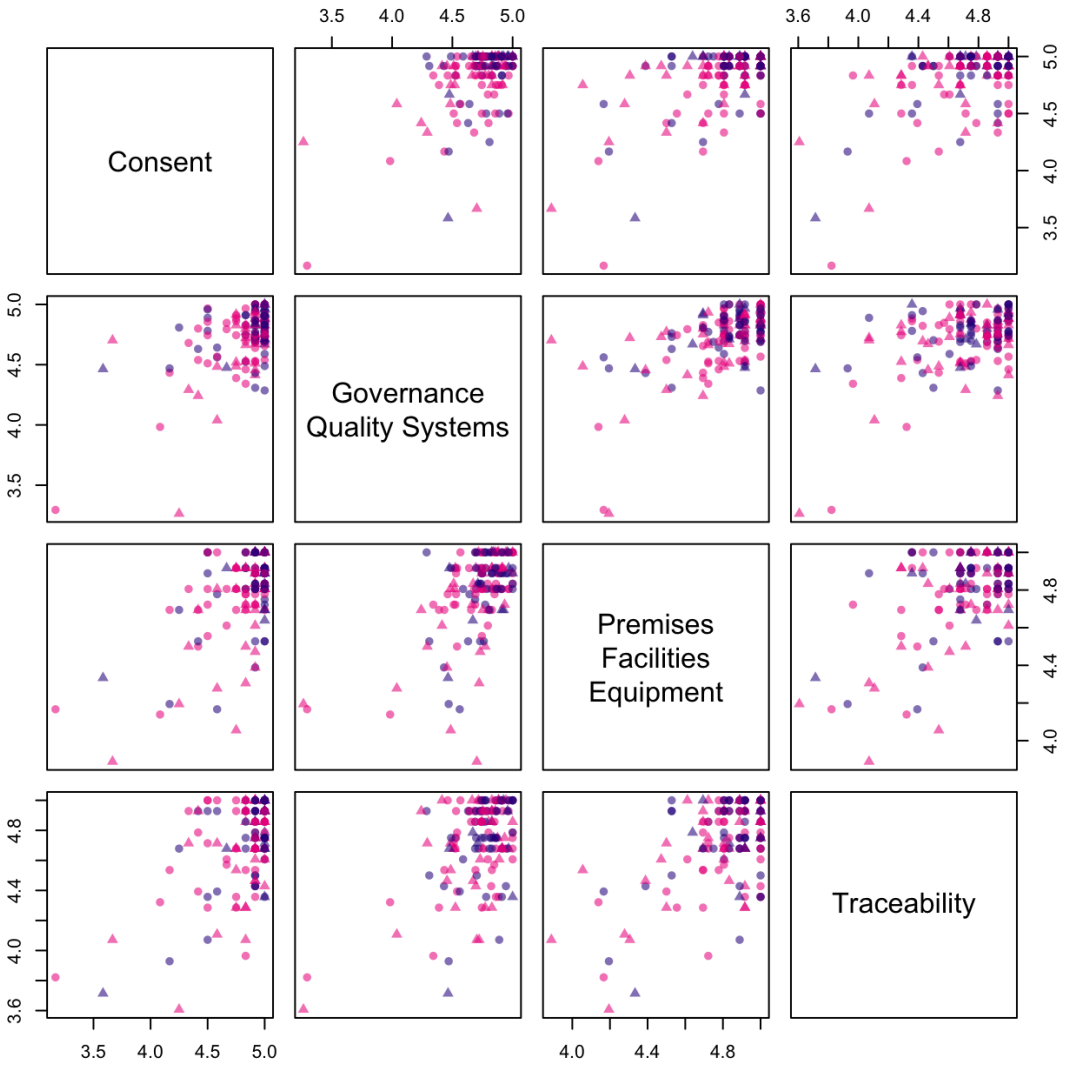

Figure 4: Matrix-scatter plot of mean scores per standard colour-coded by public (pink) / private (blue) levels and shaped by multisite (triangle) / single site (dots) levels.

It may be noted that scores were strongly related: reports showing a high score in a standard tended to show high scores in the other ones.

The matrix in Table 4 shows:

- in the upper triangle: the Spearman correlation coefficients of the scores between standards,
- in the lower triangle: the p-value of the Spearman correlation test (H0: the correlation between variables is equal to 0 *versus* H1: H0 is false).

	C	GQ	PFE	T
C	NA	3.602112e-01	0.3465849565	0.3432084
GQ	3.337813e-06	NA	0.4610101407	0.2743222
PFE	8.158836e-06	1.090325e-09	NA	0.3016885
T	1.011713e-05	4.867327e-04	0.0001170601	NA

Table 4: Spearman correlation coefficients and p-values of the Spearman correlation test.

It may be noted that all correlation estimates lied between 0.27 (T versus GQ) and 0.46 (PFE versus GQ) and were significantly higher than 0 (all p-values were smaller than 0.001), which showed a strong support for the alternative hypothesis: standard scores are correlated.

3.4 Private versus public sector

Compliance of the private and public sector was compared by calculating the global mean across all standards. See Figure 5 for more details.

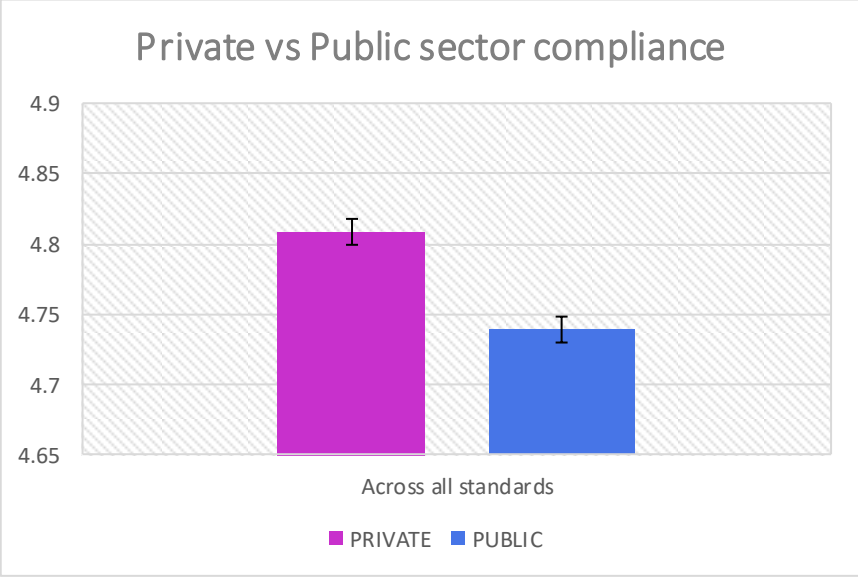

Figure 5: Global mean values with standard errors of licences from the private and public sectors.

The private sector appeared more compliant because the calculated mean was closer to the 'all good' score of '5'. A Wilcoxon rank sum test with continuity correction (W = 2403.5, p-value = 0.02335) showed that there was a significant difference in median scores between public and private establishments. The scores were also analysed using a beta regression model. The R-squared (proportion of variance of the response of the overall

score) explained by the model was small: R2 = 3.31% i.e. the effect was significant albeit small.

3.5 Multisite versus single site licences

Compliance of multisite and single site licences regardless of their source of funding was compared by calculating the global mean across all standards. See Figure 6 for more details.

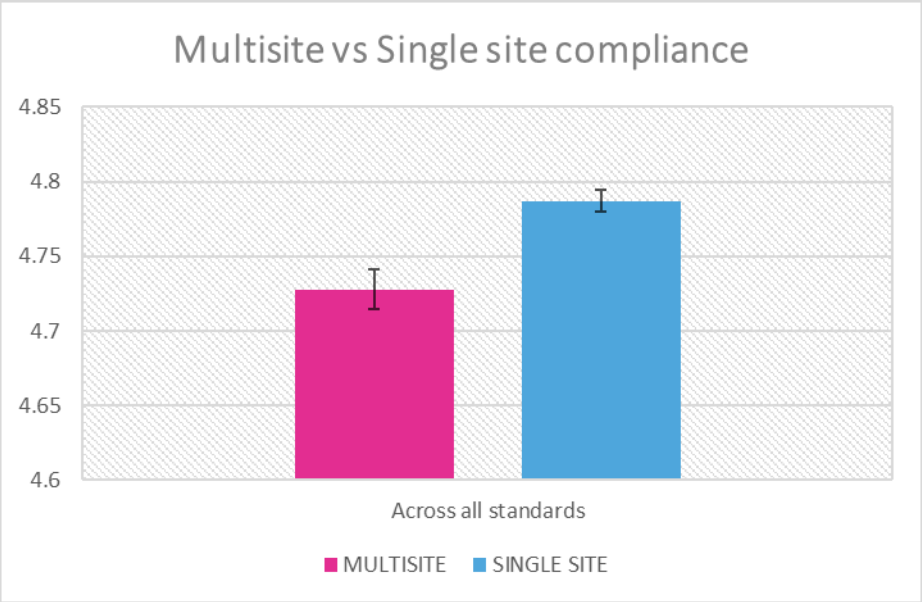

Figure 6: Global mean values with standard errors of multisite and single site licences.

Single site licences appeared more compliant than multisite licences because the calculated mean was closer to the 'all good' score of '5'. However, a Wilcoxon rank sum test with continuity correction (W = 2974.5, p-value = 0.2539) showed that the difference was not statistically significant. Therefore, there was not enough evidence to claim that there is a difference in median scores between single and multisite licensed establishments. The scores were also analysed using a beta regression model. This showed that there was not enough evidence to conclude that there was a difference in means between single and multisite establishments. Refer to Annex 5 for the full beta regression analysis.

3.6 Licence type and source of funding

A statistical analysis of mean scores between the different groups was performed. This assumed that the collected reports were a representative sample of a bigger population. A comparison of the four possible groups: public/private and multisite/single is shown in Figure 7.

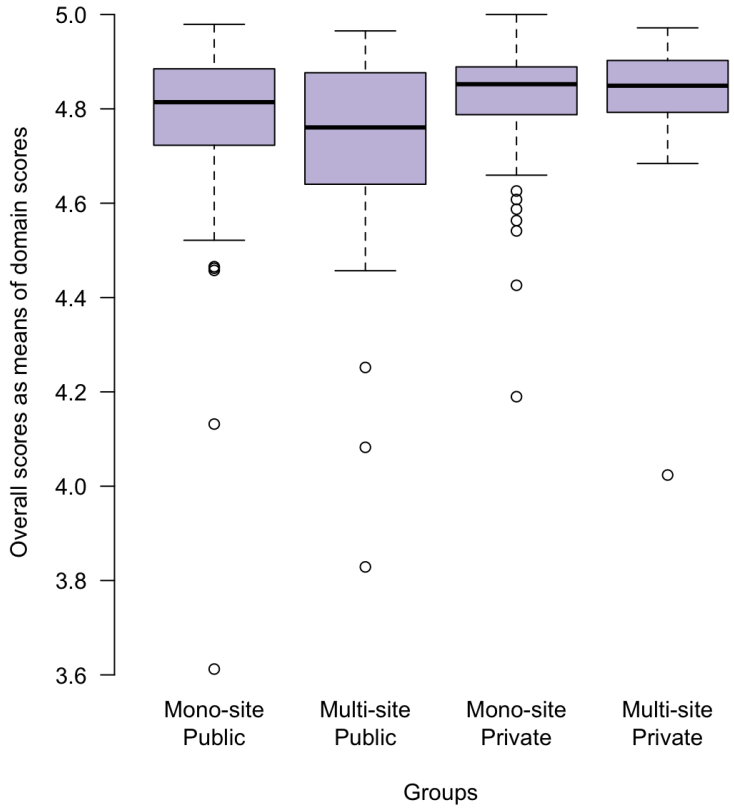

Figure 7: Boxplot of overall scores (defined as averages of standard scores) per group of interest.

There seemed to be differences in the mean values per group. A Wilcoxon's rank sum test with continuity correction (W = 750, p-value = 0.03349) showed that there was a significant difference in medians between multisite public and single site private licences. The scores were also analysed using a beta regression model. There was a significant negative effect: the mean score of multisite public establishments was significantly lower than the one of single site private establishments. The beta regression model also showed that the differences observed were driven by the scores in the private and public sector and

not by the licence type: multisite versus single site. Refer to Annex 5 for the full beta regression analysis.

3.7 Major shortfalls

A major shortfall is defined in the Authority's guidelines (15) as "*a non-critical shortfall that:*

- *poses a risk to human safety and/or dignity, or*
- *indicates a failure to carry out satisfactory procedures, or*
- *indicates a breach of the relevant Code of Practice, the Human Tissue Act and other relevant professional and statutory guidelines, or*
- *has the potential to become a critical shortfall unless addressed"*

or

"A combination of several minor shortfalls, none of which is major on its own, but which, together, could constitute a major shortfall and should be explained and reported as such. 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."

The ones recorded in this review span all four standards.

3.7.1 Consent

The Authority reported 13 major shortfalls across all the nine consent standard subcategories in the 158 establishments inspected over a 9-year period. See Figure 8 for more details. There are two consent standard categories. Consent category C1, which establishes whether consent is obtained in accordance with the Act and the HTA's Codes of Practice; and category C2, which is relevant to the training and support received by those involved in seeking consent in relation to the essential requirements of taking consent.

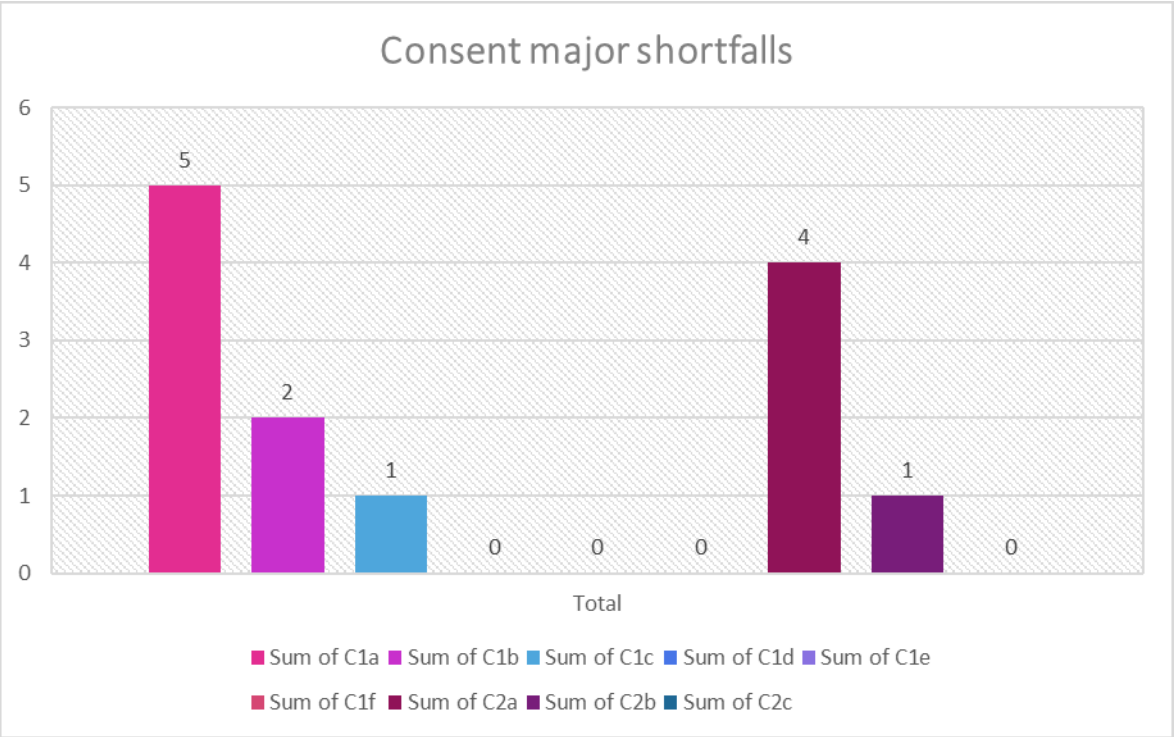

Figure 8: Consent major shortfalls reported by the Authority from December 2010 to January 2020.

Five major shortfalls were recorded under consent standard subcategory C1a - Consent procedures are documented and these, along with any associated documents, comply with the HT Act and the HTA's Codes of Practice. These were the result of deviations or incidents in the consent process reviewed during the inspection. In two establishments, two major shortfalls were reported when samples were stored illegally i.e. where samples had been held after ethics approval had expired, or where samples were stored beyond the agreed storage time.

Accumulation of minor shortfalls recorded on different subcategories of the consent standard also led the Authority to report a major shortfall under subcategory C1a in one establishment. In this particular case, there were three minor shortfalls related to the consent process. The establishment lacked SOPs for acquiring consent in accordance with the Act. There was variability in consent forms from different departments, where some did not comply with the Act and Codes of Practice. There were also inconsistencies in how consent forms were kept. Some were kept in the study records while others were kept elsewhere.

The Authority also reviewed the wording on consent forms used in those establishments that sought consent. A major shortfall in subcategory C1a was reported when permission to

store samples after use was not captured in the consent forms. On one consent form reviewed, the box capturing consent for research was ticked, presumably by the donor; however, the Authority reported that the box had been ticked at a different time from when consent was originally sought. The non-contemporaneous mark was not signed or explained on the consent form, which meant there was not an appropriate audit trail for the record. The establishment initiated an investigation after this finding, which resulted in the destruction of the sample.

Four major shortfalls were recorded under consent standard subcategory C2a - There is suitable training and support of staff involved in seeking consent, which addresses the requirements of the HT Act and the HTA's Codes of Practice. These were reported when consent forms were completed incorrectly due to the lack of adequate training of staff seeking consent. The Authority also found that there was a complete lack of training for those taking consent and, in some instances, that samples were collected with no record of consent.

Two major shortfalls where reported in consent standard subcategory C1b - Consent forms are available to those using or releasing relevant material for a scheduled purpose. This was not the case at one institution where samples were stored in contravention of the wording in the consent form. The consent form stated that samples could be used but not stored. The same staff using that material did not know of the expiry REC approval for their studies. Elsewhere, staff could not provide information about consent for samples under the licence after expired REC approval. The same establishment did not have consent information of commercially bought samples.

The Authority reported three major shortfalls in the same establishment under consent standard subcategories C1a, C1c and C2a. In relation to standard subcategory C1a, the SOPs review date was exceeded, there was no mention of the Act or Authority on the documentation, and the consent procedure was not being followed. The consent form to be used according to the SOP was not being used. In addition, donors were not informed about how to withdraw consent, consent forms used were misleading and consent was also taken in bulk.

At the same establishment, a major shortfall was reported against consent standard subcategory C1c - Where applicable, there are agreements with other parties to ensure that consent is obtained in accordance with the requirements of the HT Act and the HTA's Codes of Practice. The establishment had no third party agreements for tissue collections coming from other institutions. They also had an incomplete Material Transfer Agreement (MTA) template, and there was no consent information found for one particular study.

The Authority also reported a major shortfall in consent standard subcategory C2a at the same organisation because they found issues with the training provided. In the HTA presentation given to staff, the wrong Codes of Practice were quoted as well as the overarching standards. The legislation quoted was not relevant as it was related to the laws regarding transplantation rather than the Human Tissue Act 2004 and the research sector and also contained the wrong child age for when giving consent.

The last major shortfall reported by the Authority was in relation to the consent standard subcategory C2b - Records demonstrate up-to-date staff training. The shortfall was reported because one untrained researcher was seeking consent.

3.7.2 Governance and quality systems

The Authority reported 13 major shortfalls across all the 19 governance and quality system standard subcategories in the 158 establishments inspected over a 9-year period. See Figure 9 for more details. Governance and quality system categories encompass documented and ratified policies and procedures (GQ1), documented system of audits (GQ2), robust training programs (GQ3), appropriate management of records (GQ4), system to ensure adverse events are investigated promptly (GQ5), and that risk assessments for all practices under the licence are carried out and reviewed regularly (GQ6).

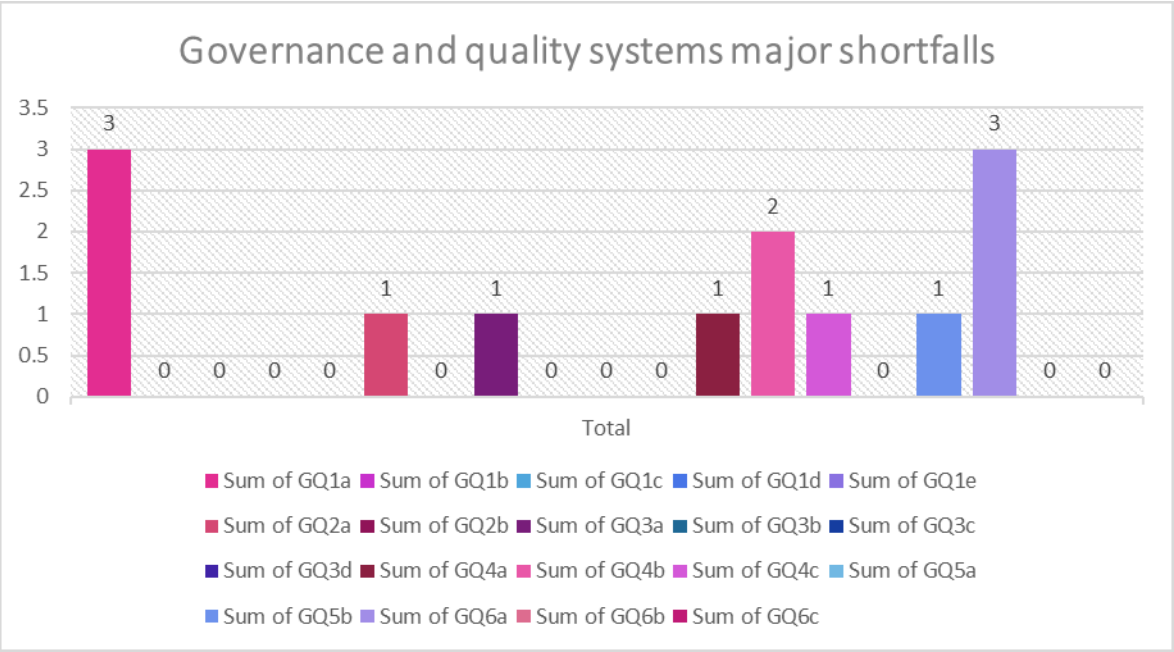

Figure 9: Governance and quality systems major shortfalls reported by the Authority from December 2010 to January 2020.

There were three major shortfalls reported under governance and quality system standard subcategory GQ1a - Ratified, documented and up-to-date policies and procedures are in place, covering all licensable activities. One establishment had insufficient SOPs and these were not being followed. In a different establishment, it was reported that there was no overarching governance framework (insufficient documented policies and SOPs to reflect procedures and practices), and that the existing SOPs only denoted laboratory protocols. Elsewhere, the Authority reported a major shortfall under GQ1a when the establishment inspected had sent samples from an expired REC approved study to an establishment that lacked an HTA storage licence. This was a breach of the Human Tissue Act 2004.

The Authority reported three major shortfalls under standard subcategory GQ6a - There are documented risk assessments for all practices and processes requiring compliance with the HT Act and the HTA's Codes of Practice. One establishment lacked risk assessments for key practices and procedures. A different establishment had insufficient risk assessments and no overarching system. Elsewhere, the risk associated with the way tissue storage was impacting sample traceability at certain tissue collections in one site was not assessed. At the same institution but different site, existing risk assessments were not reviewed and contained inaccurate address details. Here, the Authority found it difficult to assess whether enough was being done at the establishment to mitigate the risk.

There were two major shortfalls reported under standard subcategory GQ4b - There are provisions for back-up / recovery in the event of loss of records. One establishment was reported to have no centralised records for tissue registers, which made the process of recovery difficult in the event of loss of records. A different organisation recorded samples locations in paper form that were not backed-up.

One major shortfall was reported in standard subcategory GQ2a - There is a documented schedule of audits covering licensable activities. The Authority reported that insufficient internal audits were carried out at one establishment.

One major shortfall was reported under standard subcategory GQ3a - Qualifications of staff and all training are recorded, records showing attendance at training. The establishment in question had poor staff training.

One major shortfall was reported under standard subcategory GQ4a - There are suitable systems for the creation, review, amendment, retention and destruction of records. One establishment had no system in place for appropriate record maintenance. Document creation, review, amendment, retention and destruction was not being performed.

The Authority reported a further major shortfall under standard subcategory GQ4c - Systems ensure data protection, confidentiality and public disclosure (whistleblowing). In this particular case, patient information was accessible to all working at the establishment and not restricted to only those allowed to see it.

Lastly, the Authority reported one major shortfall under standard subcategory GQ5b - Effective corrective and preventive actions are taken where necessary and improvements in practice are made. At this establishment, internal audit findings captured in corrective and preventative action plans (CAPAs) were not being resolved. There was no resolution to the following internal findings: keys left in cupboards and freezers that stored human tissue, doors accessing the storage areas propped open, and sample labels on blocks and slides lost after processing.

3.7.3 Traceability

The Authority reported 16 major shortfalls across all the 9 traceability standard subcategories in the 158 establishments inspected over a 9-year period. See Figure 10 for more details. There are two traceability standard categories. Traceability category T1 - A coding and records system facilitates the traceability of bodies and human tissue, ensuring a robust audit trail; and category T2 - Bodies and human tissue are disposed of in an appropriate manner.

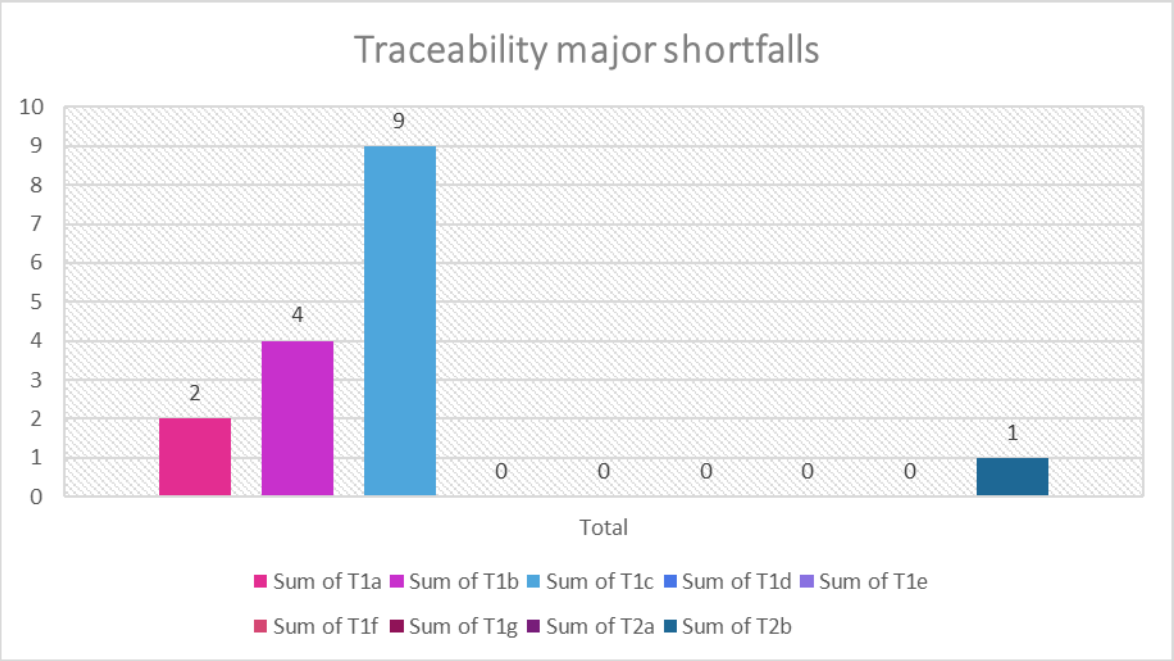

Figure 10: Traceability major shortfalls reported by the Authority from December 2010 to January 2020.

The Authority reported nine major shortfalls under traceability standard subcategory T1c - An audit trail is maintained, which includes details of: when and where the bodies or tissue were acquired and received; the consent obtained; all sample storage locations; the uses to which any material was put; when and where the material was transferred, and to whom. These shortfalls spanned organisations using different traceability systems ranging from paper based records, proprietary software databases to commercially available sample tracking tools called LIMS (Laboratory Information Management System). The types of samples being tracked also varied from FFPE blocks and sections, bones to frozen tissue and liquids such as blood, urine and saliva.

One major shortfall under standard subcategory T1c was reported at a commercial organisation that failed to record accurately the pooling of samples from different donors used in their experiments. At the same organisation, some samples had not being labelled and there were incomplete sample receipt logs. Loss of sample traceability was also evident and recorded as major shortfalls at a further four establishments. One establishment failed to record any storage location for frozen samples (including freezer number).

Traceability was also a problem for an establishment that was unable to match the actual storage location of the sample, which was recorded on the LIMS. At the same institution, samples were stored in bags that were labelled with only one identifier and the identification of human bones used was difficult because of the system used. Here, there were also missing records on the database used to capture all samples stored in liquid nitrogen. Elsewhere, a major shortfall was recorded when an establishment did not capture the date when the samples were collected and had no sample records for a collection held since 2005. No one at the establishment was aware of this collection until the respective freezer broke down and contents had to be moved.

A cumulative range of findings against the traceability standard also resulted in a major shortfall under T1c at a particular institution, which failed to risk assess the loss of sample traceability. In this case, the establishment had a range of computer proprietary databases that did not capture all necessary information in relation to sample traceability. There was one sample collection that remained uncatalogued, the number of sample vials used in research was not recorded, and there was inconsistent sample information for those samples released by the diagnostic archive.

There were four major shortfalls under traceability standard subcategory T1b - A register of donated material, and the associated products where relevant, is maintained. One establishment had no centralised tissue registry. A different organisation had FFPE blocks that were undeclared and not catalogued, which were found at the Designated Individual's office. Elsewhere, an establishment was not tracking the expiry date of the registered material. Lastly, the Authority reported one major shortfall in this subcategory in an establishment that failed to use unique samples IDs, which mixed human and non-human samples and that also failed to follow the SOP of sample labelling.

There were two major shortfalls under traceability standard subcategory T1a - There is an identification system which assigns a unique code to each donation and to each of the products associated with it. The lack of unique sample identification numbers was reported as major shortfall at one establishment. Here, the same sample identification codes were given to parent and children samples making traceability for all samples coming from the same donor difficult. In addition, the Authority observed that labels were peeling off the tubes containing the samples. Elsewhere, the Authority also reported a major shortfall under traceability subcategory T1a because unique samples IDs were not being assigned to samples, and the labelling was not following the convention stated in their SOP. At the same establishment, they were also storing human samples with other species but failed to clearly identify the provenance of each collection.

Ultimately, there was one major shortfall reported under traceability standard subcategory T2b - The date, reason for disposal and the method used are documented. The establishment, which also reported major shortfalls in the traceability standard subcategories T1a, T1b, and T1c, was reported to have inconsistent documentation in relation to sample destruction.

3.7.4 Premises, facilities and equipment

The Authority reported 10 major shortfalls across all the 10 premises, facilities and equipment standard subcategories in the 158 establishments inspected over a 9-year period. See Figure 11 for more details. There are three premises, facilities and equipment standard categories: PFE1 - The premises are secure and fit for purpose; PFE2 - There are appropriate facilities for the storage of bodies and human tissue; and PFE3 - Equipment is appropriate for use, maintained, validated and where appropriate monitored.

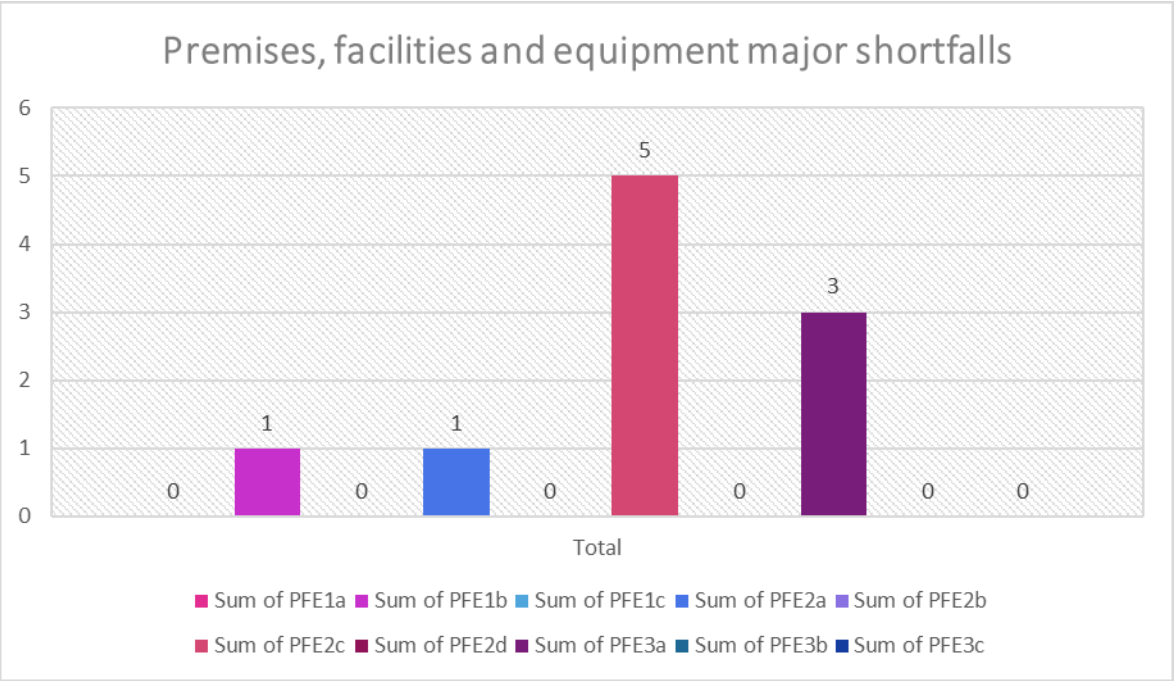

Figure 11: Premises, facilities and equipment major shortfalls reported by the Authority from December 2010 to January 2020.

The Authority reported five major shortfalls under premises, facilities and equipment standard subcategory PFE2c - Storage conditions are monitored, recorded and acted on when required. The lack of temperature monitoring and not investigating temperature deviations in sample storage units at a particular organization led to a major shortfall reported by the Authority. Here, there were liquid nitrogen tanks stored under bench areas with no oxygen monitoring in place. The lack of oxygen monitoring and risk assessment, as well as no recorded evidence of liquid nitrogen levels in the storage units at a different organisation, also resulted in a major shortfall reported by the Authority. The lack of temperature trend analysis was reported as a major shortfall at a different establishment. Here, they also found that there was no alarm call out process for the – 20 °C storage unit containing human samples.

Elsewhere, the Authority reported a cumulative major shortfall under standard subcategory PFE2c due to several under looked areas. Here, they found that the storage conditions were insufficient or unsuitable, and that they were not being monitored. There was no procedure for alarms going off, the staff was unaware of the temperature ranges of the storage units, and external temperature probes only existed in some storage locations; however, these were not being tested or challenged for optimal performance. Lastly, a major shortfall was reported at an organisation that only had internal audible alarms for the sample storage units which were not challenged. The system used was not risk assessed. The same

establishment did not review temperature data and had only one emergency contact in the call out list.

Three major shortfalls were reported under standard subcategory PFE3a - Equipment is subject to recommended calibration, validation, maintenance, monitoring, and records are kept. One major shortfall was reported at one institution that had no service contracts to cover maintenance, validation and calibration of all freezers. Here, equipment checks were not carried out and, at the time of the inspection, the service of a liquid nitrogen tank was overdue. In one establishment, there was a lack of service contracts for maintenance of the freezers being used to store samples, there was no schedule for cleaning and decontaminating the storage units, and the integral temperature probes of the storage units were not being challenged. A different establishment had no current service contract for all storage facilities.

The Authority reported one major shortfall under standard subcategory PFE1b - Arrangements are in place to ensure that the premises are secure and confidentiality is maintained. An accumulation of minor findings against the premises, facilities and equipment standard at one establishment led to a major shortfall reported by the Authority under subcategory PFE1b. Here, freezers containing human tissue samples were located in an open access room, temperature was being monitored weekly but not reviewed for trends, and freezers were not linked to a call-out system. During the inspection, a liquid nitrogen alarm was activated, but no staff attended to investigate or remediate it. At the satellite site of the same establishment, temperature checks were done ad hoc, and the weekend security patrol for the -80°C arrangement was not formalised. The Authority also reported an inadequate schedule for defrosting freezers because it was observed that a -20°C freezer's door was being shut using autoclave tape due to the ice build-up.

Lastly, the Authority reported one major shortfall under standard subcategory PFE2a - There is sufficient storage capacity. The lack of sufficient storage capacity resulted in liquid nitrogen tanks kept in an unsafe area. The Authority reported that the establishment had failed to protect their own staff by doing so. They noted that the liquid nitrogen storage space posed a significant risk to personnel because liquid nitrogen tanks were located in open corridors. These corridors were being used to access key service areas of the building, and they were poorly ventilated. In addition, not all staff was aware of the presence of the

existing oxygen monitoring system or what an audible alarm meant. There was no risk assessment in place either. The published report noted that the DI had been unable to relocate the liquid nitrogen tanks in the past.

3.8 Minor shortfalls

A minor shortfall is defined in the Authority's guidelines (15) as "*a shortfall which cannot be classified as either critical or major, but which indicates a departure from expected standards. 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 or site visit. 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*."

The minor shortfalls recorded in this review span all four standards.

3.8.1 Consent

The Authority reported 40 minor shortfalls across all the nine consent standard subcategories in the 158 establishments inspected over a 9-year period. See Figure 12 for more details.

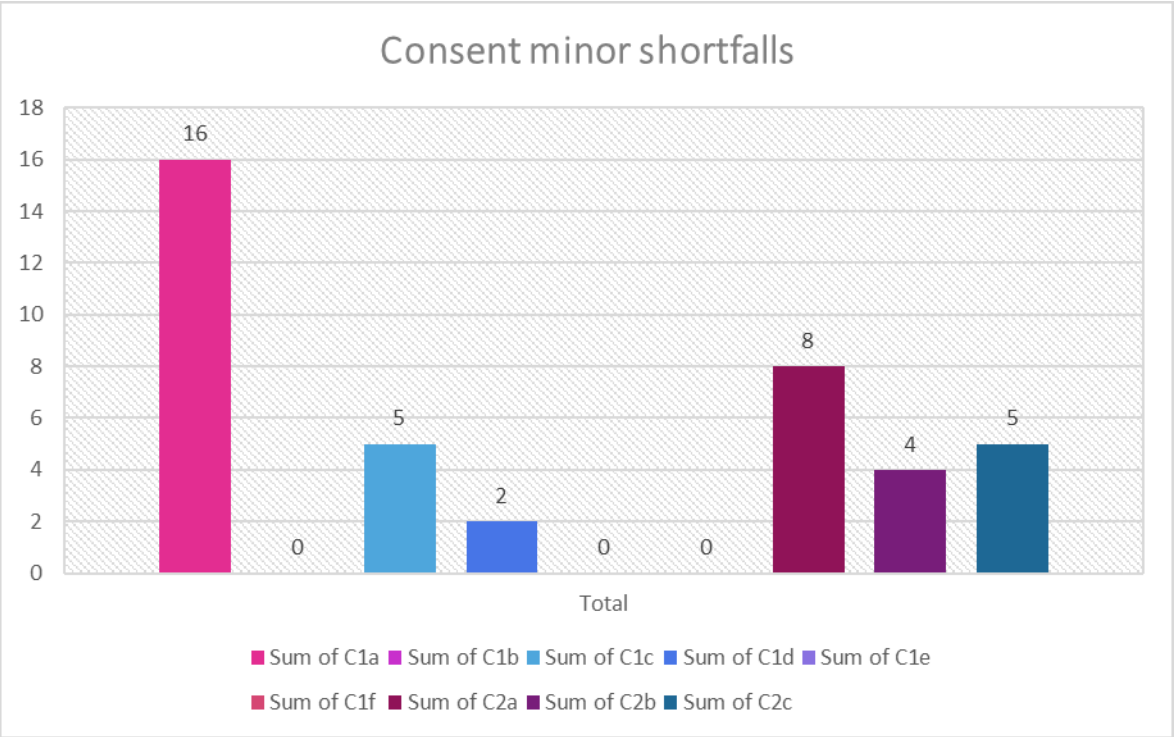

Figure 12: Consent minor shortfalls reported by the Authority from December 2010 to January 2020.

There were 16 minor shortfalls reported under consent standard subcategory C1a - Consent procedures are documented and these, along with any associated documents, comply with the HT Act and the HTA's Codes of Practice. These range from a lack of documentation, SOPs not reflecting current practices to errors in the process itself. For example, one establishment had a consent procedure in place, but this one was not being followed. People giving consent were ticking the relevant boxes on the consent forms rather than marking them as understood with initials. The same consent forms provided unclear guidance on the future use of the material once the study terminated.

One establishment was taking verbal consent instead of using paper forms. Elsewhere, a research tissue bank had no policy in place for samples held in quarantine i.e. samples awaiting confirmation as to whether they could be used or not. A different establishment used out of date consent forms, which were not in line with the current law. Here, people seeking consent had no training. These were reported as minor shortfalls and, in the case of the last two, they were not reported as major shortfalls due to the fact that the establishment self-reported this practice to the Authority.

The genome project consent forms at a different organisation lacked detail about the study itself. There was limited information explaining the use of the samples. Donors were not

given clear guidance on how the research was carried out, the implications, and the circumstances on when samples were going to be disposed of. A different establishment provided no patient information sheets in other languages. Elsewhere, the consent forms had no information on how to withdraw consent.

A different institution did not control the amount of blood taken from internal volunteers, nor offer a cooling off period for those donating. Donations happened at induction day. The consent forms and patient information sheets used in the process did not reference the Human Tissue Act. They had no explanation on how to withdraw consent, and the person taking consent did not counter-sign the forms. A different establishment also had no SOP for seeking consent from volunteers. Here, competency was also not assessed and there was no refresher training for those involved in the process.

Some establishments receiving samples donated and collected elsewhere failed to check the relevant consent documentation. For example, one organisation did not perform checks on imported material, or samples coming from private clinics, or even samples with valid REC approval. The Authority also reported minor shortfalls where consent checks were not done for samples obtained via commercial suppliers.

There were eight minor shortfalls reported under standard subcategory C2a - There is suitable training and support of staff involved in seeking consent, which addresses the requirements of the HT Act and the HTA's Codes of Practice. Some establishments did not have a training programme in place. Others did not offer a comprehensive and documented approach to the consent seeking process. Several establishments did not offer refresher training for those seeking consent.

One establishment which offered training delivered incorrect information in regards to when an HTA licence was required. Trainees were told that an HTA licence was not needed when storing samples collected prior to the 1st of September 2006 (the date the Human Tissue Act 2004 came into force). This is untrue as a licence is needed. The consent requirements, on the other hand, are the ones that do not apply to these samples. The same establishment had contradictory SOPs and was storing samples even after consent was withdrawn by the donor. It also kept a donor diary on a publicly visible space, and the donor coding used could easily identify the donor.

There were five minor shortfalls reported under standard subcategory C2c - Competency is assessed and maintained. There were establishments which had training programs for consent seekers but lacked a competency check. There were also other establishments where there was no training program in place nor competency was checked.

There were five minor shortfalls reported under standard subcategory C1c - Where applicable, there are agreements with other parties to ensure that consent is obtained in accordance with the requirements of the HT Act and the HTA's Codes of Practice. One establishment had no agreement in place with its supplier of relevant material to ensure consent was obtained in accordance with the law. A different organisation also had an agreement that lacked information with an US supplier of human tissue. There was no information about the infectious disease status information to be provided for the samples, the type of courier to be used and how to return non-conforming products.

Lastly, there were 4 minor shortfalls reported under consent standard subcategory C2b - Records demonstrate up-to-date staff training; and 2 under C1d - Written information is provided to those from whom consent is sought, which reflects the requirements of the HT Act and the HTA's Codes of Practice.

3.8.2 Governance and quality systems

The Authority reported 169 minor shortfalls across all the 19 governance and quality system standard subcategories in the 158 establishments inspected over a 9-year period. See Figure 13 for more details.

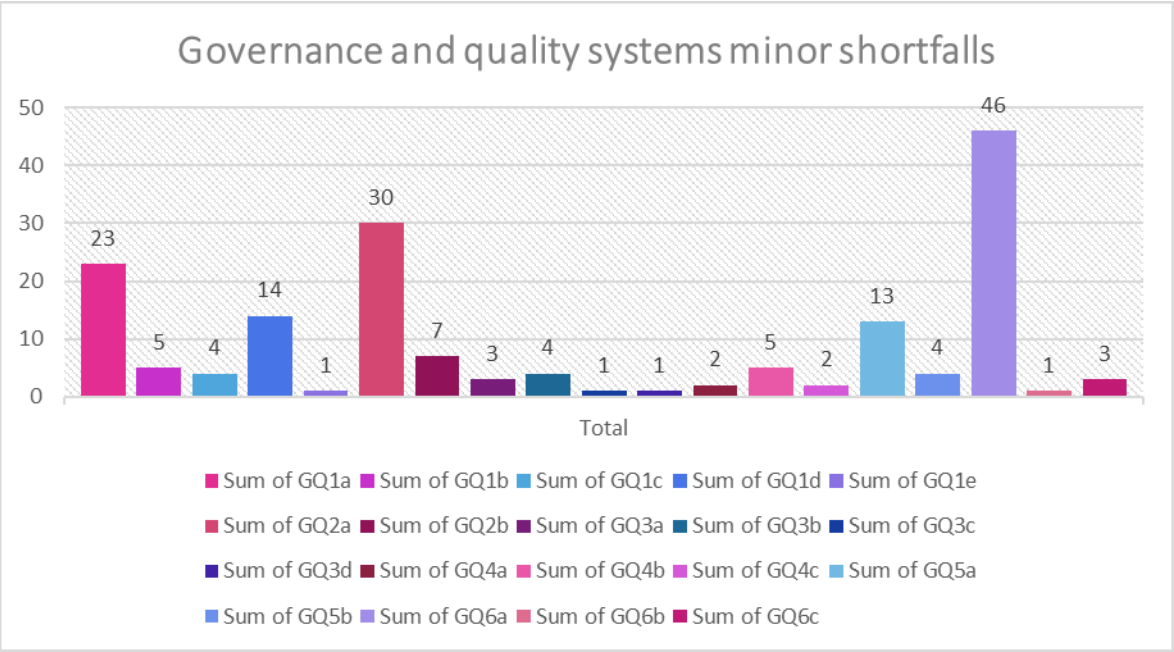

Figure 13**:** Governance and quality systems minor shortfalls reported by the Authority from December 2010 to January 2020.

There were 46 minor shortfalls reported under standard subcategory GQ6a - There are documented risk assessments for all practices and processes requiring compliance with the HT Act and the HTA's Codes of Practice. These ranged from a lack of awareness of existing risk assessments by staff working at those licenced establishments to limited or inexistent risk documentation at some institutions. In the majority of the establishments, there were risk assessments in relation to health and safety regulations, but there were not enough risk assessments in place to cover all premises, practices and procedures under the licence.

For example, at one particular institution, the risks of sample loss and consent taking were not assessed. At another establishment, the risks of storing samples after donor consent withdrawal, security arrangements for the sample storage facility, sample storage failure and transport of samples were not assessed.

Elsewhere, the Authority reported a minor shortfall when there was no risk assessment in place for samples stored in a -20°C freezer that was not temperature monitored. In addition, the same establishment did not risk assess sample transport, and the decision of not having the -80°C freezers covered under a maintenance service contract.

At a different institution, the processes to mitigate some of the risks identified were not being followed, and the level of risk identified by the assessor in one particular case was incorrect i.e. not complying with the Act was scored as low risk when it should have been scored as high. At the same establishment, it was also identified that staff lacked awareness of the risk assessments in place.

Failing to document formally the risks identified was reported as a minor shortfall by the Authority at another institution. The opposite also occurred when, at a particular establishment, comprehensive risk assessments were identified for all practices; however, an assessment in relation to sample traceability was not performed for a set of samples that were not individually labelled, and which dated prior the Human Tissue Act 2004.

There were 30 minor shortfalls reported under standard shortfall GQ2a - There is a documented schedule of audits covering licensable activities. These were reported when there were incomplete or inconsistent audit schedules, when there were no follow up actions from audits nor Corrective Actions Preventative Actions plan (CAPA plan) in place, when the standards the auditor used were out of date, or when there was a complete lack of vertical or horizontal audits carried out. In some cases, internal SOPs were not being followed, and audit schedules and supporting audit reports were missing in contravention of HTA guidelines and the establishment's own quality manuals.

In one establishment, the Authority reported a minor shortfall when there was no procedure in place to action the findings of audits, which had been carried out. At another establishment, there was no audit schedule in place; the same shortfall was identified in a previous visit to the same establishment by the HTA. At another institution, where several sample collections were being held, there were no audits of the consent process, sample traceability and relevant documentation. The HTA also reported a minor shortfall where an establishment failed to demonstrate that records were being audited for completeness, legibility and accuracy.

The lack of follow up action after an internal audit was identified by the Authority at another organisation as a minor shortfall. In this case, there was no action taken after an internal audit showed that there were samples stored with no consent documentation after the agreed quarantine period of 3 months. At a different establishment, another minor

shortfall was reported by the Authority when the audit schedule was not fit for purpose. Here, audits were carried out inconsistently and infrequently, and the information in the quality manual regarding audits was unclear. The Authority emphasised the importance of carrying out tissue traceability audits when another minor shortfall was reported against the standard because the institution in question failed to carry out these.

The Authority also reported minor findings in relation to the audit schedule in establishments with robust audit systems already in place, such as research contract organisations, or institutions where clinical trials involving human subjects were taking place. These establishments had robust systems to comply with clinical trial regulations and good clinical practice (GCP); however, they failed to include audits related to HTA licensable activities in their existing audit schedules.

A minor shortfall was also reported at one establishment when there was no evidence of audits taking place after REC approval's termination. The same establishment showed inconsistencies in auditing across the different sites under the same licence. Although all sites were audited against each HTA standard, some sites lacked a master audit schedule covering audits due to take place. At a different multisite organisation, a minor shortfall was also recorded when the audit schedule lacked enough detail, and the approach used in auditing was deemed inconsistent amongst the different sites.

There were 23 minor shortfalls reported under standard subcategory GQ1a - Ratified, documented and up-to-date policies and procedures are in place, covering all licensable activities. These included out of date governance documents such as policies, SOPs and quality manuals. In most cases, these documents contained inconsistent information or were incomplete because they lacked enough detail to carry out a procedure.

In some cases, there was no version control for policies and SOPs. The Authority also identified SOPs that were inadequate and lacked enough details. In one particular case, the SOPs in place referred to staff who no longer worked at the organisation, and also contained inaccessible links. Missing SOPs were also reported along with procedures not documented as SOPs when they should have been. Finally, there were cases where there was a complete lack of an overarching governance framework.

One establishment had HTA related documents still in draft form. A different establishment had complete SOPs at one of their research tissue banks, but not at the second tissue bank under the same licence. There was also no evidence of appropriate governance at a different establishment, which had gained a new licence for the removal of lungs from dead patients. The same establishment failed to demonstrate appropriate governance of the archived diagnostic collection.

Not documenting the expansion of material being stored at one institution was also reported as a minor shortfall by the Authority. The lack of documentation of key processes for the collection, receipt, labelling, sample storage, decontamination and cleaning of storage facilities also resulted in a minor shortfall at a different organisation. The Authority also reported a minor shortfall in one establishment when policies and procedures did not reflect existing practices. The same establishment also had incomplete SOPs and followed incorrect HTA Codes of Practice.

On 14 occasions, the HTA reported minor shortfalls under standard subcategory GQ1d - Matters relating to HTA-licensed activities are discussed at regular governance meetings, involving establishment staff. In some cases, governance meetings amongst the relevant staff working under the licences were not taking place, or when they were taking place, there were not frequent enough. For instance, at one establishment, there were no meetings being held between the different Persons Designated and Principal Investigators using tissue in their research. At a different establishment, there were no minutes being taken at meetings discussing HTA related matters. Another establishment also failed to organise formal meetings to discuss all activities under the licence carried out by a large number of staff. Finally, there was a case when the Designated Individual did not assign a Persons Designated to help overseeing the activities at the satellite site of the licence.

The Authority also reported nine minor shortfalls under the different standard subcategories of GQ4 - There is a systematic and planned approach to the management of records. One establishment, for instance, had paper records with sample information that was not backed up (GQ4b). A different establishment did not have a policy or SOP in relation to public disclosure or whistleblowing (GQ4c). Elsewhere, one establishment had no SOP for managing complaints.

The Authority reported multiple minor shortfalls at one establishment where there was no controlled document system in place, no SOP for managing complaints, an unsuitable records management policy, and an inadequate document backup and recovery strategy. The same establishment failed to demonstrate an understanding of how to report incidents and had no evidence to prove that these were investigated and corrected.

Minor shortfalls related to standard subcategory GQ5a - Staff are instructed in how to use incident reporting systems were reported a total of 13 times across all reports tabulated. Establishments were not reporting incidents, or were under-reporting, or unaware of how to report them, or even using reporting strategies based on different legislation. In one establishment, the Authority recognised an inconsistent approach to identifying, recording and following up adverse events, which led to a minor shortfall.

A different establishment was also given a minor shortfall for not having a central system to capture adverse events. Elsewhere, the Authority reported a shortfall when adverse events were being handled appropriately, but there was no documented SOP in place. There was one case where the establishment had an incident reporting system, but HTA related incidents were not listed as reportable.

The Authority reported 9 minor shortfalls under standard category GQ3 - Staff are appropriately qualified and trained in techniques relevant to their work and are continuously updating their skills. For instance, at one establishment, there was no training offered to visiting scientists. At a different establishment, there was no evidence of any staff competency assessments. A minor shortfall was also reported when staff was unaware of SOPs, or when an establishment failed to provide Human Tissue Act related training as part of their induction program. The lack of review of existing training induction programmes at a different establishment was also reported as a minor shortfall. Finally, the lack of training records at one establishment, and not having a formal appraisal system for staff at a different institution were reported as minor shortfalls by the Authority.

Lastly, there were other minor shortfalls across the governance and quality system standards, which were reported infrequently when compared with the ones previously described. Amongst these, the Authority reported five times that there was no controlled document system in place to record amendments made to the information contained within

SOPs and policies as described in standard subcategory GQ1b. One establishment was reported to have uncontrolled work instructions, and to have combined risk assessments and SOPs within the same document.

3.8.3 Traceability

The Authority reported 67 minor shortfalls across all the nine traceability standard subcategories in the 158 establishments inspected over a 9-year period. See Figure 14 for more details.

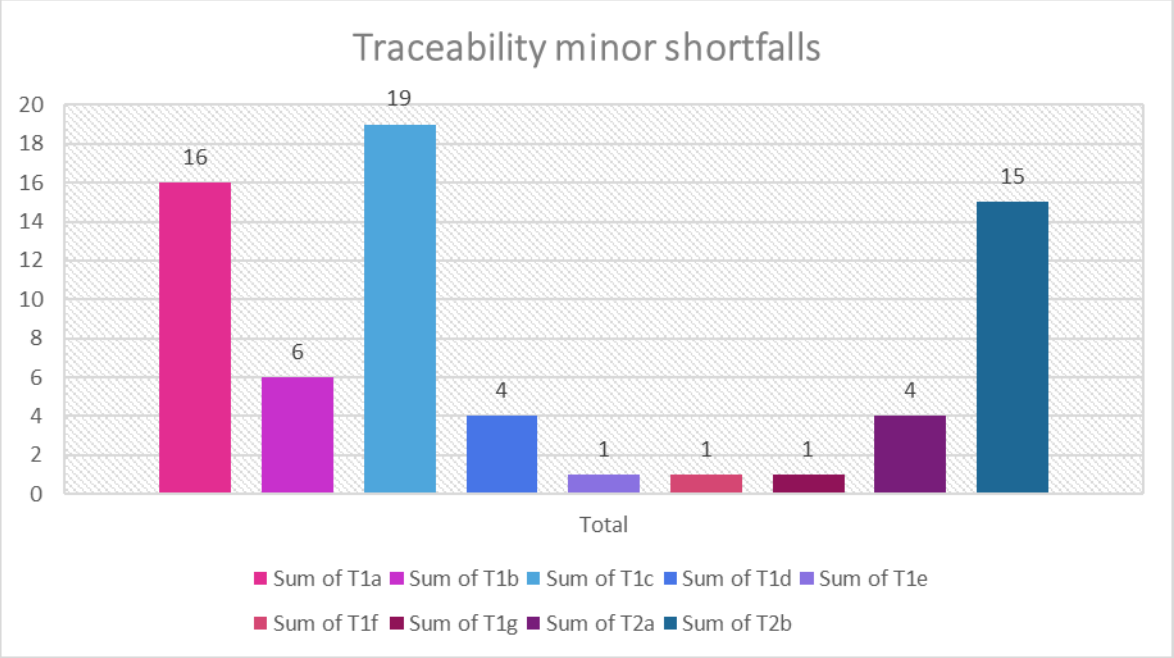

Figure 14: Traceability minor shortfalls reported by the Authority from December 2010 to January 2020.

There were 19 minor shortfalls reported under traceability subcategory T1c - An audit trail is maintained, which includes details of: when and where the bodies or tissues were acquired and received; the consent obtained; all sample storage locations; the uses to which any material was put; when and where the material was transferred, and to whom. The Authority reported shortfalls when samples' storage locations did not match the LIMS utilised for sample tracking, or, in other words, when the tissue samples were not in the correct locations. There were cases when sample labels were difficult to read or had peeled off from the sample container.

The Authority found inconsistencies between data stored in databases and data recorded in sample labels too. One establishment had no information about sample provenance. Here, the Authority also recorded the loss of traceability for one of the samples chosen on the day of the inspection. At a different institution, the contents of freezers were not labelled, and the samples chosen by the Authority were not found by the Designated Individual on the day of the inspection. Elsewhere, donor codes were not recorded in the individual consent forms.

The Authority identified samples in one box, which were not recorded in the establishment's database. Elsewhere, there were incomplete records for an archive of slides. One establishment had inventory checks as part of their compliance program; however, these were not documented or acted upon adequately. One establishment did not record the internal movement of samples on the dedicated LIMS, but in a spreadsheet, which contained inaccurate information. The Authority also found samples stored in one freezer, which the Designated Individual at a particular institution did not know about. The samples were being stained and kept for days before disposal.

One establishment entered samples on a database, which had shared login details amongst different users. In addition, samples stored at room temperature were recorded on a spreadsheet rather than the dedicated database. Staff were also unable to differentiate human from non-human material and failed to record the reason for disposal in the database. Records were later found on other laboratory documents. The same establishment did not have a system to record samples from donors who had withdrawn consent.

The training provided at one particular establishment did not detail how to accurately produce a label, and the existing documented procedures to ensure sample traceability was maintained, were not being followed by the relevant staff. In a different organisation, the consent forms could not be tracked due to incorrect database entries. The same organisation did not have a unique sample identifier system, some samples could not be located because they did not have a storage location, and one sample lacked information regarding its transport.

One minor shortfall was also reported in an establishment with a robust sample traceability system in place because the establishment failed to use the system to log a small collection from the diagnostic archive. The same establishment had three of five samples marked as disposed when these were in fact released for research. A bespoke database was also used to track samples elsewhere; however, some samples under a particular REC approved study could not be found which indicated inaccuracies in the system. In contrast, a different establishment seeking to apply for a storage licence did not possess a sample tracking system at the time of the Authority's Licence Application Assessment Visit (LAAV).

There were 16 minor shortfalls reported under standard subcategory T1a - There is an identification system, which assigns a unique code to each donation and to each of the products associated with it. Some establishments were not using a system where unique identifiers were assigned to the donated material. One establishment did not use unique sample identifiers, failed to provide complete records for all samples donated, and had samples marked up as used when they were still in storage. A different establishment recorded the same sample identifier for all the progeny of a parent sample. In LIMS terms, the same parent ID was given to all children samples. The chosen sample traceability system somewhere else failed to easily display when samples had been aliquoted. Finally, the Authority reported a minor shortfall in an establishment that did not assign unique identifiers to internal blood donors.

There were 15 minor shortfalls reported under standard subcategory T2b - The date, reason for disposal and the method used are documented. There were establishments with no disposal records in place. Others had inconsistencies in the process i.e. samples were marked as disposed of, but with no date or reason for the disposal. One particular establishment failed to record the disposal method, sample IDs, date, reason and the person who sent the sample for disposal. The same was true at other inspected establishments. Elsewhere, samples were disposed in batches with no record of individual IDs. At the same establishment, records were not kept for samples remaining after a study was completed. On a multisite establishment, one tissue collection had no system for correct sample disposal. At a different LAAV, the Authority reported that there was no provision for disposing material made by the establishment. The same place had a sample tracking system that allowed for sample ID duplication. There was also a case where the SOP

covering disposal did not explain the minimum amount of information needed when recording sample disposal i.e. date, method and reason.

There were six minor shortfalls reported under standard subcategory T1b - A register of donated material, and the associated products where relevant, is maintained. One establishment kept a register of box samples rather than an inventory of each individual sample. An incomplete register of material was evidenced elsewhere when samples were marked as used up when they were still in storage. A different establishment had a few samples not documented. One organisation had a disposal spreadsheet with a backlog of tissue to be disposed of.

There were four minor shortfalls reported under standard subcategory T2a - Disposal is carried out in accordance with the HTA's Codes of Practice. One establishment had no policy for samples disposal. Elsewhere, there was no provision for disposing material as they had never done it. Finally, one establishment disposed of samples in batches, and records of individual samples stored after a study's completion were not kept.

There were four minor shortfalls reported under standard subcategory T1d - A system is in place to ensure that traceability of relevant material is maintained during transport. One establishment failed to provide an audit trail in the form of transfer logs when samples were transported both internally and externally. A different establishment did not keep records of samples in transit between sites. Elsewhere, they had no records of who transported the samples.

There was one minor shortfall reported under standard subcategory T1e - Records of transportation and delivery are kept. One establishment did not record samples as being delivered or collected. There was also one shortfall reported under standard subcategory T1f - Records of any agreements with courier or transport companies are kept. One establishment had no formal agreement with the courier responsible for transporting the samples. Lastly, there was one minor shortfall reported under standard subcategory T1g - Records of any agreements with recipients of relevant material are kept. One establishment had no documented agreements in place with samples' recipients.

3.8.4 Premises, facilities and equipment

The Authority reported 53 minor shortfalls across all the 10 premises, facilities and equipment standard subcategories in the 158 establishments inspected over a 9-year period. See Figure 15 for more details.

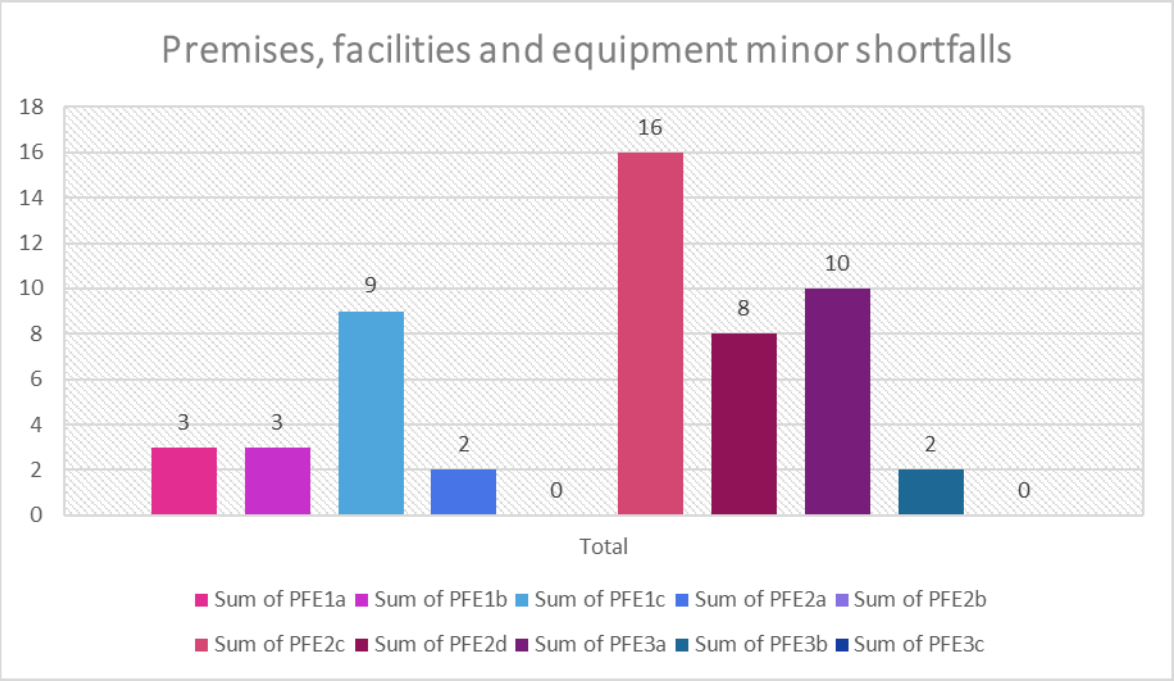

Figure 15: Premises, facilities and equipment minor shortfalls reported by the Authority from December 2010 to January 2020.

The Authority reported 16 minor shortfalls under standard subcategory PFE2c - Storage conditions are monitored, recorded and acted on when required. One multisite establishment was reported to have inconsistent temperature monitoring practices amongst the different departments or, at times, non-existent. At a different establishment, the liquid nitrogen tanks used for storing samples were not monitored at all. In some establishments, which had temperature alert systems installed in their cryostorage facilities, these were not challenged. One establishment, for example, did not challenge the alarm system and did not monitor temperature excursions. A different establishment had no routine testing of the freezer alarms, and the staff at the premises was unware of how the alarms functioned. The same site had no formal arrangement for out of hours emergencies such as freezer breakdown.

At a different establishment, there was no freezer temperature monitoring outside of normal working hours. One establishment had no alarm system for a fridge storing samples

and no external call out system for the liquid nitrogen tanks. The freezers and fridges of the same establishment were monitored on a weekly basis. A different establishment did not carry out any checks on the freezers used to store samples, nor had any maintenance records for them. The Authority also reported minor shortfalls in establishments that failed to record and analyse freezer and tanks' temperature trends. In one particular establishment, the temperature excursions of the -80°C freezers were not recorded. The same freezers had not set temperature limits. Several establishments with no temperature monitoring or checks in place had not performed a risk assessment for these practices.

There were ten minor shortfalls reported under standard subcategory PFE3a - Equipment is subject to recommended calibration, validation, maintenance, monitoring, and records are kept. There were establishments that had equipment under no maintenance contract. One establishment failed to evidence a process in place to report equipment problems. A multisite organisation had no preventative maintenance contract for -80°C freezers in some of its departments. Here, the Authority also reported that the oxygen monitoring was not working in the facility housing the liquid nitrogen tanks.

There were nine minor shortfalls reported under standard subcategory PFE1c - There are documented cleaning and decontamination procedures. Heavily frosted freezers and poor freezer door seals were identified in some inspections. Some establishments had a cleaning and decontamination schedule, but these were not documented. One establishment had no cleaning procedure or schedule in place, and several freezers were iced up. The same establishment did not review the data of the temperature monitoring system, nor had a preventative maintenance contract for those freezers outside the warranty period. This decision was not risk assessed by the establishment.

The Authority reported eight minor shortfalls under standard subcategory PFE2d - There are documented contingency plans in place in case of failure in storage area. In one establishment, the backup freezers were not empty, and the agreement for sharing storage space with another institution (as part of the contingency plan) was unclear. In a multisite organisation, there were different approaches to contingency planning across the different sites. Other institutions had no documented contingency plan in place or signed agreement with other storage facilities to move samples in case of emergencies. Finally, there were

cases where no contingency arrangements for samples stored under a licence had been made.

There were three minor shortfalls reported under standard subcategory PFE1a - An assessment of the premises has been carried out to ensure that they are appropriate for the purpose. The floor in the cryostorage facility at one establishment was in poor condition. Here, storage freezers were located in patient waiting areas with no back up power supply. The temperature at a different establishment's freezer room was too high, and there were inadequate control measures. Finally, one organisation had not carried out a risk assessment of the newly designated storage area.

There were three minor shortfalls reported under standard subcategory PFE1b - Arrangements are in place to ensure that the premises are secure and confidentiality is maintained. Two establishments stored samples in non-secure locations. A different site had one sample collection stored at room temperature, which was unlabelled, unlocked, and accessible to unauthorised staff.

There were two minor shortfalls reported under standard subcategory PFE2a - There is sufficient storage capacity. One establishment had their back up freezers unemptied. A different establishment had no space provision for possible incidents with its storage units. Lastly, there were two minor shortfalls reported under standard subcategory PFE3b - Users have access to instructions for equipment and are aware of how to report an equipment problem. Two establishments had no process in place to report equipment problems.

3.9 Advice

The HTA also provides advice to those establishments inspected to allow better practice. The ones captured in this review span all four standards and emphasised the most prevalent items of advice given.

3.9.1 Consent

The Authority gave 122 items of advice across all the nine consent standard subcategories in the 158 establishments inspected over a 9-year period. See Figure 16 for more details.

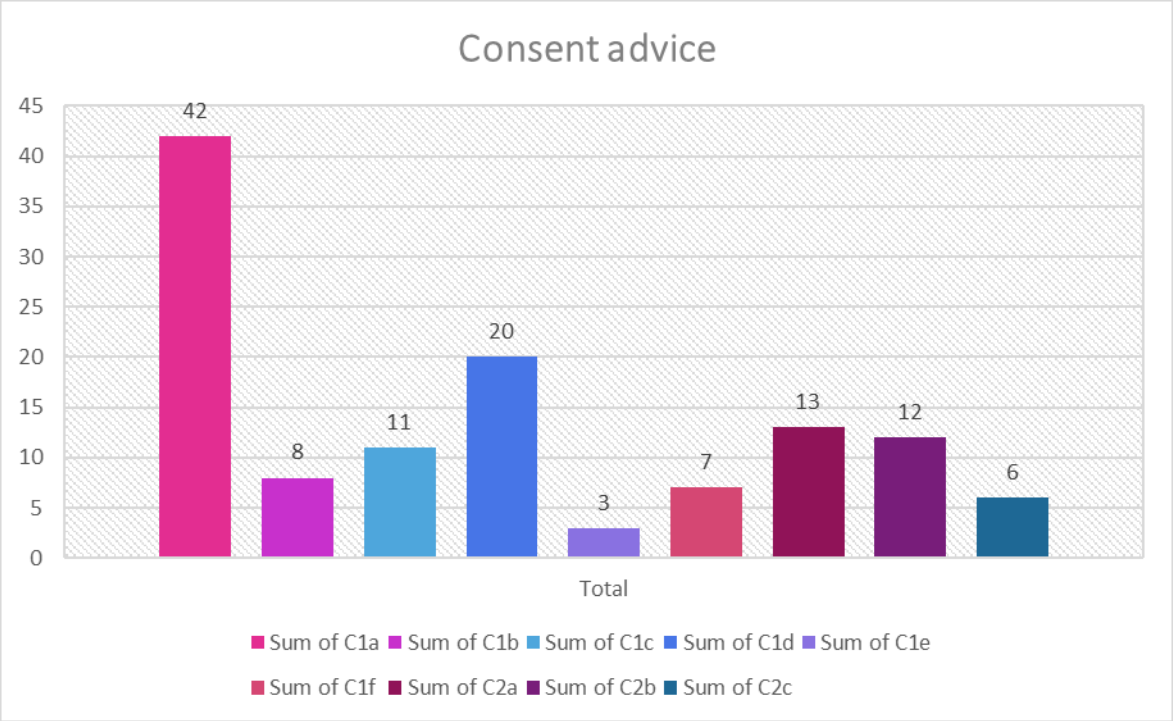

Figure 16: Consent items of advice provided by the Authority from December 2010 to January 2020.

The Authority gave 91 pieces of advice in relation to standard category C1 - Consent is obtained in accordance with the requirements of the Human Tissue Act 2004 (HT Act) and as set out in the code of practice. Subcategories were as follows: C1a (42), C1b (8), C1c (11), C1d (20), C1e (3) and C1f (7). They advised those reviewing consent forms to ensure instructions had been followed by the donor. For example, there were occasions where donors ticked rather than initialled their consent forms as requested. One establishment was asked to change their HTA policy because it contained erroneous information about licensing requirements for imported material. The establishment stated that an HTA licence was not required for imported material when in reality the opposite is true. A different establishment wrongly stated that imported material was not considered 'relevant material' under the Act.

The Authority also recommended to provide clear and sufficient information to those donating samples by following guidance on consent form and patient information sheet writing from the Health Research Authority (HRA). For instance, on several occasions, the

Authority reported cases where information on how to withdraw from a particular study was omitted in the consent form or patient information sheet. Other times information on the use, length of storage, and access to the samples was also missing. The Authority advised to document control consent forms and patient information sheets to aid the process. One establishment was advised to allow enough time for donors to arrive at a well informed decision. Here, consent was sought immediately after a tooth extraction procedure rather than before. Elsewhere, the Authority advised for the consent process to occur in a private environment allowing opportunities to ask questions. A different organisation was advised to securely file away consent forms containing patient identifiers.

The Authority advised one establishment to ask donors about health related findings that could come evident when using their samples and to document the decision. In some cases, they advised having translation services in place for those seeking consent from patients who had difficulty with the English language. Also, for those establishments collecting samples from volunteer staff, the Authority advised for an ethics committee to review the process to ensure a robust system was in place to protect donor confidentiality and potential health related findings.

The Authority emphasised the importance of knowing whether samples could be stored after a study's ethical approval had expired. They advised establishments to carry out consent documentation checks to ensure there was no holding of relevant material after a study's ethical approval had elapsed. They also advised to compile template consent forms and patient information sheets to those institutions that sourced human tissue from third parties and to keep a record of expiry dates for studies ethically approved.

For those establishments sourcing imported human tissue samples, they advised to check whether consent forms covered export and storage for future research. In addition, for those establishments receiving samples donated from within the United Kingdom, the Authority advised to have mechanisms in place to ensure correct and appropriate consent had been obtained. Similarly, for material sourced from commercial sources, the Authority advised to have a list of approved suppliers and 'due diligence forms' that captured the relevant checks on ethical approval, informed consent form, and donor information sheets.

There were a few cases where human tissue was obtained from the deceased. Here, the Authority advised establishments to apply and understand HTA guidance on qualifying relationships. Training on consent seeking for those obtaining tissue from the deceased was also advised. One establishment was asked to review the procedures related to receipt of tissue and consent checking for those tissues taken from a post-mortem examination. The establishment was asked to ensure there was consent for use in research.

The Authority gave 31 pieces of advice in relation to standard category C2 - Staff involved in seeking consent receive training and support in the essential requirements of taking consent. Subcategories were as follows: C2a (13), C2b (12), and C2c (6). The Authority advised establishments to have a robust and mandatory training program covering the Act, the consent requirements, and the latest guidance from the Authority. In some cases, they advised to use the training resources provided by the Medical Research Council (MRC). They also recommended that initial training ought to be followed by regular refresher sessions, to keep a centralised log with all the trainee names, and to assess competency for those seeking consent.

3.9.2 Governance and quality systems

The Authority gave 387 items of advice across all the 19 governance and quality system subcategories in the 158 establishments inspected over a 9-year period. See Figure 17 for more details.

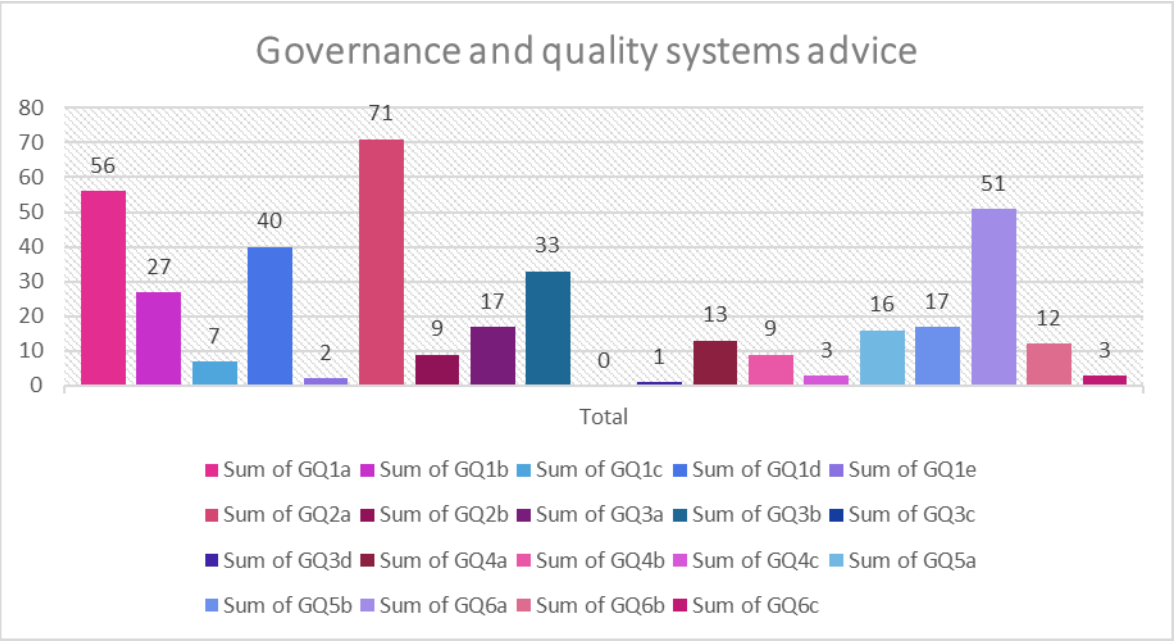

Figure 17: Governance and quality system items of advice provided by the Authority from December 2010 to January 2020.

The Authority gave 132 pieces of advice in relation to standard category GQ1 - All aspects of the establishments work are governed by documented policies and procedures as part of the overall governance process. Subcategories were as follows: GQ1a (56), GQ1b (27), GQ1c (7), GQ1d (40), and GQ1e (2). Establishments were advised to change, update, review, and disseminate SOPs and policies. SOPs should cover consent, receipt, labelling, specimen preparation/preservation, storage, transport, cleaning and decontamination of storage facilities and disposal. One establishment was advised to use a two person check approach when looking at blood samples documentation of receipt and retrieval to avoid errors. A different organisation was asked to write a policy on the length of storage for samples pending consent information because they found samples stored for months without any information. The Authority recommended destroying them.

The Authority advised to further develop QMS and manuals by adding: organisation and staff structure, guidelines from professionals and regulatory bodies, missing SOPs and risk assessments, records of governance meetings, tissue records, audit programme, how documents are controlled, reference to training and appraisal processes, non-conformities and incident monitoring as well as advice on what to audit and how to record it. The Authority advised to introduce a system, which would facilitate the dissemination of key practical information because deficiencies were found at the point of acknowledging that SOPs and policies were read by all staff. For multisite licences, where at times, some of the sites had separate documentation, the Authority advised to have a harmonised approach to

avoid duplication. They also recommended frequent communication between sites to allow staff to work under the same quality system. For those establishments also working under Good Laboratory Practice (GLP) and Good Clinical Practice (GCP) guidelines and regulations, the Authority recommended aligning all governance frameworks.

As part of the QMS review, the Authority advised establishments to collate all necessary documentation for each REC approved study such as consent forms, patient information sheets and expiry date. Particularly for expired REC approved studies, establishments ought to demonstrate that samples are allowed to be kept for future research. The Authority advised increasing the frequency of governance meetings were activities related to the licence were discussed. They also advised to include HTA topics within governance meeting already taking place and for the minutes to be taken and distributed amongst all of those working under the licence. One establishment was asked to invite all relevant staff to HTA meetings and not just senior roles. Advice was also given to those establishments, which share multiple licences, for instance, both in the post-mortem and research sector, to have joint governance meetings in order to share practices.

The Authority gave 80 pieces of advice in relation to standard category GQ2 - There is a documented system of audit. Subcategories were as follows: GQ2a (71), and GQ2b (9). Establishments either failed to demonstrate that a robust audit plan covering all areas was in place, or were not carrying out enough audits. For instance, establishments were advised to include competency assessment audits in the consent taking process. They were also advised to carry out vertical audits for donated samples where a review from the consent process to the use of the sample should take place. They were also recommended to carry out horizontal audits for particular procedures and also to do spot checks. One example given for a horizontal audit was auditing staff entering sample information into a database. They also recommended that audits should not be performed by someone involved in the SOP writing.

Closing out internal audit findings in a timely fashion by setting deadlines for completion was also advised by the Authority because, in some cases, findings were not followed up and corrective and preventative actions (CAPAs) not implemented. For those with CAPA plans in place, the Authority recommended to make the finalised reports available to all staff and to analyse the results to identify trends and systematic errors. There were

establishments carrying out audits; however, these were not formally documented. One establishment was encouraged to ask principal investigators and research groups to audit themselves.

The Authority gave 51 pieces of advice in relation to standard category GQ3 - Staff are appropriately qualified and trained in techniques relevant to their work and are continuously updating their skills. Subcategories were as follows: GQ3a (17), GQ3b (33), GQ3c (0), and GQ3d (1). The Authority advised to have staff induction programs, to provide HTA training and maintain refresher sessions, and to have staff annual appraisals. One establishment was advised to keep copies of training records. A different establishment was asked to record staff refresher training due dates. Also, and in an effort to keep on-going training, the Authority requested the dissemination of the HTA bi-monthly newsletter to keep staff abreast of new guidelines and information. In one case, the Authority advised a multisite establishment to remove the collection centres from the licence because these were either only storing samples for a few days before they were sent for analysis (incidental to transportation), or they were used entirely in the analysis within days.

The Authority gave 25 pieces of advice in relation to standard category GQ4 -There is a systematic and planned approach to the management of records. Subcategories were as follows: GQ4a (13), GQ4b (9), and GQ4c (3). One establishment was advised to include in their quality manual wider university policies on freedom of information and public disclosure (whistle-blowing). According to the Authority, SOPs and key documents ought to be reviewed every two years or after an incident. They should contain a revision history, be version controlled, have an effective from date, review date, be paginated, and have an author and reviewer name. They should not contain the HTA logo as it is proprietary. Of equal importance was the advice from the Authority in regards to the electronic back up of key paper records as some establishments were not following this practice. The Authority also advised those backing up records to audit the process for completeness.

The Authority gave 33 pieces of advice in relation to standard category GQ5 - There are systems to ensure that all adverse events are investigated promptly. Subcategories were as follows: GQ5a (16) and GQ5b (17). The Authority advised establishments to follow adverse event reporting as recommended in the Codes of Practice. Several establishments

were not aware of what constituted an adverse event and lacked staff training in how to report incidents. The Authority reminded establishments that examples of adverse events were: consent not sought according to the Act, samples used in contravention of donor's wishes, missing or incorrect documentation, specimen loss, storing and receiving samples without appropriate consent, abnormalities in storage temperature readings, inappropriate disposal, storing or using human tissue after consent withdrawal, sample mix-up, and security breaches. These ought to be reported to the Designated Individual of the licence.

The Authority gave 66 pieces of advice under standard category GQ6 - Risk assessments of the establishment's practices and processes are completed regularly, recorded and monitored. Subcategories were as follows: GQ6a (51), GQ6b (12), and GQ6c (3). The Authority advised establishments to have risk assessments covering the receipt of samples without appropriate consent, storing them after consent withdrawal, storage failure, loss of human tissue, sample mix-up or loss of traceability, transport, security and incorrect disposal. One establishment was advised to risk assess demolition works planned for an area near the cryostorage facility. A different establishment was asked to include on the risk assessment the SOPs for reference. Elsewhere, the Authority advised to risk assess storing human tissue with other species material and how out of hours deliveries were taken by security and left in the goods in area until the following morning. The Authority discouraged the same person to author and authorise risk assessments at one establishment.

Although not assigned as advice given in any of the GQS standard categories or subcategories, the Authority requested establishments to appoint Persons Designated (PD) to assist the Designated Individual (DI) of the licence. One establishment had no deputy for the DI to deal with incidents in his/her absence. A different establishment had not appointed a Contact Licence Holder (CLH). One institution had nominated the same person as the CLH and DI. Elsewhere, the chair of a tissue bank management committee was asked not to engage in decisions related to the release of samples for his own projects in order to avoid a conflict of interest. The same organisation was told to delegate to a newly appointed PD the version control of documents because the workloads where high and staff shortages had been reported. A different organisation was advised to dispose of samples that came from a company, which no longer existed, and to explore the legality when clients did not accept samples back when there was a service legal agreement in

place. Finally, the Authority advised several institutions to display copies of the licence everywhere where human tissue was stored to raise staff awareness.

3.9.3 Traceability

The Authority gave 173 items of advice across all the nine traceability standard subcategories in the 158 establishments inspected over a 9-year period. See Figure 18 for more details.

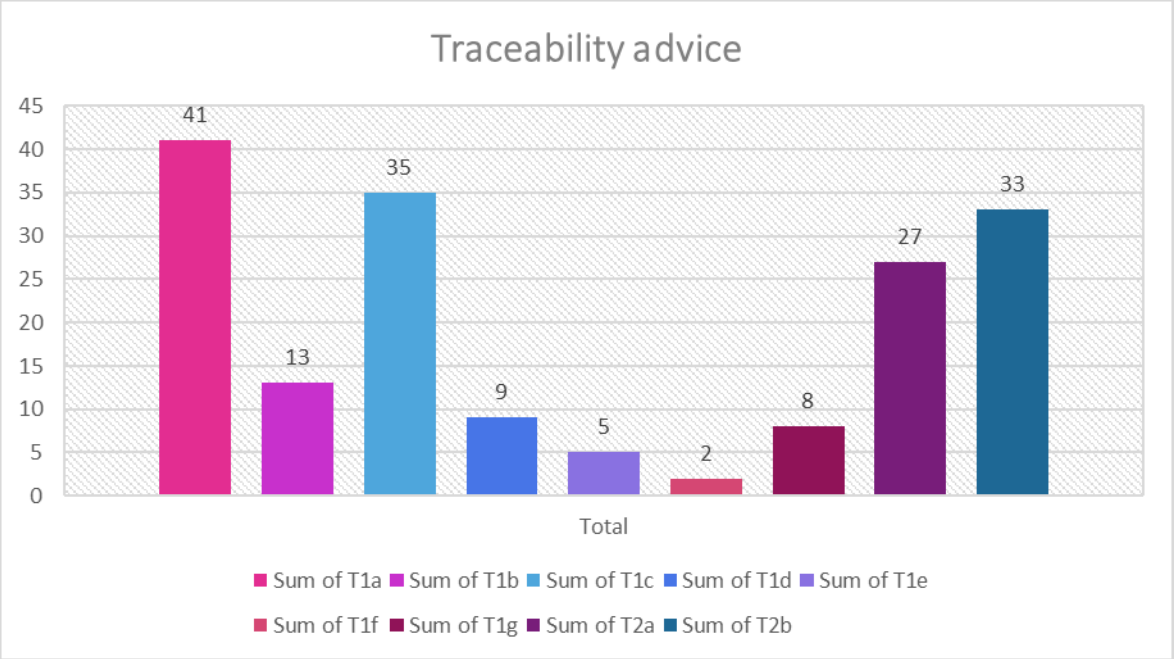

Figure 18: Traceability items of advice provided by the Authority from December 2010 to January 2020.

The Authority gave 113 pieces of advice in relation to standard category T1 - A coding and records system facilitates the traceability of bodies and human tissue, ensuring a robust audit trail. Subcategories were as follows: T1a (41), T1b (13), T1c (35), T1d (9), T1e (5), T1f (2), and T1g (8). Establishments were advised to implement a sample identification system whereby a unique identifier is given to each sample donated. The Authority advised against the practice of assigning child samples the same ID as the parent sample. This was the case at one establishment where aliquoted samples had the same ID (although volumes and locations were recorded). One establishment coded samples using the principal investigator initials and a numerical code, which the Authority deemed not to be unique and a risk for loss of traceability. A different establishment used interchangeably patient IDs and randomization numbers. Elsewhere, they used the external IDs provided by the

different tissue suppliers, which could not guarantee a unique identification system. These establishments were asked to review the process and to implement a labelling system that could be reproduced consistently.

The Authority advised on how to maintain a robust audit trail to track sample information and location throughout its life cycle. They discouraged the use of several tracking systems within the same institution. They recommended to use one database and not several for tracking human tissue. Some establishments had different tracking systems depending on whether samples were stored under the licence or under a valid approved REC study. In these cases, the Authority advised on having a harmonised approach so that one LIMS system was used for both samples under current and expired approved REC studies. As part of the audit trail, the Authority also advised establishments to track REC approved studies information and their expiry dates, as well as to ensure monitoring of REC approval coming to an end.

The use of paper records to track samples was also reported by the Authority as something to be avoided especially when not accompanied by matching electronic records. One establishment was reported to track samples in paper records, and inconsistencies were found in sample storage location most likely due to transcription errors. Differences between what was written in paper records and electronic records were also identified by the Authority at other inspections. The Authority also advised to use correctly sample logs and to have unified systems (preferably electronic) for tracking. This was also true with consent forms. In one inspection, there were difficulties linking consent forms to participants due to the filing system used.

The Authority advised to track samples down to their position within a storage box and to mark clearly the box orientation. Some establishments only recorded freezer shelf number or box number. To also aid with sample traceability, the Authority recommended to label correctly all freezers containing human tissue to differentiate them from non-relevant material and to display sample location maps. At one of the inspections, one sample could not be located because it was moved from one liquid nitrogen tank damaged rack to another one which held different size boxes. During this move, a transcription error had occurred when annotating a spreadsheet, and the sample could not be found. The

establishment was asked to review the storage contingency plan for that scenario. The Authority advised on the separation of human tissue from animal tissue.

The Authority encouraged the implementation and roll out of a LIMS system for all staff working with human tissue to improve sample tracking. This was true especially in those institutions and companies wanting to expand their tissue storage capacity. Advice was also given in regards to the use of LIMS and good practice when receipting samples. At one establishment, the Authority advised against having free text fields in the database used to track tissues. In addition, there were establishments using Excel spreadsheets to track samples. Here, the Authority advised against having free text fields, ensuring consistency of entries, and protecting the document with a password. The inventory in one of the labs inspected was handwritten and transcribed electronically a week later. The Authority advised to do this in real time.

The Authority advised on maintaining traceability whilst samples were in transport and to formalise arrangement with all couriers. One establishment was asked to record the final destination details of samples that were transferred to someone external because this was not recorded. They asked to add that information to future transfers. The Authority also advised establishments to implement a system of sample traceability while in transport by asking for an inventory in advance and sending confirmation of receipt once the samples arrived at their destination. They recommended to record courier dispatch numbers too. They also asked organisations to ensure the safety and integrity of samples arriving on deliveries out of hours. Several institutions were asked to review their SOPs on sample transport and to include instructions in the event of missing documentation. There were some cases where the same establishment had different sample quarantine arrangements depending on the collection.

The Authority found that establishments stored historical collections that no one was interested in. They asked to review this practice and to come to a solution. The Authority also asked one establishment to change its practice in regards to large numbers of tissue stored in a single bag because it posed a risk to sample integrity. A different establishment was asked to include details of the protocol for making material acellular, and therefore exempt from the Human Tissue Act 2004, into two SOPs under the licence (the blood sample separation and the centrifugation of blood samples). The Authority reminded

establishments that sufficient validation data should be available to evidence whether samples can be deemed acellular.

The Authority advised on sample preservation and integrity. One establishment storing bones was asked to remove adhesives from the specimens to ensure preservation. Elsewhere, establishments were asked to purchase suitable box lids and to use sample labels that could withstand liquid nitrogen temperatures. Some reports told of labels falling off from frozen samples. A different organisation was asked to ensure samples were labelled before they went into storage and not afterwards as the labelling had been lost by not doing it promptly. The wrong type of ink was used on plastic bags used to store samples in freezers, which at times, made the writing illegible or non-existent. One organisation was told to change the way they were bagging up samples because the plastic bags had deteriorated over time and broke down at -80 °C temperatures. Elsewhere, the Authority advised against using handwriting on vials and only labelling storage boxes on the lid.

The Authority gave 60 pieces of advice in relation to standard category T2 - Bodies and human tissue are disposed of in an appropriate manner. Subcategories were as follows: T2a (27) and T2b (33). Establishments were asked to include disposal records on LIMS and tissue logs and to have appropriate SOPs. They were also asked to include reason for disposal because this was either not recorded or recorded inconsistently. In addition, the Authority reminded establishments that human waste needs to be segregated from clinical or other laboratory waste. One establishment was asked to change their disposal SOP to capture that recording date, method and reason for disposal are a requirement and not 'good practice'. A different establishment had inconsistent disposal records.

Lastly, the Authority reminded Designated Individuals that they ought to know where all relevant material is stored. One organisation was informed that hair follicles were relevant material under the law and that they should be treated as such. The same was true in some establishments where they did not know that FFPE blocks and sections are relevant material under the Act. The Authority also reminded establishments that a traceability system is required irrespective of whether samples are stored under valid ethic approval or the storage licence, and that SOPs should be written in both cases.

3.9.4 Premises, facilities and equipment

The Authority gave 192 items of advice across all the ten premises, facilities and equipment standard subcategories in the 158 establishments inspected over a 9-year period. See Figure 19 for more details.

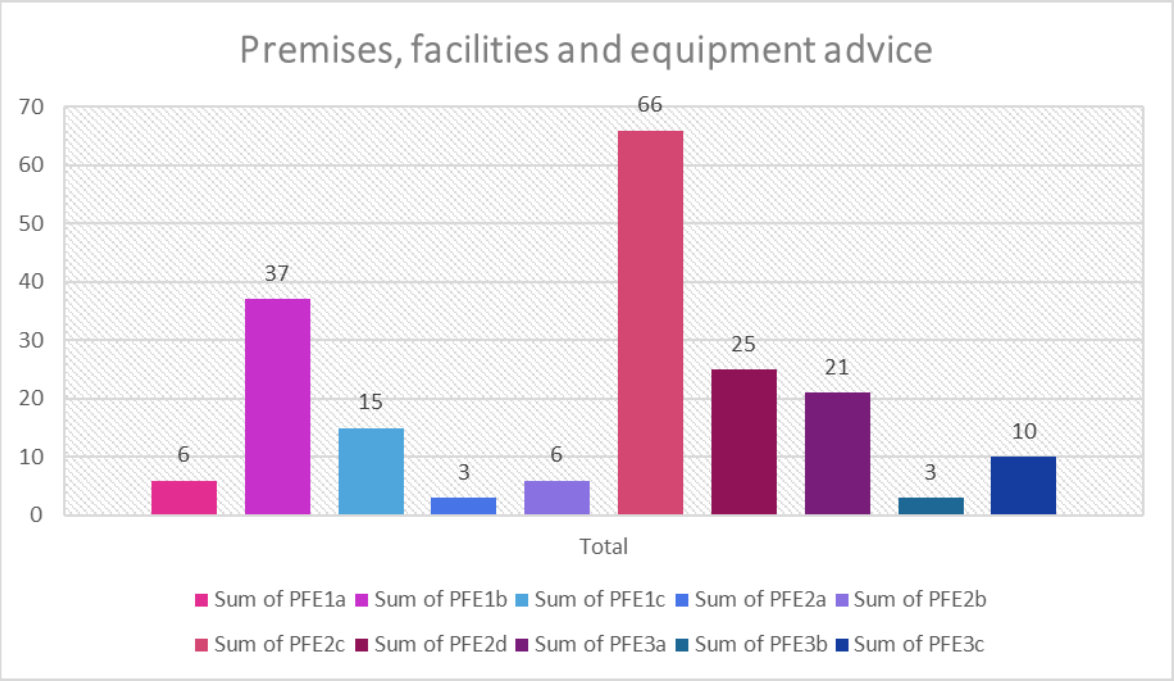

Figure 19: Premises, facilities and equipment items of advice provided by the Authority from December 2010 to January 2020.

The Authority reported 58 pieces of advice in relation to standard category PFE1 - The premises are secure and fit for purpose. Subcategories were as follows: PFE1a (6), PFE1b (37), PFE1c (15). One establishment had no arrangement in place for people not working with human tissue who had access to facilities where relevant material was stored. One establishment was advised to introduce a swipe-card access system because several staff members were sharing keys for the storage areas. The Authority recommended the use of fireproof cabinets for the storage of documents related to HTA activities. They also advised on scanning archived paper documents to ensure their perpetuity. One establishment was asked to secure the room where the liquid nitrogen tanks were stored. Elsewhere, the Authority reported that although the liquid nitrogen tank containing samples was locked, the tank itself was located in an unsecured shed. Finally, one establishment was advised to have boundaries between the cutting and archive sample area to avoid possible contamination amongst them.

The Authority reported 100 items of advice in relation to standard category PFE2 - There are appropriate facilities for the storage of bodies and human tissue. Subcategories were as follows: PFE2a (3), PFE2b (6), PFE2c (66), and PFE2d (25). The Authority advised establishments to monitor daily temperature and liquid nitrogen levels in cryostorage areas, ideally, by having an electronic monitoring system in place. They advised to install temperature monitoring in freezers and to review temperature trends because they can provide an early indication of equipment failure. They also recommended to monitor room temperature where cryostorage equipment was held. For all storage units, they recommended to add labels specifying the lower and upper temperature set points and written instructions on how to act when an alarm goes off. In those establishments where less frequent temperature checks were being performed, the Authority recommended to risk assess the regularity and potential impact on samples should a problem occur.

The Authority advised on noting the minimum and maximum temperature ranges in all areas, not just cryostorage equipment. They also recommended to challenge all freezer alarms and not just a fixed number. In addition, they reported freezers that had no alarm system. For those establishments testing temperature alarm systems, they advised on formalising and documenting the procedure. They emphasised on the importance of challenging alarms especially after freezer and fridges probes are calibrated. There were establishments where storage conditions were monitored and had contingency plans in place too; however, the procedures were not documented on SOPs. The Authority advised on ratifying these.

The Authority advised against not having oxygen monitoring in large lab areas where liquid nitrogen tanks were stored. One establishment had 16 liquid nitrogen tanks and no oxygen monitoring in place. Elsewhere, they advised against having portable oxygen monitors mounted too high on the wall and advised to test them. One establishment was asked to review the effectiveness of the ventilation system in the liquid nitrogen room. The Authority also advised on labelling all storage equipment including plugs and sockets. One establishment was asked to remove old contact details from a freezer unit. In regards to sample storage systems, the HTA advised using adequate racking system, vials and containers for the storage of human tissue. They advised against tissue being stored on top shelves which were difficult to access and storing human bones used for teaching with equipment. They ask the DI to ensure easy access to PPE and staff wearing it.

The HTA recommended establishments to improve awareness amongst staff of their existing contingency storage arrangements. Others were asked to strengthen existing contingency plans. One organisation was asked to agree on a contingency plan for the potential failure of their unique liquid nitrogen tank. A different institution had old freezers, so the Authority recommended to identify contingency arrangements in case of failure due to the storage unit's age. Elsewhere, they advised to link freezers to generators and to assess how long a freezer could hold temperature without power. Some establishments were asked to document the steps to be taken by staff if contingency arrangements were needed rather than just having a document containing a list of freezers. Others were asked to write a contingency plan SOP and to risk assess existing agreements with neighbouring facilities. The Authority recommended formalising plans with other HTA licensed premises and to risk assess the transfer of material. One establishment was asked to review their contingency plan because the freezer identified in it was being used *ad hoc.* The Authority recommended to have contingency storage space outside of the normal storage area too.

The Authority gave 34 pieces of advice in relation to standard category PFE3 - Equipment is appropriate for use, maintained, validated and where appropriate monitored. Subcategories were as follows: PFE3a (21), PFE3b (3), and PFE3c (10). Establishments were asked to include a regular freezer cleaning and maintenance schedule. In contrary, one establishment was told that their freezers were defrosted excessively (twice a year) Others were asked to evidence the existing cleaning schedule by documenting it. One organisation was asked to ensure that the newest cleaning method which included de-icing and cleaning of freezer's filters was circulated to all relevant staff. One establishment was asked to write a SOP for the maintenance of all storage locations. The Authority reported the lack of routine service for fridges and freezers and in some cases different set temperatures on -80 °C freezers. They also asked to include freezers into a service schedules after their warranty had run out. For those establishments where servicing was delegated to main service departments, the HTA recommended to obtain and file copies of all maintenance reports. The Authority identified -80 °C freezers which had servicing delayed and used inadequately. One establishment added too much weight on one of the freezer shelves.

4 Discussion

The results after analysing 158 Human Tissue Authority inspection reports based on the HTA's standards published in April 2017 (15) have shown that the research sector in the United Kingdom is mostly compliant with the regulations and guidance from the Authority. There were no critical shortfalls identified in any of the analysed inspection reports, which covered inspections carried out from December 2010 to January 2020. There were 52 major shortfalls (1%), 329 minor shortfalls (4%) and 874 pieces of advice (12%) given by the Authority in all four standards of consent (C), governance and quality systems (GQS), traceability (T), and premises, facilities and equipment (PFE). This analysis also showed that 6165 (83%) observations were categorised as 'all good', or in other words, the Authority did not report any shortfalls or give any advice against those standard subcategories.

One research sector review report published by the HTA in 2016 showed that there were no critical shortfalls, 5 major shortfalls, 103 minor shortfalls and 517 items of advice in the research sector (16). The report was based on 87 inspection visits carried out from November 2010 to March 2015 and was published after the HTA completed the first round of inspection since its launch. This review by the Authority was based on the old standards. Of the 87 reports reviewed by the HTA in 2016, 51 were reanalysed in this work using the most current standards. There were 21 reports no longer available on the HTA's website; however, the reports belonged to organisations for which later compliance reports were available. These later reports were analysed in this thesis. Finally, there were 15 reports in the HTA's review which belonged to establishments no longer listed on the HTA website; therefore, they were not included in this work.

The analysis carried out in this thesis builds on the findings of the research sector review report published by the HTA in 2016 in three ways. Firstly, it applies the standards published in April 2017 to all reports. While the HTA's review in 2016 focused on 18 standard categories, this work analysed the findings of 47 standard subcategories based on the latest standards. Secondly, it analyses and compares the level of compliance of private versus public sector and multisite versus single site establishments, something that was not published before. Thirdly, it provides an itemised and detailed description of all the findings to exemplify what constitutes a major or minor shortfall.

This work has shown that there was a greater number of shortfalls and advice given by the Authority in the GQS standard, followed by T, PFE, and finally C standard. As originally hypothesised, the greatest number of shortfalls was identified in the GQS standard with 29.95 items/subcategory. This was followed by shortfalls and advice reported under T with 28.44 items/subcategory and not by PFE with 25.50 items/subcategory as originally hypothesised. C had the lowest number of shortfalls and advice with 19.44 items/subcategory.

There were 91 establishments from the public sector (58%) and 67 from the private sector (42%). This analysis has shown that the private sector is more compliant than the public sector across all standards. Furthermore, the number of staff working under the different licences was not published in all reports; therefore, an inference of larger organisations, in regards to number of staff, and the level of compliance could not be made as originally planned. However, the number of sites for each licence was available in all reports. Typically, a multisite licence implies a larger organisation. For instance, the University of Cambridge licence has 4 sites, and the Addenbrooke's Hospital licence also located in Cambridge has 11 sites (13). These are very large organisations who employ hundreds of staff and actively use human tissue for research purposes.

Interestingly, a comparison between multisite and single site licences showed that single site licences from the private sector were more compliant than multisite licences from the public sector across all standards. The same could not be said from comparing just multisite versus single site licences (regardless of the funding source) as the overall difference was not statistically significant. These results confirm the original hypothesis; smaller organizations privately funded are more compliant than larger organisations publicly funded.

A description of shortfalls across all standards provided an insight in the regulatory activity of the HTA. Major shortfalls indicated unsatisfactory practices and a breach of the HTA's Codes of Practice and the Human Tissue Act 2004. These were reported in 23 different establishments. Minor shortfalls indicated a departure from expected standards. Almost half of the minor shortfalls were reported in the 23 establishments with major shortfalls, which suggests a 'cluster' of non-compliance rather that an even spread. The other half of minor shortfalls was reported amongst 70 different establishments. The major and minor shortfalls recorded in this thesis spanned all four standards (C, GQS, T, and PFE).

There were 13 major shortfalls reported in the C standard. They were the result of several deficiencies in the consent process and related documentation and the illegal storage of human tissue, i.e. ethical approval had expired or when samples were stored beyond the agreed time. They also resulted when untrained staff were seeking consent, and when consent training was inadequate. There were 40 minor shortfalls reported in the C standard. They were due to the lack of documentation, SOPs not reflecting current practices and errors in the process itself. They were also reported when establishments did not offer refresher training to those seeking consent, when erroneous information was given at the training sessions, and when staff competency was not being checked.

There were 13 major shortfalls reported in the GQS standard. They were related to insufficient SOPs and policies, lack of risk assessments, no provisions for back-up of records, insufficient internal audits, and unresolved CAPA plans. Poor staff training, lack of a system to maintain records and no access restriction to patient information all led to major shortfalls. There were 169 minor shortfalls reported in the GQS standard. They were reported when there were not enough risk assessments performed for all practices and procedures under the licence, when they were incomplete or inconsistent internal audit schedules, and when there was a lack of follow up actions after findings were reported. Not having up to date policies and SOPs and a review mechanism of key documents were also reported as minor shortfalls. Minor shortfalls were reported when there was a lack of governance meetings or frequency and attendance were inadequate. Finally, errors in the management of records, adverse event reporting, controlled document system, and staff training records were also reported as minor shortfalls.

There were 16 major shortfalls reported in the T standard. They were in relation to the inability to maintain a robust audit trail for the samples used. They spanned organisations using different traceability systems ranging from paper based records, proprietary software databases to commercially available sample tracking LIMS. In addition, the lack of unique sample identification codes, which is known to hinder sample traceability by enabling the possibility of having duplicate IDs used for the same sample, was reported as a major shortfall. Ultimately, not having documentation in regards to sample destruction was also reported as a major shortfall. There were 67 minor shortfalls reported in the T standard. They were in relation to the sample audit trail and when samples did not match their recorded storage location or vice versa. They were also reported when the traceability system used allowed for the duplication of samples IDs and when either the date, reason or method used to dispose of a sample was not recorded. Lastly, minor shortfalls in the T

standard were reported when sample traceability was not maintained when samples were in transit.

There were ten major shortfalls reported in the PFE standard. They were reported when there was a lack of temperature monitoring of the storage areas and when establishments failed to investigate temperature deviations. The Authority also reported major shortfalls when there was a lack of oxygen monitoring in storage areas using liquid nitrogen, which posed a risk to staff. Not analysing temperature trends and not having an alarm call out process were also reported as major shortfalls. There were also cases where storage conditions were insufficient or unsuitable, and when there was no challenge of alarms to verify whether they were operational. Lastly, the Authority reported major shortfalls when establishments had no service contracts covering maintenance, validation and calibration of freezers in place, and when there were no equipment checks performed. There were 53 minor shortfalls reported in the PFE standard. Some were in relation to the type of shortfall already described above. Others were in relation to the lack of documented cleaning and decontamination procedures of the facilities storing human tissue. Minor shortfalls were also reported in relation to inadequate contingency plan arrangements, samples stored in non-secure locations, and the lack of a process to report equipment problems.

The Authority assess compliance by inspecting licensed establishments, but, in their visits, they also take the opportunity to offer advice on how to improve practice. Someone working in a licensed establishment in the academic research sector, for instance, might not have previous experience with regulated work and how to adhere to a quality management system. Therefore, advice given by the HTA in the research sector is valuable and welcome. Although the HTA published standards are readily available, their interpretation in practice might be daunting. This thesis has shown that indeed the Authority has been very active in providing advice over the last 9 years. They gave 122 items of advice in the C standard, 387 in GQS, 173 in T, and 192 in PFE. In addition, the itemised narrative in the advice section of this work has helped freeing the ambiguity in the interpretation of the standards. After reading the advice given, the author made changes to practices in her own place of work. These changes were in relation to adverse event reporting, documenting cleaning and decontamination procedures, having a mechanism in place for checking consent documentation for human tissue obtained from commercial sources and from abroad, and finally strengthening sample audit trails while samples are in transit.

The international regulatory landscape of tissue banks providing material for research is varied. Countries like the U.S. and Canada have regulatory organisations enforcing laws and regulations in establishments that deal with human tissue for use in human applications such as transplants. However, tissue banks and biobanks created for educational and research purposes do not have oversight from governmental bodies. They instead adhere to standard setting professional bodies. One of these bodies is the American Association of Tissue Banks (AATB). The AATB in a non-governmental, not-for-profit organisation founded in 1976 in the USA with scientific and educational aims related to the safety and use of donated human tissue (17,18). The Association initiated an Accreditation Program for tissue banks in 1986 based on its standards and policies and has an inspection program for new and existing members. Current membership is voluntary and includes tissue establishments that provide human tissue for transplantation or transfer, and institutions that facilitate human tissue donations for educational and research purposes, the so-called non-transplant tissue banks. Certain AATB guidance documents are advisory only while others describe mandatory requirements for those tissue banks accredited by the AATB. In contrast with the Human Tissue Authority's legal licensing requirements in the UK, the AATB has no ability to force compliance within its members, apart from expelling them from its accredited program (19). Furthermore, there are no federal U.S. laws governing the sale of cadavers or body parts for use in research or education (20). Selling human body organs for transplant is illegal in the U.S., but procuring cadaver tissues, organs and bodies for research and education is not. The Human Tissue Authority in the UK, on the other hand, licences and inspects the organisations that do.

The U.S. government closely regulates the human transplant and therapeutic sectors. The Food and Drug Administration (FDA) Office of Regulatory Affairs (ORA) is responsible for the inspection of human tissue banks that manufacture FDA-regulated products intended for human transplantation in the U.S. (21). The ORA provides yearly inspectional observation data sets summarising the number of times an inspectional observation has been cited. The FDA also has a database called the Human Cell and Tissue Establishment Registration (HCTERS) database where tissue banks regulated by the FDA are registered (22). The U.S. Office of Infectious Disease and HIV/AIDS Policy (OIDP) published a survey of tissue establishments involved or engaged in services involving human tissue from both the living and deceased (23). This survey showed that the AATB and FDA did not exclusively inspect tissue banks in the U.S. Some were also inspected by the Clinical Laboratory Improvement Amendments program (CLIA) used by the Centers for Medicare

& Medicaid Services (CMS). The CMS regulates all laboratory testing performed on humans in the U.S. except for those used in research (24). Other tissue banks in the survey were inspected against standards from the International Organization for Standardization (ISO), and the College of American Pathologists (CAP) Laboratory Accreditation Program (25,26).

In Europe, there also seems to be context sensitive regulations. Like in the U.S., all EU countries have a governmental authority that regulates tissue banks that procure and store human tissue used for treatment in healthcare systems. The legal framework in the EU consists of three EC Directives: Directive 2004/23/EC, which is the parent Directive that provides the framework, and two technical Directives, 2006/17/EC and 2006/86/EC that detail the requirements (27). Biobanks in Europe providing samples for research purposes follow a similar format of the so-called non-transplant tissue banks in the U.S. Most hold or are working towards obtaining certificates such as ISO 9001, accreditation certificates such as ISO 15198, as well as technical specifications such as CEN (28). Research ethics committees (RECs) and Data Protection Authorities, who are responsible for reviewing the research protocols and data processing at national levels, (29) also assess biobanks providing samples for research. The Human Tissue Authority in the UK and the Norwegian Board of Health Supervision in Norway (30,31) are additional bodies sanctioned by the state to assess the compliance of biobank activities. Lastly, other levels of oversight are found in those institutions where a biobank is based or by local health authorities who might host the biobank.

A key message from the Human Tissue Authority in the UK is that "Good regulation supports good science, which in turn leads to better healthcare" (32). As shown in this work, there is a variation in how establishments interpret the regulations. For this reason, the human tissue sector in the UK benefits from the Authority. The HTA does not only highlight the shortfalls and non-compliances of those inspected, but also they provide advice to improve practice. The Human Tissue Authority adheres to the principles of good regulation: Proportionality, Accountability, Consistency, Transparency, and Targeting (33). Certainly, as a member of the research tissue sector in the UK, the author has gained insight from the HTA's transparent regulatory approach.

The Human Tissue Authority was created following the introduction of the Human Tissue Act 2004 in the United Kingdom after several tissue retention scandals came to light. The public inquiry at Bristol Royal Infirmary hospital (5) not only revealed medical

malpractice in the paediatric cardiac surgery department, but also a culture of human tissue retention taken without appropriate consent. Families had to deal with the tragic loss of loved ones, and in subsequent years, with the knowledge that organs had been taken from them without their consent. Since its inception, the Human Tissue Authority has inspected hundreds of establishments working with human tissue and has made public and accessible all the reports. The Authority stands for the fundamental principles of the Act: informed consent, dignity, quality and openness. It also gives confidence to the public and helps establishments to bring about improvement. The Authority's inspections also remind us the reason why they were put there in the first place. Quoting George Santayana's famous saying, "Those who cannot remember the past are condemned to repeat it" (34).

5 Reference list

1. Corbin J. Stolen Hearts. Transcript from TV documentary. Panorama. BBC News. 2000 Feb 21. Available from: http://news.bbc.co.uk/1/hi/programmes/panorama/archive/648151.stm
2. *BBC News.* Fury over Alder Hey report. 2001 Jan 30. Available from: http://news.bbc.co.uk/1/hi/health/1143414.stm
3. *BBC News*. Organ scandal background. 2001 Jan 29. Available from: http://news.bbc.co.uk/1/hi/1136723.stm
4. *The Guardian*. Arrogance of doctors led to organ scandal. 2000 May 11. Available from: https://www.theguardian.com/uk/2000/may/11/alderhey.sarahboseley
5. Department of Health. The Report of the Public Inquiry into children's heart surgery at the Bristol Royal Infirmary 1984-1995. Learning from Bristol. July 2001 [cited 2019 September 29]. Available from: https://webarchive.nationalarchives.gov.uk/20090811143810/http://www.bristol-inquiry.org.uk/final_report/report/index.htm
6. The House of Commons. The Royal Liverpool Children's Inquiry Report. 2001 Jan 30 [cited 2019 September 29]. Available from: https://www.gov.uk/government/publications/the-royal-liverpool-childrens-inquiry-report
7. Human Tissue Act 2004, c.30 [cited 2019 Sept 29]. Available from: http://www.legislation.gov.uk/ukpga/2004/30/contents
8. Human Tissue Act 1961, c.54 [cited 2020 June 25]. Available from: http://www.legislation.gov.uk/ukpga/Eliz2/9-10/54/contents/enacted
9. Anatomy Act 1984, c.14 [cited 2020 June 25]. Available from: http://www.legislation.gov.uk/ukpga/1984/14/contents
10. The Human Organ Transplants Act 1989, c.65 [cited 2020 June 25]. Available from: http://www.legislation.gov.uk/uksi/1989/2106/contents/made
11. Johnson, G., Wilson, A. Human Tissue Act 2004: The age of consent arrives in the UK. Journal of Commercial Biotechnology [Internet] 2005 [cited 2020 June 25] 12, 40. Available from: https://doi.org/10.1057/palgrave.jcb.3040146
12. Davies, J. The implications of the Human Tissue Act 2004. Clinical risk [Internet] 2006 [cited 2020 June 25] 12, 92. Available from: https://doi.org/10.1177/135626220601200303

13. Human Tissue Authority. The regulator for human tissue and organs [Internet] [cited 2019 Sept 29]. Available from: https://www.hta.gov.uk/
14. Adam, D. Tissue donations slump after revelations about misuse. Nature [Internet] 2001 [cited 2019 Sept 29] 409, 655. Available from: https://doi.org/10.1038/35055696
15. Human Tissue Authority. Research standards and guidance [Internet]. 2016 Jan 23 [cited 2019 Sept 29]. Available from: https://www.hta.gov.uk/sites/default/files/Code%20E%20Research%20Standards%20and%20Guidance.pdf
16. Human Tissue Authority. Research sector review: July 2016 [Internet]. 2016 August [cited 2020 June 10]. Available from: https://www.hta.gov.uk/sites/default/files/research%20summary%202016.pdf
17. American Association of Tissue Banks [Internet] [cited 2020 June 26]. Available from: https://www.aatb.org/
18. Joyce, MJ. American association of tissue banks: a historical reflection upon entering the 21st century. Cell Tissue Bank [Internet] 2000 [cited 2020 June 26] 1(1):5-8. Available from: https://link.springer.com/article/10.1023/A:1010136408283
19. Indech, B. The international harmonization of human tissue regulation: regulatory control over human tissue use and tissue banking in select countries and the current state of international harmonization efforts. Food Drug Law Journal [Internet] 2000 [cited 2020 June 26] 55(3):343-372. Available from: https://lifeguardianfoundation.org/pdfs/harmonization_of_human_tissue_regulation.pdf
20. *Reuters news*. In the market for human bodies, almost anyone can sell the dead. 2017 October 24. Available from: https://uk.reuters.com/article/uk-usa-bodies-brokers-specialreport/in-the-market-for-human-bodies-almost-anyone-can-sell-the-dead-idUKKBN1CT1F7
21. Office of Regulatory Affairs [Internet] [cited 2020 June 26]. Available from: https://www.fda.gov/about-fda/fda-organization/office-regulatory-affairs
22. Human Cell and Tissue Establishment Registration (HCTERS) [Internet] [cited 2020 June 26]. Available from: https://www.fda.gov/vaccines-blood-biologics/biologics-establishment-registration/human-cell-and-tissue-establishment-registration-hcters-public-query-application
23. U.S. Department of Health and Human Services. The 2012 and 2015 National Tissue Recovery through Utilization Survey Report [cited 2020 June 26]. Available from: https://www.hhs.gov/sites/default/files/ntrus-report-2015.pdf

24. Centers for Medicare & Medicaid Services. Clinical Laboratory Improvement Amendments (CLIA) [Internet] [cited 2020 June 26]. Available from: https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA
25. International Organization for Standardization [Internet] [cited 2020 June 26]. Available from: https://www.iso.org/standards.html
26. College of American Pathologists. Laboratory Accreditation Program [Internet] [cited 2020 June 26]. Available from: https://www.cap.org/laboratory-improvement/accreditation/laboratory-accreditation-program
27. Pirnay, J. Access to human tissues for research and product development. From EU regulation to alarming legal developments in Belgium. EMBO reports [Internet] 2015 [cited 2020 June 27] 16(5): 557–562. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4428037/
28. BBMRI-ERIC newsletter. Biobanks Europe. Trust, quality, experience, knowledge [Internet] 2017 [cited 2020 June 27]. Available from: https://www.bbmri-eric.eu/wp-content/uploads/2017/02/2017_Newsletter6_7_WEB.pdf
29. European Commission. Biobanks for Europe. A challenge for Governance [Internet] 2012 [cited 2020 June 27]. Available from: https://ec.europa.eu/research/science-society/document_library/pdf_06/biobanks-for-europe_en.pdf
30. Norwegian Act Relating to Biobanks 2003 [Internet] [cited 2020 June 26]. Available from: https://app.uio.no/ub/ujur/oversatte-lover/data/lov-20030221-012-eng.pdf
31. Norwegian Board of Health Supervision [Internet] [cited 2020 June 26]. Available from: https://www.helsetilsynet.no/en/
32. Human Tissue Authority. Guide to our key messages [Internet] [cited 2020 June 26]. Available from: https://www.nhs.uk/NHSEngland/aboutnhs/Documents/HTA_Guide_to_our_key_messages_final[1].pdf
33. UK Parliament. Improving the framework of regulation [Internet] [cited 2020 June 27]. Available from: https://publications.parliament.uk/pa/ld200304/ldselect/ldconst/68/6810.htm#note130
34. Santayana G. Life of reason: reason in common sense. New York: Scribner, 1905: 284.

Annex 1 – Table of inspected licences

License number	Final report issued date	Establishment name *(In blue those inspected against standards produced pre-April 2017 and in pink post-April 2017)*
12169	14-Dec-10	Intertek 4Front Research
12172	24-Mar-11	University of Manchester
12374	06-Jun-11	Vertex Pharmaceuticals (Europe) Limited
12534	20-Jun-11	Newcastle University
12220	22-Jun-11	Institute of Child Health
12344	07-Jul-11	Source Bioscience
12265	25-Jul-11	University of Nottingham Medical School
12508	29-Jul-11	University of Reading
12382	05-Aug-11	Durham University
12277	08-Aug-11	Eastman Dental Institute
12177	29-Aug-12	UCL Institute of Ophthalmology
12321	31-Oct-12	National Institute for Biological Standards and Control (NIBSC)
12419	07-Dec-12	Kingston University
12335	03-Jan-13	St George's University of London
12103	25-Jan-13	Peninsula College of Medicine and Dentistry, Plymouth
12402	02-Apr-13	Manchester Metropolitan University
12583	02-May-13	School of Pharmacy and Biomolecular Sciences, University of Brighton
30000	26-Jun-13	Royal Marsden NHS Foundation Trust
12585	04-Jul-13	Evotec UK Limited
12558	05-Jul-13	Eli Lilly and Company Limited
12533	17-Jul-13	Middlesex University
12322	29-Jul-13	Institute of Cancer Research
12044	24-Sep-13	Queen's University Belfast
12030	06-Jan-14	The Walton Centre NHS Foundation Trust
12121	27-Jan-14	Guy's and St Thomas' Research Tissue Bank
12590	20-May-14	Lonza Biologics Plc
12539	22-May-14	Oxford BioTherapeutics Limited
12400	10-Jul-14	Huntingdon Research Centre
12600	29-Jul-14	LGC Ltd
12055	13-Sep-14	UCL Cancer Institute
12588	15-Sep-14	ProImmune Ltd
12494	26-Sep-14	Covance Laboratories Ltd
12510	23-Oct-14	Sequani Ltd
12613	29-Oct-14	Propath UK Limited
12056	29-Oct-14	Lancashire Teaching Hospitals Foundation NHS Trust
12563	07-Nov-14	Leica Biosystems Newcastle Ltd
12532	11-Nov-14	Synairgen Research Limited
12609	12-Nov-14	LGC Ltd
12193	02-Dec-14	Newcastle upon Tyne Hospitals NHS Foundation Trust
12059	10-Dec-14	Queen's University Belfast

12575	10-Dec-14	Orchid Cellmark Ltd
12559	15-Dec-14	Almac Diagnostics
12283	23-Dec-14	MedImmune Ltd
12587	30-Dec-14	Imanova Ltd
12440	03-Feb-15	Defence Science and Technology Laboratory
12604	12-Feb-15	The University of York
12275	13-Feb-15	Hammersmith Hospital
12571	16-Feb-15	Oxford BioDynamics Ltd
12630	12-Mar-15	Hywel Dda University Health Board (licence application)
12198	17-Mar-15	Institute of Neurology, UCL
12586	31-Mar-15	Oxford Gene Technology (Operations) Ltd
12617	09-Apr-15	Re:Cognition Health Limited
12611	14-Apr-15	Syntaxin Ltd
12632	23-Apr-15	Edge Hill University (licence application)
12598	08-May-15	Crown Bioscience UK Ltd
12381	18-May-15	Aston University
12615	30-Jun-15	St Mary's University
12622	31-Jul-15	F-Star Biotechnology
12623	12-Aug-15	UK Biostores & Services Ltd
12358	14-Oct-15	College of Medical and Dental Sciences
12064	23-Oct-15	University of Ulster
12248	15-Nov-15	University of Bristol
12641	19-Nov-15	University of Huddersfield (licence application)
12240	07-Dec-15	MRC Clinical Sciences Centre
12624	22-Dec-15	NIHR-National Biosample Centre
12631	15-Jan-16	Mitomics UK Limited
12627	26-Jan-16	Antitope Limited
12645	12-Feb-16	Biofocus DPI Ltd (licence application)
12633	11-Apr-16	Quotient Bioresearch
12649	19-Apr-16	Takeda Cambridge Ltd (licence application)
12315	25-Apr-16	Addenbrooke's Hospital
12629	28-Apr-16	Clatterbridge Cancer Centre
12313	10-May-16	The School of Dentistry, Birmingham
12512	10-Jun-16	Oakfield House, School of Social and Community Medicine, Univ. Bristol
12293	30-Jun-16	London Neurodegenerative Diseases Brain Bank
12521	14-Jul-16	King's College London
12560	11-Aug-16	Chelsea and Westminster Hospital
12561	26-Aug-16	Brighton and Sussex Medical School
12638	30-Aug-16	Horizon Discovery Limited
12636	14-Sep-16	SPD Development Company Ltd
12658	30-Sep-16	York Bioanalytical Solutions Ltd.
12495	18-Oct-16	Northumbria University
12097	09-Nov-16	HistologiX Limited
12543	10-Nov-16	Brunel University London
12223	23-Nov-16	King's College London Haemato-Oncology Tissue Bank

12326	29-Nov-16	Oxford Centre for Diabetes, Endocrinology and Metabolism
12349	05-Dec-16	Keele University
12433	04-Jan-17	Weatherall Institute of Molecular Medicine
12657	05-Jan-17	Royal Holloway, University of London (licence application)
12665	27-Feb-17	RxCelerate Ltd, Babraham Research Campus, Cambridge (licence application)
12276	20-Mar-17	Royal Devon and Exeter Hospital
12514	20-Mar-17	British American Tobacco Research and Development Centre
12378	25-Apr-17	King's College Hospital
12522	28-Apr-17	King's College London
12515	05-May-17	Anglia Ruskin University (Cambridge East Road Campus)
12200	10-May-17	Bristol Dental School and Hospital
12443	30-May-17	BBI Solutions
12219	07-Jul-17	Birmingham Women's Hospital
12506	25-Jul-17	Abcam plc
12122	28-Jul-17	Astex Therapeutics Ltd
12667	03-Aug-17	ProAxsis Ltd (licence application)
12668	08-Aug-17	GammaDelta Therapeutics Ltd (license application)
12634	08-Aug-17	LifeArc
12614	08-Aug-17	Sygnature Discovery Ltd
12568	09-Aug-17	Cryo-Store Ltd
12104	29-Aug-17	University of Exeter
12199	31-Aug-17	Queen Mary University of London
12352	31-Aug-17	St James's University Hospital
12388	06-Nov-17	Royal Brompton and Harefield NHS Foundation Trust
12353	07-Nov-17	Asterand UK Acquisition Limited
12002	13-Nov-17	UK Biobank
12594	27-Nov-17	hVIVO Services Limited (first report after new codes published)
12212	06-Apr-18	Papworth Hospital
12674	09-Apr-18	Centauri Therapeutics (licence application)
12675	12-Apr-18	Novo Nordisk Research Centre Oxford (licence application)
12504	03-May-18	UCB Celltech (Slough, Berkshire)
12672	30-May-18	Caltag Medsystems Limited (licence application)
12408	04-Jun-18	Cardiff Metropolitan University
12009	06-Jun-18	University of Southampton
12528	07-Jun-18	Liverpool John Moores University
12119	05-Jul-18	University of Sussex
12676	20-Jul-18	Tusk Therapeutics Limited (licence application)
12647	01-Aug-18	Mologic Ltd
12653	08-Aug-18	Cyprotex Discovery Ltd
12066	28-Aug-18	London School of Hygiene and Tropical Medicine
12680	28-Aug-18	Stemnovate Ltd (licence application)

12577	30-Aug-18	Loughborough University
12661	17-Sep-18	University of Brighton
12678	25-Sep-18	University of Lincoln (licence application)
12681	28-Sep-18	Empyrean Therapeutics Ltd
12651	04-Oct-18	Swansea University
12422	05-Nov-18	University Hospital Wales
12572	16-Nov-18	Eurofins Pharma Bioanalysis Services UK Ltd
12397	27-Nov-18	Unilever Colworth
12635	12-Dec-18	Adaptimmune Ltd
12682	19-Dec-18	Teeside University (licence application)
12548	15-Jan-19	Liverpool School of Tropical Medicine
12196	15-Jan-19	University of Cambridge - Downing Site
12291	13-Mar-19	Salford Royal NHS Foundation Trust
12202	01-Apr-19	GlaxoSmithKline
12650	09-Apr-19	The Francis Crick institute
12664	25-Apr-19	ADC Therapeutics (UK) Ltd
12182	30-Apr-19	University of Sheffield
12643	13-May-19	Immunocore Ltd
12020	28-May-19	University of Liverpool
12074	20-Jun-19	Unilever Research and Development Port Sunlight
30004	02-Jul-19	The Christie
12015	23-Jul-19	University of Westminster
12217	26-Jul-19	John Radcliffe Hospital
12384	05-Aug-19	Leicester Royal Infirmary
12365	15-Aug-19	University of Surrey
12688	03-Sep-19	Cryosphere Services Ltd (licence application)
12692	11-Sep-19	Locate Bio (licence application)
12691	12-Sep-19	Sitryx Therapeutics (licence application)
12693	09-Oct-19	Research Donors Limited (licence application)
12297	25-Nov-19	Clinical Sciences Research Institute, Warwick Medical School, University of Warwick
12358	05-Dec-19	College of Medical and Dental Sciences
12168	16-Jan-20	Clinical Trial Service Unit and Epidemiological Studies Unit

Annex 2 – Human Tissue Authority standards post April 2017

Consent Standards

C1 Consent is obtained in accordance with the requirements of the Human Tissue Act 2004 (HT Act) and as set out in the code of practice

a) Consent procedures are documented and these, along with any associated documents, comply with the HT Act and the HTA's Codes of Practice.

b) Consent forms are available to those using or releasing relevant material for a scheduled purpose.

c) Where applicable, there are agreements with other parties to ensure that consent is obtained in accordance with the requirements of the HT Act and the HTA's Codes of Practice

d) Written information is provided to those from whom consent is sought, which reflects the requirements of the HT Act and the HTA's Codes of Practice.

e) Language translations are available when appropriate

f) Information is available in formats appropriate to the situation

C2 Staff involved in seeking consent receive training and support in the essential requirements of taking consent

a) There is suitable training and support of staff involved in seeking consent, which addresses the requirements of the HT Act and the HTA's Codes of Practice.

b) Records demonstrate up-to-date staff training

c) Competency is assessed and maintained.

Governance and quality system standards

GQ1 All aspects of the establishments work are governed by documented policies and procedures as part of the overall governance process

a) Ratified, documented and up-to-date policies and procedures are in place, covering all licensable activities.

b) There is a document control system

c) There are change control mechanisms for the implementation of new operational procedures.

d) Matters relating to HTA-licensed activities are discussed at regular governance meetings, involving establishment staff.

e) There is a system for managing complaints.

GQ2 There is a documented system of audit

a) There is a documented schedule of audits covering licensable activities

b) Audit findings include who is responsible for follow-up actions and the timeframes for completing these.

GQ3 Staff are appropriately qualified and trained in techniques relevant to their work and are continuously updating their skills

a) Qualifications of staff and all training are recorded, records showing attendance at training.

b) There are documented induction training programmes for new staff

c) Training provisions include those for visiting staff

d) Staff have appraisals and personal development plans

GQ4 There is a systematic and planned approach to the management of records

a) There are suitable systems for the creation, review, amendment, retention and destruction of records.

b) There are provisions for back-up / recovery in the event of loss of records.

c) Systems ensure data protection, confidentiality and public disclosure (whistleblowing).

GQ5 There are systems to ensure that all adverse events are investigated promptly

a) Staff are instructed in how to use incident reporting systems.

b) Effective corrective and preventive actions are taken where necessary and improvements in practice are made.

GQ6 Risk assessments of the establishment's practices and processes are completed regularly, recorded and monitored

a) There are documented risk assessments for all practices and processes requiring compliance with the HT Act and the HTA's Codes of Practice.

b) Risk assessments are reviewed regularly.

c) Staff can access risk assessments and are made aware of risks during training.

Traceability standards

T1 A coding and records system facilitates the traceability of bodies and human tissue, ensuring a robust audit trail

a) There is an identification system which assigns a unique code to each donation and to each of the products associated with it.

b) A register of donated material, and the associated products where relevant, is maintained.

c) An audit trail is maintained, which includes details of: when and where the bodies or tissue were acquired and received; the consent obtained; all sample storage locations; the uses to which any material was put; when and where the material was transferred, and to whom.

d) A system is in place to ensure that traceability of relevant material is maintained during transport.

e) Records of transportation and delivery are kept.

f) Records of any agreements with courier or transport companies are kept.

g) Records of any agreements with recipients of relevant material are kept.

T2 Bodies and human tissue are disposed of in an appropriate manner

a) Disposal is carried out in accordance with the HTA's Codes of Practice.

b) The date, reason for disposal and the method used are documented.

Premises, facilities and equipment standards

PFE1 The premises are secure and fit for purpose

a) An assessment of the premises has been carried out to ensure that they are appropriate for the purpose.

b) Arrangements are in place to ensure that the premises are secure and confidentiality is maintained.

c) There are documented cleaning and decontamination procedures.

PFE2 There are appropriate facilities for the storage of bodies and human tissue

a) There is sufficient storage capacity.

b) Where relevant, storage arrangements ensure the dignity of the deceased.

c) Storage conditions are monitored, recorded and acted on when required.

d) There are documented contingency plans in place in case of failure in storage area.

PFE3 Equipment is appropriate for use, maintained, validated and where appropriate monitored

a) Equipment is subject to recommended calibration, validation, maintenance, monitoring, and records are kept.

b) Users have access to instructions for equipment and are aware of how to report an equipment problem.

c) Staff are provided with suitable personal protective equipment.

Annex 3 – Human Tissue Authority standards pre April 2017

Consent standards

C1 Consent is obtained in accordance with the requirements of the Human Tissue Act 2004 (HT Act) and as set out in the code of practice

- Consent forms comply with the HTA's Code of Practice
- Consent forms are in records and are made accessible to those using or releasing relevant material for a scheduled purpose
- If the establishment obtains consent, a process is in place for acquiring consent in accordance with the requirements of the HT Act 2004 and the HTA's Codes of Practice
- Where applicable, there are agreements with third parties to ensure that consent is obtained in accordance with the requirements of the HT Act 2004 and the HTA's Codes of Practice
- Consent procedures have been ethically approved

C2 Information about the consent process is provided and in a variety of formats

- Standard operating procedures (SOPs) detail the procedure for providing information on consent
- Agreements with third parties contain appropriate information
- Independent interpreters are available when appropriate
- Information is available in suitable formats, appropriate to the situation
- Consent procedures have been ethically approved

C3 Staff involved in seeking consent receive training and support in the implications and essential requirements of taking consent

- Standard operating procedures (SOPs) detail the consent process
- Evidence of suitable training of staff involved in seeking consent
- Records demonstrate up-to-date staff training
- Competency is assessed and maintained

Governance and quality system standards

GQ1 All aspects of the establishments work are supported by ratified documented policies and procedures as part of the overall governance process

- Policies and procedures in place are in place, covering all activities related to the storage of relevant material for research in connection with disorders, or the functioning, of the human body
- Appropriate risk management systems are in place
- Regular governance meetings are held; for example, health and safety and risk management committees, agendas and minutes
- Complaints system

GQ2 There is a documented system of quality management and audit

- A document control system, covering all documented policies and standard operating procedures (SOPs)
- Schedule of audits
- Change control mechanisms for the implementation of new operational procedures

GQ3 Staff are appropriately qualified and trained in techniques relevant to their work and are continuously updating their skills

- Qualifications of staff and training are recorded, records showing attendance at training
- Orientation and induction programmes
- Documented training programme, (e.g. health and safety, fire, risk management, infection control), including developmental training
- Training and reference manuals
- Staff appraisal / review records and personal development plans are in place GQ4 There is a systematic and planned approach to the management of records
- Documented procedures for the creation, amendment, retention and destruction of records
- Regular audit of record content to check for completeness, legibility and accuracy
- Back-up / recovery facility in the event of loss of records
- Systems ensure data protection, confidentiality and public disclosure (whistle-blowing)

GQ5 There are documented procedures for distribution of body parts, tissues or cells

- A process is in place to review the release of relevant material to other organisations
- An agreement is in place between the establishment and the organisation to whom relevant material is supplied regarding the tracking and use of material and eventual disposal or return

GQ6 A coding and records system facilitates traceability of bodies, body parts, tissues and cells, ensuring a robust audit trail

- There is an identification system which assigns a unique code to each donation and to each of the products associated with it
- An audit trail is maintained, which includes details of when and where the relevant material was acquired, the consent obtained, the uses to which the material was put, when the material was transferred and to whom

GQ7 There are systems to ensure that all adverse events are investigated promptly

- Corrective and preventive actions are taken where necessary and improvements in practice are made
- System to receive and distribute national and local information (e.g. HTA communications)

GQ8 Risk assessments of the establishment's practices and processes are completed regularly and are recorded and monitored appropriately

- Documented risk assessments for all practices and processes
- Risk assessments are reviewed when appropriate
- Staff can access risk assessments and are made aware of local hazards at training

Premises, facilities and equipment standards

PFE1 The premises are fit for purpose

- A risk assessment has been carried out of the premises to ensure that they are appropriate for the purpose
- Policies in place to review and maintain the safety of staff, authorised visitors and students
- The premises have sufficient space for procedures to be carried out safely and efficiently
- Policies are in place to ensure that the premises are secure and confidentiality is maintained

PFE 2 Environmental controls are in place to avoid potential contamination

- Documented cleaning and decontamination procedures
- Staff are provided with appropriate protective equipment and facilities that minimise risks from contamination
- Appropriate health and safety controls are in place

PFE3 There are appropriate facilities for the storage of bodies, body parts, tissues and cells, consumables and records.

- Relevant material, consumables and records are stored in suitable secure environments and precautions are taken to minimise risk of damage, theft or contamination
- Contingency plans are in place in case of failure in storage area
- Critical storage conditions are monitored and recorded
- System to deal with emergencies on 24 hour basis
- Records indicating where the material is stored in the premises

PFE 4 Systems are in place to protect the quality and integrity of bodies, body parts, tissues and cells during transport and delivery to a destination

- Documented policies and procedures for the appropriate transport of relevant material, including a risk assessment of transportation
- A system is in place to ensure that traceability of relevant material is maintained during transport
- Records of transportation and delivery
- Records are kept of any agreements with recipients of relevant material
- Records are kept of any agreements with courier or transport companies

PFE5 Equipment is appropriate for use, maintained, quality assured, validated and where appropriate monitored

- Records of calibration, validation and maintenance, including any agreements with maintenance companies
- Users have access to instructions for equipment and receive training in use and maintenance where appropriate
- Staff aware of how to report an equipment problem
- Contingency plan for equipment failure

Disposal Standards

D1 There is a clear and sensitive policy for disposing of human organs and tissue

- Documented disposal policy
- Policy is made available to the public
- Compliance with health and safety recommendations

D2 The reason for disposal and the methods used are carefully documented

- Standard operating procedures (SOPs) for tracking the disposal of relevant material detail the method and reason for disposal
- Where applicable, disposal arrangements reflect specified wishes

Annex 4 – Author's comparison of Human Tissue Authority standards pre and post April 2017

Key: green for standards that have been kept after April 2017 and red for newly introduced standard subcategory codes (shown here for reference) and purple for standards which have been removed

Consent standards

C1 Consent is obtained in accordance with the requirements of the Human Tissue Act 2004 (HT Act) and as set out in the code of practice

- C1d,e - Consent forms comply with the HTA's Code of Practice
- C1b - Consent forms are in records and are made accessible to those using or releasing relevant material for a scheduled purpose
- C1a - If the establishment obtains consent, a process is in place for acquiring consent in accordance with the requirements of the HT Act 2004 and the HTA's Codes of Practice
- C1c- Where applicable, there are agreements with third parties to ensure that consent is obtained in accordance with the requirements of the HT Act 2004 and the HTA's Codes of Practice
- C1a - Consent procedures have been ethically approved

C2 Information about the consent process is provided and in a variety of formats

- C1a - Standard operating procedures (SOPs) detail the procedure for providing information on consent
- C1c - Agreements with third parties contain appropriate information
- C1e - Independent interpreters are available when appropriate
- C1f - Information is available in suitable formats, appropriate to the situation
- C1a - Consent procedures have been ethically approved

C3 Staff involved in seeking consent receive training and support in the implications and essential requirements of taking consent

- C1a - Standard operating procedures (SOPs) detail the consent process
- C2a - Evidence of suitable training of staff involved in seeking consent

- C2b - Records demonstrate up-to-date staff training
- C2c - Competency is assessed and maintained

Governance and quality system standards

GQ1 All aspects of the establishments work are supported by ratified documented policies and procedures as part of the overall governance process

- GQ1a - Policies and procedures in place are in place, covering all activities related to the storage of relevant material for research in connection with disorders, or the functioning, of the human body
- GQ6a,c - Appropriate risk management systems are in place
- GQ1d - Regular governance meetings are held; for example, health and safety and risk management committees, agendas and minutes
- GQ1e - Complaints system

GQ2 There is a documented system of quality management and audit

- GQ1b - A document control system, covering all documented policies and standard operating procedures (SOPs).
- GQ2a - Schedule of audits
- GQ1c - Change control mechanisms for the implementation of new operational procedures

GQ3 Staff are appropriately qualified and trained in techniques relevant to their work and are continuously updating their skills

- GQ3a - Qualifications of staff and training are recorded, records showing attendance at training
- GQ3b - Orientation and induction programmes
- GQ3b - Documented training programme, (e.g. health and safety, fire, risk management, infection control), including developmental training
- GQ3b - Training and reference manuals
- GQ3d - Staff appraisal / review records and personal development plans are in place

GQ4 There is a systematic and planned approach to the management of records

- GQ4a - Documented procedures for the creation, amendment, retention and destruction of records
- GQ2a,b - Regular audit of record content to check for completeness, legibility and accuracy
- GQ4b - Back-up / recovery facility in the event of loss of records
- GQ4c - Systems ensure data protection, confidentiality and public disclosure (whistle-blowing)

GQ5 There are documented procedures for distribution of body parts, tissues or cells

- T1b,c - A process is in place to review the release of relevant material to other organisations
- T1g - An agreement is in place between the establishment and the organisation to whom relevant material is supplied regarding the tracking and use of material and eventual disposal or return

GQ6 A coding and records system facilitates traceability of bodies, body parts, tissues and cells, ensuring a robust audit trail

- T1a - There is an identification system which assigns a unique code to each donation and to each of the products associated with it
- T1c - An audit trail is maintained, which includes details of when and where the relevant material was acquired, the consent obtained, the uses to which the material was put, when the material was transferred and to whom

GQ7 There are systems to ensure that all adverse events are investigated promptly

- GQ5b - Corrective and preventive actions are taken where necessary and improvements in practice are made
- System to receive and distribute national and local information (e.g. HTA communications)

GQ8 Risk assessments of the establishment's practices and processes are completed regularly and are recorded and monitored appropriately

- GQ6a - Documented risk assessments for all practices and processes
- GQ6b - Risk assessments are reviewed when appropriate

- GQ6c - Staff can access risk assessments and are made aware of local hazards at training

Premises, facilities and equipment standards

PFE1 The premises are fit for purpose

- PFE1a - A risk assessment has been carried out of the premises to ensure that they are appropriate for the purpose
- Policies in place to review and maintain the safety of staff, authorised visitors and students
- PFE2a - The premises have sufficient space for procedures to be carried out safely and efficiently
- PFE1b - Policies are in place to ensure that the premises are secure and confidentiality is maintained

PFE 2 Environmental controls are in place to avoid potential contamination

- PFE1c - Documented cleaning and decontamination procedures
- PFE3c - Staff are provided with appropriate protective equipment and facilities that minimise risks from contamination
- Appropriate health and safety controls are in place

PFE3 There are appropriate facilities for the storage of bodies, body parts, tissues and cells, consumables and records.

- PFE1b - Relevant material, consumables and records are stored in suitable secure environments and precautions are taken to minimise risk of damage, theft or contamination
- PFE2d - Contingency plans are in place in case of failure in storage area
- PFE2c - Critical storage conditions are monitored and recorded
- PFE2c - System to deal with emergencies on 24 hour basis
- PFE1b - Records indicating where the material is stored in the premises

PFE 4 Systems are in place to protect the quality and integrity of bodies, body parts, tissues and cells during transport and delivery to a destination

- Documented policies and procedures for the appropriate transport of relevant material, including a risk assessment of transportation
- T1d - A system is in place to ensure that traceability of relevant material is maintained during transport
- T1e - Records of transportation and delivery
- T1g - Records are kept of any agreements with recipients of relevant material
- T1f - Records are kept of any agreements with courier or transport companies

PFE5 Equipment is appropriate for use, maintained, quality assured, validated and where appropriate monitored

- PFE3a - Records of calibration, validation and maintenance, including any agreements with maintenance companies
- PFE3b - Users have access to instructions for equipment and receive training in use and maintenance where appropriate
- PFE3b - Staff aware of how to report an equipment problem
- Contingency plan for equipment failure

Disposal Standards

D1 There is a clear and sensitive policy for disposing of human organs and tissue

- T2a - Documented disposal policy
- T2a - Policy is made available to the public
- Compliance with health and safety recommendations

D2 The reason for disposal and the methods used are carefully documented

- T2b - Standard operating procedures (SOPs) for tracking the disposal of relevant material detail the method and reason for disposal
- T2a - Where applicable, disposal arrangements reflect specified wishes

Annex 5 – Beta regression analysis

In this section, we model the scores by means of a beta distribution with common nuisance parameter and means possibly different means per group. We considered 5 models:

- model 1: no difference in means,
- model 2: difference in means between the public/private institutes,
- model 3: difference in means between the mono/multisite institutes,
- model 4: difference in means per group **without interaction** between the public/private and mono/multisite variables,
- model 5: difference in means per group **with interaction** between the public/private and mono/multisite variables.

The model checks (not shown here) suggest a good fit of the model to the data. Sensitivity analyses considering different nuisance parameters per group led to the same conclusions.

Comparison of models was assessed by means of Likelihood ratio tests comparing embedded models.

Model 2 is better than model 1 (there is a difference in means between private and public institutes):

```
##  Likelihood Ratio Test for nested GAMLSS models.
##  (No check whether the models are nested is performed).
##
##        Null model: deviance= -673.7275 with  2 deg. of freedom
##  Altenative model: deviance= -679.0493 with  3 deg. of freedom
##
##  LRT = 5.321795 with 1 deg. of freedom and p-value= 0.0210603
```

Model 3 is not significantly better than model 1 (there is not enough evidence to conclude that there is a difference in means between mono- and multi-site institutes):

```
##  Likelihood Ratio Test for nested GAMLSS models.
##  (No check whether the models are nested is performed).
##
##        Null model: deviance= -673.7275 with  2 deg. of freedom
##  Altenative model: deviance= -675.3476 with  3 deg. of freedom
##
##  LRT = 1.620102 with 1 deg. of freedom and p-value= 0.2030776
```

Model 4 is close to significance when compared to model 1 (this result is driven by the difference in means noted between private and public institutes) but there not enough evidence to show that model 4 is better than model 2:

```
##  Likelihood Ratio Test for nested GAMLSS models.
```

```
##  (No check whether the models are nested is performed).
##
##        Null model: deviance= -673.7275 with  2 deg. of freedom
##  Altenative model: deviance= -679.638 with  4 deg. of freedom
##
##  LRT = 5.910406 with 2 deg. of freedom and p-value= 0.05206809
```

```
##  Likelihood Ratio Test for nested GAMLSS models.
##  (No check whether the models are nested is performed).
##
##        Null model: deviance= -679.0493 with  3 deg. of freedom
##  Altenative model: deviance= -679.638 with  4 deg. of freedom
##
##  LRT = 0.5886106 with 1 deg. of freedom and p-value= 0.4429569
```

Model 5 is not significantly better than model 4 (the interaction between the public/private and mono/multisite factors does not improve the fit):

```
##  Likelihood Ratio Test for nested GAMLSS models.
##  (No check whether the models are nested is performed).
##
##        Null model: deviance= -679.638 with  4 deg. of freedom
##  Altenative model: deviance= -679.6733 with  5 deg. of freedom
##
##  LRT = 0.0353516 with 1 deg. of freedom and p-value= 0.8508608
```

The following output shows the results of the beta regression fit corresponding to model 2:

```
## ******************************************************************
## Family:  c("BE", "Beta")
##
## Call:  gamlss(formula = score ~ private, sigma.formula = ~1,
family = BE, data = dataw)
##
## Fitting method: RS()
##
## ------------------------------------------------------------------
## Mu link function:  logit
```

```
## Mu Coefficients:
##                Estimate Std. Error t value Pr(>|t|)
## (Intercept)     2.91701    0.07543  38.670   <2e-16 ***
## privatePrivate  0.25942    0.11292   2.297   0.0229 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## ------------------------------------------------------------------
## Sigma link function:  logit
## Sigma Coefficients:
##             Estimate Std. Error t value Pr(>|t|)
## (Intercept) -1.61158    0.06889  -23.39   <2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## ------------------------------------------------------------------
## No. of observations in the fit:  158
## Degrees of Freedom for the fit:  3
##       Residual Deg. of Freedom:  155
##                       at cycle:  9
##
## Global Deviance:     -679.0493
##             AIC:     -673.0493
##             SBC:     -663.8616
## ******************************************************************
```

Please note that the R-squared (proportion of variance of the response [overall score]) explained by the model is small: R2 = 3.31%. (so, the effect is significant but small).

Finally, one of the hypothesis was that multi-site public has a lower mean than mono-site private. The following output shows the beta regression fit of the model comparing multi-site public to the group mono-site private (reference):

```
## GAMLSS-RS iteration 1: Global Deviance = -305.8724
## GAMLSS-RS iteration 2: Global Deviance = -347.544
## GAMLSS-RS iteration 3: Global Deviance = -379.7557
## GAMLSS-RS iteration 4: Global Deviance = -394.799
## GAMLSS-RS iteration 5: Global Deviance = -398.0886
## GAMLSS-RS iteration 6: Global Deviance = -398.4475
```

```
## GAMLSS-RS iteration 7: Global Deviance = -398.4741
## GAMLSS-RS iteration 8: Global Deviance = -398.4759
## GAMLSS-RS iteration 9: Global Deviance = -398.476
## ******************************************************************
## Family:  c("BE", "Beta")
##
## Call:  gamlss(formula = score ~ group, sigma.formula = ~1,      family
= BE, data = dataw)
##
## Fitting method: RS()
##
## ------------------------------------------------------------------
## Mu link function:  logit
## Mu Coefficients:
##                          Estimate Std. Error t value Pr(>|t|)
## (Intercept)                3.1841     0.1084  29.376   <2e-16 ***
## groupMulti-site\nPublic  -0.3326     0.1462  -2.276   0.0253 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## ------------------------------------------------------------------
## Sigma link function:  logit
## Sigma Coefficients:
##             Estimate Std. Error t value Pr(>|t|)
## (Intercept) -1.60696    0.09058  -17.74   <2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## ------------------------------------------------------------------
## No. of observations in the fit:  92
## Degrees of Freedom for the fit:  3
##       Residual Deg. of Freedom:  89
##                       at cycle:  9
##
## Global Deviance:     -398.476
##             AIC:     -392.476
##             SBC:     -384.9106
```

```
## ************************************************************
```

We can note a significant (negative) effect: the mean score of **multi-site public** institutes is significantly lower the one of **mono-site private** institutes.