WHAT INFLUENCES THE HARMONISATION OF CANCER TISSUE BANKS IN THE UK?: AN ETHNOGRAPHIC STUDY

Thesis submitted for the degree of Doctor of Philosophy at the University of Leicester

by

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ABSTRACT

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What influences the harmonisation of cancer tissue banks in the UK?:
An ethnographic study

Persuasive arguments exist as to why the harmonisation of tissue banks is important. Yet harmonisation has not happened on a large scale and empirical research has not investigated the reasons for this in detail. This thesis presents the results of ethnographic research using the case study of cancer tissue banks to identify influences on harmonisation. The research involved 40 interviews and over 117 hours of observations with professionals working across 15 organisations. Data analysis was based on the constant comparative method with use of sensitising constructs from literatures on standards and diffusion of innovation. A new model of the tissue supply chain was developed and refined against the findings.

Harmonisation depends on the creation, implementation and outcome of standards. The empirical work showed that a complex picture of harmonisation emerges when the creation, implementation and outcome of standards are considered separately. Different factors act as barriers or facilitators, or as both, at each stage. Standard creation in cancer tissue banks is obstructed by a lack of agreement between organisations and professionals, who may have differing interests and views on the appropriate type and scope of standards, who should create them and how. Standard implementation can be enabled or hindered by standard design, the actions and features of organisations, and individual and professional factors. Critically, the outcome of implementing standards has not always increased harmonisation; in some cases the result is fragmentation, duplication or exclusion.

The thesis describes cross-cutting political, social and technical issues that arise during the tissue supply chain and throughout the stages of standard creation and implementation, making harmonisation complicated and difficult to achieve. Eight recommendations are offered for how harmonisation can be facilitated in practice.
ACKNOWLEDGEMENTS

Dedicated to a man I can’t forget and his wife I wish I’d met.

I dedicate this thesis to my grandfather Albert Errington (1920–2012), without whose support I would not have been able to attend university to undertake the Master’s degree that preceded this thesis. I also dedicate it to his wife, Sheila Errington (1923–1969), who sadly I never met in person, but wish I had.

My first acknowledgement must be to the participants in my study, whose kind contributions allowed me to begin to understand cancer tissue banking. They offered me many opportunities including attending private meetings or waiving conference fees, sometimes going so far as to collect me from train stations across the UK. One tissue bank manager was generous enough to allow me to spend a week trying not to obstruct activities at a busy tissue bank. Other participants told me engaging stories about their experiences of conducting research using human tissue and gave me tours of their labs, even letting me look inside their lab notebooks. Several clinicians let me observe their clinics or procedures and consultants put hours of their time aside to let me question them. People working at a pharmaceutical company invited me in and showed me their custom designed facilities. Due to the kindness of all the professionals involved, I enjoyed this part of the research immensely.

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<td>BBMRI</td>
<td>Biobanking and Biomolecular Resources Research Infrastructure</td>
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<td>BMA</td>
<td>Biomedical assistant</td>
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<tr>
<td>BRIF</td>
<td>Bioresource research impact factor</td>
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<td>BRISQ</td>
<td>Biospecimen reporting for improved study quality</td>
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<td>CaBIG™</td>
<td>Cancer Biomedical Informatics Grid, US</td>
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<td>CaHUB</td>
<td>The Cancer Human Biobank, US</td>
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<td>CaTissue</td>
<td>Cancer tissue banking information management system, US</td>
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<td>CCB</td>
<td>Confederation of Cancer Biobanks</td>
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<td>CCLG</td>
<td>Children’s Cancer and Leukaemia Group</td>
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<tr>
<td>CEN</td>
<td>European Committee for Standardisation</td>
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<td>CRO</td>
<td>Contract research organisation</td>
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<td>CRUK</td>
<td>Cancer Research UK</td>
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<td>EC</td>
<td>European Commission</td>
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<td>ECMC</td>
<td>Experimental Cancer Medicine Centre</td>
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<td>EHR</td>
<td>Electronic health record</td>
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<tr>
<td>ELSI</td>
<td>Ethical, legal and social implications</td>
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<td>ENCODE</td>
<td>ENCyclopedia Of DNA Elements Project</td>
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<td>ENGAGE</td>
<td>European Network for Genetic and Genomic Epidemiology</td>
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<td>EPIC</td>
<td>European Prospective Investigation into Cancer and Nutrition</td>
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<td>Abbreviation</td>
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<tr>
<td>ESBB</td>
<td>European, Middle Eastern &amp; African Society for Biopreservation &amp; Biobanking</td>
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<tr>
<td>FP</td>
<td>Framework programmes, European Commission</td>
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<tr>
<td>GCP</td>
<td>Good clinical practice</td>
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<td>HE</td>
<td>Dr Helen Eborall (PhD supervisor)</td>
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<td>HTA</td>
<td>Human Tissue Authority, UK</td>
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<td>ICGC</td>
<td>International Cancer Genome Consortium</td>
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<td>ICH</td>
<td>International Conference on Harmonization</td>
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<td>IP</td>
<td>Intellectual Property</td>
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<td>ISBER</td>
<td>International Society for Biological and Environmental Repositories</td>
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<td>ISO</td>
<td>International Organization for Standardization</td>
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<tr>
<td>JW</td>
<td>Jessica Wright (Author)</td>
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<tr>
<td>MDW</td>
<td>Professor Mary Dixon-Woods (PhD Supervisor)</td>
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<tr>
<td>MHRA</td>
<td>Medicines and Healthcare Products Regulatory Agency, UK</td>
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<tr>
<td>MI</td>
<td>Minimum information</td>
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<td>MIABIS</td>
<td>Minimum data set for sharing biobank samples, information and data</td>
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<td>MMI</td>
<td>Molecular Medicine Ireland</td>
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<td>MRC</td>
<td>Medical Research Council</td>
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<tr>
<td>MTA/MDTA</td>
<td>Material (and data) transfer agreement</td>
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<tr>
<td>NCI</td>
<td>National Cancer Institute, US</td>
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<td>NCRI</td>
<td>National Cancer Research Institute, UK</td>
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<td>Abbreviation</td>
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<tr>
<td>NCRN</td>
<td>National Cancer Research Network, UK</td>
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<td>NHS</td>
<td>National Health Service</td>
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<td>NHSBT</td>
<td>National Health Service Blood and Transplant, UK</td>
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<td>NIH</td>
<td>National Institutes of Health, US</td>
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<td>NIHR</td>
<td>National Institute for Health Research, UK</td>
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<td>NRES</td>
<td>National Research Ethics Service (now named the Health Research Authority), UK</td>
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<tr>
<td>OBBR</td>
<td>Office of Biorepositories and Biospecimen Research (now named the Biorepositories and Biospecimen Research Branch), US</td>
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<tr>
<td>OECD</td>
<td>Organization for Economic Co-operation and Development</td>
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<td>onCore UK</td>
<td>Oncology Tissue and Information Resource in the UK</td>
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<td>P3G</td>
<td>Public Population Project in Genomics</td>
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<td>PHOEBE</td>
<td>Promoting Harmonisation of Epidemiological Biobanks in Europe</td>
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<tr>
<td>PI</td>
<td>Principal investigator</td>
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<tr>
<td>R&amp;D</td>
<td>Research and development (also see RG)</td>
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<tr>
<td>RCP</td>
<td>Royal College of Pathologists</td>
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<tr>
<td>REMARK</td>
<td>Reporting Recommendations for Tumor Marker Prognostic Studies</td>
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<tr>
<td>RG</td>
<td>Research governance (also see R&amp;D)</td>
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<td>RTB</td>
<td>Research tissue bank</td>
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<td>SOP</td>
<td>Standard operating procedure</td>
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<td>SPIDIA</td>
<td>Standardisation and Improvement of Generic Pre-analytical Tools and Procedures for In-vitro Diagnostics</td>
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<tr>
<td>SPREC</td>
<td>Standard Preanalytical Coding for Biospecimens</td>
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<td>STRATUM</td>
<td>Strategic Tissue Repository Alliance Through Unified Methods</td>
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<td>TMA</td>
<td>Tissue microarray</td>
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<td>TSC</td>
<td>Tissue supply chain</td>
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<td>TuBaFrost</td>
<td>European Human Frozen Tumour Tissue Bank</td>
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<td>UK</td>
<td>United Kingdom</td>
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<td>UKCRC</td>
<td>UK Clinical Research Collaboration</td>
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<tr>
<td>UNESCO</td>
<td>United Nations Educational, Scientific and Cultural Organisation</td>
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<td>US or USA</td>
<td>United States of America</td>
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LIST OF LAWS, RECOMMENDATIONS AND DECLARATIONS


Data Protection Act 1998 (UK)

Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects [2008] Adopted at the 59th General Assembly of the World Medical Association (Declaration of Helsinki)


Human Tissue Act 2004 (UK)

Human Tissue (Scotland) Act 2006 (asp 4) (UK)

CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

Biobanking has the potential to be the most powerful single platform for health innovation and knowledge generation, provided that it is adequately resourced and networked. Maximizing the use, productivity, and value of biobanks worldwide will depend on a transition of the way in which biobanking is perceived and conducted. Harmonization across biobanks is crucial in order to make investigations more robust, more targeted, and more economical (Harris et al. 2012).

Harmonisation and standardisation have always underpinned civilisation, helping promote cooperation and coordinate tasks (Busch 2011) and forming an invisible infrastructure enabling everyday life. Moves towards harmonisation in biomedical research have been evident since the Enlightenment period (Busch 2011), and are most clear in the international harmonisation of regulatory and other requirements for clinical trials and drug development. Strikingly, however, the processes of standardisation, harmonisation and regulation seen in clinical trials are far from characterising the situation for research involving human tissue and related data. In this thesis, I will use the case of cancer tissue banking to explore why, despite the strength of arguments in favour of tissue bank harmonisation, only limited progress has been made.

I begin in this chapter by outlining why tissue banks are seen as an increasingly valuable scientific resource and will summarise the rationale for their harmonisation. I summarise the available literature on challenges to harmonisation, and will show that further research is needed to gain full understanding.

Tissue Banks

Tissue-based research is now used to increase understanding and classification of disease, the development and testing of drugs and other treatments, and investigations into complex diseases and personalised treatments. Basic and translational research projects increasingly rely on human tissue as a research resource. Powerful technology has evolved which is capable of extracting molecular
and other types of useful data from tissue samples (Harris et al. 2012, OECD 2007, Sebire and Dixon-Woods 2007, Riegman et al. 2006) enabling researchers to: (1) understand the biological functions of normal and diseased tissue, and the effects of environment and lifestyle factors upon these (Oosterhuis, Coebergh and van Veen 2003, Clotworthy 2012, UKCRC 2011); (2) identify or validate biomarkers (measurable properties such as genes, enzymes or hormones) that are targets for therapy, detection or prevention (Clotworthy 2012, National Cancer Institute 2011b, ECMC 2010); and (3) assess the safety and efficacy of drugs and other treatments prior to clinical trials (Clotworthy 2012). Large international collaborations now depend on the supply of human tissue, including the International Human Genome Sequencing Consortium, the International HapMap Project, the International Human Epigenome Consortium, the Encyclopedia of DNA Elements project, and the International Cancer Genome Consortium.

Tissue research usually requires more than just the tissue. A combination of both tissue and data about and associated with the tissue is what researchers need for maximally useful research. The value of a tissue sample is likely to increase in proportion to its association to data about the sample, the participant, or the participant’s environment (Harris et al. 2012, Riegman et al. 2006, Vaught et al. 2011b, Fortier et al. 2010, Jackson and Banks 2010, Confederation of Cancer Biobanks 2012b, Hodgson, Wellings and Harbron 2012). For these reasons, tissue samples are increasingly organised into collections known as tissue banks or biobanks. As I discuss later in more detail, no consensus exists on what defines a tissue bank (Shickle, Griffin and El-Arifi 2010, Heeney 2012), but typically they store tissue samples annotated with information of value to researchers.

Tissue banks are seen by many in the research community as crucial in providing the raw material needed to support progress in biotechnology and scientific investigations (Harris et al. 2012, OECD 2007, Clark 2006). Tissue banks help to optimise tissue supply to researchers by enabling more ready access to samples and related data (UKCRC 2011, Vaught et al. 2011b, Clark 2006). Tissue banks can also allow the researchers or organisations to: work more efficiently with clinical trials (which have high quality requirements), avoid having to collect new samples for novel projects, decrease the
time spent processing samples (due to the implementation of best practices), and share the tissue bank database across projects (Rogers et al. 2011).

**Harmonisation: What is it and why is it Important to Researchers?**

Recent years have seen a proliferation of tissue banks, and at the same time calls for their harmonisation. I will begin by considering what harmonisation might mean before turning to why it is seen as desirable and problems with attempts to harmonise.

Defining harmonisation is remarkably fraught, with competing views as to the extent to which it involves full standardisation. Clearly, harmonisation must involve standards (Salter 1988), but harmonisation may occur along a spectrum. The extent to which harmonisation should involve interoperability (at one end of the spectrum) or full standardisation (complete uniformity, at the other end of the spectrum) has posed challenges in the area of tissue banking (Harris et al. 2012).

Interoperability is the ability of two or more systems to exchange valid information or samples that can then be used (Public Population Project in Genomics 2005). Harmonisation, under an interoperability model, is then a process for unifying things (for example, procedures, methodologies or IT) to the point that interoperability is possible (Public Population Project in Genomics 2005). From this perspective, differences between tissue banks can exist, as long as the exchange of information and samples between studies is possible (Fortier et al. 2010). Some harmonisation efforts aim for interoperability. For example, the Public Population Project in Genomics (P3G), established in 2007, aims to attain interoperability and share both tools and methods across large tissue banks (Knoppers et al. 2008). The P3G DataSHaPER (DataSchema and Harmonization Platform for Epidemiological Research) tool deems harmonisation complete when data collection occurs “in a manner that is sufficiently similar in the different studies to allow valid synthesis to take place (Fortier et al. 2010)”.  

By contrast, at the other end of the spectrum, full standardisation might be seen as aiming towards complete uniformity: Timmermans and Epstein describe “standardization as a process of constructing uniformities across time and space,
through the generation of agreed-upon rules (2010, 71)”. Projects such as the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) embrace the goal of more complete standardisation (Yuille et al. 2008). Areas they aim to standardise across their network include sample management, data quality, epidemiological data and logistics (Yuille et al. 2008).

**What would harmonisation involve?**

Much of the existing literature on harmonising tissue banks appears to be organised around three key themes: ethico-legal aspects, methods, and how to coordinate tissue banks. First, debates have focused on how far it is possible to achieve consensus or agreement on general ethical, governance and legal principles across tissue banks, acknowledging that contextual factors such as the type of tissue bank, or the country it is based in may limit moves towards complete standardisation (Harris et al. 2012, Wallace, Lazor and Knoppers 2009, Cambon-Thomsen et al. 2005, Ravid 2008, Kiehntopf and Krawczak 2011, Knoppers, Abdul-Rahman and Bédard 2007). Second, some have argued that the methods used to collect and store tissue and data, or standard operating procedures (SOPs) can be standardised to some extent (Harris et al. 2012, Yuille et al. 2008, Ravid 2008, Kiehntopf and Krawczak 2011, Vaught and Lockhart 2012). Third, much discussion has focused on how best to coordinate tissue banks through organisations or networks in order to facilitate harmonisation (Ravid 2008, Kiehntopf and Krawczak 2011, Knoppers, Abdul-Rahman and Bédard 2007, ESFRI 2006, OECD 2001). Across the three areas, different types of standards were suggested, including policy-focused, procedural, technical and contractual. However, the field is an active one, and new considerations and potential solutions continue to arise (Harris et al. 2012).

**Arguments in favour of harmonising tissue banks**

Leaving aside the issue of what exact form on the continuum from interoperability to full standardisation that harmonisation might take, five key arguments in favour of the harmonisation of tissue banks recur through the literature:
1. to encourage higher quality samples and data,
2. to allow larger, more (statistically) powerful research projects to take place, faster,
3. to stop needless duplication of effort and prevent under-utilisation of resources,
4. to encourage stakeholder participation in tissue banking, and
5. to increase economic competitiveness.

To encourage higher quality samples and data The availability of high quality tissue is critical for researchers, especially as the technology used to extract molecular data (for example on the DNA, RNA or proteins) from tissue becomes more sensitive (Harris et al. 2012, National Cancer Institute 2011b). Improved quality standards would reduce the possibility of error or bias and enable comparison of similar experiments. Low quality molecular and other data mean increased sample sizes are needed in order to account for the possibility of error or bias, increasing the cost to the researcher in both time and money (Burton et al. 2009). Variation in tissue and data quality across tissue banks also leads to ambiguity and unreliability when comparing the results of similar experiments conducted using tissue from different tissue banks – a particular issue when conducting systematic reviews (Yuille et al. 2008).

A key way in which harmonisation can assist in this endeavour is by providing guidance on what factors have an impact on the quality of the sample (or data) and how the sample should be annotated with information about these factors. Factors that influence the quality of tissue include technical aspects linked to how the tissue was collected and stored, for example the length of any delay between removal of sample and processing for the tissue bank. This is because the longer the delay, the more detrimental this is to the quality of the sample, which begins to degrade (Jackson and Banks 2010). Quality considerations are important when collecting data too. For example data on individuals’ weight is more reliable if measured by trained medical staff rather than self-reported (Fortier et al. 2010). Harmonisation might be able to help with ensuring samples and data are of high quality.
To allow larger, more (statistically) powerful research projects to take place, faster
To study complex diseases and the gene-gene or gene-environment interactions that cause them, a large number of cases is needed (Harris et al. 2012, Shickle, Griffin and El-Arifi 2010, Yuille et al. 2008, ESFRI 2006, Burton et al. 2009). The effect of some interactions is very small, so large numbers are required to take into account the potential for noise, confounders or low quality data (Burton et al. 2009). Harmonisation of tissue banks might enable researchers to obtain large numbers of samples (Kiehntopf and Krawczak 2011, Friede et al. 2003), thus leading them to conduct the research faster and accelerate other types of research, including translational research that uses biological data to identify disease biomarkers and linked drug targets (Harris et al. 2012, Knoppers, Abdul-Rahman and Bédard 2007).

To stop needless duplication of effort and prevent under-utilisation of resources
Funders of tissue research are interested in minimising duplication of effort in terms of sample and data collection (UKCRC 2011, The Wellcome Trust 2011, Lord et al. 2005), and are keen to obtain value for money from the samples and data already collected (The Wellcome Trust 2011). In order to pursue these aims, funders may: require applicants to consider the potential for collaboration or re-use before granting funding, attach access and sharing conditions to the samples and data after they have been used for the research, or fund initiatives that encourage the sharing of samples or data, such as catalogues or databases (UKCRC 2011, The Wellcome Trust 2011). Despite these intentions, funder policies vary, resulting in many challenges in achieving those goals. Thus, funding for long-term data and sample sharing is not always available, and multiple catalogues exist, making discovery, access and re-use difficult (UKCRC 2011, The Wellcome Trust 2011).

To encourage stakeholder participation in tissue banking One argument suggests that harmonised governance guidelines could build the trust of participants and encourage investors by providing transparency and accountability of tissue banking activities (Kiehntopf and Krawczak 2011, Knoppers, Abdul-Rahman and Bédard 2007, Knoppers and Joly 2007, Kaye 2006). Tissue bank representatives argue that quality standards would reassure both tissue donors and researchers of the high quality (Betsou et al. 2007, onCore UK 2008a).
To increase economic competitiveness

The European Strategy Forum on Research Infrastructures, part of the European Commission, has argued that the harmonisation of biological resources could give institutions, countries, or economic areas a competitive advantage in terms of pre-clinical and/or clinical research (ESFRI 2006). The Organization for Economic Co-operation and Development (OECD) also recognised that a global network of tissue banks (it included non-animal tissue) could contribute towards international economic development (OECD 2001).

Problems with attempts at harmonisation

Despite the existence of what appear to be sound and persuasive arguments for the harmonisation of tissue banks, it has still not happened on a large scale. In the UK for example, various, mostly small harmonisation initiatives have been undertaken by professional groups, funders, industry and research centres, but they are not well-coordinated (UKCRC 2011). Connections between individual tissue banks in Europe remain limited and fragmented (OECD 2007, Zika et al. 2011). Standard operating procedures (SOPs) for sample collection and analysis remain varied across the UK and Europe – none has emerged as dominant (UKCRC 2011, Yuille et al. 2008, Kiehntopf and Krawczak 2011, Vaught and Lockhart 2012, Zika et al. 2011, Jury et al. 2012, Vaught, Caboux and Hainaut 2010, Marko-Varga et al. 2012). Researchers are still making calls for high-quality tissue samples and data (National Cancer Institute 2011b, Thompson et al. 2008, Massett et al. 2011, Carter and Betsou 2011). Ethico-legal controversies have not been solved (Vaught and Lockhart 2012). The continuing lack of harmonisation on a large scale points to the existence of challenges to collaboration that would benefit from further investigation.

One challenge is that harmonisation in the area of tissue banking is not always seen as an unqualified good; arguments exist against the rationale, implementation and outcome of activities that aim to harmonise. A dispute exists over whether it is value for money to use harmonisation to enable larger studies to identify gene-gene or gene-environment interactions with ever smaller effects (Day 2009). Discussions have arisen when tissue banks, driven by the desire to standardise, have incurred costs in implementing standards that have little relevance to them (Carter, Betsou and Clark...
Money is not the only issue. Much has been written about the tendency of full standardisation to crush variety, water down creativity, and lead to the dumbing down and imposition of one set of views on those of others (Busch 2011, Day 2009, Bowker and Leigh Star 2000, Timmermans 2003, Swann 2010). Throughout my thesis the potentially negative consequences of harmonisation are highlighted and explained along with the positive.

**Literature on Professionals’ Views on Harmonisation**

Despite the scale of these issues, the challenges to harmonisation have not yet been fully characterised. What is missing is an empirically-informed understanding of what influences the success or failure of initiatives to harmonise tissue banking activities. The small body of literature that has questioned professionals or described their experiences has provided some intriguing hints about what influences harmonisation but left major conceptual gaps. I introduce and critique this literature below and then identify some of its limitations and lacunae.

**Method of review**

During the period 2010 to the end of 2012 I searched for literature that either conducted empirical studies on professionals (broadly defined to include research scientists) working in tissue banking and harmonisation, or that described their experiences when engaging with harmonisation efforts. I focused on literature on professionals rather than research study participants or patients because professionals (and the organisations they work for) are directly involved in the initiation of harmonisation activities (for examples see Wallace, Lazor and Knoppers 2009, Betsou et al. 2007 and Downey and Peakman 2008). Professionals are responsible for the implementation of standards in the area as they approach patients, seek consent, remove the tissue, label it, and arrange for its storage and analysis – yet few studies have approached them (Sebire and Dixon-Woods 2007, Meir et al. 2011). I have not included any studies that engage directly with tissue bank donors or the general public. While such input is vital on important questions related to the ethical and societal context of standards, a great deal of literature has focused on these issues and the challenges are well-characterised (Meir et al. 2011).
My search strategy was to conduct formal literature searches using databases such as SCOPUS, the British Library Catalogue, EBSCO Business Premier, PubMed and Google Scholar and supplement this with information gathered informally from contacts and conferences (see Appendix 1). I identified 14 empirical studies that investigated professionals’ views, using either qualitative or quantitative methods such as interviews or surveys on subjects that contributed towards an understanding of what influences tissue banking harmonisation efforts (UKCRC 2011, Hirtzlin et al. 2003, Hoeyer 2006, Human Tissue Authority 2009b, Jackson et al. 2009, Kaye et al. 2012, McLean et al. 2005, Myles et al. 2011, NCRI, National Cancer Intelligence Network and onCore UK 2008, NCRN 2009, onCore UK 2009b, Pathological Society 2010, Prior 1987, Zika et al. 2010).

Only one of the empirical studies on professionals’ views – the so-called “environment scan” in the UK Funders’ Vision for Human Tissue Resources (referred to as the Funders’ Vision) – considered harmonisation directly, but even this does not capture detail about what makes harmonisation efforts successful or not (UKCRC 2011). Six of the other studies focused on the response of professionals to regulation or governance (Human Tissue Authority 2009b, Jackson et al. 2009, Kaye et al. 2012, McLean et al. 2005, NCRI, National Cancer Intelligence Network and onCore UK 2008, onCore UK 2009b). Of the rest, two studies focused on profiling pathologists (Pathological Society 2010, Prior 1987), two surveyed tissue banks internationally about their organisation and legal and ethical context (Hirtzlin et al. 2003, Zika et al. 2010), two consulted professionals on the design of or access to tissue banks (Myles et al. 2011, NCRN 2009), and one aimed to understand the implementation of ethics policy in a Swedish tissue bank (Hoeyer 2006).

I also examined 20 further papers that were editorials or viewpoint commentaries, rather than reporting on original research. Many of these publications described or compared the experiences of harmonisation organisations devising standards or the tissue banks implementing them, but were not necessarily based on empirical research. They included reports of tissue banking experiences (Riegman et al. 2006, Downey and Peakman 2008, Davis et al. 2012, Yuille et al. 2010, National Cancer Institute 2007b, Matzke et al. 2012, Herpel et al. 2010, Morente et al. 2006, Lopez-
CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW


Influences on harmonisation

The following section summarises the main findings of the literature on what influences the harmonisation of tissue banks in the UK. Because standards are crucial for harmonisation, the review is split into two phases: creation and implementation of standards following Timmermans and Epstein (2010).

Creation of standards

Timmermans and Epstein (2010) identify creation as a key phase in the life-course of standards. The reviewed literature suggests several aspects of standard creation that are important for the harmonisation of tissue banks:

- availability of resources for standard creation,
- who is involved in standard creation, and
- how standards are designed.

The availability of resources for standard creation

Creating standards requires time and resources. Despite this, professionals in the studies rarely report that the costs of standard creation have an impact on the success of harmonisation initiatives. Resources are needed to coordinate activity and to obtain the support of key stakeholders (UKCRC 2011). Activities relating to creating standards include: individuals to manage the process, consultation procedures, visits to tissue banks to observe practice, networking meetings and activities to encourage uptake of the resulting standards (Lord et al. 2005, Meir et al. 2011, Yuille et al. 2010). The financial costs of these initiatives can be considerable. The US National Cancer Institute cancer biomedical informatics grid (caBIG™), which aimed to provide a “standardized
biomedical informatics platform” connecting cancer patients, doctors and researchers, reported spending $20 million in its first year “building community”, consulting professionals, including them in workgroups, and developing the standards to enable the sharing of data (National Cancer Institute 2007a, 20).

**Who is involved in standard creation?**

Standards relevant to harmonisation are typically developed by diverse actors including governments, regulatory bodies, funders, networks, institutions and individual tissue banks. Research funders and Research Ethics Committees (RECs) are the key oversight bodies for professionals who note the need to follow funder requirements on topics such as open access, data handling, consent and access (Gibbons and Smart 2012c). However, the influence does not extend to following guidance that is not a requirement of obtaining funding or approvals (onCore UK 2009b, Gibbons and Smart 2012c). Instead, the main bodies professionals turn to for guidance and advice are social and professional networks, NHS Research and Development Offices and, occasionally, applicable regulators (onCore UK 2009b, Gibbons and Smart 2012c).

The International Organization for Standardization (ISO) is a striking example of an organisation with so much influence internationally that some tissue banks choose to accredit themselves against its standards despite the fact that no ISO standard applies directly to the process of tissue banking (Carter, Betsou and Clark 2011). For example, some tissue banks implemented the ISO 9001 quality specification standard (UKCRC 2011, Downey and Peakman 2008, Davis et al. 2012) and/or the ISO 17020:2004 standard for inspection bodies (Herpel et al. 2010). Benefits included improving external confidence, acting as a tool to justify and gain funding, and providing quality assurance for industrial partners (Herpel et al. 2010). Because the provisions of such standards have no direct application to tissue banking they may have been obtained primarily to provide reassurance to funders and users of the tissue bank (Carter, Betsou and Clark 2011).

The literature also shows that **who is involved in setting standards in the harmonisation process is important for other reasons: professionals report wanting to**
feel that their points of view were represented in the harmonisation process and that they are often dissatisfied with current representation. Biomedical professionals feel that lawmakers, policymakers and regulatory bodies should consult more widely, and include researchers, scientists, patients (and representatives), participants, data holders and those who collect the data (Gibbons and Smart 2012d). Pathologists are seen as working in isolation and not taking part in group discussions (McLean et al. 2005), or as having a difficult time mediating between the scientific and the social aspects of their job (Prior 1987), which may stop pathologists from volunteering to take part in efforts to create standards.

Practical implications also exist; the literature shows that professionals may opt out of research if they feel that standards have been set in ways that are irrelevant or illegitimate. A key example of this is the drafting process of the UK Human Tissue Act (2004). Some pathologists felt underrepresented during the legal process, perhaps because of negative media attention at the time (McLean et al. 2005, Pathological Society 2010). A large number of professionals found parts of the resulting Human Tissue Act (2004) irrelevant, that it had struck the wrong balance between individual rights and wider societal needs, that the licensing requirements put them off conducting research, and that the regulatory framework made it difficult for them to conduct certain types of research (Human Tissue Authority 2009b, Pathological Society 2010, Gibbons and Smart 2012a). These challenges illustrate the problems in practice of representing particular groups during the creation of standards.

The design process for standards

Different ways of designing standards may meet with different levels of success and acceptance in terms of harmonisation. Three models for the creation of standards are apparent in the literature: management or government designed high-level standards, network-driven efforts and initiatives generated by the relevant community of professionals.

The first model is to obtain agreement on standards at the highest (and perhaps international) level (Harris et al. 2012) because tissue banking involves such a large number of individuals, organisation and countries with different interests. A notable
example in the UK is the attempt by the National Cancer Research Institute (NCRI) to develop a cancer biosample directory and a template for access policy (UKCRC 2011, NCRI, National Cancer Intelligence Network and onCore UK 2008).

Network-driven initiatives are standards designed by representatives of professional tissue banking networks with the goal of reaching harmonisation within that network. The *Funders’ Vision* highlights two UK networks that have been working towards the harmonisation of tissue bank operating procedures, NCRI’s Confederation of Cancer Biobanks (CCB) and the MRC-led UK Brain Banks Network (UKCRC 2011). The CCB has produced a set of guiding principles, but otherwise both networks were reported as making little progress so far (UKCRC 2011). Internationally, networks make a large contribution to harmonisation efforts. One, P3G, created a searchable directory of population-level tissue banks; model consent forms, information sheets, and access clauses; and tools that enable the identification and harmonisation of key variables (Public Population Project in Genomics 2012). Other types of standards developed by international networks include: technical standards relating to informatics; policy type guidance on governance and data sharing; and procedural standards on quality management (Meir et al. 2011).

The third type of design process involves community-led initiatives designed by researchers, projects, biobanks or their institution (for example, hospital or university). The impact of the harmonisation effort is thus likely to be local or project-specific. Different types of standards covering sample annotation, quality standards, technical protocols, cost recovery models, mechanisms for sharing, publication guidelines and metrics for judging success are often devised locally due to a lack of UK or international agreement on optimal requirements (UKCRC 2011). One example of many in the UK was the Breast Cancer Campaign tissue bank, where researchers managing the tissue bank oversaw the process of harmonising standard operating procedures across participating centres (UKCRC 2011). Similarly, the European Prospective Investigation into Cancer and Nutrition (EPIC) project had to standardise methods of collecting information on diet because this had not previously been done internationally (Slimani et al. 2000).
Evidence from the empirical studies does not give enough detail to allow comparison of which of these methods is more effective in terms of implementation of standards and harmonisation. In the UK, legislation and other high-level standards may not have been widely accepted, and network-driven efforts have not always got very far (UKCRC 2011, Jackson et al. 2009, McLean et al. 2005, Gibbons and Smart 2012c). Despite this, respondents to the Funders’ Vision were hopeful about the outcome of the network and community-led harmonisation efforts (UKCRC 2011).

**Implementation and enforcement of harmonisation efforts**

Once standards are created, they need to be implemented and enforced if they are to result in harmonisation. Ways of securing compliance with standards include the use of sanctions, licensing, audits or training sessions (Busch 2011, Timmermans and Epstein 2010, Heimer 2008). My review of the tissue banking literature suggests that seven features explain the extent to which harmonisation is implemented and enforced for tissues banks: characteristics of the standards themselves, competitive research environment, use of regulation, the actions of organisations that create or impose standards, the impact of networks and success stories, characteristics of the organisation where the tissue banking is being conducted, and individual factors. I also briefly consider the outcome of the implementation of standards in the area.

**1. Characteristics of standards that are relevant to implementation**

A number of features appear to be important in to the extent to which standards end up being implemented: ensuring fairness, evidence-base, length, clarity, degree of standardisation, building-in flexibility, and other forms of encouragement.

*Ensuring fairness* Finding an equitable way of recognising all the different interests that arise in relation to tissue banking appears to be crucial for engendering support for implementing standards and harmonisation. Professionals who do not agree with standards or view them as flawed are less likely to engage with them (Gibbons and Smart 2012b). Professionals express concerns about whether their efforts towards tissue banking are properly recognised (UKCRC 2011, NCRI, National Cancer Intelligence Network and onCore UK 2008), how the intellectual property (IP) would be distributed (Myles et al. 2011, NCRI, National Cancer Intelligence Network and onCore
UK 2008) and how to balance the need to protect individual rights with the wider societal need for tissue banking in legislation (McLean et al. 2005, Pathological Society 2010).

One of the major questions relating to fairness is access to the samples (UKCRC 2011, Myles et al. 2011, NCRI, National Cancer Intelligence Network and onCore UK 2008). In a UK consultation the majority of respondents thought that open access to samples was most fair, and should be restricted only by the scientific value of the research and qualifications of the applicants (NCRI, National Cancer Intelligence Network and onCore UK 2008). Nevertheless, further comments revealed that they thought access should be prioritised for the original collectors or those willing to collaborate with them, for researchers in the UK or for non-profit organisations (NCRI, National Cancer Intelligence Network and onCore UK 2008). Reaching a fair compromise between those who collect and use the tissue can be difficult and there is huge variation in existing access policies (Meir et al. 2011, Vaught, Kelly and Hewitt 2009, Fortin et al. 2011). The UK DNA Banking Network and TuBaFrost both view their access policy as a valuable way to incentivise participation in their tissue banking networks. They both allow the original collector to retain a level of control and encourage collector and researcher to form new collaborations in order to conduct the research (Yuille et al. 2010, Lopez-Guerrero et al. 2006).

Evidence-base Ensuring that the contents of standards are evidence-based appeared to be critical to obtaining buy-in from professionals. A lack of evidence to support the contents of standard operating procedures (SOPs) for tissue banks leaves professionals unmotivated to change their own procedures in order to follow new ones (UKCRC 2011).

Length Professionals are often critical about the length of standards; for example, the length of the research ethics application form (a type of standard) is typically reported as off-putting for small projects (McLean et al. 2005, Pathological Society 2010, Gibbons and Smart 2012a).

Clarity Standards that are not clear may lead to misunderstandings and misinterpretations that threaten the success of harmonisation in the area. For example
professionals find UK regulatory and governance procedures complicated and difficult to understand, and it is thought that misunderstandings have led to tissue banks preventing access to samples (UKCRC 2011, Human Tissue Authority 2009b, McLean et al. 2005, onCore UK 2009b). Bodies such as RECs and NHS data protection offices are seen to interpret laws inconsistently (Gibbons and Smart 2012a).

The degree of standardisation The point on which standards sit on the spectrum from interoperability to full standardisation can affect whether they are implemented: full standardisation can cost money for individuals or organisations. TuBaFrost acknowledged this and took the approach of splitting their SOPs into two categories – essential and recommended – aiming for harmonisation but not complete uniformity (Morente et al. 2006). TuBaFrost recognised that the cost and effort involved in implementing the full standards would be a potential disincentive for potential network members (Morente et al. 2006).

Building-in flexibility Professionals report that diversity in tissue bank type and associated practicalities means that governance frameworks should be designed flexibly (Gibbons and Smart 2012d). For example, the UK Breast Cancer Campaign tissue bank aims to design SOPs for its contributing centres based around a core set of procedures that allow for local variability (UKCRC 2011, 13). These procedures are not planned to be set in stone and will be subject to assessment and improvement where necessary (UKCRC 2011, 13).

Other forms of encouragement Other ways of encouraging people to comply with the standards necessary for harmonisation vary from a simple ‘thank you’ through to access to investment, technology and other types of support, including:

- stipulating that publications arising from research using the tissue banks contain acknowledgement of the bank’s contribution (NCRI, National Cancer Intelligence Network and onCore UK 2008),
- building a metric that evaluates and recognises the value of tissue banks (Harris et al. 2012),
- using certification or accreditation as a quality mark in order to attract customers or funders (Herpel et al. 2011),
- rewarding those who collaborate with improved access to funding, skills, resources and infrastructure; greater support for business processes and securing intellectual property (IP); or the possibility of influencing policy (Chataway et al. 2012),
- offering the use of latest technology, feedback on research results and histopathology reviews (Lopez-Guerrero et al. 2006),
- setting periods of privileged access to data (Lord et al. 2005), or
- providing staff salaries and equipment in hospitals to assist with tissue banking (Vaught, Kelly and Hewitt 2009).

2. The impact of the competitive research environment on implementing standards

The second feature the literature highlights as influencing the harmonisation of tissue banking is the competitive research environment. First, currently dominant career paths and training initiatives may not include the skills required to follow the standards for harmonisation, such as data management (Lord et al. 2005). Second, the ‘publish or perish’ culture where employers and funders judge success by the publication of research papers in peer-reviewed journals can deter professionals from engaging with standards that require them to share tissue, data or their results (Pisani and Abou-Zahr 2010).

This explains why recognition and rewarding effort in relation to tissue banking and resulting research is a dominant focus of concern in the empirical research both in terms of authorship and intellectual property (UKCRC 2011, Myles et al. 2011, NCRI, National Cancer Intelligence Network and onCore UK 2008, Gibbons and Smart 2012a). Professionals working in, or investigating, tissue bank harmonisation and data sharing see prevailing academic culture as a major barrier. Suggestions for how to change it include: taking contributions to databases into account when considering promotions and funding applications, investing in relevant training, developing ways of describing and citing tissue and data resources, developing supporting infrastructure, and supporting initiatives to measure the value of tissue banks and databases (Harris et al. 2012, Lord et al. 2005, Pisani and Abou-Zahr 2010).
3. The use of regulation to implement and enforce standards

Professionals working towards harmonisation of data-sharing in the life sciences describe legislation as a double-edged sword (Lord et al. 2005); this description also fits regulation around human tissue. Positive features include the requirements of the Human Tissue Act (2004) and work of the Human Tissue Authority (HTA), which has led to improved standards for consent and storage and encouraged collections to consolidate (UKCRC 2011, Human Tissue Authority 2009b). Another important benefit is the joint HTA and National Research Ethics Service (NRES) scheme for the generic ethics approval of Research Tissue Banks (RTBs), broadly welcomed by the community with approximately 120 RTBs now approved (UKCRC 2011).

On the other hand, negative aspects of regulation are evident. Some legislation is not UK-wide; a separate law was implemented in Scotland – the Human Tissue (Scotland) Act 2006 (UKCRC 2011). Professionals felt that this could cause complications and that Scotland could fall behind the rest of the UK in terms of standards (UKCRC 2011, Human Tissue Authority 2009b, Pathological Society 2010). Larger tissue banking networks report that differences between legislation across jurisdictions cause issues for the exchange of tissue and data between them (Riegman et al. 2006).

Aside from these complications, professionals report that licensing requirements and sanctions cause them to think twice about whether to engage with regulation (UKCRC 2011, Human Tissue Authority 2009b, Jackson et al. 2009, McLean et al. 2005, Pathological Society 2010, Gibbons and Smart 2012a and 2012c). Tissue researchers are deterred from conducting research (particularly when using tissue from deceased persons) by sanctions including fines and imprisonment, and may change their plans to avoid getting a licence (52 per cent of 237 respondents, Human Tissue Authority 2009b)(McLean et al. 2005, Pathological Society 2010, Gibbons and Smart 2012a).

4. How the actions of organisations creating or imposing standards can influence implementation

In the UK, research funders have led the discussion on what actions could be taken to encourage implementation of standards. Some funders (the US National Institutes of Health and the UK-based Wellcome Trust) have changed their funding criteria and
procedural requirements to allow for recognition of team work and the value of roles such as data management (Pisani and Abou-Zahr 2010). Publishers have also begun requiring data-sharing as part of the agreement to publish (Pisani and Abou-Zahr 2010). In practice, funders use various mechanisms to monitor researcher compliance including project audits, and requiring reports and/or attendance at meetings (Gibbons and Smart 2012c), but enforcement may not be straightforward – respondents to the Funders’ Vision note that funders have done little to enforce the terms of grant funding that relate to sharing (UKCRC 2011).

5. The impact of networks and success stories on the implementation of standard

The current literature suggests that professionals in the UK largely base their decisions on what tissue banking standards to implement on information from informal professional social networks and projects or companies they viewed as successful (onCore UK 2009b, Gibbons and Smart 2012b and 2012c). Thus, these relatively informal sources are consequential for whether standards are implemented and harmonised. More formalised professional tissue banking networks are relatively new but may be a useful conduit for sharing standards and infrastructure (Meir et al. 2011).

6. The impact of the characteristics of the organisation where tissue banking occurs on standard implementation

Characteristics of the organisation (hospital, tissue bank, university, private company) engaged in tissue-banking activities affect whether standards are implemented successfully. If the standards are not implemented correctly harmonisation will not be attained. Four characteristics of organisations are important for the success of harmonisation efforts: the type of organisation, the availability of resources for implementation, whether they offer training, and the oversight and monitoring system.

The type of organisation in the UK – whether academic, NHS or commercial – influences the degree of understanding, acceptance and implementation of standards. Employees of private companies are more likely to be positive about existing standards than those in the NHS – who report finding standards strict, complex and difficult to
access (Human Tissue Authority 2009b, onCore UK 2009b). In terms of following standards, industry employees (in the US) report issues linked to long-term funding, infrastructure and the nature of access parameters (Myles et al. 2011). Professionals working in the NHS may experience pragmatic difficulties linked to lack of resources for taking consent or problems accessing tissue or specialists (UKCRC 2011, Jackson et al. 2009). Culture in the NHS is often blamed for some problems. For example, paternalism is seen to prevent approach of suitable tissue donors and pathologists are portrayed as reluctant to release blocks containing human tissue needed for research due to worries they would not be returned (UKCRC 2011, NCRN 2009).

The availability of financial resources for implementation is a key determinant of the successful adoption of standards. Specific costs include putting the requirements of standards into practice, purchasing licenses and work to obtain accreditation or certification. As well as the issues with finding resources in the NHS (see above), professionals also mention the cost of obtaining a HTA license, which they view as too high and something they may not receive extra funding to cover (Human Tissue Authority 2009b, Gibbons and Smart 2012a). Accreditation or certification schemes can cost money for the organisation to implement, for example high direct and indirect costs relate to the adoption of the ISO 17020:2004 standard (Herpel et al. 2010).

Training offered by organisations also influences standards implementation. Training events are reported as beneficial as they provide professionals with guidance (Gibbons and Smart 2012c). The kinds of training respondents mentioned includes those run by funders (largely on regulation, through both tools and events), courses (including good clinical practice or research governance courses), alongside the more general training available through attending conferences or meetings (UKCRC 2011, Gibbons and Smart 2012c).

The final crucial characteristic of organisations relevant to standard implementation is the nature of their internal governance structure and monitoring systems. This has a critical role in enforcing standards and ensuring they are followed accurately. In the literature, oversight is reported as common but variable. Of biomedical professionals taking part in the Governing Genetic Databases project, 18 of 49 reported feeling
overseen by, or answerable to, institutional governance arrangements or internal supervisory actors (Gibbons and Smart 2012c). Systems differ between private and public organisations – with the former feeling answerable to management and in-house compliance experts and the latter to audit, monitoring, lawyers, Caldicott guardians, and hospital Research and Development (R&D) teams (Gibbons and Smart 2012c). A large number of professionals feel they are overseen by written documentation such as contracts or agreements or answerable to steering committees and other structures (Gibbons and Smart 2012c).

7. Individual factors and implementation

The beliefs, education, experience and background of an individual can affect whether standards are implemented successfully and harmonisation attained. Decisions about whether and to what extent to engage with regulation or governance in the area of tissue banking is affected by whether the professional:

- agrees with it or views it as flawed,
- views it as unnecessary to comply because it does not apply to them,
- already feel like they are already complying,
- decide to engage with some provisions but not others, or
- interpret the provisions to suit themselves (Gibbons and Smart 2012b and 2012c).

Thus, “at the extremes, there were admissions that pointed to practitioners deliberately avoiding, if not violating, relevant laws or governance, whilst feeling themselves to be justified in so doing (Gibbons and Smart 2012b, 159)”. Underlying implicit forms of guidance also inform decisions about what is acceptable, including professional culture and experience gained through practice (Gibbons and Smart 2012b). Additionally, different backgrounds, education, shared experience and culture of professional groups may lead to variation in what individuals regard as ethically, legally and socially acceptable (Gibbons and Smart 2012b).
The outcome of implementing standards – harmonisation or more complication?

Even when standards are successfully created and implemented, they do not necessarily contribute towards the harmonisation of tissue banking activities. Overall, a given standard may act positively to streamline activities, or it may introduce more complication or add unforeseen problems to the area. Both positive and negative UK examples can be found. Activities in relation to the generic ethics approval of Research Tissue Banks (RTBs) and the Human Tissue Act (2004) are identified by some as having contributed towards harmonisation (see above). But in many other areas efforts to harmonise are perceived as erecting barriers to harmonisation either by causing regional divisions within the country (for example the Human Tissue Act (2004), see UKCRC 2011, Human Tissue Authority 2009b, Pathological Society 2010), overlapping with other similar standards and causing duplication and conflict (for example the governance systems linked to ethics, HTA licensing, NHS R&D, and funding applications, Gibbons and Smart 2012a), or being implemented inconsistently resulting in a lack of harmonisation in practice (examples included inconsistent interpretation by RECs, NHS data protection offices and administrators, Gibbons and Smart 2012a and McLean et al. 2005). Thus, the situation in the UK is characterised by a large number of actors issuing overlapping (or divisive) standards and no dominant body or organisation (McLean et al. 2005, onCore UK 2009b, Gibbons and Smart 2012c). The result is a lack of harmonisation.

The limitations of previous empirical studies

The literature review above suggests that a small body of empirical social research of relevance to the problems around harmonising tissue banks exists. While clearly it offers much of value, it also has some limitations, addressed below. Common limitations of the current literature relate to the: scope, timing, methods and interpretation of results.

Scope — Most studies explored professionals’ reactions to regulation and governance more broadly or associated topics such as consent rather than focusing specifically on their attitudes towards tissue bank harmonisation. The Funders’ Vision
environment scan was the only study to do this directly (UKCRC 2011), but it focused solely on issues of relevance to funders: efficiency, economies of scale and reducing duplication and barriers to re-use. Alongside this, it did not include information on the logistics of tissue collection and collaboration or how this works in the context of the NHS. It was further limited because it did not make the distinction between opinion and research results clear.

**Timing** Two relevant studies are now outdated due to changes in the regulatory and governance context in the UK; research for the key qualitative studies with a focus on regulation and governance (Kaye et al. 2012, McLean et al. 2005) was undertaken between 2005 and early 2007. The regulatory and governance context has changed since then, in particular: the Human Tissue Act (2004) has been fully implemented, the Human Tissue Authority has amended guidance, and the Research Tissue Bank generic ethics approval scheme was put in place in 2009 (Human Tissue Authority 2009a, Human Tissue Authority and NRES 2009).

**Methods** I identified weaknesses and gaps in methodological approach used in many studies, leading to the potential for bias and missing information. In some studies the potential for sampling and response bias arose from the choice of sample. Quantitative studies reported difficulties finding a representative sample, or even knowing what one may look like (Human Tissue Authority 2009b). Response bias may have occurred for those professionals interviewed for the *Funders’ Vision* as they were often funded by or otherwise linked to the funders (UKCRC 2011).

Regarding sampling, there was little coverage of views from members of private companies and clinical institutions. Problems were reported with gaining access to pharmaceutical companies (Zika et al. 2010). In clinical institutions, studies often focused on pathologists and did not speak to others involved in the process of tissue banking (UKCRC 2011, McLean et al. 2005, Pathological Society 2010). Empirical studies did not consult surgeons, nurses or non-elites such as technical staff, thus there is little information about what is important to these groups who have experience of engaging with and implementing standards (a small number of non- elites replied to the onCore UK 2009b survey).
Observational approaches were rarely used in the studies, limiting knowledge about harmonisation at the different steps of the tissue banking process, who is involved in creation and implementation, how guidelines are used and implemented, and whether behaviour aligns with information given during surveys and interviews. Only one of the studies (Hoeyer 2006) included observations of practice in tissue banking, and this was outside of the UK context.

Interpretation of results The majority of the empirical studies did not apply any theory when interpreting their results (with the exception of Hoeyer 2006 and McLean et al. 2005), and the area is generally under-theorised. Factors identified as influencing harmonisation are rarely explained in any detail.

There is a need for a theoretically-sensitive study looking into influences on tissue bank harmonisation from the perspectives of the numerous professionals involved, including observations to identify how they create and use standards. This is what my thesis has aimed to do. Specifically, it addresses the question of: what influences the harmonisation of tissue banks in the UK?
CHAPTER 2: INTRODUCING THE CASE STUDY –
HARMONISATION OF CANCER TISSUE BANKING IN THE UK

An international harmonisation effort as broad and diverse as that of tissue banking is
difficult to study comprehensively during a single research project. A case study
enables focused, in-depth research to take place in this continually developing area,
where context matters (Flyvbjerg 2011). This chapter explains the choice of
harmonisation of cancer tissue banks in the UK as the case study and traces the use of
cancer tissue in research, how tissue banks can assist in tissue collection and the
progress towards harmonisation. In order to further understand the detail and
rationale behind efforts to harmonise I describe the different ways in which tissue
banking might be conceptualised (as a process, life-cycle, network or supply chain). I
conclude that each of these approaches aids understanding of tissue banks and
incorporate elements of each into a new model of cancer tissue banking. Finally, I
outline the ‘sensitising concepts’ from the literature that have assisted in structuring
the empirical inquiry.

Introducing the Case Study

Chapter 1 suggested that there is a need to explore why the harmonisation of tissue
banks is not occurring on a large scale despite a convincing set of reasons in its favour.
What influences the harmonisation of tissue banks is thus the key research question to
which this thesis is directed. The question is very broad given that tissue banks are
common and their characteristics diverse (Harris et al. 2012, Shickle, Griffin and El-Arifi
2010, Technopolis 2010, European Commission 2012); surveys have confirmed this
(Zika et al. 2011, Hirtzlin et al. 2003). Harmonisation efforts take different forms and
occur at multiple levels (Harris et al. 2012, Yuille et al. 2008, Kiehntopf and Krawczak
2011, Vaught and Lockhart 2012). The answer to such a general research question
covering a wide and variable subject matter would necessarily be generic. I therefore
decided to use a case study to enable me to provide more useful, informed, timely and
specific answers.
Three key reasons explain why case study research is a useful tool with which to study tissue bank harmonisation. First, the focus, depth and richness that case study research allows can give a deeper insight into what influences harmonisation and the reasons bearing on any failures (Flyvbjerg 2011). Second, tissue bank harmonisation is an active field which is still maturing (Fortier et al. 2010, Kiehntopf and Krawczak 2011, Carter and Betsou 2011, Matzke et al. 2012, Moore et al. 2011, Wolfson et al. 2010) and using a case study approach allows harmonisation activities to be studied as they take place, rather than historically (Flyvbjerg 2011, Yin 2003). Third, in contrast to an experiment, a case study can be designed to take the wider context or environment surrounding a phenomenon into account (Flyvbjerg 2011, Yin 2003). A case study approach allows the harmonisation of tissue banking to be studied in-depth, as it is occurring and taking the context into account. Of course, as with any research approach, there are limitations to case studies, which I will explore in more detail in the methods chapter.

I have identified cancer tissue banking in the UK as an appropriate case study. I explain the reasons for the selection of this case below.

**Why choose the harmonisation of cancer tissue banking in the UK as the case study?**

A case study of the harmonisation of cancer tissue banks in the UK has the potential to provide useful and relevant information (an "information-oriented selection", see Flyvbjerg 2011) for three salient reasons:

1. **Arguments for the harmonisation of cancer tissue banks for research purposes have been made repeatedly**  As with arguments made for tissue banking more generally (see Chapter 1), harmonisation of cancer tissue banks is seen by many as critical for the rapid and effective progress of research in order to improve diagnosis and treatment, but of cancer specifically (Oosterhuis, Coebergh and van Veen 2003, Massett et al. 2011, Morente et al. 2006, Suh et al. 2009, von Eschenbach and Buetow 2006, National Cancer Institute 2011a). Harmonisation could, for example, facilitate the study of rare cancers (which make up 20 per
cent of cancers) and enable the development and application of personalised cancer treatment, as discussed further below (European Society for Medical Oncology 2008, De Palma and Hanahan 2012).

2. **Cancer tissue bank harmonisation activities have taken place across the UK**
A variety of efforts to harmonise activities at national and network levels have been initiated in the UK, and many are still ongoing. These include a national cancer tissue bank (onCore) that was founded in 2005 and has since ceased operating (onCore UK 2008b). Several cancer tissue bank networks and projects working across multiple sites now exist that are working towards harmonisation (UKCRC 2011): the Confederation of Cancer Biobanks (CCB), the Cancer Research UK Stratified Medicine Programme, Children’s Cancer and Leukaemia Group (CCLG), Wales Cancer Bank, and the Breast Cancer Campaign Tissue Bank (Confederation of Cancer Biobanks 2012a, Peach et al. 2012, CCLG 2012, Breast Cancer Campaign 2012, Wales Cancer Bank 2013). Cancer is therefore an area of action and activity.

3. **Cancer tissue banks are spearheading tissue bank harmonisation efforts in the UK**
Cancer tissue banks have taken the lead on several key developments of interest to tissue banks in general: governance principles, a tissue bank accreditation scheme and useful template documents. In relation to the former, in 2006 the CCB issued the Human Research Tissue Banks/Resources/Biobanks Guiding Principles – the first consensus statement on the governance and management of tissue banks of any kind in the UK (Confederation of Cancer Biobanks 2006). In the same year the European human frozen tumour tissue bank (TuBaFrost) released in-depth international standards (Riegman et al. 2006) covering tissue collection and sharing; and one year earlier International Society for Biological and Environmental Repositories (ISBER)(2005) had released the US and quality-focused best practices for the management of tissue banks.

Regarding accreditation, in 2007, onCore collaborated with others involved in cancer research and the Marble Arch Working Group on an initiative to bring together existing laws and standards to provide an international framework for
accreditation of tissue banks (Betsou et al. 2007). Finally, regarding templates, a tissue and data access policy, with associated material transfer agreement, was developed in 2009 by NCRI, onCore, and the National Cancer Intelligence network after a consultation process (National Cancer Research Institute 2009b). The document was the first of its type in the UK and can be used by any tissue bank. In summary, cancer tissue banks are working towards harmonisation and in the process creating principles, standards and templates that others in the tissue banking field can utilise.

The involvement of cancer tissue banking in harmonisation efforts supports its use as a ‘critical’ and ‘paradigmatic’ case study, to use Flyvbjerg’s terms. It is critical because the leadership of cancer tissue bank harmonisation activities puts them in a position of strategic importance in relation to the wider area of tissue banks (Flyvbjerg 2011). Further, since on some occasions cancer tissue banks set the standard and act as exemplars, it can be seen as a paradigmatic case (Flyvbjerg 2011). I discuss these types of case study and their implications in more detail in the methods chapter.

Practical arguments also exist to reinforce the choice of cancer and related research as an area to study. Cancer is a common disease with a high level of research funding, including that specifically for collecting and storing research samples (Medical Research Council (MRC) 2012). Cancer research is an existing bounded research community as evidenced by the existence of networks for researchers and tissue banks and the existence of the NCRI and the National Cancer Research Network (NCRN) which represents the major cancer research funders and associated research (National Cancer Research Institute 2008).

My research question therefore can be most clearly stated as: what influences the harmonisation of cancer tissue banks used for research in the UK? In order to begin addressing the question I first address why tissue banks are seen as valuable to cancer researchers and why the harmonisation of those banks might be beneficial.
Cancer research, tissue banks and harmonisation

The section below explains the value of tissue and data for cancer research, the convenience and other advantages of using a tissue bank, and the progress towards harmonisation.

**Use of cancer tissue and associated data in research**

Cancer researchers rely on access to tumour and normal tissue, and associated data, for study. First, the study of cancer tissue under the microscope (histopathology), coupled with information about clinical outcome, enables greater understanding of different cancer sub-types, which leads to better classification of the disease and assignment of patients into risk categories (Sebire and Dixon-Woods 2007, Jackson et al. 2009). Second, investigating cancer tissue at the molecular level (for example genetic studies (DNA), gene expression studies (RNA) or looking at proteins such as enzymes (proteomics)) alongside medical, environmental and lifestyle data, generates important knowledge about the nature of the disease and highlights potential targets for new therapies (Riegman et al. 2006, Oosterhuis, Coebergh and van Veen 2003). Third, cancer tissue and associated data are also needed to validate, test and confirm both the potential new therapeutic targets and any therapies that have been developed (National Cancer Institute 2011b). Fourth, an important application for well-annotated cancer tissue is to understand how and why patients (and cancers) respond differently to cancer therapies to allow patients to be given the therapies that will be most effective (also termed stratification, personalised medicine and when applied to pharmaceuticals, pharmacogenomics, see Box 1 for an example for this type of research)(Clotworthy 2012, Chataway et al. 2012, Arnedos et al. 2012, Hall et al. 2011).
How tissue banks help cancer researchers access tissue, data, technology and expertise

Large (international) multicentre cancer research projects such as The Cancer Genome Atlas project (US), Cancer Genome Project (UK) and the International Cancer Genome Consortium (ICGC) have become more common; harmonisation across tissue banks is required in order to undertake them (Morente et al. 2006, International Cancer Genome Consortium 2010). These large projects are generating new sub-types of cancer (Garay and Gray 2012) that will in turn need to be studied in order to understand the links between sub-types and treatment possibilities (De Palma and Hanahan 2012, Arnedos et al. 2012). The discovery of new rarer cancer sub-types links to a further benefit of harmonisation across tissue banks, which supports the identification, collection and combination of rarer cancer tissue types within research projects, for example through catalogues or networks. At least 20% of cancer cases are
rare, with rare defined as fewer than 5 cases in a population of 10,000 (European Society for Medical Oncology 2008).

Tissue banks can address problems of tissue availability for cancer researchers. The amounts of tissue available vary across the many types of cancer because the methods of diagnosis and treatment are different (Patlak and Levit 2010). Taking tissue biopsies and undertaking surgery for cancer is still very common, but advances in clinical treatment mean that cancer may be identified and removed earlier or even destroyed before or during removal of samples (Teeley and Bashe 2005, Chan 2007, O'Halloran, Guyers and Henderson 2004). As a result, sample sizes may be small and there may be little left-over for researchers after processing in pathology departments (Sebire and Dixon-Woods 2007, Riegman et al. 2006, O'Halloran, Guyers and Henderson 2004, Reck et al. 2011, Grizzle, Bell and Sexton 2011, Gaffney, Madden and Thomas 2012). Tissue from some cancer types is rare because these are not treated surgically, for example large pancreatic or lung cancers, resulting in a general lack of tissue samples for researchers (Grizzle, Bell and Sexton 2011).

Normal tissue from close to the cancer is often available to researchers as it is also extracted during surgery so pathologists can confirm whether the cancer has been completely removed (Coleman 2006). Normal tissue can be used to understand molecular changes in cancer by comparing it to cancerous tissue, but it is not available in every case, for example if the tumour is in a vital organ like the heart or brain little normal tissue is removed (Grizzle, Bell and Sexton 2011).

Tissue banks may therefore have an important role in enabling access to difficult-to-obtain tissue, often in ways that would be expensive or hard for researchers to arrange individually. Some tissue banks collect tissue post-mortem, this enabling use of tissue not usually treated using surgery and normal tissues for comparative purposes (Grizzle, Bell and Sexton 2011, Vonsattel et al. 2008, Eiseman et al. 2003, Vaught et al. 2011a). In some cases tissue banks can access other sources of normal comparative tissue such as that left-over from cosmetic surgery (Grizzle, Bell and Sexton 2011, McDonald 2010). If an alternative supply of tissue is not available, some tissue banks enable access to the paraffin embedded (fixed) or frozen diseased and normal tissue in
pathology archives (Riegman et al. 2006, Morente and Alonso 2005). Going through a tissue bank is not always an advantage – a researcher may obtain less tissue than if they approached a hospital directly because tissue banks often portion out the tissue they receive (Bell, Sexton and Grizzle 2009).

Tissue banks can also help to address issues of tissue quality. Delays in processing the tissue after removal, for example, can affect the genes and proteins expressed in the tissue (Jackson and Banks 2010, Marko-Varga et al. 2012, Bell, Sexton and Grizzle 2009, Balch 2011). Most tissue banks implement their own standard operating procedures (SOPs), which in turn decreases the time spent processing samples and leads to better quality samples (Rogers et al. 2011). Larger tissue banks supply dedicated staff to assist in the collection of tissue to the researchers’ criteria (Grizzle, Bell and Sexton 2011).

In cancer research, high quality annotated tissue has become crucial due to new technology that can conduct in-depth molecular studies to support translational research and therapy development (National Cancer Institute 2011b, Morente et al. 2006). For the information derived from these studies to be reliable across numerous studies and tissue banks, professionals argue that harmonisation of technical procedures for collecting, processing and storing of tissue samples is required (National Cancer Institute 2011b, McShane et al. 2005, William et al. 2010). Tissue banks can help in collecting associated clinical and lifestyle data on tissue samples, including those relating to patient outcomes, tissue quality, patient treatment information, medical history, family history, health behaviour and patient lifestyle (Massett et al. 2011). These data are often difficult to obtain, mainly because collating such data is costly for clinical staff, especially when transcribing information from paper medical records or obtaining information from other hospitals (Shaw and Patterson 2011, Cole et al. 2012). Tissue banks can assist by collecting required clinical and lifestyle data along with the samples (Vaught et al. 2011b).

A further role for cancer tissue banks is facilitating review of tissue samples by pathologists, which is useful in order to confirm that the tissues researchers receive are what they are looking for (McDonald 2010, Hainaut et al. 2011). Researchers often report problems engaging clinical pathologists in research (National Cancer Research
Institute 2009a), but tissue banks may have established access to pathology expertise (Vaught et al. 2011b, McDonald 2010, Womack and Gray 2009).

**Overview of progress towards harmonising cancer tissue banks**

Harmonisation efforts are currently working at three different but interlinked levels: (a) describing the procedures cancer tissue banks must follow to ensure the collected samples are high quality, (b) coming to agreement on how to annotate the samples or research projects to inform future researchers about how the samples have been treated or used and (c) providing guidance on what clinical and lifestyle data to collect from research participants. For example, cancer tissue bank networks are working towards agreement on quality standards, while the Canadian Tumour Repository Network have already put an accreditation scheme in place (Matzke et al. 2012). Sample and project labelling schemes have been developed to assist researchers to understand how samples were processed and allow combination of samples from different tissue banks including REMARK (Reporting Recommendations for Tumor Marker Prognostic Studies)(McShane et al. 2005), and more widely: SPREC (Standard Preanalytical Coding for Biospecimens)(Betsou et al. 2010), BRISQ (Biospecimen Reporting for Improved Study Quality) guidelines (Moore et al. 2011) and MIABIS (Minimum Data Set for Sharing Biobank Samples, Information and Data)(Norlin et al. 2012). Harmonisation initiatives, such as the Public Population Project in Genomics (P3G), have also begun to provide general guidance on the type and format of clinical or lifestyle data on the participant that should be collected alongside the samples (Fortier et al. 2010).

Despite the arguments for harmonisation of cancer tissue banks, progress has been uneven. Cancer researchers still claim that there is a shortage of high quality, well-annotated, and fit-for-purpose tissue samples (National Cancer Institute 2011b, Vaught et al. 2011b, Thompson et al. 2008, Massett et al. 2011, Carter and Betsou 2011, Beishon 2008). Despite the existence of networks, many cancer tissue banks still work separately in terms of procedures, databases and ethical and legal frameworks (Massett et al. 2011, Wagstaff 2011).
The need to avoid the duplication of effort when developing databases and computer programs in cancer research was recognised by US funders who initiated caBIG™ (cancer biomedical informatics grid) in 2004 (von Eschenbach and Buetow 2006, National Cancer Institute 2011a). However, a review in 2011 found that the tools they had developed were not widely accepted by the cancer research community (except, interestingly, those that were developed alongside already existing projects) and that results were not commensurate with funder investment (National Cancer Institute 2011a). However, the project succeeded in building collaboration and reaching a consensus on relevant terminology that was widely adopted (National Cancer Institute 2011a).

Several major projects other than caBIG™ were judged as failing to meet their goals. In the UK, a centralised national cancer tissue resource (onCore – oncology tissue and information resource) was set-up in 2005. However, in 2009 tissue banking activity was wound down; this was blamed on lack of success of the centralised approach to tissue banking (onCore UK 2008b and 2009a). The UK Confederation of Cancer Biobanks (CCB) did not meet its goal of standardising or harmonising operating procedures for tissue banks (UKCRC 2011). In Europe, a human frozen tumour tissue bank (TuBaFrost) was established to enable identification, exchange and use of residual frozen cancer tissue samples across Europe – but despite receiving European funding it was still unused after two years (Riegman et al. 2006, Riegman, Bosch and OECI TuBaFrost Consortium 2008). Absence or failed implementation of harmonised procedures has caused direct problems for large cancer research projects aiming to use samples from different tissue banks, such The Cancer Genome Atlas (US) project, which did not find the number of usable high quality samples they needed after asking tissue banks across the US and the rest of the world (Carter and Betsou 2011, Silberman 2010).

Notwithstanding high-profile failures in harmonisation efforts, new initiatives continue to be established. The US, for example, has set-up a national cancer human biobank (caHUB)(Eastman 2009). In the UK the Cancer Research UK Stratified Medicines Initiative and Breast Cancer tissue bank intend to put in place harmonised procedures (UKCRC 2011, Peach et al. 2012). Thus, it is clear that the harmonisation of cancer tissue banks is an on-going process with numerous failures, successes and unknowns.
This thesis seeks to explain why progress towards harmonisation has been variable and to investigate and characterise the main factors that influence this. In order to do that I need to elaborate upon the nature of tissue banks and understand more about what kind of activities take place, and who must be involved, in order to collect, bank and use tissue and data.

Understanding Tissue Banking

The varied examples of harmonisation efforts I have given above show that it can take place on many levels and at times can be quite technical. In order to be able to understand the possibilities for harmonisation it is necessary to examine tissue banks and banking in more detail. This section considers tissue banking generally, rather than focusing solely on cancer, because many features are generic.

In offering this account, a major challenge is absence of consensus on the definition of tissue banks (or biobanks)(Shickle, Griffin and El-Arifi 2010, Heeney 2012). The literature (implicitly or explicitly) describes tissue banking in different ways: as a process, a lifecycle, a network or a supply or value chain. In what follows, an analysis is offered of the advantages and disadvantages of each model before presenting a proposed novel approach, combining important aspects from each. I first introduce a working definition of tissue banks to define the scope of my research.

Defining tissue banks

I propose the following working definition for the purposes of my research. A tissue bank:

1. has medical research as a major use,
2. contains human tissue, and does not solely contain blood, embryos, foetuses or gametes, and
3. includes both the tissues and associated data required for research.

In order to arrive at this definition I considered various definitions of tissue banks available in relevant guidance, laws and ethical opinions (see PRIVILEGED 2010), noting key features. Three of these features were particularly important to include and clarify
(either through inclusion or exclusion) in the definition because they have a significant influence on the breadth of what could be classified as a tissue bank, and by implication the size of the case study: (1) the use or purpose of the tissue bank, (2) the nature of the tissues in the tissue bank and (3) whether data is included. Other features, including the scale of the collection, the period of storage, whether collection was prospective or retrospective, the public or private nature of the collection, though useful to consider when sampling tissue banks, have less of an effect on the scope of the concept of tissue banks.

This definition provides a general outline which requires further detail in order to understand tissue banking in any depth – in order to do this, different ways of conceptualising tissue banks are explored.

How does tissue get banked and used?

Four existing approaches (process, life-cycle, network and supply or value chain) can be identified that allow insights into the activities, organisations and persons involved in tissue banking. I draw on these existing approaches, and consider their strengths and limitations, in order to produce a new model of tissue banking that is especially useful in explaining the possibilities for harmonisation.

1. Process approach for understanding tissue banking

One popular way of conceptualising tissue banking is as a process or set of processes (Betsou et al. 2007, Downey and Peakman 2008, Morente et al. 2006, Gaffney, Madden and Thomas 2012, McDonald, Velasco and Ilasi 2010). Models of business processes often appear similar to flow diagrams (for an example see Figure 2-1 below) and the aim is to present complex organisational processes in a simple way (Aguilar-Savén 2004). Two harmonisation efforts exemplify the process approach: the Marble Arch Working Group on International Biobanking when harmonising quality standards (see Figure 2-2)(Betsou et al. 2007); and Pfizer Inc. when designing a new software package for their internal tissue banks (see Figure 2-3)(McDonald, Velasco and Ilasi 2010).
These two examples provide a great deal of information about what kind of activities and people are involved in tissue banking. At a basic level, Betsou et al. (2007) show that the process involves acquisition, preparation, aliquoting, maintenance and provision (Figure 2-2).

Figure 2-2 Schema of biobank processes (reproduced from Betsou et al. 2007)

Pfizer Inc.'s sample receiving detail (Figure 2-3) shows how complicated a process can get and some of the mistakes that may occur when receiving samples, such as the sample going missing or thawing out if frozen (McDonald, Velasco and Ilasi 2010). However useful these examples are in giving preliminary information about tissue banking, numerous gaps are evident. The question of how data about the patient is collected and stored is unanswered. The examples offer no understanding of any
overarching management activities or other cross-cutting processes that take place in the tissue banks. As the examples are often limited to a particular context, a picture of any of the wider interactions, partnerships and networks that occur in tissue banking (for example with other organisations) is lacking. One solution could be that modelling tissue banking activities using the process approach could be most useful for self-sufficient tissue banks such as UKBiobank. The fact the processes described are specific to individual organisations could also explain why little information exists about transportation of the tissue.

**Figure 2-3 Pfizer business process flow diagram for receiving samples (copied from McDonald, Velasco and Ilasi 2010, 204)**

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2. **Life-cycle approach for understanding tissue banking**

A second approach is to describe tissue-banking as a life-cycle (Moore et al. 2011, Office of Biorepositories and Biospecimen Research 2012, Public Population Project in Genomics 2013, Gee et al. 2013) rather than a process. The life-cycle approach covers production from raw materials to transportation, use, disposal and re-use of the product. In industry, life-cycle models encourage product manufacture to occur more efficiently by considering the usage of raw materials, how waste is dealt with and when transportation is required (for a generic example see Figure 2-4)(Westkamper, Alting and Arndt 2000, Hagelaar and van der Vorst 2001). In business, life-cycle management also includes consideration of supporting activities such as product research and development (R&D), technical support and commercialisation (Price and Coy 2001).
Figure 2-4 Life cycle of a product. Transportation processes are shown with a "T" and waste treatment processes with a "W" (copied from Westkamper, Alting and Arndt 2000, fig. 17)

This figure was removed due to copyright restrictions, please refer to the publication, Fig. 17.

Two organisations have used the life-cycle or lifespan approach in order to support harmonisation activities: the US Office of Biorepositories and Biospecimen Research (OBBR) when looking at sample handling (see Figure 2-5)(Office of Biorepositories and Biospecimen Research 2012), and the UK Strategic Tissue Repository Alliance Through Unified Methodology (STRATUM) Project in order to identify costs associated to sample and data collection (see Figure 2-6)(Gee et al. 2013).

Figure 2-5 Lifecycle of biospecimens (reproduced from Office of Biorepositories and Biospecimen Research 2012).

Copyright information: This material originated from the website of the National Cancer Institute (http://www.cancer.gov).

The two examples shed further light on tissue banking activities. For example, STRATUM shows that steps specific to data may exist including collecting data, transferring the data to electronic format, anonymising and later archiving it (Figure 2-6). The life-cycle approach encourages tissue banks to outline what takes place before and after acquisition and distribution of the samples. Examples prior to acquisition
include obtaining approvals and funding (Figure 2-6). Examples after distribution of samples include re-stocking (Figure 2-5) and sample disposal (Figure 2-6). Including consideration of the transportation or physical distribution of samples is also a key element in the life-cycle approach (Figure 2-6). These approaches expand our comprehension of tissue banking but, as in many of the process approaches, it is hard to understand where the activities take place and who undertakes them. Again, wider collaborations and interactions between organisations are also not evident, nor are any overarching management or cross-cutting processes conducted by the tissue bank (despite technical support being a consideration of life-cycle management).

Within harmonisation initiatives, the lifecycle approach has been used particularly by those interested in exactly what happens to tissues during tissue banking either because there are quality (OBBR, BRISQ) or cost (STRATUM) implications. The fact that this approach generally incorporates factors important before collection (for example R&D), transportation and issues around waste such as re-use or disposal lends itself to these uses. As with the process approach, it is also informative to understand how harmonisation initiatives separate areas that require different types of guidance. In this regard, P3G split their guidance into four different but overlapping stages (design, building, using and closing the tissue bank).
Figure 2-6 Simplified sample life cycle (copied from Gee et al. 2013, 41).

Copyright information: This material originated from the STRATUM project, website http://stratumbiobanking.org.
3. Network approach for understanding tissue banking

A third approach is to characterise tissue banking as a network, either within or between organisations (Shickle, Griffin and El-Arifi 2010, Zika et al. 2011 and 2010, Technopolis 2010). Networks can be analysed and mapped at the level of the organisation or individual, and often focus on the nature of the relationship between actors (Conway and Steward 2009). Different techniques can be used to analyse and present networks, with social network analysis often used in relation to science and tissue banking (Technopolis 2010, Conway and Steward 2009, Newman 2001). Social network analysis collects information about who has a relationship with who via questionnaire, interview or other publicly available data including publication details (for an example see Figure 2-7 below)(Conway and Steward 2009, Newman 2001). The focus is therefore less on the specifics or detail of processes, activities or overall management, but on relationships.

**Figure 2-7 The formal organization and informal networks of engineers working in R&D (copied from Allen 1977, 208)**

This figure was removed due to copyright restrictions, please refer to the publication, page 208.

Two groups exemplify a network approach to understand tissue banking and harmonisation: BBMRI (Biobanking and Biomolecular Resources Research Infrastructure), which commissioned a social network analysis to map cooperation in the area of tissue banking (see Figure 2-8 and Figure 2-9)(Technopolis 2010) and GeneBanC (Genetic Bio and Databanking: Confidentiality and Protection of Data), which interviewed tissue banks and made conclusions about their involvement in networks (Shickle, Griffin and El-Arifi 2010).
The network approach enables a greater understanding of which organisations are involved in tissue banking and the relationships between them. Academic organisations (over 50% of organisations, see Figure 2-9) dominate European research projects that include tissue banking (Technopolis 2010, 91). The BBMRI social network analysis also shows that collaborations may be international – and often dominated by the UK (14.7% of all possible participations) and four other countries (Italy, France, Germany and the Netherlands) (Technopolis 2010, 89). The UK is therefore one of the leading countries in terms of tissue banking and as such, useful to study.

*Copyright information:* This material originated in a report by the Technopolis group, freely available on website http://www.technopolis-group.com/.
Contradictory information exists on whether tissue banks are members of networks. Shickle et al.’s (2010) interview study found that all tissue banks could be classified as being part of a network either because they were networking internally or externally. On the other hand, Zika et al.’s (2011) survey found that the majority of tissue banks are single or stand-alone (68%) with their own databases in most cases and no partnership with other tissue banks. This difference could be due to the definition of ‘network’ and Shickle et al.’s idea of tissue banks as networking internally. Considering tissue banks as networks is therefore helpful.

Networks are clearly important for implementing harmonisation but may have different priorities or goals for harmonisation, or be more or less amenable to harmonisation. The nature of the network may therefore influence the desire for, nature and extent of harmonisation. Shickle et al. (2010) showed that some networks harmonise in order to produce a shared catalogue of samples, IT systems, facilities, overall management or best practices.

4. Supply or value chain approaches for understanding tissue banking

A fourth approach to characterising tissue banking is that of the supply chain (Confederation of Cancer Biobanks 2012b, Downey and Peakman 2008, Vaught et al.
This approach considers processes that are integrated across more than one business, from developing and manufacturing the product to providing the goods to the consumer (Cooper, Lambert and Pagh 1997). The supply chain includes consideration of transportation (physical distribution) and management of the raw material found in life-cycle approaches, see Figure 2-10. The supply chain model aims to integrate the different types of members across the chain (for example customers, suppliers, contractors, or other linked organisations), and as such it can also be viewed as a type of network (Hagelaar and van der Vorst 2001, Croom, Romano and Giannakis 2000, Harland 1996). The overall management of the chain and the information flow across it is seen as important for the chain to function correctly (see Figure 2-10) (Cooper, Lambert and Pagh 1997, Croom, Romano and Giannakis 2000). The model is limited by less in-depth representation and analysis of processes than other models.

An important concept relating to the supply chain is 'lean' thinking, which focuses on continually reviewing and improving processes along the chain in order to increase value and remove wasteful steps; standardising to remove process variation is a major aspect of this (Radnor, Holweg and Waring 2012). (UKBiobank took concepts from 'lean' supply management when designing their facility, Downey and Peakman 2008.) The concept of value has led some organisation to create “value chains”, looking at the costs and benefits of each step in the supply chain (Vaught et al. 2011a, 26).

Vaught et al. (2011a) identified five main steps on the value chain: biospecimen collection and shipping; processing; storage management; retrieval and distribution; and an overarching pillar on infrastructure and administration (Figure 2-11). Of special interest is the infrastructure and administration pillar, which illuminates activities that must take place centrally to support the different stages of tissue banking. While
Vaught at al.’s model begins to bring in relational elements such as human resources, it does not include consideration of the network of organisations and individuals involved in collecting the tissue, while the supply chain approach in general does consider these aspects (see Figure 2-10). Using chains as a metaphor also leads to the main limitation of supply chain management: that the ‘links’ in the chain slow down the flow of goods or information (Downey and Peakman 2008, SM Thacker & Associates 2012). UKBiobank, for example, highlight that control must be maintained over the input and output of the different process steps otherwise things can become chaotic (Downey and Peakman 2008).

**Figure 2-11 Biobanking value chain framework (copied from Vaught et al. 2011a)**

![Biobanking value chain framework](image)

Towards a new model of tissue banking

The different approaches for conceptualising tissue banking all have something to offer and tissue banking can be seen as a combination of process, life-cycle, network and supply chain. I have developed a provisional model (Figure 2-12) based on the tissue supply chain approach and Vaught et al.’s (2011) value chain diagram (Figure 2-11), but also incorporating useful aspects of the other approaches into account.
The model expands on Vaught et al.’s in five aspects. First, it includes data within all the different steps (I have highlighted the importance of data in Chapter 1, and this was incorporated into process diagrams including Figure 2-3. Second, it incorporates the idea that managing information flow is of overarching importance (based on the generic supply chain model, Figure 2-10). Third, it acknowledges that different individuals and organisations may be involved at different stages of the supply chain and that relationships between them (see the generic supply chain model, Figure 2-10) are of key importance. Fourth, it incorporates phases pre- and post-tissue banking activities, such as set-up, tissue destruction, archival or closure (see life-cycle model Figure 2-6). Fifth, it incorporates the idea of processes that cut across the whole supply chain (based on the generic supply chain model, Figure 2-10).

The cross-cutting processes in question are partly based on those from the generic supply chain diagram and life-cycle management: customer service management (providing the customer with one point of contact and product information), demand management (forecasting demand and minimising variability), order fulfilment (delivery of orders as promised and on time), procurement (building a relationship with suppliers of key items, incorporating them into the development of processes), and product development (Cooper, Lambert and Pagh 1997). The literature mentioned some of these processes as important for tissue banks to consider, for example
knowing what types of tissue cancer tissue researchers need, and aliquoting (see Figure 2-2) it appropriately to meet demand (Myles et al. 2011, Bell, Sexton and Grizzle 2009). I have retained several processes that cut across the tissue supply chain: informed consent management; maintaining audit trail and barcode tracking; quality control and pathology review; and shipment and transport (Vaught et al. 2011a).

I used this model derived from the literature and my own conceptualisation as an organising framework when trying to interpret my fieldwork on the practical side of tissue banking and targets for the harmonisation efforts. Chapter 4 explains how it was tested against what I observed during my research, and as a result was modified and updated. I used further sensitising concepts from the literature, as discussed below, in structuring my inquiry and interpreting my findings.

**Sensitising Concepts: What may Influence the Harmonisation of Cancer Tissue Banks?**

In what follows I introduce two theoretical approaches used to create sensitising concepts before entering the research field: sociology of standards and a model of the diffusion of innovations in service organisations.

**Sociology of standards**

The sociology of standards literature is useful for a broader view on the process and outcomes of standard creation. In terms of creation, it emphasises that who takes part in and is excluded from standard creation is important – which is mirrored in the findings from the empirical studies in Chapter 1 (Timmermans and Epstein 2010, Lampland and Leigh Star 2009). Different stakeholders bring different interests to the table that need to be negotiated between and who is present shows whose interests matters (Timmermans and Epstein 2010, Bowker and Leigh Star 2000, Lampland and Leigh Star 2009). Being part of the team designing the standard may confer advantages on some at the expense of others (Heimer, Coleman Petty and Culyba 2005).

The sociology of standards literature also makes it clear that implementing standards can have consequences beyond those anticipated, for example because people or
activities become marginalised (Lampland and Leigh Star 2009). Some standards may create new, different, barriers to harmonisation, or obstruct the activity they are trying to harmonise – a finding that appeared to emerge from empirical literature in relation to tissue research under the Human Tissue Act (2004) (Cullen Dunn 2009). The literature also argues that the effect of standards depends on the context surrounding the implementation, and there is a need for any study of standards to take this into account (Cullen Dunn 2009).

**Diffusion of innovations in service organisations**

Greenhalgh et al.’s model on diffusion of innovations in service organisations, such as the National Health Service (NHS), provides further factors that may influence adoption of innovations, including:

- **the contents of the innovation** – innovations are easier to adopt if they are feasible, workable, simple and easy to use.

- **the existence of opinion leaders or champions** – obtaining the support of opinion leaders is useful for a successful innovation but identifying them is not easy; supportive and positive champions can also influence success.

- **the existence of social networks** – social networks powerfully influence the adoption of innovations by individuals, including networks of organisations. A well-connected organisation is more likely to be influenced by the other organisations in its network.

- **the presence of critical organisational factors** – the success of innovations depends on the wider context, and particularly the characteristics of the organisations adopting the standard. Important characteristics include: the support, involvement and commitment of managers; the provision of timely and high quality training; the availability of resources to support implementation; and receptiveness to change.

- **the impact of individual aspects** – if an innovation meets an identified need of an individual, they are more likely to adopt it; people also liked to be clear before the innovation was adopted how it would affect them personally.
- **the existence of incentives** – one of the characteristics supporting diffusion is that a technological innovation should offer relative advantage over existing technologies. A conducive socio-political climate encourages innovation in organisations, especially when it occurs at an early stage of implementation (Greenhalgh et al. 2004, 2008).

Linked studies on the management of change in healthcare organisations illuminate a contradictory position in relation to whether and what type of evidence is required to support standards, both showing the need for well-described scientific evidence (Grol et al. 1998) and that it is not always required for successful implementation (Timmermans 2003).

Table 2-1 summarises the major influences from the cancer tissue banking literature (see Chapter 1), supplemented by literature on factors linked to the clinical side, the definition or work of a tissue bank (Chapter 2). I present these as sensitising concepts – general concepts to sensitise a researcher into pursuing certain questions throughout the research project (Charmaz 2006). The layout of Table 2-1 was influenced by Greenhalgh et al.’s (2008) summary of their model on diffusion of innovation in the health services. The adapted version considers design issues, incentives and legislation.
Table 2-1 Areas that may influence the harmonisation of cancer tissue banking, anticipated by Greenhalgh et al.’s diffusion of innovation model

<table>
<thead>
<tr>
<th>Design – Issues at the design stage that affect the creation and acceptance of standards include:</th>
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<tbody>
<tr>
<td>- the availability of resources to create and design the standards,</td>
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<tr>
<td>- the players involved in standard creation,</td>
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<tr>
<td>- how the standards are designed,</td>
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<tr>
<td>- the clinical context linked to cancer and the processes of banking the tissue, and</td>
</tr>
<tr>
<td>- the scope of the harmonisation effort.</td>
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<table>
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<tr>
<th>Implementation and Enforcement – Decisions to follow cancer tissue banking harmonisation efforts are influenced by:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- the contents of the standards in terms of: fairness, incentives, evidence, relevance, length, clarity, degree of standardisation and flexibility,</td>
</tr>
<tr>
<td>- various aspects of the competitive research environment including whether and how effort is recognised and different views on ownership of samples,</td>
</tr>
<tr>
<td>- law and legislative bodies influence harmonisation by:</td>
</tr>
<tr>
<td>- offering threats and disincentives to abhorrent behaviour,</td>
</tr>
<tr>
<td>- being backed up by a strong political impetus for change,</td>
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<tr>
<td>- requiring licensing, which:</td>
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<tr>
<td>- leads to cost implications for the applicant, and</td>
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<tr>
<td>- requires professionals to go through a process of obtaining the license,</td>
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<tr>
<td>- creating the possibility that standards are accepted by some regions and not others,</td>
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<tr>
<td>- or creating barriers (real or perceived) to cancer tissue banking in practice.</td>
</tr>
<tr>
<td>- the actions of organisations that create or impose standards, for example the incentives offered, such as making compliance a condition of funding, or ease of access to guidance about standards,</td>
</tr>
<tr>
<td>- the existence of networks and success stories, for example:</td>
</tr>
<tr>
<td>- social networks sharing knowledge and advice about standards,</td>
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<tr>
<td>- professional networks may vary in their desire for harmonisation and the nature and extent of it, or</td>
</tr>
<tr>
<td>- the existence of successful tissue banks or organisations that can be emulated.</td>
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<tr>
<td>- the characteristics of organisations conducting cancer tissue banking, including:</td>
</tr>
<tr>
<td>- the type of organisation (academic, NHS or industry) and how they are monitored,</td>
</tr>
<tr>
<td>- the availability of resources for implementation,</td>
</tr>
<tr>
<td>- the availability of training, and</td>
</tr>
<tr>
<td>- the existence of systems of internal oversight and monitoring, including audit.</td>
</tr>
<tr>
<td>- numerous individual aspects, including:</td>
</tr>
<tr>
<td>- personal views on the standard and whether it is seen as fair or flawed,</td>
</tr>
<tr>
<td>- educational background or practical experience that leads to certain behaviour, and</td>
</tr>
<tr>
<td>- rationalised selective compliance.</td>
</tr>
<tr>
<td>- existing standards that cause overlap, confusion, duplication or wider variation in practice.</td>
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</tbody>
</table>
Research Questions

Following the literature review and conceptualisation presented in Chapters 1 and 2, it is now appropriate to specify my research question precisely. My overall question is: what influences the harmonisation of cancer tissue banks in the UK? The following sub-questions will be relevant to answering this:

- Does the tissue supply chain model apply well to practice?
- Which actors are involved in the tissue supply chain?
- Do professionals support harmonisation in the area of tissue banking?
- Why has the harmonisation of cancer tissue banks not taken place?
- What do existing standards cover and does this match with what professionals request?
- Who is involved in creating standards and what are their motivations?
- What is the process for designing standards?
- What design, organisational and individual factors influence implementation of standards?
- What effect does the outcome of implementation have on harmonisation?
- Do common areas of complexity exist across the different stages of harmonisation?
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With recourse to the methodological literature, this chapter describes the study design and the justification for this design. It also includes reflections on potential influences on the research. It concludes by explaining the major ethical issues relating to the conduct of the research and their management.

Rationale for Research Method Selection

The final research questions were open-ended and exploratory, reflecting the gaps in the literature. The literature review (Chapter 1) showed that professionals (defined to include individuals working for organisations involved in tissue banking, tissue research or harmonisation) would be the most appropriate group to approach. Using quantitative methods such as surveys would be inappropriate as the relevant variables (i.e. the influences on harmonisation) were unknown. Who, precisely, was involved in devising and implementing harmonisation efforts in the UK was also unclear. Thus, the survey method was unviable, not least because obtaining a representative sample in the area of human tissue regulation is known to be problematic, as previous attempts to do this have demonstrated (Human Tissue Authority 2009b).

Three further problems with using a quantitative approach can be identified. First, little directly relevant social theorisation existed; thus the possibility of deductive or hypothesis-driven research was limited. Second, a quantitative approach was inappropriate for investigating the wider context of UK cancer tissue banking and harmonisation. Questions such as: how cancer tissue banking takes place in the UK, who is involved in harmonisation and why, and does the method used for creating the standard affect the possibility of implementation, would be impossible to address. Third, tissue banking is a complex and distributed process involving numerous sites and actors. It is unfeasible to study a process that occurs across contexts using quantitative techniques requiring that variables be tightly defined a priori.

Qualitative research methods can address some limitations of a quantitative approach. For example semi-structured interviewing enables discussion of:
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- the background context of cancer tissue banking and related harmonisation initiatives,
- the views of professionals on what influences harmonisation,
- and relevant new, previously unknown, issues (Pope and Mays 1995, Bryman 2008).

Observations of practice enable:

- checking of whether professionals’ recollections matched what occurred in the field,
- a better understanding of implicit beliefs, routines or tacit actions the professionals were not aware of,
- and study of the whole process of tissue banking, from collection of tissue in surgery to use in research in the university (Mays and Pope 1995, Silverman 2005).

In addition, documents can help to build contextual detail (Atkinson and Delamont 2005), while photographic images allow place and space to be included (Harper 2005).

I decided that an ethnographic approach would be the best way of enabling different data collection techniques to be combined in the selected case study (Brewer 2000, Hammersley and Atkinson 2007); it was especially attractive because ethnography is a flexible method that can be adapted to accommodate emergent findings (Hammersley and Atkinson 2007).

In order to support transparency, an objective of this chapter is to clearly and comprehensively describe the methods and analysis, while Chapters 4–6 aim to give a straightforward account of the empirical findings.

Research Methods and Design Strategy

In order to underpin discussion in this chapter, this section provides an outline of the research methods and design strategy for the study, accompanied by an overview diagram (Figure 3-1). The study commenced with a literature review (see Chapters 1 and 2, and Appendix 1), which clarified the main research questions, gave rise to sensitising concepts and informed the choice of methods – an ethnographic approach.
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coupled with a case-study focus. A pilot study allowed refinement of the research design, particularly in terms of sampling, and further development of the sensitising concepts. Following on from this, an initial plan was developed involving three NHS hospitals and associated universities as the major sites for the research, alongside visits and observations at relevant organisations and meetings.

Data collection commenced in March 2010, and involved a combination of semi-structured interviews, observations, photographs and document collection (see sections below, under ‘ethnography’). Data analysis started in October 2010 and fed back into the data collection phase, informing sampling decisions, ensuring potentially disconfirming data was sought, and leading to the evolution of interview topic guides (see section on data analysis below). Findings were consolidated with attention paid to: ensuring transparency of research methods, providing illustrative quotes, and ensuring fair-dealing in terms of considering the full range of opinions. Vignettes were used within the text provide context to, and explanation of, the findings.

Before explaining the research process in more depth I explain how I addressed one of the key challenges when conducting qualitative research – the potential influence of me (as the researcher) on the research and resulting data.
Figure 3-1 Research methods and design strategy overview

- Literature review
  - Elucidated main research question
  - Highlighted sensitising concepts
  - Informed choice of methods: ethnographic approach & case study focus

- Pilot
  - Informed refinement of research design
  - Informed choice of sample & sites for main study
  - Developed sensitising concepts

- Initial plan
  - 3 hospitals and linked universities chosen as major research sites
  - Visits & observations at relevant organisations and meetings

- Data collection
  - Purposive and strategic sampling
  - Semi-structured interviews
  - Observations and photographs
  - Document collection

- Data analysis
  - Constant comparative method
  - Open-coding
  - Initial themes & coding framework
  - Memos produced
  - Focused coding for subsequent data
  - Constant comparison of new data to existing categories to develop categories or create new ones
  - Attention paid to disconfirming data
  - Coding frameworks integrated and finalised

- Consolidation of findings
  - Transparency in methods & quotes
  - Context illuminated with vignettes
  - Considered full range of opinions

See Appendix 12 for participant details
Reflexivity and Researcher Influence

One of the cited challenges to the reliability of qualitative research is the researcher’s influence on the setting and the results (Mays and Pope 1995, Denzin and Lincoln 2003). Each researcher has potential biases, a distinctive personality and different levels of influence (Denzin and Lincoln 2003). Reflexivity throughout my research was important to reveal potential influences (Critical Appraisal Skills Programme (CASP) 2006). It took the form of an ongoing detailed written record of reflections on my involvement and possible influence on the research, through fieldwork diaries and field notes. The remainder of this section considers how assumptions, experience or personality may have impacted on the research generally. Reflexive observations are included at relevant points in the remainder of this chapter.

One assumption embedded in the main research question was the idea that harmonising tissue banks was a priori a good thing. This was also evident in much of the literature (see Chapter 1). However, I set this presumption aside in favour of thinking more critically about the enactment of harmonisation and what acts as a barrier or facilitator. I was careful to avoid presenting myself as either for, or against, harmonisation whilst in the field.

A further assumption was that the cancer tissue banking community was easily separable from wider tissue banking to form the limits of the case study. In practice it became difficult to distinguish between the two, as many tissue banks collect both cancer and non-cancer tissues; many hospital departments handled both. Further, other relevant stakeholders who were not directly involved in cancer tissue banking but who participated in tissue banking more generally were approached, for example regulators and funders.

My own assumptions were revised as the project progressed, including a commonly held view that the involvement of the pharmaceutical industry in tissue banking and research was a ‘bad’ thing. Over time, I was constantly surprised at the cooperation and amiability of pharmaceutical companies’ representatives, and the welcome I received at relevant conferences:

See Appendix 12 for participant details
The small size of the conference made it easier to do some networking; it was easy to talk to people high-up in pharmaceutical companies, to talk to anyone. Pharmaceutical companies often offered for me to visit. People were friendly, so friendly that I wondered if pharma purposely employs nice people (field notes, meeting 5).

My prior academic experience and training in both law and biological sciences may have influenced the research. My previous research work on the ethical and legal governance of tissue banks (Townend et al. 2009, Rouillé-Mirza and Wright 2005) might have led to undue focus on the major law in the area, the Human Tissue Act (2004), consent or privacy. In order to avoid this, during interviews professionals were not asked questions on these topics until their importance had been established through the emerging research findings (see preliminary interview topic guide in Appendix 7 versus the later stage topic guide in Appendix 8).

Another specific research interest of mine, due to its implications for tissue bank governance, was whether professionals viewed tissue samples and the associated data as two separate things or as combined for the purposes of research (Wright et al. 2010). It was crucial to address this from the outset as it defined the scope of the study and it was included in the topic guides (see Appendices 7 and 8). If professionals felt that the tissue and data could be viewed separately, this project could have solely focused on the tissue and the tissue supply chain. If, on the other hand, the professionals viewed data as crucial for tissue banking and research, it needed to be included. Professionals did, in the event, view the data as important (see Chapter 5) and it was incorporated into the study.

My previous experience as a scientist (a degree in genetics) had also given me practical laboratory experience. Thus, during tissue bank and laboratory tours, I often understood techniques and equipment were used for. This enabled more time to discuss research matters. An additional benefit to a background as a scientist was that professionals appeared to be more accepting, often making comments like ‘well you’ll understand this’. Although some social scientists observe that these kinds of

See Appendix 12 for participant details
statements just create the illusion of being accepted and are not actually acceptance, in practise, it was advantageous (Czarniawska 2007).

Finally, personality clearly influenced my research practice. On the positive side, I was well-organised throughout the research, and particularly skilful at meeting professionals and arranging visits, tours or observations. Less positively, I occasionally found it difficult to be spontaneous and take the initiative or ‘chance’ to request further observations or interviews:

after the day I felt a bit dirty, I think because I’d pushed my way in. I wondered if that’s what journalists feel like. However, despite this I met some wonderful people who spent a lot of time chatting to me and offered me a lot of opportunities (field notes: Colham (a large NHS Trust with linked hospital)).

It became clear during early observations that taking the initiative could be important and I became more proactive when appropriate. This facilitated access to a wide variety of meetings and locations (see sampling and access below).

**Case Study**

As described in Chapter 2, a case study of cancer tissue banks was judged to be an appropriate design for this research. Two limitations to ethnographic case study research are often mentioned in the literature. The first relates to understanding the significance of concepts and findings and how often they occur (Flyvbjerg 2011). As this study aimed to identify and characterise previously unrecognised factors that may influence harmonisation, I do not claim to have complete coverage or exact information on occurrence. However, when results are presented in the chapters below some indication as to the relevance and pertinence of a viewpoint or activity is provided.

A second concern is whether the results from the case study are generalizable to the wider phenomenon or context being studied, in this case tissue banking (Flyvbjerg 2011). Clearly, this is much more likely to happen in an analytical or conceptual sense rather than a statistical sense (Yin 2003). It is likely that any analysis would be generalizable to wider harmonisation efforts because cancer tissue banking was a

*See Appendix 12 for participant details*
‘paradigmatic’ case that led the harmonisation initiative in the UK (see Chapter 2). This remained evident during my research:

within cancer, ... you've obviously got xxCanbankxx [a national cancer tissue bank] ... , but then also xxOnconetxx [a network of cancer tissue banks] which were a central way of harmonising .... Nothing like that exists in cardiovascular and for someone who’s come from a cancer background I found that very strange (P12, tissue bank manager).

Additionally, as mentioned above, the research extended beyond the case study to professionals and settings involved in tissue banking more generally.

**Pilot Studies**

An initial pilot study was conducted to refine the research design and develop ‘sensitising concepts’ (Charmaz 2006). This included an informal discussion with a pathologist and attending a two-day human tissue research conference. This pilot work influenced the design by confirming that the NHS is the primary place in the UK that human tissue is collected, and by drawing attention to the important role of industrial actors. It informed decisions about sampling, and the research plan was developed to include visits to pharmaceutical companies and tissue supply intermediaries. Access was also assisted as key contacts were met who were later approached during the fieldwork. The pilot study also enabled a better understanding of how to communicate with relevant professionals, and especially ‘elites’ (see semi-structured interviews below).

The pilot study influenced the sensitising concepts, showing that tissue banking was part of a complex supply chain and resulted in preliminary information on who was involved. Table 1 (May 2010) in Appendix 9 illustrates the conceptual development after the pilot study, compared to earlier ideas. They included a new focus on industry and other amendments. This table was the basis for the first interview topic guide (Appendix 7) and informed the start of the ethnographic research. In month 14 of the research period, six interview transcripts from *Conversations with Pathologists*, a collection of interviews with pathologists conducted by Sue Armstrong, were analysed,
with interviewee and author consent, to generate ‘sensitising concepts’ around the response to the Human Tissue Act (2004) (Pathological Society 2010, Armstrong 2010). The results of this analysis were subsequently included in the literature review (Chapter 1).

Ethnography

Ethnographic research combined with a constant comparative method of analysis meant that sampling, data collection, reviewing the literature and analysis were conducted concurrently and iteratively throughout the research. The initial study plan (March 2010) was developed after the pilot study and in conjunction with the ethics applications. The plan was flexible and could accommodate emergent findings, for example on who was involved. The research plan revolved around interviews, observations, document collection and photography within three main research sites (incorporating hospitals and linked universities) to understand how the harmonisation of cancer tissue banking was working in practice as well as further interviews and observations outside of these specific sites, for example at conferences and in organisations with a stake in tissue banking. As shown in Table 3-1 and Table 3-2 below, 81 individuals participated in the research; 40 professionals were interviewed and 41 were observed across the three main research sites and eight other organisations (for further details see Appendix 12). Additionally, eight conferences or meetings were attended and three tissue banks visited.

The next section gives details on sampling and access, followed by an account of the data collection methods used: semi-structured interviews, observations, photography and documents.

Sampling and access

The sampling strategy for the three tissue-banking sites was ‘purposive’ (Silverman 2005, Mason 2002). Hospitals had been shown to be sites of key importance on the tissue supply chain in the literature review, confirmed by the pilot study. Three main research sites including NHS teaching hospitals and linked universities already involved in supplying and conducting tissue research were selected as the main locations to

See Appendix 12 for participant details
CHAPTER 3: METHODS

conduct observations. Each hospital, or group of hospitals, served a different sized local population, and as such were classified into small (Report, a small NHS Trust with linked university), medium (Novelburg, a medium sized NHS Trust with linked university) or large (Colham) sites. Findings, including variation and similarities, were compared and contrasted across the three research sites.

The flexible nature of the research led to the need for what Hammersley and Atkinson term ‘sampling in the field’ (2007). More strategic or ‘theoretical’ sampling is often thought difficult to achieve but in this study, because the data analysis was happening alongside the sampling, it was possible (Charmaz 2006, Silverman 2005, Brewer 2000, Hammersley and Atkinson 2007). As the scope of the research narrowed, sampling became more strategic.

Sampling was planned to cease when a degree of ‘theoretical saturation’ was reached, or little new could be added to the ideas that have emerged from the data (Bryman 2008, Glaser 1965). In terms of interviews, the initial research plan anticipated this after 36–41 interviews (see Table 3-1), based on the previous research experiences of my PhD supervisors, Mary Dixon-Woods (MDW) and Helen Eborall (HE). 40 interviews actually took place. Theoretical saturation occurred within the remit of the project, but a number of alternative and potentially valuable lines of enquiry emerged from the research that would benefit from future exploration (see Chapter 7).

Access

In each major research site and organisation, ‘gatekeepers’ assisted with access to locations for observations and professionals to interview (Hammersley and Atkinson 2007). These varied between ‘official’ gatekeepers who were named as collaborators on the project, and ‘unofficial’ gatekeepers who emerged as helpful for facilitating access as the research progressed. Site gatekeepers were different types of professionals, including oncologists, pathologists, clinical trials coordinators, tissue bank managers and facilitators, funder representatives and PhD students. The main route that relevant professionals were identified and approached, for interview, was by introductions from gatekeepers to their colleagues either by email or face-to-face. My fieldwork diary records that: “the best results come from introductions from local

See Appendix 12 for participant details
collaborators or PIs in the case of my case studies, or from snowballing when in the hospitals or universities (21 October 2011).

Overall, the majority of individuals contacted agreed to an interview or period of observation. Six individuals did not reply to email contact. On four further occasions interviews or observations had been arranged and then I was unable to contact the potential participant at some stage after distributing the information sheet and agreeing to a date. A further two potential participants said no, in one case because she felt she was not involved enough in cancer tissue banking. In another a pharmaceutical company representative refused longer observations or photographs, but was happy to host a visit and allow informal interviews.

**Table 3-1 Expected (plan March 2010) vs. Actual (end Feb 2012) interview totals**

<table>
<thead>
<tr>
<th>Activity</th>
<th>Expected No.</th>
<th>Actual No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colham – Interviews</td>
<td>6-7 NHS staff</td>
<td>14 (9 NHS)</td>
</tr>
<tr>
<td>Repton – Interviews</td>
<td>6-7 NHS staff</td>
<td>6 (4 NHS)</td>
</tr>
<tr>
<td>Novelburg – Interviews</td>
<td>6-7 NHS staff</td>
<td>7 (6 NHS)</td>
</tr>
<tr>
<td>Key stakeholders outside main research sites</td>
<td>–</td>
<td>13 (3 Uni)</td>
</tr>
<tr>
<td>Interviews</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interviews – NHS staff</td>
<td>18-21</td>
<td>19</td>
</tr>
<tr>
<td>Interviews – University staff</td>
<td>18-20</td>
<td>11</td>
</tr>
<tr>
<td>Interviews – Other</td>
<td>included in 18-20</td>
<td>10</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>36-41</strong></td>
<td><strong>40</strong></td>
</tr>
</tbody>
</table>

**Semi-structured interviews**

Interviews were conducted before observational work at each site in order to understand the tissue banking that was taking place there and to provide information on useful locations for observations to occur. Professionals inside research sites, and other relevant organisations, were also interviewed to obtain opinion and knowledge.

See Appendix 12 for participant details
on tissue banking and harmonisation efforts. The initial research plan expected 36–41 interviews to take place, and of these 18–21 would be with NHS hospital staff, and 18–20 with university and other relevant professionals (see Table 3-1). The number interviewed fell within this expected range. In order to obtain a variety of viewpoints a range of professionals were interviewed, including: a PhD student, a university administrator, university researchers, tissue bank staff, tissue bank managers, a lawyer, funder and regulatory body representatives, clinical trial facilitators, research nurses, a pathology lab manager, research governance staff and hospital consultant surgeons, pathologists, oncologists and a clinician (see Appendix 12).

Many of the professionals interviewed could be considered ‘elites’ such as hospital consultants or funder representatives. One issue with speaking to these groups was that they were clearly accustomed to public speaking and often repeated the official message of the wider organisation rather than their personal views. For example, one member of tissue bank staff said that many tissue bankers did not want to harmonise because “they’re going to be self-sufficient (P5)”, echoing comments of the manager on “the cottage industry style of self-sufficiency (P4)” of tissue banks. In some cases it took time, more probing questions and the assurance of confidentiality for the professionals to share their less ‘public’ views. One example was a discussion with a tissue bank manager about closure of the tissue bank:

*about a year and a half ago for economic reasons we took the decision to back out of the active biobanking side because it was actually, it’s a very expensive thing to do and also very time consuming thing to do …*

**WHO TOOK THAT DECISION?**

*our funders took that decision*

**SO IT WASN’T IT WASN’T YOU FOR EXAMPLE?**

*No, although there was inevitability to it … (P4, tissue bank manager).*

I felt the need to get behind the official company message in order to understand the reasons that lay behind the decision and its impact:

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See Appendix 12 for participant details
BUT HOW DID YOU FEEL ABOUT THAT DECISION?

I wasn’t surprised to be perfectly honest. There was the inevitable uncomfortableness of closing down systems, contracts, relationships and laying off staff that we had built from scratch. ... So there’s always a little personal thing about the destruction of something you’ve made (P4, tissue bank manager).

Unfortunately in several cases professionals requested that such statements be kept ‘off the record’ and so they could not be used.

In some cases interviewing elites could be intimidating either because of an impressive location or a sense of the professional’s importance. For one interview “I got there and she had to deal with multiple emergencies at the other place she works at on the phone before she spoke to me, and this heightened my sense of her importance (fieldwork diary: 16 May 2011)”. Telephone interviews were often more straightforward as such face-to-face aspects did not need to be dealt with.

Topic guides based on my literature review, pilot work and extensive discussions within my supervisory team were used to structure the interviews, and these evolved as the research progressed in order to test new ideas. Guides were tailored to the professional’s role to ensure that maximum usefulness was obtained from each interview. An example of the process of updating topic guides was as follows:

I initially copy the topic guide for the new interviewee from a person working in a similar role. I then read all relevant previous interview transcripts and meeting reports. I brainstorm all the possible questions I could ask for a few hours and then go through and organise them into themes before writing them up as ‘proper’ questions. In this way all topic guides are different, but the same questions can run through them. I file all used topic guides (fieldwork diary: 24 October 2011).

Semi-structured topic guides meant that professionals were able to raise and discuss relevant topics, thus allowing for new points to arise. All interview audio recordings were transcribed either fully or partially. If professionals asked to check their transcripts they were able to, although in practice only one professional requested this and made minor spelling corrections.

See Appendix 12 for participant details
Observations and photography

Observations took place both within the three main research sites (inside both the hospitals and associated universities) and at tissue banks and meetings outside them. Photography was used when permission was given. Across the hospital sites, I spent 103.25 hours conducting observations, with 11 of those on tours or visits. Outside the main sites, the initial research plan envisaged attending up to 16 meetings, four tissue bank visits and three observations. In the end, I attended eight meetings which ranged from one to three days, and made three visits lasting approximately 14 hours in total, but no other external observations occurred (see Table 3-2). Overall, practice was observed in pathology departments, oncology and other clinics, interventional radiology, tissue banks, and relevant committee meetings, workshops or conferences. I also visited and spoke to people in university labs, tissue storage facilities, tissue banks, clinical trials units, funders and pharmaceutical companies.

Observations revealed the mundane routines around tissue banking. When appropriate, these were recorded photographically. In order for data collection to be as naturalistic as possible, the initial aim was to be ‘non-participatory’ and simply observe practice (Mays and Pope 1995, Hammersley and Atkinson 2007, Potter 2002). However, this is not what happened. The most naturalistic observations were during shadowing (Czarniawska 2007, Murphy and Dingwall 2003) tissue bank facilitators in Novelburg, but, even then, I ended up participating in the work of the tissue bank:

I was doing a few more things today including shredding something in the morning, helping stack papers, helping with boxes, helping unload samples into freezers, opening and shutting doors, sitting with researchers while they waited to collect samples, and carrying samples. I possibly shouldn’t be doing these things but I was helping out (field notes: Novelburg).

Other researchers have observed that the choice of the degree of participation in the research site is never entirely in the researcher’s control when shadowing because the researcher may be told, asked or expected to assist in some activities (Czarniawska 2007, Murphy and Dingwall 2003).

See Appendix 12 for participant details
Table 3-2 Expected (plan March 2010) vs. Actual (end Feb 2012) observation totals

<table>
<thead>
<tr>
<th>Activity</th>
<th>Expected</th>
<th>Actual</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observations at Colham</strong></td>
<td>Sept 2010 to Feb 2011 (6 mths)</td>
<td>Sept 2010 to May 2011 (9 mths)</td>
</tr>
<tr>
<td>Observations – professionals</td>
<td>-</td>
<td>24 individuals (12 NHS)</td>
</tr>
<tr>
<td>Observations of practice – hours</td>
<td>-</td>
<td>33 hrs, pathology (14.5), clinical trials unit (10), oncology (5.5), tissue board meetings (3)</td>
</tr>
<tr>
<td>Tours and visits – hours</td>
<td>-</td>
<td>6.5 hrs, university</td>
</tr>
<tr>
<td>Observations – professionals</td>
<td>-</td>
<td>7 individuals (4 NHS)</td>
</tr>
<tr>
<td>Observations of practice – hours</td>
<td>-</td>
<td>17 hrs, pathology (14.25), interventional radiology (3)</td>
</tr>
<tr>
<td>Tours and visits – hours</td>
<td>-</td>
<td>2.5 hrs, university</td>
</tr>
<tr>
<td><strong>Observations at Novelburg</strong></td>
<td>Sept 2011 to Feb 2012 (6 mths)</td>
<td>Feb 2012 (1 week)</td>
</tr>
<tr>
<td>Observations – professionals</td>
<td>-</td>
<td>5 individuals (1 NHS)</td>
</tr>
<tr>
<td>Observations of practice – hours</td>
<td>-</td>
<td>42 hrs, university tissue bank and related activities, including hospital pathology and wards</td>
</tr>
<tr>
<td>Tours and visits – hours</td>
<td>-</td>
<td>2 hrs, tissue bank</td>
</tr>
<tr>
<td><strong>Observations outside research sites</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total key stakeholder observations –</td>
<td>-</td>
<td>5 individuals (1 Uni)</td>
</tr>
<tr>
<td>individuals (not incl. conferences)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organisation observations –</td>
<td>3 organisations</td>
<td>0 organisations</td>
</tr>
<tr>
<td>organisations outside NHS trusts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observations at relevant meetings and</td>
<td>16 observations</td>
<td>8 observations</td>
</tr>
<tr>
<td>conferences – number</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visits to tissue banks – number (hrs)</td>
<td>4 tissue banks</td>
<td>3 tissue banks (total 14 hrs)</td>
</tr>
<tr>
<td><strong>Individuals observed</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Individuals observed – NHS staff</td>
<td>-</td>
<td>17 individuals</td>
</tr>
<tr>
<td>Individuals observed – University staff</td>
<td>-</td>
<td>20 individuals</td>
</tr>
<tr>
<td>Individuals observed – Other</td>
<td>-</td>
<td>4 individuals</td>
</tr>
<tr>
<td><strong>TOTAL individuals observed</strong></td>
<td>-</td>
<td>41</td>
</tr>
</tbody>
</table>
Due to tight timescales many observations were ‘tours’ of hospital departments or tissue banks, where I would be taken around, have everything explained to me, and be able to ask questions. Often, I would be left to observe individual professionals at work for short periods of time when I could ask questions. This kind of observation has been termed a ‘go-along’ (Kusenbach 2011). Advantages of go-alongs are that they allow researchers to understand what participants do, their views on locations, activities or experiences encountered during the observation (Kusenbach 2011). The major disadvantage is that go-alongs can disturb normal events and potentially lead to what is termed the ‘Hawthorne effect’, when the researcher’s presence modifies others’ actions (Mays and Pope 1995, Kusenbach 2011). Evidence of this effect was evident in the research; for example in two different pathology departments:

*it was a little bit awkward sat there because I think she felt that she had to show me interesting things – people seem to get paranoid that they aren’t showing me interesting things and I have to reassure them that their routines are very interesting to me (field notes: Colham).*

*I think I did cause problems because she said she did things a bit slower with me around, and she said this was due to me being a distraction. On the other hand, she also said it was quite nice to have somebody there who was actually interested in what she was doing (field notes: Repport).*

Even though observations could not always be classed as ‘naturalistic’, they allowed a wider understanding of the locations tissue banking took place in, how tissue was stored and distributed, pragmatic issues associated with this, and the impact of laws and other standards.

Observations identified deviation between what professionals said in interviews and what occurred in practice. For example, the Novelburg University tissue bank manager said during an interview that: “we've put in place a costing process so that the pathology time it's taken to provide a sample to the tissue bank is reimbursed back into their laboratory (P67, tissue bank manager)”. However, observations indicated that the costing process was not working: “P72 (tissue bank facilitator) was of the opinion that they keep reformulating the costs at the moment and that the costings

See Appendix 12 for participant details
were very much works in progress and sometimes made upon the spot (field notes: Novelburg)”. A difference existed in this tissue bank between the official and unofficial versions of events, indicating the value of triangulating what is said by actors during interviews against what was happening in practice.

Further, observations were a useful way of collecting the opinion of those conducting the work in practice:

*I’ve just been to Colham where I spoke to a Research Technician. I’m really impressed at how useful it was – I think the conclusion would be that it’s very important to speak to the people doing the practical work, and not just the Professors. It really struck me how much she (P62) had thought through all these issues, and how clearly she stated her position and ideas. When I spoke to the archivist in the hospital, she also gave me an incredible amount of useful information – more than many of the pathologists (fieldwork diary: 21 October 2011).*

Formal interviews with support staff, assistants or students were rare, ‘informal interviews’, or conversations during observations were more usual. These professionals appeared to be more open and I developed close relationships with some of them, meaning that I had to remind people of my ‘researcher’ status (see ethics section on consent below).

During observations, everything was treated as ‘anthropologically strange’ and the following recommendations were followed (Silverman 2005 and 2007, Hammersley and Atkinson 2007, Emerson, Fretz and Shaw 1995):

- consider and note initial impressions,
- try to get behind public statements and behaviour,
- take note of tacit behaviour,
- think about place and space,
- take note of non-verbal actions,
- observe how professionals create and use categories,
- consider the mundane as well as the remarkable, and
- be reflexive about emotions and feelings as the observations progress.
Despite preparation, some observations provoked extreme reactions, for example when viewing human tissue in pathology:

*they were just throwing it in the colander, it was all draining into a sink, and then the stuff that was in the colander (which looked really gruesome to me), bits of flesh and everything, just went into a yellow bin (clinical waste I think). The idea of different people’s tissue all mixed together like this quite disturbs me, but I don’t know why (field notes: Colham).*

I viewed my reactions to situations as useful to highlight when what was being observed diverged from something expected to something abnormal. Thus, the reactions helped to highlight when activities or situations in new research sites deviated from those in other sites or what policy or other documents dictated should be happening. In this way my feelings and reactions were a research tool (Czarniawska 2007).

**Note-taking, observation reports and photography**

Notes were taken overtly during observations using small notepads, rather than after the event. One advantage to this was transparency; professionals could see the notes being made this served as a reminder of my status as a researcher. A disadvantage was that this occasionally led to some participants watching or waiting for the note-taking to stop before speaking, or once even asking for specific things to be written down: “when I was talking to the Biomedical Assistant (BMA) she seemed to get enthusiastic about me making notes and said things like ‘you must write this down’ (field notes: Colham)”. In this way note-taking could have an effect upon naturalism of the setting, with professionals narrating or pausing their work to assist the researcher. Notes taken in the field were limited to ‘key words’ and ‘jottings’ intended to jog the memory when later compiling a report (Hammersley and Atkinson 2007, Emerson, Fretz and Shaw 1995).

Following each observation, or when next convenient, notes from the observation were gathered, themes selected, and audio reports made (Czarniawska 2007). A computer programme, Dragon Naturally Speaking version 10, was used to create initial
transcripts of the observation reports, which were checked for consistency with the original recording. Meeting reports were compiled using Microsoft Word.

Note-taking was accompanied by photography to record details that would be difficult and time-consuming to describe in textual form. An example of this was photographs of buildings, storage facilities and other aspects of place and space. Figure 3-2 illustrates how photography can demonstrate the size and scale of storage facilities. Occasionally, pictures of useful documents were taken (Hammersley and Atkinson 2007). Accompanying contextual details were noted for each photograph, including where and when it was taken and details on what it illustrated (Hammersley and Atkinson 2007).

**Figure 3-2 Inside a tissue storage facility, view of liquid nitrogen storage vats**

![Inside a tissue storage facility, view of liquid nitrogen storage vats](image)

**Deviations from the research plan**

Several deviations from the research plan occurred (see Table 3-2). It was anticipated that more observations other than tours or visits would be done in organisations outside the main research sites; but often tours were offered as the only sanctioned form of access. The three relevant organisation types highlighted after the pilot study were: a pharmaceutical company, an institute or organisation outside the UK and a
CHAPTER 3: METHODS

company that provides access to fresh materials for commercial companies. In two cases, efforts to set up observations in pharmaceutical companies failed. In both, initial goodwill was apparent but complexities arose when details about the visit were discussed; one company did allow a tour and informal interviews. In relation to organisations outside of the UK, international professionals were interviewed, but these were undertaken while attending international meetings. Funding and time were not sufficient to support a period of observation abroad. Finally, companies collecting tissue from the NHS in order to supply it to commercial or other organisations were difficult to identify and contact.

Further, eight of an estimated 16 meetings were attended. The initial estimate was based on the number of relevant conferences advertised during the first six months of the research when four meetings were attended. In the final 18 months of the study a further four meetings were observed. The original target was not met due, in the main, to logistical issues and expensive conference registration fees (for example, £1558.80 for Biobanking 2011 in London). Additionally, the amount of data collected from each conference was extensive and as a result time-consuming to consolidate.

Finally, the number and length of observations in the main research sites achieved varied. More hours of observation (44) occurred in Novelburg than the other two sites. There, I had the opportunity to shadow tissue bank facilitators for five full working days as they collected, processed and stored tissue. At other sites hours were spent at different departments, units or clinics when it could be arranged. In addition, a lower amount of observations took place in Refport, where the key relevant individual went on leave.

Document collection

As part of the ethnographic study, documents were collected to support interview and observational data, these included:

See Appendix 12 for participant details
- screenshots of tissue bank databases,
- tissue bank SOPs,
- forms, logs, labels, agreements, questionnaires, protocols, information sheets and consent forms relating to tissue banking,
- university department standards, manuals and guidance documents,
- university committee documents,
- hospital lab guidelines and tissue banking SOPs,
- PowerPoint presentations outlining organisation policy,
- funder reports,
- regulatory authority policy,
- documents distributed at meetings and conferences, and
- organisational webpages.

Professionals were generally willing to provide examples of documents when asked. The format varied, some documents were sent or available digitally, in other cases paper versions were photographed, photocopied or collected during the research. In several cases, I copied information (for example from notice boards) into a notebook. After anonymisation, paper versions were scanned and, alongside digital files, incorporated into NVivo (QSR international), a computer programme used to assist with organising and analysing data.

**Data Analysis**

Analysis of the qualitative data was based on the constant comparative method first outlined by Glaser (1965). This method involves the allocation of collected data (coding) to categories to structure and interpret it (Glaser 1965). I used this approach for both organisation and analysis of data. In terms of analysis, I commenced with broader open coding (Bryman 2008) to allow ideas to emerge and later moved towards more focused coding (Charmaz 2006) when developing the categories (see data analysis pathway in Figure 3-3).
Prior to coding the first 14 interviews, they were re-read in order to ensure familiarity with their contents (Bryman 2008, Braun and Clarke 2006). Following this, open coding (Bryman 2008) was conducted, initially on paper, following the idea of coding incidents and statements to as many categories as possible, and where relevant on a line-by-line basis (Charmaz 2006, Glaser 1965). Category names were kept succinct and aimed to capture the content of the data coded to them (Charmaz 2006). Structures relating the categories to each other, or ‘coding trees’, were developed and inputted into NVivo (see Appendix 11 for examples). All data were imported into NVivo and coded.

Initial coding trees assisted with locating salient or key categories in the data and enabled some categories to be integrated into others, a process Charmaz (2006) terms ‘theoretical integration’. Consequently, focused coding assigned any new data to these initial coding trees to help understand the breadth of the categories and to continually develop the coding trees to ensure best fit to the collected data. Open coding was conducted, again, when new data was collected, such as the first international tissue banking conference attended. Seven coding trees arose from the data, three of those pertained to a broad analytical level (analytic coding trees). Four served to structure the data (structural coding trees) to enable ‘scene setting’ or vignettes to be built within the results chapters.

See Appendix 12 for participant details
As the data collection and coding continued it became clear following literature reviews and meetings with MDW and HE that particular social theories (such as those on cooperation and the sociology of standards) could offer analytical utility (see Appendix 9, December 2011, theoretical sensitising concepts). This influenced theoretical integration in the analytic coding trees (see cooperation coding tree in Appendix 11), which were organised with reference to these concepts. The final coding trees incorporated sets of categories and links to existing social theory, as well as new emergent concepts and ideas which had arisen from the data.

The constant comparative method recommends the use of memos to support and develop the process of analysing the data (Charmaz 2006, Glaser 1965). Memos and notes were used to assist with understanding and developing ideas about the concepts and categories that arose during the different stages of coding the data, for excerpts see Appendix 10. These memos were continually added to throughout the research and led directly to writing-up the results of the research.

One method of ensuring that the developed categories represented the data, and being sure that theoretical saturation was reached, was to identify (rather than ignore) deviant cases and test whether they fitted into the framework, or suggested new categories or ideas (Silverman 2005). One example of this was that an emerging theme of the research was that the Human Tissue Act (2004) was holding-up tissue research and causing problems for tissue banking. In order further explore this I spoke to a range of professionals across numerous sites about the law and found individuals who felt the case was the opposite. Information from these supportive professionals was carefully analysed to produce a section of the coding tree on the advantages of the law (see Appendix 11), which broadened my understanding of the outcome of the implementation of this law. Selecting varied professionals from different types of organisations ensured the study incorporated diverse perspectives (Hammersley and Atkinson 2007). Identification and exploration of deviant cases also contributed other emerging themes.

Finally, when writing up the data it was important to ensure that the different viewpoints collected were represented in the results, termed ‘fair dealing’ or ‘justice’
by some commentators (Hammersley and Atkinson 2007, Murphy and Dingwall 2001). During my research this was linked to the concept of triangulation and ensuring that any potentially competing versions of events were compared. When writing up I also used vignettes and mini-case studies to provide context and illustrate the analysis.

**Ethics and Ethnography**

As the ethnographic research was highly exploratory, decisions on who, how and what to observe, interview or photograph were often taken spontaneously. Thus, *a priori* project plans could not cover all of the situations that arose and anticipate all ethical issues. Ethnographic researchers who aim for immersion in the field and conduct observations often report continuously having to make ethical decisions (Czarniawska 2007). I followed Murphy and Dingwall’s (2007) idea of being an ‘ethically sensitive’ researcher who could respond to such situations as they arose. I supported this by obtaining relevant training and questioning other researchers about their experiences prior to commencing observations. I undertook training on good clinical practice, taking consent, ethnographic methods and interviewing. Knowledge of research ethics, data protection and privacy was held from previous educational and work experience. I organised an ‘ethnographic experiences’ meeting with others in my researcher group undertaking ethnographies in hospitals in order to share practical advice and ethical reflections. Next, I reflect on the particular ethical issues associated with consent.

**Consent**

Obtaining informed consent is a particular concern of research ethics committees (REC) (Department of Health 2005). Approvals demanded that certain principles needed to be followed for interviews, observations, photographs and conferences. For interviews, the participant had to be provided with the study information sheet at least 24 hours prior to the interview unless they decided that less time was acceptable. In practice, the vast majority of professionals had the information sheets one week in advance, with only one or two professionals met in the field having less time.

Whilst obtaining consent, professionals were given more information about the study and the opportunity to ask any questions. In practice, few professionals asked
questions and most wished to skip going through every provision on the consent form, preferring to sign it and proceed to interview. Research ethics approval was given for email consent when the interview was by telephone, and this option was used in five of 40 interviews. During two face-to-face interviews, professionals did not give consent for the interview to be audio recorded and extensive notes had to be taken. While professionals were given the opportunity to withdraw consent, this did not occur.

The approved principles for observations within organisations were different depending on whether they were NHS hospitals or not due to differing requirements of the two RECs approving the research. In both cases, where possible, information sheets had to be distributed to staff before the observation. A particular problem existed within NHS hospitals with multiple departments and when certainty did not exist about where the observations would take place. In several cases heads of departments were asked to distribute this information, but I cannot be sure to what extent it occurred. I ensured that I carried information sheets with me and I distributed them during observations and took steps to explain the research and seek assurance that people understood it and were comfortable. Within the NHS, verbal consent to observation noted in the field notes was considered to be sufficient by the REC, and this principle was followed in practice by always ensuring participants’ permission was sought and recorded.

Both RECs accepted that verbal individual permission needed to be sought before taking photographs during observations and where possible supervisors or department heads would review and agree to the photos. In practice this worked well. However, in one case a laboratory manager vetoed several photographs and insisted that the photographs were retaken in order to cast the department in a better light. On my return she gave explicit directions on how to re-take the photographs, and some cleaning took place before the photos were taken. These photographs were not natural data and were excluded from analysis.

Outside the NHS, the University of Leicester ethics committee required written consent when conducting observations, unless this was impossible or undesirable (the latter principle was aligned with the Framework for Research Ethics, ESRC 2010).
Situations where the requirement for written consent might not be possible were foreseen. For example when individuals entered the setting for a small amount of time, worked in a different area of the lab, or were too busy to give written consent. In practice, these situations often arose, and very few people completed written consent form for observations and instead gave verbal consent.

Informed consent in ethnographic observations can be understood as a continual process of verification and renegotiation (ESRC 2010, British Sociological Association 2002). Although the aim was to be sufficiently unobtrusive so as not to affect the actors’ behaviour, this was not always straightforward. Sometimes, in informal settings, participants would engage in conversations that they perhaps would not have done had they not become habituated to my presence. In these cases I felt it was good ethical practice to remind them about the research.

Consent was difficult to negotiate and ensure during the conferences and meetings I observed. Little guidance is available in training courses or textbooks on this issue. It was decided to contact the organisers to request distribution of study information in advance to delegates. In practice, this only happened once. Many were large international corporate events and identifying the relevant person to distribute such information was often not possible. While at the conferences, the aim was to ask the organisers to make an announcement about the research. This happened twice, but again, due to the size of some of the meetings it was difficult to approach the organisers. The goal of obtaining an announcement was unrealistic at larger events. As an alternative to announcements, I presented a poster at two conferences and carried ethically approved leaflets about the research to distribute. Individuals directly spoken to were informed about the research and given the opportunity to ask questions.

At this conference I did not speak to the organiser. However I did a poster presentation that clearly told everyone what I was doing. I also spoke individually to the people I met and often said ‘I might use this in my PhD, do you mind?’ (field notes: meeting 7).

See Appendix 12 for participant details
CHAPTER 3: METHODS

Privacy: data protection, anonymisation and confidentiality

Participants’ and organisations’ identities were protected during the research to limit any harm that might be caused on publication (Hammersley and Atkinson 2007). Enacting and protecting these principles while conducting ethnographic research is a challenge due to the tensions between retaining detailed information and achieving anonymity. Following a review of the literature and relevant legislation, ten principles were developed to guide the research:

1. Give the participants, organisations and conferences a code or pseudonym

   Interviewees were given a number (for example P1, P2) when they agreed to take part and this was used when reporting the results. Observation study participants were also given codes. Research sites and organisations were given pseudonyms such as Colham, Novelburg and Onconet. The names of conferences and meetings were coded simply, for example, ‘meeting 1’. Some organisations were not anonymised as they were unique in the area and would easily be re-identified. Participants working for these organisations were informed about, and agreed to, this.

2. Remove directly identifying information from transcripts, reports, documents and photographs

   Directly identifiable information was removed (or replaced with a code), including names (individual or organisational), addresses (postal and email), telephone numbers, professions, location of work, gender, organisational logos or signs, voices, people’s faces and car number plates (see the Data Protection Directive 95/46/EC)(Article 29 Data Protection Working Party 2007, US National Institutes of Health 2013, Medical Research Council (MRC) 2003). When dictating observation or writing meeting reports, potentially identifying contextual information was routinely excluded. To ensure that professionals could not be identified from their job title, they were asked to frame their roles in general terms before the interview. The rationale behind this was that some professions are rare or unique, and this was borne out in the research when some professionals said they were the one of the few people with a particular profession in the country. In several cases, people or

See Appendix 12 for participant details
organisations wished to be identified but this would have caused the identities of linked respondents to be revealed (Kaiser 2009).

3. **Consider whether other contextual information could indirectly identify an individual** Incidental information left in quotes or transcripts could be combined (Social Research Association 2003), or associated with other information the reader holds, to identify a person. Such indirect clues could include: verbal mannerisms in a quote, dates, places, amounts, small contextual details such as events (Kaiser 2009, Tolich 2004). One individual’s verbal mannerisms had to be altered in order to obscure their nationality. Incidental details replaced in transcripts included the names of colleagues, organisations, places and projects. For photographs anything potentially identifying was blurred using a computer program. For documents, particular attention was paid to removing logos and information from the headers and footers.

4. **Do not collect identifying information if not required** The principle of data minimisation in Data Protection Directive 95/46/EC (Article 6) requires that personal data should not be collected if it is not required. In this research, no irrelevant personal information, for example, the age and sex of the professionals was collected.

5. **During observations store identifying information separately to field notes and then destroy it** When in the field, any personal information required to conduct the research (such as names, address and telephone numbers) was stored in the final pages of the field notebook and removed and destroyed once observations were concluded.

6. **Limit access to the original data** In order to prevent unauthorised access, electronic personal data, including voice recordings, were either encrypted or held on secure drives and password protected within the University (Data Protection Directive 95/46/EC, Article 17). I alone had access to all of the full transcripts and audio recordings.

*See Appendix 12 for participant details*
7. **Store consent forms and equipment securely**  
When not in transit or use, all consent forms and research equipment (for example, cameras and audio recorders) were stored in locked cabinets in offices with restricted access.

8. **Limit the transcribing to the primary researcher**  
I transcribed most interviews and all observation reports myself, removing any identifying information in the process. Where other transcribers were used, they signed a confidentiality agreement and the audio files were transferred securely.

9. **When writing-up, use a different example if an individual may be identified**

10. **Check acknowledgements or co-authors do not reveal identities.**

Issues of confidentiality arose separately to privacy in cases when participants specifically requested that certain pieces of information were not divulged (Pattinson 2011). This information often took the form of photographs taken, or comments made after a more formal interview or off the record at a conference. I respected participants’ requests in all cases.

**The Presentation of Research Data**

Chapters 4–6 comprise the research results. Six notes assist with understanding how the research data is presented. First, the professionals involved in the study are referred to throughout as ‘participants’ or ‘professionals’. Second, all professionals are referred to as ‘she’, especially in excerpts from field notes. Third, within quotes from interviews, capital letters denote the researcher (JW) speaking. Fourth, research sites and involved organisations have been given pseudonyms which are italicised and followed by an explanation in brackets at first mention in the text. See Appendix 12 for more extensive information on the organisations, participants and referenced throughout. Fifth, much of the research took place at the three main research sites previously described (Colham, Novelburg and Repport), each of which included a hospital or hospitals and an associated university. Finally, I had many informal conversations during observations; these have been referenced using a citation of the style ‘field notes: participant number, job title’.

See Appendix 12 for participant details
CHAPTER 4: RESULTS – SETTING THE SCENE FOR CANCER TISSUE BANKING AND HARMONISATION IN PRACTICE

This chapter presents findings that set the scene on cancer tissue banking in a UK context, leading to a more thematic presentation of my results in Chapters 5 and 6. Part 1 of this chapter explores study participants’ conceptualisations of ‘harmonisation’ and the process of harmonisation, showing that some view the process as complicated and not necessarily desirable. Part 2 offers an introduction to each of the actors important to tissue banking in the UK. I consider the influence of each, and the relationships between them, highlighting the social and political complexity of the UK tissue banking environment. Part 3 begins to show the technical complexity of tissue banking, by testing the provisional tissue supply chain model based on literature review that I proposed in Chapter 2 against observations of what happens in practice, and then updating the model in light of my findings. Part 1 demonstrates that harmonising tissue banks is complicated by a myriad of social, political and technical issues, and Parts 2 and 3 support this.

Part 1: Participant Understandings of, and Views on, Harmonisation

Interpreting my research findings requires, first, some background on the views of participants on what harmonisation means; second, a description of motivations for supporting or not supporting it; and third an explanation of my approach to presenting findings in the following chapters.

Participants generally aligned themselves with the ‘continuum’-based definition of harmonisation presented in Chapter 1; they considered harmonisation an umbrella concept representing a spectrum of possibilities with full standardisation at one end and ‘laissez faire’ application at the other. Standardisation was perceived as an extreme form of harmonisation involving “identical protocols in all respects .... [s]tandardisation in my view is ... the ultimate of harmonisation, it’s where you ... have predefined protocols for data collection (P6, university researcher)”. These
professionals also linked harmonisation to the goal of interoperability across tissue banks. Thus, many professionals viewed the outcome or ‘goal’ of harmonisation as an important feature.

Other participants considered the process itself as what defined harmonisation and which involved “persuading everybody to do the same thing (P40, pathologist)” or undertaking “actions and processes that bring about agreement, reconciliation or standardisation (document: meeting 6)”.

The majority of professionals appeared to be ideologically committed to the idea of tissue bank harmonisation, and a significant proportion were involved in harmonisation efforts. Participants supported harmonisation because it: encouraged the re-use of samples; minimised duplication of effort; led to economies of scale; and allowed the combination of samples and data in tissue banks, enabling the study of rare diseases or the creation of large sample sizes. Several also said that harmonisation could make the country a more attractive place to conduct research, attracting investment from large companies.

Some novel motives for harmonisation also emerged that have not previously been reported in the literature in any detail (Chapter 1). Within BigPharma, an international pharmaceutical company, data harmonisation was seen as useful because it led to people across the company speaking the same language and helped to ensure that they were “comparing apples with apples and not apples with pears (P41, tissue bank manager)”. Participants also proposed that harmonisation improves practice through the sharing of knowledge and expertise that takes place:

*through the harmonisation process, people are also learning from one another .... [I]t’s also a way not only to repeat what has been done but to improve, to improve it, to bring it to another level. Because you get this extra knowledge that just comes to you (P2, ELSI researcher).*

Motives occasionally mentioned by professionals included the ideas that harmonisation on quality would illuminate how samples and data had been collected and enable more targeted research use; while harmonisation on ethics approvals would reduce paperwork and bureaucracy.

*See Appendix 12 for participant details*
Reasons harmonisation was not supported

Discussions on the reasons why tissue banks should not be harmonised were rarely as explicitly stated or well-rehearsed as those supporting harmonisation. But those I uncovered began to give an indication as to why harmonisation is technically, socially and politically complicated. From a scientific perspective, some professionals were unconvinced that connecting tissue banks was required to support research into common cancers because individual centres already saw thousands of cases a year.

Other professionals felt that the current diversity in technical procedures in tissue banks should be preserved so as not to exclude unknown future research possibilities:

*this year’s research questions and next year’s research questions will be different.*

*... [H]armonisation, standardisation could ... say things like ... it has to be frozen within a certain time from the sample coming out the patient. ... if you say half an hour, to start with there’ll be some projects for where that’s not fast enough ... so how do you make your minds up? (P40, pathologist).*

One participant was concerned that scientific creativity would be dampened if in-depth sample collection procedures narrowed research possibilities. Several professionals felt that standards should not be in-depth as the fine detail would be too difficult to implement in hospitals where variables such as timings could not easily be controlled:

*if it is a resected tumour or biopsy which needs to be frozen down there’s a lot of ways of doing it. There are overriding principles but ultimately it probably can’t be uniformly standardised. .... I don’t think you can put too much in terms of standardisation of what ... must be done between the sample coming out of a patient and ending up in nitrogen. Cos you can’t (P52, clinician and tissue researcher).*

Furthermore, participants identified social reasons why harmonisation efforts would struggle. Some of these concerns related to the process of harmonisation and the difficulty of reaching agreement on new documents, tools or databases. Another concern was the perception that ‘other’ professionals understood the arguments for harmonisation but were still ‘resistant’ to implementing new standards.
People know they can’t escape the harmonisation agenda because intrinsically the argument makes sense, but they’re happy to harmonise as long as everyone else harmonises to their standard (P4, tissue bank manager).

Participants felt that these ‘others’ may view new standards either as an implicit criticism of their own existing procedures and methods or be wary because they do not want to change.

Other concerns were more political in nature. Some participants felt that harmonisation initiatives led by large powerful organisations (including the Government) would not be supported due to a lack of trust. Thus, who was involved in the harmonisation effort could be important to people’s willingness to cooperate. A further apprehension was that organisations taking part in harmonisation initiatives might not communicate with others running similar projects:

[t]he one potential disadvantage … is that... I hope they [different local harmonisation projects] are all having some discussions with each other, because it would be very sad if we ended up with a system inxxFinkleborough xx [a local cancer tissue bank] … that can’t align with the system inxxColhamxx (P55, funder representative).

Though the major reason participants supported harmonisation was to avoid duplication of effort, they were also concerned about not imposing “a one size fits all model (P2, ELSI researcher)”. This could be linked to the general perception that standardisation is an extreme form of harmonisation, and something that many actors wished to avoid.

Harmonisation as complicated

Thus, participants gave accounts both in favour and against harmonisation; harmonisation of tissue banks was seen as technically, socially and politically complex. It is no surprise that professionals were caught between seeing harmonisation as simple and as something that was too difficult and so should not be attempted:
there’s two dangerous perspectives that a lot of people hold. Both of which prevent it [harmonisation]. One is the group who feel that it’s so difficult it’s not even worth trying to start … who will argue with every single proposal you make about how you could harmonise two things together. And there’s another group that say it’s so straightforward you don’t need to harmonise, if two studies have collected information about smoking then it’s the same and you don’t worry about it. … Both of those two viewpoints are naïve and ridiculous but nevertheless they are held by a lot of influential people (P6, university researcher).

If harmonisation is not impossible, it is certainly complicated. To tackle the inherent complexity it is helpful to separate the larger problem of what influences harmonisation into three smaller constituent problems: stages of creation, implementation and the related outcomes, as foregrounded in my earlier discussion in Chapter 2.

In order to further simplify the discussion the products of harmonisation are referred to as standards whether they are guidelines, operating procedures, agreements, contracts, laws, directories, registries or IT systems. While the majority of participants used the term standards similarly broadly, some saw a difference between standards and ‘softer’ best practice or guidance documents. Additionally, funder representatives saw a separation between standards and ‘systems’, with the former term referring to guidance and standard operating procedures (SOPs) and the latter to directories, registers and IT systems. Nevertheless, the concept of standards is used throughout this thesis, with attention to different possible interpretations.
Part 2: Actors Involved in Tissue Banking and Relations Between them

Part 2 introduces the role and extent of involvement of the major organisations (termed actors) that conduct, or have an external influence on, tissue banking (see Figure 4-1). These actors are referred to in later discussions on who creates standards (Chapter 5) and how actors can support (or not) the implementation of standards (Chapter 6). Relations between actors are complex; initial reflections on interactions are provided at the end of Part 2.

Actors conducting tissue banking

Observations and interviews suggested that six main actors were active in obtaining, storing or distributing tissue and data (see Figure 4-1). The tissue banking environment was characterised by “massive variation, it’s a really heterogeneous sector the research sector, ... very mixed – from very small amounts of activity to commercial to academic (P61, Human Tissue Authority staff member)”. Descriptions of the key tissue banking sites below illustrate the extent of activity, variety and complexity.
Figure 4-1 Actors involved in UK tissue supply chains

See Appendix 12 for participant details
Universities

Universities held a wide variety of tissue banks. Larger tissue banks set up by universities either had a general focus (Novelburg and Refport University tissue banks) or were cancer specific (Finkleborough, a local cancer tissue bank). The banks were collaborations between one university (or group of linked universities) and numerous hospitals either in purpose-built or adapted facilities in the university or within a hospital building. This represented a drive by some universities to integrate internal tissue banking activities, motivated by transparency, regulation and a desire to improve quality for researchers and improve research infrastructure:

*I think the University is definitely engaged with it and trying very hard to channel as much activity as they can through the tissue bank ... I mean one of the major reasons, is that they want to increase research output and ... it's generally perceived that tissues that come out of a properly run tissue bank are better quality, ... there are other aspects such as institutional risk in terms of compliance and regulatory issues (P67, tissue bank manager).*

Staff from the larger university tissue banks often took part in wider harmonisation activities and/or joined Onconet (a network of cancer tissue banks), but little evidence of other cross-university harmonisation existed. Internally, many universities had established pan-university tissue boards which monitored tissue collection and research at an institutional level, covering both large and small collections.

Smaller tissue banks for individual researchers existed that ranged in size from a few paraffin blocks to 30,000 frozen samples. These collections were heterogeneous in terms of types of samples stored, standard operating procedures, storage facilities, equipment used for analysis and databases. Social complexity could arise in relation to these collections. Participants described university researchers as working separately and in some cases either in competition or disagreement with other researchers in the same institution, although there were also reports of groups working together, for example in terms of freezer storage space.

See Appendix 12 for participant details
P63 talked a lot about the professors that are based at the hospital and work with Colham university. She hinted that there have been squabbles between them and some have tried to steal each other’s research work. She described them as existing in separate ‘silos’ (field notes: P63, research technician).

Universities were sites of massive technical and social heterogeneity, but some had moved towards integration and harmonisation.

**NHS Hospitals**

National Health Service (NHS) hospitals were the primary provider of tissue and data from clinics, surgery, pathology, or via clinical trials units, to tissue banks. Several hospital-specific tissue banks also existed and a number of hospital pathology department archives were directly accessed by researchers. As such the NHS was very influential, but hospitals were not joined-up in tissue-banking endeavours and the variation between them led to technical, social and political complexity:

> the UK is meant to be in a unique situation by having comprehensive health care for the whole population through a so called National Health Service. The reality of it, however, is that it’s actually a fragmented local health service, Trusts are not centrally controlled, they make local decisions, they hire and fire people locally, they set priorities locally (P4, tissue bank manager).

The lack of harmonisation was evident everywhere: pathology SOPs, databases, archives, consent procedures, recompensing costs, funding and Research and Development (R&D, or Research Governance) practices. All of these caused issues for harmonisation efforts and tissue collection across multiple sites.

**Pharmaceutical companies and contract research organisations**

Pharmaceutical companies acquired tissue and data from a number of sources including collaborations with hospitals and universities, tissue supply intermediaries or tissue banks:
a researcher at BigPharma said that they have established a network to meet tissue supply needs, including clinical trials, historical collections and commercial suppliers. She said ultimately the samples come from hospitals, universities or public/charity tissue banks. She said currently commercial suppliers are providing the most tissue, but they are looking to use clinical trials samples. They also have a connection with a local cancer tissue bank (field notes: meeting 7).

The tissue and data were stored inside the company either in large centralised tissue banks or locally by individual researchers. Some companies had worked to harmonise internal processes and databases but there was little evidence of harmonisation across companies.

After collection, samples and data were rarely distributed outside companies, except under a contract with a Contract Research Organisation (CRO)(see Figure 4-1). CROs offered research services to, and coordination of clinical trials on behalf of, pharmaceutical companies (as well as other actors). For trials, CROs typically received samples linked to trials directly from hospitals and may be based abroad. CROs have developed connections to particular hospitals and held tissue banks around the world. Again, little evidence existed of harmonisation between CROs.

**Tissue supply intermediaries**

I devised the term ‘tissue supply intermediaries’ to refer to commercial companies that acted as intermediaries between tissue sources and research-focused customers, but were not set up specifically as a tissue bank. Some intermediaries were large with access to a wide range of sample types, others, often smaller and more specialised, relied on a few key suppliers. Tissues were sourced from the UK and abroad, and both prospectively and retrospectively. These companies were influential as they were the main suppliers for some pharmaceutical companies. A tissue bank manager at BigPharma described how their tissue procurement strategy worked:

*when she receives a tissue request she looks to see if the tissue bank has got it. If the bank does not, she asks if they want it sourcing. If they did she would apply to a company on the approved suppliers list such as Asterand or Tristar (field notes: P70, tissue bank manager).*
I found little evidence of discussions or guidance relating to tissue supply intermediaries sourcing tissue in the UK and even fewer when the tissue was sourced from abroad.

**Independent tissue banks**

Independent tissue banks are those detached from the overarching control (financial, governance or otherwise) of any one organisation. Some were influential in terms of providing an example that others followed, for example professionals referred to documents prepared by CanBank, Wales Cancer Bank and the Rare Cancer Association of Biobanks (a national cancer tissue bank).

*The tissue bank manager* said that she had a role model at Wales Cancer Bank, and often called xxthemxx on the telephone. *She likes the way that things are done at Wales Cancer Bank* (field notes: P67).

Independent tissue banks varied in both size and funding arrangements and sometimes maintained connections to local universities and hospitals.

**Actors with external influence on tissue banking**

This section introduces the six main actors who create environments for and external pressures on (but who do not themselves conduct) tissue banking and discusses the extent of their influence, variance and harmonisation (see Figure 4-1).

**Regulators**

The UK Government creates legislation and associated regulators that govern the actions of professionals taking part in tissue banking. The Human Tissue Act (2004) and regulator (the Human Tissue Authority or HTA) proved to be influential as they were mentioned by a large number of participants and observations showed that they had changed practice for tissue banks. The regulator aimed to ensure that premises obtained licenses and certain legal and ethical requirements were followed:

*And that’s the key really to the Human Tissue Act and what we’re expected to do. It’s to try and ensure that when tissue is used and stored for use, that it comes there with consent* (P61, Human Tissue Authority staff member).

See Appendix 12 for participant details
Ironically, any resulting harmonisation did not extend across the across the whole of the UK, as Scotland followed different legislation where licensing was not required:

so what they’re doing in Scotland is they’ve had a different approach. They don’t have a Human Tissue Authority … and their legislation just covers … removal and use of tissue from the deceased (P51, funder representative).

The result was divergence between Scotland and the rest of the UK. As noted in the literature review, this is a good illustration of some of the difficulties of securing harmonisation through legal instruments; unless they are adopted uniformly they may not result in the same standards being met.

Good clinical practice (GCP) requirements, which are quasi-legal standards, were frequently mentioned by research participants. Despite this, one regulator’s (the Medicines and Healthcare Products Regulatory Agency) guidance on ensuring that laboratories follow the requirements of Clinical Trials Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC was only mentioned once in my interviews and observations. Similarly, data protection requirements received only a minor mention, and not one that suggested that the legal standards on data protection had led to harmonisation:

most people think that the data protection act is totally unworkable, and is to the detriment of research, and therefore, choose to ignore it. I certainly do (P52, clinician and tissue researcher).

Guidance from inter-governmental bodies also lacked influence in the UK. For example, the Organization for Economic Co-operation and Development’s Best Practice Guidelines for Biological Resource Centres 2007 and the Council of Europe’s Rec(2006)4 on Research on Biological Materials of Human Origin were only ever mentioned at meetings and conferences, and never in practice.

**NHS Research Ethics Committees (RECs)**

Professionals saw RECs as influential: if they wished to collect and store human tissue and data for research they normally had to apply for approval through the centralised NHS REC application system. Tissue bank managers often placed particular importance
on having “a very good working relationship with our xxRECxx (P12, tissue bank manager)”. A specific centralised ethics application scheme for ‘Research Tissue Banks’ (RTBs) had been developed by the Human Tissue Authority and the National Research Ethics Service (now Human Research Authority). The voluntary scheme originally aimed to cover research use of diagnostic archives, but had expanded to apply to other types of tissue bank:

and that’s been a very popular scheme, there are now over 200 Human Tissue Authority licensed banks that have that generic approval.

AND HAVE YOU HAD GOOD FEEDBACK ABOUT THAT SCHEME?

Yeh we have, and I think the feedback that we’ve got is that it’s something that more and more banks want to take advantage of really (P61, Human Tissue Authority staff member).

All approved RTBs needed a Human Tissue Authority license and to follow linked research sector standards devised by the HTA, resulting in a level of ‘procedural’ harmonisation.

**Funders**

Government funders, endowment trusts and charities supported tissue banking activities through a patchwork of funding initiatives with little harmonisation. No national government funding scheme for supporting tissue banking infrastructure or networking existed. Instead, funders supported individual institutes, centres and units and distributed pump-priming money for independent, university or disease-specific tissue banks. Outside units or centres, a funding gap for investment in longer term infrastructure was evident.

Funders did coordinate with each other in three important ways. First, evidence existed that government funders worked closely together to ensure tissue collection is funded. Second, cross-funder groups had been established on relevant topics, for example the National Cancer Research Institute (NCRI) and the UK Clinical Research Collaboration Experimental Medicine Funder’s Group. The NCRI supported a cancer
tissue bank registry and the production of a template access policy for research involving samples and data (2009), both of which had been used by tissue banks.

Third, twelve funders collaborated by signing up to the policy document the *UK Funder’s Vision for Human Tissue Resources* supporting greater harmonisation in the areas of generic consent, directories, access, and justifying new sample collections. However:

*how each funder will implement through terms and conditions of grants or through new policies, or whatever, however they decide to implement this vision, will differ, and I don’t think we could ever get a unanimous agreement on how to do that. Because each funder obviously has got their own ways and systems and processes (P51, funder representative).*

Thus, the *Funder’s Vision* did not represent a joint funding commitment for development of the standards and in reality it could lead greater variation; differences already existed between funder requirements for researchers and policies on topics such as patient involvement, post project data sharing and researcher exclusivity periods. Although political pressure had driven funders to greater cooperation, this was limited by the internal processes of individual funders.

A Scottish Governmental body had devised a scheme to harmonise tissue banking and support related infrastructure:

*researchers will be able to go to one contact point in their local health board and say this is the tissue I want. … [T]he money from the collaboration doesn’t just go into biorepositories, it also goes into R&D and to some extent universities as well to have that infrastructure in place. In some places it is equipment, in others it is people … we want to have as much research taking place in Scotland as is possible (P65, Scottish Government representative).*

The initiative, with a connected accreditation scheme, had the potential to encourage harmonisation and to raise standards across Scotland, at least within the main NHS Scotland health boards, though new research would be needed to determine if it succeeded in this aim. While this appears to have further separated Scotland from the

*See Appendix 12 for participant details*
rest of the UK, underlying principles of the accreditation scheme were derived from
HTA standards so interoperability could result.

**Suppliers**

Suppliers of the products, equipment or services that enable or automate tissue banking had an external influence on tissue banks. These commercial enterprises provided: software, sample storage or collection equipment, sample storage facilities, digital pathology, assays, technology for analysis of samples, quality control, reagents and logistics. Variation existed between these products; this benefited the suppliers because tissue banks became tied to particular suppliers to obtain reagents for particular machines or the correct tubes to fit inside purchased sample storage facilities. Tissue bank databases were a strong example of this:

> at meeting 7 many companies offered sample management databases. But when I asked a representative they said that none of the companies had agreed the same minimum data set so all of the databases would contain different data fields. In terms of working with other pieces of software, she said that for each new piece of technology whether that could be linked into the database depended on whether those companies had an agreement or not! (field notes: meeting 7).

All of the tissue banks included in the ethnographic study had approached different companies for databases, and as a result they were all different and technically difficult to connect together for the purposes of harmonisation.

**Patient organisations**

In the context of tissue banking, patient organisations represent people living with a particular disease or patients taking part in tissue banks. They were influential because tissue banks consulted them through donor forums, public-patient engagement panels, or local involvement networks, when establishing procedures or plans. However, whether such patient involvement was required (consultation was required by at least one funder) and what it meant was not harmonised across tissue banks.

In some cases patient representatives had a more direct involvement; in one tissue bank, trained patient advocates spoke to potential donors as part of the consent
process. Patient organisations outside the UK had set up tissue banks to offer their samples and/or data to researchers, especially in the case of rare diseases:

>a patient representative had a child who developed a rare disease in 2006, which affects one in one million people. At the time there was fragmented patient care, few isolated researchers, few cell lines, no animal models and only a few clinical trials that had failed. She founded a patients’ association and drove the setting up of a biobank with associated database. The patients’ associations were the people running and managing the biobank (field notes: meeting 7).

Thus, while patient organisations had an undefined but important and increasingly influential role in tissue banking, the level of involvement was not harmonised.

Professional organisations
There are a few key professional membership bodies with an interest in tissue banks. The most influential organisation – the Royal College of Pathologists (RCP) – published clinical guidelines for taking tumour tissue and producing pathology reports and was instrumental in developing the UK Clinical Pathology Accreditation scheme which many clinical pathology labs are subscribed to. Several pathologists and researchers argued that these two documents could be adapted for use in the research sphere:

>so there are also national guidelines about processing and reporting of cancer tissue ... and they are published by the Royal College of Pathologists. So there is a defined way of processing tissue and I think that must have been adapted now to include or to allow for tissue bank type facilities. So I am assuming there is a uniform approach (P8, surgeon).

I found little evidence, however, that they were appropriate for or adapted into the research context, so the RCP’s influence related primarily to clinical practice. Another professional organisation whose guidance was mentioned in practice was the (international) World Medical Association, which drafted the Declaration of Helsinki (2008), referenced when writing a protocol for a clinical trial that involved tissue banking:

>I wrote the Protocol. ... [w]e refer very vaguely to things like the Declaration of Helsinki (P7, oncologist).


Relationships between actors

The number of different actors in the field, and relationships between them, gave rise to social and technical complexity that made collecting tissue and related harmonisation difficult. Tissue banks needed to be skilled relationship managers to deal with all the issues that arose. Interactions highlighted in the sections above (and see Figure 4-1) were between:

- tissue banks and regulators,
- tissue banks and funders,
- tissue banks and research ethics committees,
- tissue banks and suppliers,
- tissue banks and local universities or hospitals,
- pharmaceutical companies and tissue suppliers, whether hospitals, tissue banks or tissue supply intermediaries,
- pharmaceutical companies and contract research organisations, and
- tissue supply intermediaries and collection sites, often hospitals.

To illustrate some of the complexities, it is useful to consider as a case in point the relationship between Novelburg University tissue bank and a nearby hospital that provided it with tissue.

Socially, barriers existed to communication between the hospital and university. Professionals felt that the two organisations spoke a different language and reaching shared understanding was difficult:

\[ \text{so I’m a histopathologist and I was involved in helping get it [the University tissue bank] up and running really. So prior to me taking over there were problems, it was \ } \text{almost like the university and the NHS spoke a different language and because I’d been part of the university before I was able to translate if you like and so I was able to bridge the gap and get things moving, so xxP67 Tissue Bank Managerxx and I worked really quite closely together to get this up and running (P76, histopathologist).} \]

Staff based in Colham University also found the different routines and systems (for example surgery schedules, rigid rota) in a hospital hard to understand and adapt to.

See Appendix 12 for participant details
Technical issues between the two types of organisations made it difficult for the university to work alongside the hospital to access clinical databases and enter facilities to collect tissue and data:

The NHS – university barrier seems to be a hard one for the tissue bank to navigate because of technological issues linked to computer systems, access cards, and access to patient information and databases. In the main office area of the tissue bank, one of the computers is NHS and another is University and information cannot be exchanged between them. One staff member working there for two months had only just received a pass that allowed her to get into hospitals and into the tissue bank (field notes: Novelburg tissue bank).

Problems relating to cybersecurity were evident when Novelburg tried to manage relationships between different contributing hospitals along the tissue supply chain:

[t]he LIMS [tissue bank database] is based on the web on this hospital’s servers. But this brought its own problems, because this hospital will not allow access to it from the other hospitals involved in our tissue bank. There are firewalls in place (P68, tissue bank manager).

Thus, technical and other issues may multiply when a tissue bank needs to interact with numerous examples of each actor and manage the relationships between them. Another context in which this occurred was when tissue banks had to manage numerous funders with different, possibly overlapping, requirements.

Communication between tissue banks was evident but not harmonised. In some cases relations were formalised, as in the case of Onconet, but a UK-wide informal network of tissue bank managers also existed. In this informal network, tissue bank managers consulted each other for advice by telephone and email and visited each other’s facilities:

P67 (Tissue Bank Manager) mentioned that the wider network of people biobanking in the UK would often visit and talk to each other. She said there was ‘love and brotherhood’ amongst people running biobanks. She said a lot of people visit each other’s biobanks and that she visited some when they were setting up, and people often visited theirs (field notes: P67, tissue bank manager).
Observations at relevant meetings and conferences showed that this informal tissue bank network also met at events. Besides communications with other actors and tissue banks more generally, relationships with individuals had to be carefully managed. Consideration of the tissue supply chain model in practice begins to illustrate this further level of complexity.

I have described the main actors involved in conducting, or with an influence on, tissue banking, and the relationships between them. I move on to consider how the tissue supply chain works in practice.
Part 3: The Tissue Supply Chain Model in Practice

Chapter 2 presented a provisional tissue supply chain model founded in the existing literature (see Figure 4-2). This model was used to structure my research findings on tissue banking practice into a series of steps covering (1) tissue bank set-up (step 1a. funding, governance and legislation; step 1b. infrastructure and standards); (2) tissue and data collection; (3) shipment and transport; (4 & 5) processing, aliquoting and storage; (6 & 7) retrieval, distribution and scientific analysis; and (8) post-tissue bank. Emphasis is given to the first stage (tissue bank set-up) both in order to understand the specific UK context and to consider in more detail the types of infrastructure and standards developed prior to starting tissue collection. Following consideration of each step, the initial, provisional model was refined and a new updated model is presented at the end of Part 3.

Figure 4-2 Provisional tissue bank supply chain model (as discussed in Chapter 2)

Step 1a. Tissue bank set-up: funding, governance and legislation

Finkleborough (a local cancer tissue bank), was part of my research. It provides a useful example for explaining the external funding, governance and regulatory pressures facing such banks when establishing themselves in England (requirements are different in Scotland).

See Appendix 12 for participant details
Based in England, *Finkleborough* tissue bank sat within a university department closely linked to several hospitals. It relied on four funding avenues to support the infrastructure of the tissue bank and the NHS service costs relating to sample collection: the university, a cancer charity, a pharmaceutical company, and a system of charging researchers to cover costs (cost-recovery). This type of funding patchwork was common to many tissue banks in England, but no ‘standard’ pattern of funding existed, with other banks obtaining support from government funders, public donations or intellectual property rights. The funding arrangements had political implications for the tissue bank; university researchers could access samples and data at reduced costs and the pharmaceutical company that funded six technicians could “basically get the pick of what they want from the biobank (P68, tissue bank manager)”.

*Finkleborough* took one year applying for a research tissue bank (RTB) ethics approval and as part of this had to design access policies and consider the scope of applicable research. The application needed to be renewed every five years. Committing to this regular process on the part of clinical and administrative staff required either altruism or organisational pressure because the main advantages were for researchers: “if they [the researchers] ask us, they could come under our ethics approvals so they don’t have to get their own and the samples are already there (P68, tissue bank manager)”.

In other examples that I identified in interviews, professionals had chosen not to apply for a RTB approval for their small tissue bank or diagnostic archive due to a lack of these social or political pressures with the consequence that researchers needed to obtain their own ethics approval for each narrowly defined study.

Alongside the ethics approval, *Finkleborough* had to apply and pay for a Human Tissue Authority (HTA) license to cover the geographical location or ‘premises’ of the tissue bank. Research use of a linked hospital pathology diagnostic archive was obtained at no extra cost by extending the already existing license to cover research. The HTA required *Finkleborough* to nominate a ‘Designated Individual’ for the collection who had to undergo “training within 12 months of being issued with a license (P61, HTA staff member)”. Another license requirement was that four groups of HTA research
sector standards were followed covering: consent; governance and quality; premise and equipment; and disposal.

Certain monitoring requirements arose as a result of holding a HTA license. *Finkleborough* had to complete a self-assessment exercise every two years where they rated themselves against the HTA standards:

> *we have a risk profile that is ... a living, breathing thing really so if adverse events occur in an establishment, then this score can be changed and that might bring their inspection forward if we know that’s something that we need to look at in more detail.... And to be fair ... we consider research as a low risk sector* (P61, HTA staff member).

*Finkleborough* had been inspected by the HTA, as had all of the other tissue banks included in the ethnographic study.

*Finkleborough* was planning to expand into hosting clinical trials so they would also be subject to another regulator, the Medical and Healthcare Regulatory Authority (MHRA): “[i]t is just a different regulatory body that manages the trials ... the MHRA ... [it would] make us auditable by them ... it means we would have to operate slightly differently (P68, tissue bank manager)”.

Finally, *Finkleborough* had to apply for the agreement of the Research and Development (R&D) (or Research Governance – RG) office in each NHS trust from which they were collecting tissue:

> *you don’t ... have to go down the official R&D approval route to set-up the tissue bank, but I think in the letters it says you are expected to have had interaction with management, and the HTA certainly expect us to have some kind of agreement in place with what they call our collecting centres* (P67, tissue bank manager).

No formal R&D application procedure existed for RTBs, and as a result substantial variation occurred in how each NHS trust dealt with a request, causing delays. Other research tissue banks had experienced similar set-backs, revealing the absence of central harmonisation in terms of forms or processes, and a lack of governmental (or political) support for this.

*See Appendix 12 for participant details*
Step 1b. Tissue bank set-up: infrastructure and standards

Novelburg (a medium sized NHS Trust with linked university) tissue bank was a cross-university tissue bank collecting (but not limited to) cancer tissue, which had recently been established in newly built facilities. It is a particularly useful example for illustrating three different aspects of setting up infrastructure and standards relating to tissue banks: premises and equipment, informatics, and devising documents and procedures.

Premises and equipment

Many aspects of the design of the Novelburg tissue bank enabled flow of materials and data through the tissue supply chain or supported the provision of services to researchers. The location of tissue bank premises, in terms of proximity to local hospitals, was a key feature in this regard. Novelburg was established very close to the university and two linked hospitals. This example and others suggested that the closer the tissue bank was to associated hospitals and university, the easier the collection and distribution of ‘fresh’ tissue and other samples. Long transit times could lead to the degradation of fresh tissue and problems for researchers: “the tissue bank facilitator showed me an overview of what typical researchers want each week and the clear majority of researchers want fresh tissue, with only a couple who want frozen or fixed (field notes: Novelburg)”. Additionally, to support the collection of fresh tissue, Novelburg had amended the normal hospital procedure of placing samples in preservative immediately after removal from the patient. Surgeons could send fresh tissue straight to pathology because the pathology department was close to surgical theatres; in other hospitals where this was not the case, collection of fresh tissue was difficult.

Novelburg tissue bank appeared well-resourced. It had: a specimen reception room, a sample processing laboratory, a room containing liquid nitrogen storage vats, a freezer room, further laboratories for cell culture and containing equipment used to provide services to researchers, and space for staff offices and file storage. In common with other large tissue banks, Novelburg had disaster mitigation systems including back-up power and temperature monitoring and alarms for freezers and tanks. It was thus a
good example of the types of facilities common in large tissue banks. Nevertheless, some variation existed between banks: some had space for ambient storage or labs for dealing with viruses or for conducting flow cytometry. Smaller tissue banks did not always have liquid nitrogen storage or disaster mitigation systems. Samples in smaller tissue banks may have thawed and re-frozen an unknown number of times, affecting the value of samples for research.

*Novelburg* offered services to researchers such as conducting immunohistochemistry, digitising slides, laser dissection microscopes and culturing cell lines. As a result it had to purchase specialist equipment: “the idea was that they would charge for these services and this would make some money for the biobank, at least that’s what they said in the business plan (field notes: P67, tissue bank manager)”. Purchasing particular equipment during tissue bank set-up could lead to an ongoing relationship with suppliers, and reagents for these machines could cost thousands of pounds:

*when you’ve got the machine, that’s not the end of it, all the reagents and probes and various things that you need cost thousands of pounds. Also it took a long time (four hours) to set up and even with two experts there, they had to call their representative at the company to try and sort things out (field notes: Novelburg).*

Tissue supply chains were prone to disruption according to the availability of appropriate equipment in particular locations. *Novelburg* had invested in equipment outside the tissue bank in order to support the tissue supply chain, mainly in the pathology department:

*the tissue bank facilitator showed me the medium-sized -80 freezer on top of the counter which was for the tissue bank. Attached to the side there was a clipboard with a form that needed to be completed when samples were collected. On top of the freezer there was a roll of labels and cryovials to put the samples in. The liquid nitrogen was in a small flask which had to be filled up every day by tissue bank staff (field notes: Novelburg).*

Other tissue banks also offered services but varied as to the type of equipment they had, for example *Finkleborough* had a tissue microarray machine and tissue processor

*See Appendix 12 for participant details*
but this equipment was not found everywhere. Other tissue banks and clinical trials units had equipment, normally freezers, within clinical departments.

My observations suggested that it was important not to overlook the significance of apparently mundane pieces of equipment and their contribution to supply chain functioning. Tissue bank staff in Novelburg, for example, identified the lack of a photocopier close to one of the hospital wards as the reason that the relevant consent forms were not copied and sent down to pathology with tissue samples. This caused huge problems for the running of the tissue bank.

**Informatics**

Databases chosen or designed for tissue banks sometimes led to harmonisation across the individual tissue bank and occasionally the wider institution. The Novelburg database (see Figure 4-3) was a package bought ‘off-the-shelf’ from a commercial supplier and configured to their needs. The database had led to some level of harmonisation for information stored by the tissue bank and it allowed centralised audits and stock control. In the Refport (a small NHS Trust with linked university) tissue bank, the database functioned as a ‘virtual biobank’, uniting tissue collections across the organisation and enabling them to be searched.

Technical differences between tissue bank databases meant, however, that harmonisation (conceived either in terms of shared standards or interoperability) had not occurred in the UK. Databases, especially when highly customised, often responded to the local context and could not be used by others. The Novelburg database was not technically interoperable with other local tissue bank databases (which also often collected different data), nor could data be exchanged with NHS hospital pathology databases, which were also all different.
Indexing of personal information was one example of where different databases did things in different ways. For example, donor medical or lifestyle information was not collected in standard ways across databases. Novelburg intended to collect it only when asked by researchers due to the time it took for them to collect it from patient records. Tissue banks assembled for project-specific purposes, for example clinical trials, were more likely to collect this information in the form of (electronic) case report forms or participant questionnaires:

well it varies, most case report forms have to have your vitals, by vitals it is blood pressure, your pulse, your resps, your weight, your performance status, the date if you have taken any bloods or if there is any quality of life .... questionnaires .... If they ... had any sickness while they were on chemotherapy or ... are they getting worse .... [T]he whole of the blood count, [or] ... CT scan results (P30, clinical research assistant).

Technical differences were also evident. Databases in some tissue banks that I examined were designed by companies such as StarLIMS, LabWare and Labvantage or using software such as Microsoft Excel or Microsoft Access. Several tissue banks, including one I termed Canbank (a national cancer tissue bank), purchased a customised database from a commercial supplier: “[you can take] a basic shell of their
programme and then customise it your circumstances ... and that’s the route we went ... because it was customised to us, it’s not really very usable by anyone else (P4, tissue bank manager)

Scotland had trialled a project to harmonise activities involving a free, open-source, sample management database developed in the US called ‘caTissue’. Sample tracking software could be incorporated into this database allowing details about samples to be shared with the wider research community. But connecting hospitals was not straightforward and concerns about data sharing arose: “it is probably less of a problem here than it is in England but each health board does have its own lawyers and their own IT security people that are very wary (P65, Scottish Government representative)

Information security was an issue for other tissue banks, including Canbank, Finkleborough, Noveldburg and Refport, who all wished to implement a direct connection between tissue bank databases and NHS databases or external cancer registries. None had been successful. Major challenges for data sharing and communication between hospitals were data security concerns and lack of agreement between IT departments. These remained despite the agreements put in place between tissue banks and different hospitals during the tissue bank set-up phase.

**Devising documents and procedures**

Each tissue bank I looked at designed documents and procedures during its set-up stage usually without referring to national or international guidelines, thus the resulting documents were never identical.

**Novelburg** first focused on producing documentation needed to engage with external actors: donor consent and information sheets, researcher application forms, tissue request forms (with costings) and material transfer agreements. The tissue bank manager explained the process of developing these:
I concentrated for the first year to 18 months on getting the paperwork done…. Getting ethical approval was of paramount importance …. At the same time I was trying to develop … the consent process. So that was about embedding a tissue consent into the surgical consent form. And I had to work quite closely with the clinical governance team for that, and that took a long time to get organised and approved and sorted out …. The ethics committee did actually stew over that for a while. But we got that through and so, then the other thing that’s very important to develop as a licensed tissue bank, is agreements for tissue in and tissue out …. And when I started this there wasn’t one so I wrote one myself, which took quite a long time. And it took a long time to get through because the trust haven’t seen anything, the like of it at all. But what I found was that once one trust has signed up to it, then it snowballed, and we now have them in place with eight different trusts in the xxthis areaxx. …. And we have a lot of internal researchers who are employed by the University, so the agreement that we have in place with our own staff is different to the agreement that we would have with an external researcher (P67).

The quotation illustrates the political elements in developing documents in terms of both the negotiation required with external actors such as Research Ethics Committees and R&D (or clinical governance) offices and obtaining the agreement of NHS Trusts. This political complexity meant that it took both effort and time to develop documents.

**Standard operating procedures**

One set of documents that Novelburg had not finalised during the set-up phase was in-depth technical standard operating procedures (SOPs): “P67 (tissue bank manager) said that it was very difficult to write SOPs for quality purposes at the beginning of the biobank because the procedures kept changing, but now they’re calming down, she felt that she would be able to finish them (field notes: Novelburg)”. Data gathered from observing practice at Novelburg supported the idea that the procedures put in place when tissue banks were setting-up could change over time, for example when professionals working in hospitals including surgeons, pathologists and research nurses requested amendments.

See Appendix 12 for participant details
In at least two of the clinics the procedures were not actually working yet and negotiations were happening to get them to such a state where they would run smoothly. Getting consent forms down from surgery to pathology was also not happening as it should (field notes: Novelburg).

This suggests that designing concrete SOPs may be difficult during the set-up phase, and that any point during the operation of the tissue bank, procedures may need to change. In so doing, coordination and harmonisation with others may easily slip.

Other tissue banks that had been operating for a number of years had also devised detailed SOPs. Topics covered included: sample collection, labelling, processing, storage, traceability; data collection, protection and security; obtaining consent; and reporting misconduct. Many of these covered similar areas to the Human Tissue Authority (HTA) standards, which RTBs were required to follow: “the tissue bank manager had set-up 11 SOPs or guidelines which matched the HTA standards, for example on consent, transport, traceability and disposal (field notes: P57)”.

Because the HTA standards did not contain detailed technical guidance on what to include in SOPs, the actual detailed content of SOPs varied by tissue bank.

Devising local SOPs was based on common sense applied to the local context rather than national or international guidance. At Finkleborough: “xxthe lab managerxx wrote a lot of the technical SOPs like the sample processing and I think xxshexxx took those from SOPs from studies or just developed them in terms of best logistical practice (P68, tissue bank manager)”. One of the explanations given for the local development of SOPs was a lack of scientific evidence to support specific methods:

[now let’s say that you’ve got investigator 1 with his or her own biobank and investigator 2 with his or her own biobank. The likelihood that their SOPs are the same are zero. …] [H]armonisation/standardisation at the moment basically says that one of them has to adopt the other, or they both have to abandon theirs and come to a common ground. What we actually don’t know what the arguments are for coming to the common ground … And then if a sort of independent third party sort of thought leadership group be it BBMRI or whoever says actually you’re all

See Appendix 12 for participant details
wrong, you need to come to this new SOP, people are all going to say but why? Where’s the evidence for it? There isn’t any (P4, tissue bank manager).

The quotation illustrates how a lack of evidence supporting SOPs could play a role in non-harmonisation of tissue bank SOPs. However, tissue banks did sometimes engage with accreditation schemes that encouraged tissue banks to put in place SOPs:

P5 said that some Biobanks have ISO 9001 accreditation. They are doing that in the absence of a standard. She said that ISO 9001 was meaningless and expensive, ‘a red herring’, and does not lead to a level playing field. ISO 9001 is about putting a management system in place to do what your company does e.g. giving people rooms for the night in a hotel etc. The management can choose the needs of the organisation; so this is good if management decides to validate freezers, but you don’t have to do these things to get ISO 9001 (field notes: P5, funder representative).

Thus, just like HTA standards, ISO9001 had failed to provide the specific guidance needed to achieve technical harmonisation. Accreditation schemes with more relevance, such as the Clinical Pathology Accreditation scheme, did not cover research. Due to this gap, Onconet had commenced work towards certification on quality for cancer tissue banks. The lack of harmonisation at the level of SOPs or other documents meant that further stages of the tissue supply chain were similarly variable.

**Step 2. Tissue and data collection**

As Colham (a large NHS Trust with associated University) did not have one central tissue bank, rather a large number of researchers collecting, storing and processing tissue and data in different ways, it is the ideal example to illustrate the variation and challenges faced for steps 2 to 7. Observations in Colham suggested that three different avenues for the collection of tissue and data existed in hospitals. The first avenue was to collect tissue and data leftover following normal diagnostic procedures, primarily through accessing the hospital pathology archives and existing (paper) medical records. The second avenue involved modifying normal diagnostic procedures to allow tissue or data to be collected more easily for research. Modifications in Colham included obtaining a piece of fresh tissue at surgery before it was sent to
pathology. The third avenue involved completely new procedures to collect tissue and data for research, for example alongside clinical trials.

Despite the existence of different avenues, all led to similar technical, social or political difficulties, including those relating to relationship management and informed consent. Additionally, specific issues arose as a result of NHS hospitals being the major source of human tissue, the need to allow for the variety inherent in clinical practice, and the impact of financial pressures on the NHS. I explain these two issues below.

**Relationship management and informed consent**

All avenues of sample collection required careful relationship management, and banking tissue in practice had significant social and political elements. A variety of hospital staff were involved in collecting tissue and data, including: research nurses, surgeons, pathologists, oncologists, interventional radiologists, clinical research associates, clinical trials coordinators, biomedical scientists (or assistants), technicians, research governance coordinators, IT specialists and laboratory and hospital management. *Colham* tissue bank had to manage relationships with staff in order to obtain the tissue and data, often accomplished by negotiation, favours, incentivising or sweet-talking: “the people who get the tissue aren’t necessarily the people with the best strategic project, it’s the people who actually happen to be in with the surgeons (P14, departmental administrator)”.

Pathologists and surgeons were seen as particularly important to keep ‘onside’ in the tissue banking process. In *Colham*, a pharmaceutical company incentivised one surgeon by offering free use of expensive research equipment at their facilities:

> so we would provide xxcells for BigPharmaxx, and they would allow us to use their equipment .... Some of the bits of kit were a million quid each. So that was mutually beneficial (P12, surgeon).

In *Novelburg* the tissue bank did favours for surgeons in order to bank tissue:
in the lab P74 (tissue bank facilitator) was splitting some samples received from a particular surgeon. This was after an agreement with P67 (tissue bank manager) that half of the samples collected from the surgeon would go back to the surgeon for ethically approved research projects. This was to keep the surgeon ‘onside’ (field notes).

Tissue banks often employed friendly staff who could be relied on to maintain complicated relationships.

The informed consent procedure was an activity where relationships were especially key. Who obtained consent for tissue banking (as distinct from consent to procedures) was not harmonised across different tissue banks and hospitals. In Colham, researchers asked clinical trainees registered on research degrees to take consent because academic researchers could spend hours waiting to access patients. Advantages of doing it this way included clinicians’ experience in taking consent and their ability to answer the patients’ clinical questions: “it looks stupid to not know anything about the patient’s clinical treatment (field notes: P25, clinical research fellow)”. For Finkleborough tissue bank, technicians took consent and so it was important to employ technicians who were confident and happy to approach patients: “all our technicians have scientific degrees but we actually employ on interpersonal skills because we want people here who are confident and can speak to patients, because it is amazing how intimidating it can be to approach people and even go into theatres so we are quite careful (P68, tissue bank manager)”. P68 went on to explain that one technician “struggled with that part of the job [taking consent] and it affected our collections (ibid.)”. It seems clear that the profession and personality of the person taking consent could influence success.

Efforts had been made to harmonise consent procedures within individual NHS trusts by implementing generic consent procedures, but none had been entirely successful. In Colham efforts to incorporate consent for research into the surgical consent form had failed for political reasons:
When I asked P37 if she’d been involved in efforts to change things at the trust she said that she does not have the authority. Generic consent to research has been suggested on many occasions and driven by clinicians. In order to set up generic systems you need someone driving it from the top. She said they want it but have to convince a large number of doctors, surgeons, and pathology services, which is not an easy job (field notes: P37, university researcher).

Generic consent for research within the surgical consent form had been incorporated elsewhere following extensive negotiations (see ‘devising documents …’ above). However, it tended to move the responsibility for taking consent for tissue banking from individual researchers and tissue bank staff onto doctors, surgeons and surgical teams. This was why surgeons were particularly important to the tissue supply chain in these trusts and effectively became a gatekeeper to the tissue. But they were unreliable links in the supply chain. Novelburg estimated that only one in ten surgeons sent the consent forms to pathology, despite repeated requests and emails from tissue bank staff. Missing consent forms was an issue for fresh tissue where the existence of consent must be very quickly verified, and researchers sometimes had to destroy fresh tissue that emerged without consent: “If the surgeon forgot to consent the patient we couldn’t use it, and that did happen to us, and we had to destroy some tissue (field notes: P79, university researcher)”.

The NHS context

A number of difficulties arose when collecting tissue and data for research within the NHS which could not be adequately explained as a simple matter of hospitals being insufficiently well organised. To begin to comprehend what was happening requires, first, an understanding of cancer diagnosis and treatment pathways and the technical implications for research; second, a description of common practical issues in hospitals; and third, consideration of potential political explanations for the wider problems.

The patient diagnosis and treatment pathway created numerous implications for research tissue collection. The procedures for creating the ‘blocks’ and slides used for diagnosis in hospital pathology departments varied across hospitals. Differences were

See Appendix 12 for participant details
found within SOPs for labelling, fixing, and cutting up samples as well as in how recommended procedures were enacted. In Colham, when tissue was received it was: labelled and given a number, ‘fixed’ to stop biological activity, cut, embedded in wax blocks, slides were taken from the blocks, stained and used for diagnosis under a microscope. All hospitals followed similar steps to prepare the tissue, but the detailed workings of this procedure were not identical, even though the end result looked similar – a wax ‘block’ and a set of associated slides (see Figure 4-4 below). A trainee pathologist and researcher explained how variation occurred:

*the Royal College of Pathologists sets out guidelines for how we should deal with specimens. If somebody has a colon cancer taken out it should be dealt with [fixed] ... for ... 48 hours. But just to use an example, in a hospital where there’s a backlog of histopathology samples, that might fix for four days. In a hospital where ... there are lots of consultants doing one speciality ... they’re inclined to do ... [a] case even though it hasn’t fixed for the regulation 48 hours (P24).*

Variations of this kind could later lead to differences in the outcomes of research, for example if researchers developed tests to detect cancer that only worked when samples had fixed for 24 hours, rather than 48.

**Figure 4-4 Slides associated with one case, Colham hospital**

Procedures for diagnosing and treating cancer affected the volume of cancer and associated normal tissue available for research. In Colham, the cancer type and location was linked to how much affected and/or normal tissue was removed during
surgical treatment. A resection for colorectal cancer might result in around 1m of colon tissue, with cancer and proximal normal tissue leftover for research. Conversely, a tiny volume of tissue removed in the case of skin cancer (melanoma) might have little or no tissue left over. Normal unaffected tissue such as tonsils and fat, potentially useful to researchers as control tissue, was often unavailable because it was discarded after surgery: “I do obesity surgery and ... my hope is that we try in xxColhamxx to have ... a fat bank, and there is no fat bank (P8, surgeon).”

In Refport the method of diagnosis and normal treatment pathway affected the volume of cancer available. Needle biopsies were used to investigate potential cancer, and while the resulting cores were likely to be left over for research, they were very small. If cancer was confirmed, the normal cancer treatment pathway would involve treatment with chemotherapy before surgery, with the result that when removed the tissue was often calcified, necrosed or dead, which was not always useful for researchers.

*Sometimes it’s quite easy when the tumour arrives fresh to see which bits are alive and which bits are dead so you can preferentially take bits for ... freezing or research from the live bits. But in many cases you can’t, so you may take samples for freezing and it turns out they are all dead (P42, pathologist).*

Practical issues made it difficult to collect data for research purposes in Colham hospital. Patient records were largely held in paper form; a university researcher (P37) explained why these were a challenge for researchers:

*clinical data is difficult to collect from notes. The notes are not written in a format that makes it easy, unless you are a clinician yourself, to find it. She said they were big bundles up to 50 years old and in order to do an appropriate statistical analysis, you may need 20 to 30 pieces of information from each patient (field notes: P37).*

One way of getting relevant clinical information was to ask patients themselves. In Colham, the only direct patient consultations appeared to take place on clinical trials either as an extension to a normal consultation with a clinician, or with clinical trials coordinators while the patient was waiting for an appointment: “[t]he CRA [Clinical Research Assistant] asked if she could have a few minutes with the patient before the
procedure and the registrar agreed (field notes: P34)”. Such interviews took time, patients did not always know accurate answers to questions and they frequently asked for information about their clinical treatment.

Further difficulties in collecting tissue and data for research existed in Colham, see Table 4-1 below. At a practical level, the paper-based nature of forms recording sample information or consent often got lost, mislaid or took some time to arrive at the correct department. Similar issues arose in other hospitals, where operational and social issues included: the consent form being lost, not sent or not completed correctly by those obtaining it; the tissue bank staff being too busy to collect samples; the pathology archives being off-site and difficult to access; and pathologists refusing to take part in research.

Practical and operational problems must be considered within the wider context, including the priorities of NHS hospitals and budgetary constraints. Hospitals were seen primarily as places for the treatment of patients and use of the staff and facilities for research was a secondary purpose, at best:

there is a big research agenda, but I think always their [Novelburg hospital’s] main priority is going to be service. Clinical service. So, so I think we’re down the pecking order in that .... [T]hey’re very active research wise, but I don’t think it can ever be a priority (P67, tissue bank manager).

This was especially significant as NHS hospitals provided the majority of tissue to the different kinds of banks (see Figure 4-1). When professionals worked across the clinical and academic spheres they often felt unsupported in their research efforts: “you know what the NHS is like, you have to find a way of doing research, they’re not gonna help you (P11, surgeon and researcher)”. In terms of research, tissue research was viewed by NHS staff as a lower priority than clinical trials: “the obsession with randomised controlled trials has kind of devalued all other type of participant research (P4, tissue bank manager)”. This low prioritisation of tissue research could be linked to increasing financial pressures on the NHS and a drive towards efficiency: “trusts ... have to deliver a clinical service and they have quite tight budgets and ... collecting all this tissue ... the pathology time to do it and the storage costs, are not inconsiderable and there’s no
reward for the trusts, ... it’s just an extra cost (P55, funder representative)”.

Professionals working across clinical and academic spheres felt that budgetary slack existed in the past when staff or equipment were used for tissue collection or research when not required for clinical care. But this slack no longer existed and the use of staff and equipment was controlled through job plans and hospital R&D offices.

Table 4-1 Practical issues that affected tissue and data collection in Colham

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<th><strong>Patient related</strong></th>
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<td>Patients cancel or do not attend hospital appointments</td>
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<td>Patients do not stay for tests after hospital appointments</td>
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<td>Patient decides not to go through with procedure</td>
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<td>Patient has gone for a walk, shower or scan when professionals arrive to ask for consent</td>
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<td>Timings change for appointments</td>
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<td>Beds not available for patients</td>
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<td>Consultant does not arrive on time for clinic or procedure</td>
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<td>Academic staff cannot access patients to obtain consent</td>
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<td>Surgeon decides not to proceed in operating theatre</td>
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<td>Surgeon refuses to take part in tissue banking</td>
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<td>Particular clinics not receptive to, or accommodating of, research</td>
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<td>Samples mislabelled</td>
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<td>Tissue wasted or lost when cutting it</td>
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<td>Tissue collected too small</td>
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<td>Staff (e.g. research nurses) not available to collect tissue if operation is an emergency or during personal, bank or religious holidays or maternity leave</td>
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<tbody>
<tr>
<td>Pathology staff not available to access pathology archive for research purposes</td>
<td></td>
</tr>
<tr>
<td>Labels on pathology blocks or slides are not easy to anonymise</td>
<td></td>
</tr>
<tr>
<td>Archive disorganised, making blocks and slides difficult to find</td>
<td></td>
</tr>
<tr>
<td>Required blocks or slides have been removed from the archive and not returned or lost</td>
<td></td>
</tr>
<tr>
<td>Required blocks thin and worn down</td>
<td></td>
</tr>
<tr>
<td>Required slides smashed or stuck together</td>
<td></td>
</tr>
<tr>
<td>Required slides or blocks have been returned to patient or next-of-kin</td>
<td></td>
</tr>
</tbody>
</table>
**Step 3. Tissue and data shipping**

*Colham* further illustrates the lack of harmonisation that existed when shipping tissue and data. After collection tissue was transported in various ways and at varying points on the supply chain; options included pathology vans, hospital buses, taxis, private vehicles, couriers (see Figure 4-5) and the postal system. Couriers were more likely to be used when tissue was to be transported fresh or collection was part of a clinical trial. They generally provided information tracking the location of the samples but company practices varied and practical issues persisted. Exact timings were difficult to obtain and sometimes samples went missing: “yeh, sometimes samples do get lost (field notes: P28, clinical trials coordinator)”.

*Figure 4-5 Inside a courier's van*

*Canbank* had installed a tissue bank database online so that local collection centres could provide data distantly and instantly. In other tissue banks it was common for staff to travel to a central location to input data:

* THEY PERSONALLY BRING THE SAMPLES BACK HERE AND THEN PROCESS THEM AS WELL AND THEN DO THE DATA ENTRY?  

Yes. *The frozen tissue processing happens on the collection site so they will literally be coming back and putting samples in the freezer or dropping the formalin pots off in the lab and then entering the data in the system so Friday afternoons are a bit of a fight for a computer (P68, tissue bank manager).*
Steps 4 & 5. Tissue processing, aliquoting and storage

Prior to storage and in preparation for future research use, the samples had to be aliquoted into smaller sample sizes or processed specifically for certain types of research. In Colham, considerable variation existed as to how this was done, particularly in relation to SOPs, sample logs and labelling procedures. One department had published in-depth SOPs for processing samples on a webpage but these had not been adopted across the university. Clinical trials, laboratories and researchers also had their own methods to log sample processing details for traceability purposes, often using forms (see Figure 4-6) or notebooks.

Figure 4-6 Sample log form from a cancer clinical trial

Labelling practices had a downstream effect on research and tissue banks, both due to technical aspects of the procedure and the number of different approaches. In Colham pathology department, labelling procedures meant that the cartridges holding ‘blocks’ were labelled with a special ink “that resists the processes of sample fixation and treatment, in the past they had used pen or pencil (field notes: P15, laboratory manager)”. But this meant that the ‘blocks’ were difficult to anonymise for use in research:

See Appendix 12 for participant details
P28 showed me one block ready to go to a contract research organisation (CRO) where she had struck through the surname on the cartridge using a black pen. I could still see the surname. She said she supposed they could see the surname if they wanted to (field notes: P28, clinical trials coordinator).

Labelling in hospital pathology departments, tissue banks and clinical trials, varied widely from written labels to 2-D barcodes, and no evidence existed that tissue bank specific labelling conventions such as SPREC (see Chapter 2) were being used. Due to this variation, researchers and tissue banks had to design systems to record the different labels in order to ensure traceability. BigPharma (an international pharmaceutical company) had to redesign the company sample registration database to incorporate them:

the samples may have gone to many different places before coming to the biobank, including hospital pathology departments, CROs and analysing labs, and each one would put on a new label or code. P70 felt she needed to record each one in order to ensure traceability (field notes: P70, tissue bank manager).

In several tissue banks some of the aspects of sample processing or storage were automated. At relevant meetings automation was presented as a way of standardising procedures. At BigPharma, machines and related databases had been customised for the storage and retrieval of DNA samples. But these were specifically designed to fit the space at, and requirements of, BigPharma, and it was questionable whether they could be adapted into other contexts. Automation may be useful to obtain a high degree of standardisation within organisations but if it is highly customised it may be hard to place in other contexts.

Steps 6 & 7. Tissue and data retrieval, distribution and scientific analysis

Prior to requesting the retrieval and distribution of samples and data for analysis, researchers had to discover where they might be available and apply to access the collection. They might, for example, search the NCRI tissue bank register, which contained minimal information including tissue types available and contact details: “data’s presented … in a harmonised way for people to be able to search it in a harmonised way (P5, funder representative)”. However, throughout my research,
professionals repeatedly called for a new, in-depth and systematically updated register of samples and data with improved searchability to assist researchers.

After finding out where the samples they wanted were stored, the steps the researcher needed to follow were similar across tissue banks: the researcher completed an application that was reviewed by the tissue bank’s access committee (or similar). The requirements of the application and the composition of the access committee were variable; some access committees had fixed membership where a quorum was needed to approve the access request, while on others membership varied depending on the application. Committees could also attach varying conditions to the approval, for example on what to do with the samples and data after the study has ended.

Following approval, sample retrieval and distribution to researchers who were approved to use samples were influenced by social factors. At Colham pathology archive, as in other hospitals, staff did not trust researchers to return blocks or slides. As a result some hospitals would not release whole blocks to researchers, and instead processed the block on the researcher’s behalf to make new slides. Distributing fresh tissue was a particular issue. In Novelburg, tissue bank facilitators saw researchers as ungrateful:

*P72 said that they no longer go out of their way to take the tissue immediately to the researchers because, no matter what we do they’re not grateful for the samples. She said ‘they get it when I can give it to them’ (field notes: P72, tissue bank facilitator).*

From a researchers’ perspective, they felt that it was hard to plan their days, they never knew when a sample would arrive and the samples were seen as small.

I have shown that the tissue supply chain was difficult to establish and complicated by practical, social and technical factors, which makes sustainability a particular problem.
Step 8. Post-tissue bank: sustainability and destruction

The long-term stability of tissue banks was not guaranteed due to lack of funding for tissue banking infrastructure and regulatory issues. Canbank, for example, ceased functioning after operating for several years. Its funders took the decision not to continue providing financial support and as a result samples had to be returned to the local collection centres, the customised database was decommissioned, staff were laid off and some samples that could not be distributed had to be destroyed. Other tissue banks closed because pharmaceutical companies were closing down sites in the UK, or, on a smaller scale, because researchers retired or moved. Funding was the crucial element to sustaining (or moving) a tissue bank, and without this samples and databases often had to be destroyed.

Some professionals felt that English legal and governance requirements were responsible for the destruction of samples. Their understanding was that when a tissue research project with specific ethics approval and consent ended, the samples had to be destroyed if the researcher was unable to move the samples to a HTA licensed site:

\[s]o what happens? If your brilliant research project comes to an end, you haven’t got funding to carry on and or you’re changing tack, and you’ve got these samples, you destroy them. ... The alternative, the only alternative being pay someone money and they haven’t got the money cos the project’s finished, of course it’s finished, course they haven’t got the money. So the way that the legislation has been set up is forcing people to destroy tissue samples (P40, pathologist).

The need for a specific ethics approval was also blamed for this: “we have risked having to destroy specimen selection collections at the end of research studies because people have made it insistent that the researcher took specific consent and that the ethical approval was only for that specific process (P54, clinician and researcher)”. My research did uncover a small amount of evidence that a tissue throw-away culture had begun to exist as a result, with researchers routinely disposing of samples no longer required for specific projects.
**Modifications to thesis tissue supply chain model**

Based on my observations and interviews, I suggest that Figure 4-7 (below) represents a more accurate model of the tissue supply chain that the provisional model I proposed based on the literature review.

**Figure 4-7 Revised tissue bank supply chain model**

The tissue banking supply chain can be seen as seven distinct but overlapping stages which comprise the outside of the circle. These stages are supported by four cross-cutting internal processes which are important throughout each stage. One of the cross-cutting processes is infrastructure, administration and informatics which incorporates outfitting labs, procurement, security, finance and regulatory compliance, audit, inspection, human resources and the construction and maintenance of the tissue bank information management system or database. Relationship management is crucial throughout the different stages of the tissue bank supply chain, both between
individuals, actors externally influencing tissue banks and other tissue banks. Owing to the importance of the Human Tissue Act (2004), informed consent management is a critical cross-cutting aspect of the tissue supply chain. The final process is shipment and transport, which can occur between or within any of the stages of the supply chain.

In relation to the individual stages, I have made three significant amendments to my original model. The first was to combine the stages of aliquoting and processing with that of storage, as these often took place together. The second amendment, modifying the retrieval and distribution step to include ‘access’, was because researchers often needed to locate relevant tissue and data and apply to use them. Third, an optional stage was added for services for researchers as the majority of tissue banks involved in the ethnographic research had purchased equipment and outfitted labs so as to offer services, at a cost. In terms of the coverage of the different stages, producing SOPs and labelling had not been given the prominence in the original model that they deserved, and these should be viewed as crucial parts of project set-up and storage stages respectively.

This new model emphasises the importance of relationship management and the consequent social and political complexities throughout the supply chain, a theme that runs throughout the remaining chapters and influences harmonisation. Discussion about each stage also highlighted the technical complications in the process of tissue banking. The updated model can be used to consider what type of standard is appropriate and what impact it might have upon other parts of the supply chain.
CHAPTER 5: HARMONISATION IN PRACTICE – STANDARD CREATION

This chapter presents findings on why and how standards are created in the area of (cancer) tissue banking, and what affects this process. The chapter first considers what type of standards have been created or requested, then who should create them and ends with a model of how standard creation takes place in the area of tissue banking.

What Should Standards Cover?

This section aims to give an overview of the types of standards that have been both created and suggested for the tissue supply chain at local (tissue bank), national or international levels. These are grouped into standards about sample collection, processing, storage and transport; data; consent and relationships between organisations. Different types of standards are relevant for each of these areas. Procedural standards such as SOPs or forms harmonise the steps to be taken to achieve a particular aim, and were often used to describe processes around sample collection, processing, storing and transport. Technical standards including computer databases, programs and websites, often addressed data. Policy standards include (often generic) statements about what should or should not ideally happen and often applied to areas such as consent. Contractual standards such as agreements cover exchange of tissue and data, and thus are useful when governing relationships between organisations. The discussion below assists understanding of what type of standard is appropriate in what situation and illustrates the importance of considering wider questions such as how specific or generic to make a standard or when it is important to fully standardise. The section finishes by highlighting the gaps and ambiguities.
Sample collection, processing, storage and transport

Local standards revolved around the supply chain stages of sample collection, processing, storage and transport (a cross-cutting issue). These standards were both technical and procedural and included the design of databases, labelling systems, automated storage systems and standard operating procedures (SOPs). Developing SOPs and embedding procedures was difficult (see Chapter 4) because the procedures frequently changed as clinical or tissue bank staff found the best way to operationalise them. Specific details such as the following had to be included, alongside more generic clauses, in order to attain procedural harmonisation:

*The person taking consent should ensure the correct information is presented to each patient for one of the following categories:*

8.1.2.1. *Patients with cancer (solid tumours)* ...
8.1.2.3. *Patients with a potential diagnosis of cancer*
8.1.2.4. *Patients without cancer (document: consent SOP)*.

Tissue banks walked the line between producing overly generic standards on the one hand and too detailed to put into practice in busy hospitals on the other. National or multi-site standards had to take into account variations between hospitals in ways of collecting and preparing tissues, the availability of different types of tissues (for example fresh or normal) and storage mechanisms (see Chapter 4).

Despite the use of SOPs to define and describe local operations, national guidance on tissue sample collection, processing and transport was repeatedly requested:

*I think you should have some gold standard SOPs out there that people can use because biobanking now is done a local level. It is not done nationally and I guess when people are using samples, they may have to get samples from different places and you want to be guaranteed that samples are of good quality from everywhere (P68, tissue bank manager).*

Onconet took the initiative to design national standards (see vignette below), and the STRATUM (Strategic Tissue Repository Alliance Through Unified Methods) project to develop general standards was just commencing as the period of my research ended.
Professionals were concerned that Onconet’s standards would lead to “a highly regimented system dictating how banks must work (document: meeting 6)”. In-depth SOPs could render aspects of the standard impossible to implement in individual organisations. For example it was not possible to put liquid nitrogen storage facilities into Refport pathology department “due to ventilation issues (field notes)”, so if it was required by a standard it would be impossible to implement. Yet other professionals felt that national standards would be useless unless they were very detailed on different sample collection pathways and methods.

The only existing national standards on sample collection, processing, storage and transport took the form of policy and general guidance about what should or should not happen, rather than technical or procedural standards to. These standards – the Human Tissue Authority (HTA) research sector standards – took a policy format and lacked detail on implementation.

**Figure 5-1 HTA Research Sector Standards, excerpt (document collected, undated)**

<table>
<thead>
<tr>
<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Documented policies and procedures for the appropriate transport of relevant material, including a risk assessment of transportation</td>
</tr>
<tr>
<td>● A system is in place to ensure that traceability of relevant material is maintained during transport</td>
</tr>
<tr>
<td>● Records of transportation and delivery</td>
</tr>
<tr>
<td>● Records are kept of any agreements with recipients of relevant material</td>
</tr>
<tr>
<td>● Records are kept of any agreements with courier or transport companies</td>
</tr>
</tbody>
</table>

As a consequence, professionals argued that the HTA standards (see Figure 5-1) did not guarantee high quality samples and data or harmonisation:

*I know that the Human Tissue Authority has got standards under their licensing scheme, I don’t think they go into nearly enough detail mind, to make sure that people harmonise practice (P51, funder representative).*
But these generic requirements allowed a degree of flexibility to those following them. The HTA was flexible during inspections and willing to take into account different ways of working: “she said that the HTA conducts very good inspections and they are friendly and helpful and take on board your point of view (field notes: P70, tissue bank manager)”.

Internationally, the situation varied; the International Society for Biological and Environmental Repositories, (ISBER, 2012) and the US based National Cancer Institute (NCI, 2011), had developed best practices covering sample collection, processing, storage and transport, whereas Molecular Medicine Ireland (MMI) had developed a set of SOPs (2010). A focus on sample labelling requirements shows that these documents were more policy than procedural. Following ISBER, “[e]ach aliquot or container should be labeled with a unique barcode/number (section I3.200)”. MMI SOPs gave the illusion of being procedural standards, but were better understood as policy in terms of more generic requirements that will require local interpretation:

2. The appropriate allocated unique study identification number and/or bar-coded label will be applied to the specimen container immediately following collection from the research participant thereby ensuring correct labelling ...

4. Where barcode labels are not in use research personnel will ensure that the research participant’s unique study identification number is written legibly in permanent marker on the specimen container immediately following collection (SOP 1.5 on Specimen Identification and Labelling).

In contrast, a tissue bank SOP illustrates the difference between a generic international and a specific local standard, with the SOP far more specific, detailed and procedural in character: “[o]nce the registration form is complete the sample should be transferred into a cyrovial labelled only with the [Rare Cancer Association] case number and the [Rare Cancer Association] specimen code e.g. [000123 LN04](document: tissue banking SOPs, Report Pathology Department)”. Thus, a pattern of decreasing specificity was evident, and potentially required, when standards moved from the local to international contexts.

See Appendix 12 for participant details
Data

SOPs for data collection, confidentiality, management or databases tended to be less common in the organisations I studied than those on tissue samples. In general, tissue banks appeared to focus on clarifying procedures around collecting tissue rather than the associated clinical or lifestyle data. SOPs occasionally made passing reference to collecting or processing data:

8.2 Recording Sample Information

8.2.1 Any information relating to the acquisition of tissue should be recorded on the Finkleborough tissue bank Sample Request Form ... (document: tissue acquisition SOP).

National HTA Research Sector Standards focused on collecting and processing tissue, although organisations were encouraged to keep ‘records’ of activities that took place within the tissue bank, including where tissue was stored, storage conditions and transport and delivery. These records translated into highly specific technical standards such as databases, programs or webpages, capable of storing and displaying this information. For example, the Finkleborough database had been configured to give an overview of the different tissue collection totals from different contributing hospitals.

Different approaches to standards on data and tissue was a problem in that that all professionals questioned on the topic felt that both tissue and data were required for optimal research using human tissue:

you can collect samples and you can collect information about those samples but what researchers want is the clinical data that goes with it so they want to know what treatments the patients have had and obviously the diagnosis of those samples. They just want it linked to as much information as possible to inform their research (P68, tissue bank manager).

During the conferences and meetings observed, researchers repeatedly called for higher quality data accompanying tissue samples. No national standards existed in the area outside data protection legislation. Locally, procedural standards such as forms

See Appendix 12 for participant details
(see Chapter 6) were being used to collect the data accompanied with little explicit guidance on how to complete them.

Tissue banking professionals I spoke to or observed were interested in harmonising ‘minimum datasets’ containing the minimal amount of information that should be collected about each person or patient the samples related to. While national standards had begun to be considered, some international efforts already existed. Biogov International (an international harmonisation organisation) focused on harmonising aspects linked to data collection:

> [t]he method that has been developed by the team here consists of identifying some key variables and seeing how these variables can be … expressed differently in different questionnaires … in order to make sure that … the data … will be comparable (P2, ELSI researcher).

Technical solutions had been developed for understanding whether data collected by tissue banks could be combined. In practice, tissue bank databases used varied, but those designed by the same company often had similar characteristics. Internationally, caTissue designed by NCI in the US was an open-source database, with a user community, that could be adopted and adapted by any tissue bank so it allowed both standardisation and customisation.

Many professionals saw national or international harmonisation relating to data as more important than on tissue collection or processing:

> The tissue bankers might get together and discuss current good practice, but the one thing that really needs harmonisation is the data that goes with it so that people know what they’re getting (P40, pathologist).

If information about how the tissue was collected or processed could be stored individual tissue banks could be left to collect and process tissue in their own way as long as they recorded identical information about what they were doing:

*See Appendix 12 for participant details*
A big biobank would ideally have procedures for all eventualities. But no biobank is like that. So the best way is to keep records of what you’ve done. Who cares how the hospital got the sample as long as it is annotated in a standard way and is searchable? (field notes: P5, funder representative).

While this meant standardisation on the one hand, it would allow tissue banks greater flexibility on the other. The idea had developed internationally, with codes already being developed (SPREC, REMARK, BRISQ and MIABIS see Chapters 2 and 4) that could be attached to samples as labels or metadata. The SPREC code includes seven fields covering what could happen to the sample before it is stored for use in research, an example being: “SER-SST-A-E-N-A-G”, which indicates the type of sample, how it was collected, processed and stored (Betsou et al. 2010). At a national level these codes had not been adopted and internationally ISBER and NCI supported different coding systems (SPREC and BRISQ respectively). A European project, SPIDIA (standardisation and improvement of generic pre-analytical tools and procedures for in-vitro diagnostics) aimed to contribute evidence to assist in the development of these codes.

How far to move towards full standardisation and when was a critical question when designing such standards for tissue banks. Nationally, “the general consensus was that the kinds of things you should be harmonising were procedures and processes, and only standardising things like data fields (field notes: meeting 6)”. As discussed in Chapter 4, some resistance to complete standardisation was apparent:

[w]e don’t want to impose a one size fits all model, because we don’t think that’s the way it should go. We think that there’s a need for a diversity of biobanks (P2, ELSI researcher).

Nonetheless, the biggest advances in, and most convincing arguments for, complete standardisation, were in relation to data.

Other professional requests for data standards included registers of tissue banks that contained a standard dataset on each tissue bank. I found that institutions including pharmaceutical companies and universities were mapping and registering tissue banks centrally. Nationally, a cancer tissue bank register was run by the National Cancer Research Institute (NCRI), but no register existed outside this. Discussions were taking
place as to what data fields were required for an optimal register. Internationally, Public Population Project in Genomics (P³G) had established a register covering large tissue banks that contained searchable information on the types of samples and data collected. Additionally, movements had been made to give tissue banks unique identifiers to identify and measure the impact of tissue banks. At a European level, the BRIF (Bioresource Research Impact Factor) project aimed to produce “a standardised tool to quantify the use of bioresources (field notes: meeting 7)” that could be used when citing tissue banks in publications or measuring their impact.

**Consent**

Nationally, SOPs on obtaining consent to tissue banking were widespread and largely procedural:

> *The purpose of this document is to provide clear guidance on the procedures to be followed during the taking and recording of informed consent from patients wishing to donate samples to the Finkleborough tissue bank (document: consent SOP).*

The focus on consent can be attributed to national-level policy documents in the form of legal requirements (Human Tissue Act 2004) and accompanying guidance that emphasised the importance of consent. Licensed tissue banks were inspected against standards for consent that required SOPs, systems and evidence that the tissue bank followed policy such as “[s]taff involved in seeking consent receive training and support in the implications and essential requirements of taking consent (document: HTA Research Sector Standards)”. The requirement for consent led to the design of consent forms that recorded the donor’s agreement to take part in the research. While the National Research Ethics Service (NRES) provided generic guidance on doing this for research, it was not specific for tissue banks. Thus, while containing similar elements, each local hospital trust and tissue bank designed their own consent form (procedural standard) and associated information sheet.

Often what was contained in local documents could be tracked back to national and international norms. One consent SOP stated that: “[t]he person taking consent should ensure that the participant knows they are free to withdraw from their consent at any
stage without providing a reason (document collected, consent SOP)”. This was very similar to NRES guidance on producing patient information sheets (2011) which offers the sample wording: “[y]ou are free to withdraw at any time, without giving a reason” while internationally, the World Medical Association Declaration of Helsinki (2008) states “the potential subject must be informed of the right to ... withdraw consent to participate at any time without reprisal”.

**Relationships between organisations**

Relations between organisations on the tissue supply chain were dealt with primarily through contractual standards, such as material and data transfer agreements (MDTAs) and service level agreements. Locally, each document was specific to the relationship in question, for example, a tissue bank and a researcher, and the actual nature of these relationships were extremely variable. Nationally, the National Cancer Research Institute (NCRI) had also issued guidance on MDTAs with legalistic sample wording such as: “[t]he Custodian agrees to supply the [data] [samples and data] described at Appendix 1 (“the Materials”) upon the terms and conditions of this Agreement (document collected, access policy)”. Internationally, the US NCI had developed a more prescriptive and specific template, published with its best practices document in 2011. However, these agreements only go part way to addressing all of the different types of relationships that exist along the tissue supply chain, and for example they were not used always when tissue was transferred within organisations.

**Gaps and ambiguities**

Differences were apparent between what standards existed and what participants in my study wanted. Comparison of the existing standards to the tissue supply chain diagram in Chapter 4 shows that a grey area exists around the responsibilities of tissue banks to create SOPs or standards in areas that cross over to researcher or clinical activities. For example, few standards existed that covered the types of services tissue banks may offer to researchers. Further areas where standards were often requested by professionals but rarely existed included specific guidelines for quality management and cost recovery.
CHAPTER 5: STANDARD CREATION

In part these gaps and ambiguities were due to differences in who wanted what. Quality managers wanted standards to allow them to measure and monitor quality, funders wanted registers so they could check whether sample collection had happened previously and the pharmaceutical industry made repeated demands for associated clinical data. The next section considers the question of who should create the standards, given these competing interests.

Who Should Create the Standard?

Creating standards took place in an institutional context where different organisations and professional groups had different motivations for taking part. This section aims to understand what types of organisations were taking part (or not) in efforts to create national and international standards and why. In doing so, it illustrates the political complexity that exists when designing standards, with some actors enjoying a large degree of influence over activities, while some are effectively excluded from discussions.

Organisations involved in efforts to create standards and their interests

Understanding who is involved in creating standards is important because organisations that fund projects or conduct the design work have a degree of influence on the result in terms of its nature, content and scope. Using findings from an analysis of who is involved in creating standards, Figure 5-2 is an adapted and expanded version of the diagram of actors involved in tissue banking. Figure 5-2 depicts the extent of the organisation type’s involvement with the aid of ‘traffic light’ colours: green for high levels of engagement in relevant initiatives, amber for some involvement and red for low engagement. The process of distinguishing the different organisational interests at stake revealed standard creation to be an area of political complexity where different organisations had disparate incentives and disincentives to taking part.

Funders, formal tissue bank networks and universities had large (‘green’) roles in efforts to create standards across the UK. Individual national funders had significant influence over activities in the UK, but smaller influence abroad. Funders were
interested in standards that allowed funded tissue banks to be used (and re-used) efficiently, not duplicated and they encouraged the collection of good quality tissue and data that led to reliable research results. However, funders were often not able to extensively support or enforce standards themselves, and preferred standards that did not raise barriers for researchers:

the funder board had to approve the project’s direction. She waited three months and it came back and said: don’t make it onerous, don’t make it burdensome, give them something they’ll find useful, and don’t give them regulation (field notes: P5, funder representative).

In interviews, funders described themselves as being ‘unconvinced’ that tissue banking was worth investing in, this was of concern because they had a large amount of influence over the sustainability of tissue banks (see vignette E below). Cross-funder agreement was politically difficult to achieve. Nevertheless, funders were heavily involved in producing guidance, agreeing policies, setting up committees and collaborations, funding meetings and conferences, funding staff to work on harmonisation and supporting registers. Funders frequently had important consultative roles on standard creation projects (see vignettes A and E below).

Formal networks of tissue banks were influential both nationally and internationally, and had expertise to draw on when developing standards. Networks were interested in providing standards to encourage members to join the network and subsequently to trust other members enough to collaborate with them. In some cases standards were seen as a means to improve the reputation of the network to external funders and researchers:

A [network] quality mark was perceived as providing reassurance to patients, researchers and funders and making banks that achieve the quality mark more attractive to funders and researchers, thus attracting funds (document: official minutes, meeting 6).

Standards were also seen by networks as a mechanism for sharing experience and offering support to new members. But network members were nonetheless concerned that standards might impact upon their autonomy or entail a cost or burden. Formal
networks were involved in efforts to harmonise SOPs, quality procedures and directories in the UK and internationally (including ISBER, European, Middle Eastern & African Society for Biopreservation & Biobanking, ESBB, and Public Population Project in Genomics, P3G).

Universities were involved in all identified harmonisation projects and networks in the UK and internationally. Their motivations were to encourage the types of collaborations that could lead to improve their reputations and in turn attract more funding. Harmonisation efforts within universities were aimed to support researchers, through sharing infrastructure, knowledge, or minimising bureaucracy. Reduction of regulatory risk by registering or harmonising tissue banks was also important.

Internationally, universities formed the vast majority of partners on European projects such as PHOEBE (Promoting Harmonisation of Epidemiological Biobanks in Europe), Bio-SHaRE.EU (Biobank Standardisation and harmonisation for research excellence in the European Union), ENGAGE (European Network for Genetic and Genomic Epidemiology), and members of the steering group for BBMRI (Biobanking and Biomolecular Resources Research Infrastructure). However, universities were sometimes hesitant about collaboration due to academic competition; individual researchers often resisted harmonisation too. One conference keynote speaker felt that:

*currently scientific competition stimulates small research groups and cooperation only happens when there is no other way, this enhances fragmentation and inhibits sample sharing (field notes: meeting 7).*

Organisations with an ‘amber’ level of involvement included NHS hospitals, pharmaceutical companies and suppliers. The involvement of hospitals in tissue banking activities rarely extended further than cooperating with local universities or commercial companies. Hospitals did take part in initiatives that spanned multiple hospitals including the Breast Cancer Campaign and the CRUK Stratified Medicines Initiative (which had value for the clinical domain as it assisted with genetic analysis and transferred results back). Representatives of hospital tissue banks took part in UK harmonisation projects and networks including Onconet and STRATUM. But generally,

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*See Appendix 12 for participant details*
the sole motivation for hospitals in taking part in harmonisation efforts was an interest in the clinical side benefiting in terms of more funding or infrastructure. Reasons against included a general lack of support for tissue banking and a reluctance to relinquish local control over finances, samples, data or research governance. Hospitals were also described in interviews as risk averse with little money to create or implement standards.

If you’ve got a multi-centre thing you have to get the approval of every R&D office don’t you? There’s no central go ahead and do it. Which I suppose becomes inevitable with the splitting up of hospitals into Foundation Trusts that are all independent financial entities. Course they’ll want their own checks (P40, pathologist).

In the pharma sector, I found that individual companies were generally well-disposed towards harmonisation as they wished to maximise the use of their samples, services, facilities and expertise and to secure ethical and legal compliance to conserve reputation. From a research perspective, companies were also interested in national and international projects to improve the quality of samples and data. The negative aspects of taking part in harmonisation efforts included failures to monetise the outcome of harmonisation efforts, for example, if it were an open-source IT solution. Additionally, pharmaceutical companies appeared to be only interested in collaboration as long as they received the samples, but did not wish to share them (see Figure 4-1). Consequently, much of the involvement of pharmaceutical companies in harmonisation activities in the UK was limited to the Strategic Tissue Repository Alliance Through Unified Methods (STRATUM) project, which aimed to improve the availability and quality of tissue and data. Small pharmaceutical companies appeared to have a higher level of involvement internationally than larger companies, for example as part of the ESBB Executive Committee.

Involvement of tissue bank suppliers was limited to efforts to aiding harmonisation within organisations by providing systems or equipment. However, suppliers had an interest in being involved in harmonisation projects to develop new products they could later commercialise, or to encourage their own product to become gold
standard. (Suppliers advertised and gave plenaries on their products at key international harmonisation meetings, and also sponsored the meetings.) Disincentives to their involvement in harmonisation efforts also existed: if another product was preferred, or if new requirements led to their products being unsuitable, their profits might be reduced. Despite this, suppliers took part in international projects, and they were involved on the boards of several formal networks and on the ‘Standardisation and Improvement of Generic Pre-analytical Tools and Procedures for In-vitro Diagnostics’ (SPIDIA) and ENGAGE projects. In SPIDIA, suppliers were required to develop the tools (sample quality indicators and guidelines) that supported harmonisation, and assisted with co-funding the project.
Figure 5-2 Level of involvement in harmonisation of tissue banking
**Political complexity and excluded organisations**

Patient organisations, professional organisations, NHS RECs, government regulators, publishers, independent tissue banks, tissue supply intermediaries and contract research organisations generally had low involvement in standard creation in the UK. In some cases organisations were excluded because they were not members of the formal networks designing the standards, for example ISBER and ESBB had no patient representatives or organisations on their executive committees. Yet patient organisations had strong interests in being involved in harmonisation efforts, particularly when they were linked to rare diseases (see Chapter 4). However, there were signs of increasing involvement of patients in some harmonisation efforts, which is why they were designated as ‘amber’ on Figure 5-2. Across the UK, patient representation occurred on Onconet (a network of cancer tissue banks), the Scottish accreditation system and STRATUM, but was in other ways limited. Internationally, patient organisations were involved in BBMRI and Public Population Project in Genomics (P3G).

Another reason for exclusion of some actors was a lack of awareness on the part of the standard creators of that actor’s importance in the tissue supply chain, this explains why tissue supply intermediaries and contract research organisations (CROs) have not been part of standard creation projects in the UK (one notable exception was the STRATUM project). Internationally, CROs have prominent positions on the boards of ISBER and ESBB and take part in SPIDIA and BBMRI. Tissue supply intermediaries, on the other hand, had limited involvement outside being part of the ESBB. Little is known about these companies and how they operate (both because they were not included in my sample and due to lack of literature), but it is clear that their importance is rising in the UK as suppliers of human tissue and data: “the plenary speaker said that currently commercial suppliers are providing the most tissue to BigPharma (field notes: meeting 5)”.

While considering involvement in harmonisation efforts, two further actors were identified that may be important but as yet were given few roles in harmonisation projects: publishers and standards organisations. My fieldwork indicated that
involvement of publishers was seen as important to: support open access to pre-competitive data, request information about sample quality or assist with the citation and recognition of tissue banks. At a European level, the Bioresource Research Impact Factor (BRIF) project set out to engage with publishers and journal editors. The project requested that journal editors supported the need for and implementation of BRIF so it can be used to track publications emanating from use of the tissue bank.

One barrier to harmonisation arising from the conference was a lack of recognition for biobanks and when a biobank is acknowledged in publications, where this happens is varied. For example it could be in the abstract or another place, or there may be typing errors (BRIF presentation) (field notes: meeting 7).

BRIF’s discussions with journal editors had met with limited success, except for the European Association of Science Editors, which amended its guidance to include a note about acknowledging tissue banks in the methods section.

SPIDIA was the only (international) project that included a standards organisation – the European Committee for Standardisation (CEN) – directly. CEN was involved in order to assist the project produce the ‘official’ guidelines and quality assurance scheme that are one of the key project outputs.

The results of the research carried out under activity 1 [gathering evidence and writing guidelines], will be provided to CEN/TC 140 In vitro diagnostic medical devices as an input and a potential basis for technical work on European Standards, Technical Specifications or Technical Reports in the field of pre-analytical procedures (document: SPIDIA webpage).

How Should Standards be Created?

There’s two definitions of harmonisation that we use. One of them is a scientific statement of the philosophy of it … and one of the key points is that it is completely context specific and so that two sets of data which may be harmonised for one purpose may not be for another purpose (P6, university researcher).

Decisions relating to the process of creating and designing standards were influenced by context, as demonstrated in the quote above. For this reason, I will present a series
of vignettes to describe some of the different standard creation projects that I observed. Observations from the vignettes result in a model of the process of standard creation and information on the impact of political, social and technical considerations when creating standards.

**Creating tissue banking standards: six vignettes**

Six vignettes are used here as outline examples of work towards standards that enable or harmonise tissue banking:

A. cancer tissue bank network quality standards,
B. changing a federated cancer tissue bank to a centralised one,
C. joint funder statement on human tissue resources,
D. international pharmaceutical company harmonising tissue banking across its organisation,
E. setting up an independent national cancer tissue bank, and
F. setting up a university tissue bank linked to local hospitals.

Vignettes A and C refer to national standards and vignettes B, D, E, and F to more localised standard creation projects. The narratives provide a glimpse of a normally invisible world behind the scenes, considering who is involved, the design process and the particular issues faced during these efforts.

**Vignette A – Cancer tissue bank network quality standards**

A few years after its inception the cancer tissue bank network Onconet recognised a need to design quality standards following politically motivated concerns from one of its members:

*Discussions at the ... [Tissue Bank] Advisory Board highlighted a risk management issue that is directly related to membership of groups, such as xxOnconetxx. Where constituent members are invited to join the group with no stated quality criteria for either management or samples, it could lead to reputation issues ... which could spill over directly to member banks (document: Onconet).*

Onconet initially gathered ideas relating to a possible accreditation system allowing external measurement against a known standard. One year later the project was being
supported by Association of Cancer Funders and its board wished to review plans for the scheme. The board gave the opinion that it should be what the network members want, useful and not onerous or burdensome. After this there was a degree of soft-pedalling and the scheme was termed ‘benchmarking’ rather than accreditation.

Over one year after the initial idea for the scheme, a workshop was organised. Those running the event invited network members who were already broadly supportive of such a scheme as well as funders and a patient representative. The workshop was designed to capture the attendees’ views on ‘quality marks’ (terms such as accreditation and certification were rarely mentioned) with the aim of devising a scheme that was “generated from the community (P5, funder representative)”. The consensus was that a quality mark was required, with the most popular option being a supportive scheme where tissue banks assess themselves against standards (‘self-assessment’) but being subject to peer review inspections. Around two years after the initial workshop, standards and best practices that aimed to be used to check quality of a tissue bank’s samples and data were distributed for consultation.

This example shows how a scheme can develop and change after social interaction with the funders and the research community, in this case from an accreditation scheme with external measurement to a potentially lighter touch scheme involving self-assessment and peer review.

**Vignette B – Changing a federated cancer tissue bank to a centralised one**

The Rare Cancer Association of Biobanks (RAB)(a national cancer tissue bank), which had a central office and local NHS collection sites, had two major issues: whether to operate as a federated or centralised facility and how much flexibility to allow contributing centres in terms of SOPs. The RAB collection sites collected and stored frozen and fixed tissue samples and distributed them to researchers when requested to do so. The central office produced and disseminated guidance including protocols, consent documentation and registration forms, and kept the main project database updated. The central SOPs for frozen tissue stated:

*See Appendix 12 for participant details*
The local pathologist will primarily work to locally approved standard operating procedures for the sampling and storing of frozen tumour (document: RAB tissue bank protocol).

RAB had little control over how the samples were taken and stored and RAB could not do any quality control checks before the samples were released to researchers, as a result the quality of the samples was viewed as variable. The priority for the local centres was clinical work and despite being paid for samples and transport they did not always distribute samples to researchers quickly.

About eight years after the bank was established, RAB began to consider transporting all samples to a central location so that a central lab could check quality and ensure that samples were released on a timely basis. It took another four to five years before the major funder agreed to support this and the process started. The tissue bank manager took time to survey the pathologists’ opinions at each centre, either through a questionnaire or one-to-one meeting, in order to understand their preferences in relation to sending the samples. The manager had to take account of the different preferences at each contributing centre, particularly in relation to the paraffin blocks that are part of the medical record, which in some cases amounted to resistance to relinquish samples: “I know of several centres that currently bank with us that are not willing to send out paraffin blocks at all to anybody (P33, tissue bank manager)”. Putting SOPs in place was viewed as necessary in order to support the process of centralisation, and RAB placed slightly stricter requirements on centres covering the collection of data about sample collection timings, storage methods and transfer of samples to the central location. It remains to be seen how the move to centralised sample storage has affected the participation of local centres, but one centre visited had trouble finding the human resources to send the samples: “[i]t’s not being awkward, physically there will be nobody .... banking is not built in to anyone's job (P42, pathologist)”.

This vignette illustrates the struggle many tissue banks face between centralisation and federation, and how to address the question of whether to retain central control or allow local centres the discretion to undertake their own activities.

See Appendix 12 for participant details
Vignette C – Joint funder statement on human tissue resources

The impetus for UK funders to come to a national vision on human tissue resources arose from high-level discussions on pan-funder groups (UKCRC Experimental Medicine Funders Group) and boards. The project was run by staff from several funding bodies and overseen by a pan-funder board. Prior to drafting the vision and related actions, a degree of consultation took place in order to obtain evidence to support it. Key contacts in the area were interviewed, opinion was canvassed at a major conference, and results of previous projects that had investigated public opinion were considered.

How the harmonised vision was presented in terms of scope and contents was influenced by the funders themselves. In terms of scope, some of the key issues and opinions found during the consultation stage were not included in the final vision because they were judged to be outside the remit or power of funders. The final document included an overarching vision and individual action points. While one professional working on the vision said that it:

has been agreed between most of the UK funders of medical research and it's been no mean feat actually. We were surprised (P51, funder representative).

Another funder board member felt that:

It’s very easy to get people to sign up to nice visions and statements …. Even for xxFunder 1xx ourselves, we can at a policy level say we think this very good. The difficulty comes when things come to the boards and of course they are then competing with all the other research projects …. The boards have to be convinced that it’s actually worth putting the extra funding in … (P55, funder representative).

The document did not describe how the activities and goals should be implemented because each funder had its own systems and processes and would be likely to choose different mechanisms. Thus, the funders have only agreed at a policy level and have not committed to any specific actions, and challenges could be faced putting it into practice.

See Appendix 12 for participant details
This example demonstrated the social activities important for gathering evidence for the development of standards, and the political complications inherent in obtaining agreement across different organisations.

Vignette D – International pharmaceutical company harmonising tissue banking across its organisation

*BigPharma* (an international pharmaceutical company) had been through over ten years of mapping and consensus building in order to produce harmonised internal processes and policy on tissue banking, but had still not achieved all their objectives. The company had two major projects to harmonise activities across its different sites. The first took two years to produce a global best practice policy, a position paper, guidelines, templates, a website, pilot tissue banks in certain disease sites and an interim computer database.

*One of the problems we had actually at that point was ... getting discovery, the research arm, to buy-in to what was seen as important to deliver across the company. ... [D]iscovery always viewed us [Clinical] as a service department providing them with the samples they needed for their research. But actually that was really quite short-sighted because R&D is across a company, but that's how companies were, they were working very much in silos (P41, tissue bank manager).*

As the company was international, different ethical, legal and political frameworks needed to be negotiated when writing policy. After this first project an effort to develop a global computer database failed after organisational changes.

Four years later a second project was initiated in order to improve tissue banking across the organisation and a working group was set up. This project was seen as a ‘change’ programme. The aims of the group were broad and included to: update the policy and produce recommendations for organisational and global governance; harmonise SOPs linked to sample life-cycle and data management across the organisation; consider how to optimise sample storage; build a computer database tracking samples and storing related data. Various mapping exercises took place in order to meet these goals.

*See Appendix 12 for participant details*
The first question was how many samples do we have? The answer was they didn’t know. So the first thing she did was go around one site identifying all of the stores of human tissue and making a site inventory in Excel (field notes: P71, pathologist).

In order to understand how people were working, internal workshops were set up to map the processes around tissue banking and it was difficult to get agreement from all relevant groups in the organisation for these. Different cultures were described within BigPharma: research groups were more informal and less used to following processes and standards than groups working on the clinical side. After the process workshops, ‘use cases’ or specifications were developed for a computer database by relevant professionals, on topics such as receiving, storing and requesting samples.

The mapping underpinned later actions including establishing dedicated biobanking facilities within sites and the two year process of putting together SOPs and international integrated operating procedures on life-cycle management, acquisition, handling, storage, research use and disposal. The computer database was still in the process of being developed and implemented five years after the second project had started. This was partly because initial process workshops had not captured the incredible amount of detail needed for such a system. Standardising and cataloguing all possible data fields that could be entered in such a database was a massive task, involving obtaining agreement from information standards and regulatory teams within the company.

This vignette shows that gathering evidence and coming to a consensus can be especially difficult for technical standards such as computer databases, and competing interests can be present even inside the same organisation.

Vignette E – Setting up an independent national cancer tissue bank

The example of Canbank illustrates that the creation of standards takes investment in terms of both time and money, and without high-level support such as that provided by funders, may fail. Sample collection finally began after around two years and three months and an investment of over £1.7 million in setting up the organisation and related standards. First, the organisation had conducted consultations to inform business strategy and captured requirements for a computer database accessible from

See Appendix 12 for participant details
hospitals via the internet. Tissue bank staff then appointed a commercial partner to
develop the database, a process that continued up until and throughout sample
collection and cost more than £475,000, with similar amounts required for
maintenance. SOPs were designed in-house around how to obtain consent and how to
collect, label, process and transport the samples. ‘Sample donation kits’ were
produced and sample storage and transport solutions selected. The organisation also
began to conduct research to provide evidence about the optimum methods of sample
storage. Identifying hospitals willing to contribute samples and completing extensive
and complex contract negotiation took around one year. While Canbank developed
SOPs centrally, individual hospitals had flexibility in terms of which patients to
approach and how, what kind of role the funding supported and how tissue banking
was incorporated into the hospital routine.

Despite a significant (and ongoing) investment in creating standards such as the
computer database and SOPs, the funders decided not to support follow-on funding
after only one and a half years of sample and data collection. This collection ceased,
contracts were ended, staff laid off, and the computer database was mothballed.

This vignette highlights the dependency of (independent) tissue banks on funders
during the initial set-up and establishment phase, before the tissue bank can return on
the investment by cost-recovery, which Canbank had intended to do. In this case the
funders were capricious:

*the sort of thinking and responses of the funders seem to come and go and you
know they seem to change their own ideas and change their own focus

YEH

on a regular basis

THAT’S THE DANGER, THAT’S A DANGER ISN’T IT?

Yeh, and I’m not too sure they themselves knew … what they wanted out of it and
what they expected out of it (P4, tissue bank manager).
Despite an ongoing relationship and communication with the funders throughout the whole project, Canbank staff were unable to convince them that the collection was worth continuing, and to manage their expectations.

**Vignette F – Setting up a university tissue bank linked to local hospitals**

Novelburg University tissue bank took over 18 months to set up through a process of negotiation, reaching agreement and convincing staff to accept changes to routine. The tissue bank manager, supported by an executive committee comprising of high-level university and hospital staff, oversaw amendments to hospital consent procedures, the information sent out with appointments letters and the tissue supply chain to support tissue banking. The tissue bank manager held discussions with and gave talks to the different stakeholders involved, including university management and key stakeholders in hospitals: pathologists, surgeons, management and R&D: “it meant lots of meetings and lots of talks at seminars and lots of networking locally (P67)”.

However, this was not always easy, for example because the university and hospital management did not trust, and found it difficult to communicate with, each other – “it was almost like the University and the NHS spoke a different language (P76, pathologist)” – and a level of ‘translation’ was required.

The tissue bank manager’s approach to devising standards (harmonisation at a local level) involved holding individual discussions with clinicians and surgeons in order to establish procedures within their clinics or surgeries. The manager worked to maximise incentives and minimise disincentives in order to make the tissue bank work. Individual incentives included doing favours for some surgeons (see Chapter 4, relationship management). Disincentives to clinicians were minimised by providing tissue bank staff to distribute information sheets or collect samples. Perhaps as a result of this personalised approach, the tissue bank did not have harmonised SOPs (see Chapter 4, developing SOPs). The procedures also evolved over time and were constantly being re-negotiated to respond to new clinical situations or clinician requirements, and so setting up the tissue bank and related processes was in a sense harmonisation in action. This vignette demonstrated that SOPs for any tissue bank based in a clinical environment need to be flexible and capable of amendment.

See Appendix 12 for participant details
This example shows that it can take time to develop and gain acceptance for standards and that due to variation within hospitals, standards can be difficult to put into place and need to be able to evolve.

**A model of the process of standard creation**

The vignettes above show that common steps in designing standards exist, but that individual contexts give rise to potentially unique political, social or technical issues. I propose a model based on the common features of standard creation before looking into the types of specific issues that can arise. I describe the model with reference to the vignettes, but also draw other examples from my research.

The model contains four stages (see Figure 5-3), outlined individually below.

**Figure 5-3 The four stages of standard creation**
Stage 1: Finding funding and support

The idea for a standard must find funding and support either from within an organisation or from a funding body. In most of the vignettes, the impetus for, and ideas behind standard creation emanated from a high level, for example a funding board or from executive management in an organisation. This may have increased the likelihood of successful standard creation, perhaps in part due to the general requirement for financial support and resources. Thus, internal or external funders were vital stakeholders in the development and acceptance of standards. Vignette E highlights the impact of losing the high-level funding and support – in this case it meant the end of the tissue bank and related standards.

Stage 2: Deciding who will work on it

The standard creation initiative must then consider who will put the idea into practice. Typically an executive committee, termed either a board (vignette C), steering committee (vignette A) or working group (vignette D), was formed to oversee the project. Committee membership varied and included individuals from different types of organisations: tissue bank committees contained members of university and hospital governance (vignette F), the funder-led project had representatives from different funders (vignette C), and the independent tissue bank contained both funder and patient representatives (vignette E). Thus, membership was linked to who was supporting or funding the project, which allowed funders a level of control over standard development. Composition did not always include all relevant stakeholders involved in tissue banking in practice (see Chapter 4), but some allowance for this occurred through later mapping or surveying exercises (stage 3).

In larger projects high-level committees devolved the actual work between task forces (vignette D) or working groups (vignette A). Membership of the task forces was decided centrally (for example by the executive committee) through considering job roles (vignette D) or experience (vignette A, although members of the network had first identified themselves as interested in taking part). On smaller or local projects, tissue bank managers or other staff conducted the majority of the work themselves, in some cases together with external commercial suppliers (vignettes B, C, E and F).

See Appendix 12 for participant details
Finally, certain characteristics were seen as desirable in individuals who took part in standard creation. One common theme was that they must be skilled at relationship management, facilitation and negotiation. Professionals who could bridge ‘different worlds’, for example between university and hospital or IT and laboratory, were seen as useful when creating standards (see vignette F). Study participants described individuals involved in standard creation as altruistic, with a commitment to working out of hours and a willingness to do long and detailed work to support developing the standard. When asked about barriers to developing standards, a participant involved in an international harmonisation initiative said:

*OK well first of all, it’s difficult, it’s boring .... [T]here aren’t many people who enjoy doing it ... you’ve got to be the sort of person who wants to do something well for the sake of doing it (P6, university researcher).*

**Stage 3: Mapping and discovering evidence**

Mapping or surveying was undertaken in order to understand the context the standard was being created in or to gather evidence to support the process (vignettes B, C and D). Outside the vignettes, an employee of *Bio-gov International* described their methods:

*A lot of the work started with knowing what’s already out there. Because we can’t just start it from scratch ... a lot of the work was just so who has a biobank? And what have they done so far? And what kind of IT system do these use? And what kind of consent form have they used?*

*YEH YOU DO SEEM TO DO A LOT SURVEYS AND QUESTIONNAIRES

A lot of surveys. And I think that’s really the first step (P2, ELSI researcher).*

How this was undertaken depended on whether the project was intended to be applied across numerous organisations or solely internally. When across numerous organisations, mapping included conducting telephone interviews with key relevant contacts (vignette C), holding stakeholder meetings (for example, BBMRI did this), conducting structured workshops (vignette A) or sending out questionnaires (vignette B). In some projects documents such as patient questionnaires or consent forms from...
n numerous tissue banks were sourced to analyse the differences between them to support the creation of a harmonised standard.

Internal harmonisation efforts generally conducted more detailed censuses or surveys, but people did not always collaborate with these. Prior to establishing centralised tissue banking facilities, organisations conducted surveys to discover and characterise internal tissue banks and/or held workshops to map internal processes (vignettes D and F). In vignette D those running the exercise felt that despite surveying, “the biobank doesn’t know what’s out there (P71, pathologist)” . This difficulty of obtaining information also occurred within universities who had asked researchers to declare their activities, and externally at an international level when requesting information from different tissue banks.

Some projects sought public or scientific opinion to inform development of the standard. Public opinion was obtained through relevant publications (vignette E), interviews, focus groups and questionnaires. However, on some projects (vignette C), this was mentioned but not done comprehensively. Scientific opinion, particularly on topics such as how to optimally collect and store samples, was often identified as lacking – “the science behind the science ... there’s a need for evidence based standards there (P2, ELSI researcher)” – and this led to internal experimentation and development of techniques (vignette E). Nevertheless in some cases professionals based guidance and procedures on their own experiences rather than on available scientific evidence (also see Chapter 4).

**Stage 4: Building consensus and creating standards**

Final development of standards relied on collaboration, both inside and between organisations, to produce a standard. Participants referred to this stage as the least transparent and many dismissed questions about it, often referring to other individuals who had designed the standard:

> the tool is still under development ... and they are developing it as it goes along ... in discussion between xxNHSScotlandxx and the Biorepository managers. ... I leave that to them and they give me regular updates but it seems to be going pretty well (P65, Scottish Government representative).
The three main features of this stage were:

- drafting, often done by one or two individuals (see vignettes B, C, E and F),

- continual discussions between individuals collating evidence and drafting standards, relevant stakeholders and executive committees: “I ... draft it, it goes out to our committee, gets reviewed, comes back, back and forwards, gets approved by the Executive, and becomes a policy of the xxConsortiaxx (P1, university researcher)”, and

- external review or consultation, usually when the standards had reached an initial draft or prototype form (vignette A). For example, signatures may be required from other organisations (vignette C) or, for tissue banks, approvals from research ethics committees or R&D departments (see vignettes E and F).

A common finding was that standards started small and increased in size and scope over time: “[s]o when I say that it’s being done in the back rooms, it’s being done a little bit at a time (P1, university researcher)”. The standards were often created in phases, each building on the last to add to them or broaden their scope. BigPharma had two phases of producing standards (vignette D) and Onconet intended to develop the quality standards over time (vignette A). Novelburg University tissue bank (vignette F) intended to gradually broaden the scope of their ethics approval from covering adults, to also including children or incapacitated adults. Standards such as SOPs frequently built-in this need for evolution by requiring review and update at a future time-point. Thus, tissue banking standards generally evolved over-time to fit the context or to allow early initial implementation and later expansion of the standard.

Well when we had the working group it was always our idea to put technicians in and it just kind of evolved that they would be doing the consent (P68, tissue bank manager).

As such the creation of standards was not static and the four stages in the model may be repeated several times. The process should therefore be understood as cyclical in character.
Standard design and political, social and technical considerations

The vignettes have usefully highlighted the influence of political, social and technical considerations when designing standards. The impetus for standard creation often either arose from, or had to be approved by, executive boards who maintained a level of control and influence over the standards and their contents or scope (vignettes A, B, C and E). Thus, the remit of these standards was dictated by management or funders, who were not necessarily those who would be directly implementing the standard. In vignette A the funder supporting the standard gave specific requirements about its contents. In vignettes A, C and D the tissue banking community was included either within working groups or through consultation. In one case this led to modification of the initial idea in-line with community interests; vignette A showed that a proposed accreditation scheme became less strict after inviting tissue bankers to a working meeting. On occasion, when numerous organisations were involved the interests of one organisation could dominate those of others; in vignette A one member of a formal network instigated the network-wide standards.

Politics were also important when tissue banks designed local standards, especially within the NHS, where difficult decisions had to be made as to how tissue banking could be incorporated into the clinical environment (vignettes B, E and F). One solution to this was more generic or flexible standards (vignette B). Another case where standards were flexible was when agreement had to be reached between numerous organisations (vignette C). Two different models existed when tissue banks engaged with multiple organisations: a central office that controlled procedures and stored all samples (centralised system), and a central office existed but samples were collected and stored locally, with some variation in procedures (federated system). The choice of model could have political implications. Vignette B shows that when moving from a federated to a centralised storage model some of the original collection and storage centres had resisted the release of samples to a central location, despite these being registered with the tissue bank.

Social interaction was important when mapping and discovering evidence and building consensus. When discovering evidence, professionals were frequently interviewed or
questioned for their opinions, which were then fed back into standard development. When building consensus, dissemination, negotiation and reconciliation was important, especially when standards were new and seen as a potential change. In Bigpharma, two departments involved originally held divergent opinions on the need for a standard, but they were eventually reconciled (vignette D). Due to the social aspects, standard creation often took a long time, such as when: reaching agreement on workflows in BigPharma (vignette D), negotiating special requirements (vignette F), or encountering resistance to proposed changes (vignette B).

The vignettes frequently referred to the development of technology in the form of a tissue bank database as costly and lengthily, encountering significant problems or delays. A significant problem was clarifying the tissue bank’s processes in enough depth to design an appropriate database (vignette D). The creation of company-wide ontologies to catalogue and define the different clinical or research terms used across the company was a massive task, and was still not complete after other policy standards and SOPs were developed. Thus, developing appropriate technology can take longer than more general policy statements due to their specificity and requirement for detail. For these reasons, developing computer databases had commensurately large cost implications (vignette E).

Chapter 5 has shown that standard creation was obstructed by a lack of agreement between organisations and professionals on the appropriate type and scope of standards, and who should create them and how. A neat division did not always exist between standard creation and later implementation. Chapter 6 describes how the choices made when designing standards can influence implementation, and shows how the evolution of standards happens through standards moving back and forth across creation and implementation phases.
CHAPTER 6: IMPLEMENTATION OF TISSUE BANKING
STANDARDS AND RELATED OUTCOMES

This chapter considers the influences on the implementation of standards and whether the outcomes of this are always harmonisation. The array of factors that encouraged implementation could be grouped into four categories, described further below: the nature or design of the standard, the actions of standard creators or external actors, issues with implementing standards within organisations (specifically the features of implementing organisations) and individual and professional factors. Table 6-1 provides an overview of the factors identified. The chapter ends with consideration of how the outcome of implementing standards can have important consequences for whether harmonisation is achieved.

The Nature or Design of the Standard

The nature of a standard influenced implementation and whether harmonisation resulted. In order to understand which design factors were important, the vignettes that follow explore different types of standards: the Human Tissue Act (2004), clinical trial protocols, forms and databases. In some cases factors influencing implementation other than the nature or design of the standard are mentioned when overlap occurs.
Table 6-1 Summary of factors influencing implementation

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<th>Pressures or enablers to implementation</th>
<th>Factors working against implementation</th>
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<td></td>
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<td>Impractical classifications</td>
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<td>Standard designed with user community</td>
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<td>The standard can evolve</td>
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<td><strong>The actions of standard creators or external actors</strong></td>
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<td>Funder, network or publisher requires it</td>
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<tr>
<td>Incentive to implement standard provided</td>
<td>Incentive not provided</td>
</tr>
<tr>
<td>Sanction, licensing, inspection or reporting</td>
<td>Enforcement poor or light-touch</td>
</tr>
<tr>
<td>Advice or training provided</td>
<td>No advice or training offered</td>
</tr>
<tr>
<td>Standards disseminated effectively</td>
<td>Lack of effective dissemination</td>
</tr>
<tr>
<td><strong>The features of organisations implementing standards</strong></td>
<td></td>
</tr>
<tr>
<td>Prioritisation of standard by organisation</td>
<td>Standard is low priority</td>
</tr>
<tr>
<td>Support and leadership from high level</td>
<td>Lack of high-level support</td>
</tr>
<tr>
<td>Provision of resources to support initiative</td>
<td>No resources available</td>
</tr>
<tr>
<td>Cooperation between departments</td>
<td>Low inter-department cooperation</td>
</tr>
<tr>
<td>Low number of different sites</td>
<td>High number and location of different sites</td>
</tr>
<tr>
<td>Collaboration with other organisations</td>
<td>Little collaboration with those outside organisation</td>
</tr>
<tr>
<td><strong>Individual and professional factors</strong></td>
<td></td>
</tr>
<tr>
<td>Research mindedness and altruism</td>
<td>Lack of research agenda</td>
</tr>
<tr>
<td>Collaboration supported and lack of egos</td>
<td>Academic competition and egos exist</td>
</tr>
<tr>
<td>No proprietary feelings over the tissue</td>
<td>Feelings of ownership or localism exist</td>
</tr>
<tr>
<td>Acceptance of standards, rules or change</td>
<td>Resistance to standards, rules or change</td>
</tr>
<tr>
<td><strong>The outcome of implementing standards</strong></td>
<td></td>
</tr>
<tr>
<td>Standards are complementary</td>
<td>Standards overlap and cause duplication</td>
</tr>
<tr>
<td>Standards are inclusive</td>
<td>Standards cause exclusion and marginalisation</td>
</tr>
<tr>
<td>The outcome of implementation is perceived as positive</td>
<td>The outcome is perceived as negative</td>
</tr>
</tbody>
</table>

See Appendix 12 for participant details
**Human Tissue Act (2004): impractical classifications**

The Human Tissue Act (2004) and the Human Tissue Authority (HTA) research sector standards were referred to by professionals as the most relevant legal standards for tissue banks and they had a major impact on practice (in Scotland, the relevant law was the Human Tissue (Scotland) Act 2006). Supporting this finding, tissue collections and pathology archives were frequently split into samples collected pre- and post-September 2006, the date the law took effect, see Figure 6-1 below:

> OK, well I suppose a significant amount of the stuff that we do presently, this’ll have to change, but a lot of the stuff we do presently is on existing archival holdings. So pre-HTA, and the reason we do lots of research on those is because we can (P42, pathologist).

**Figure 6-1 Excerpt from specimen registration form, Refport hospital, pathology department**

<table>
<thead>
<tr>
<th>Consent</th>
<th>On the Biological Studies Tumour Banking Consent form, the patient / parent / guardian has consented for the material to be used for:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Research: Yes / ☒</td>
<td>Multi-centred collaborative Research: Yes / ☒</td>
</tr>
<tr>
<td>Signed</td>
<td>Full Name (CAPITALS):</td>
</tr>
<tr>
<td>Date: / /</td>
<td>Position</td>
</tr>
</tbody>
</table>

Three examples of classifications within the legislation illustrate how political decisions made when designing a legal standard about what to include or not within the scope of the law can have a direct effect when implementing it in practice.

The first example shows how some classifications can lead to new practices that appear to go against scientific ‘common sense’. The definition of human tissue (relevant material) in the Act is:

> *material, other than gametes, which consists of or includes human cells (S. 53(1)).*

This definition was viewed as set in stone:
the Act is very clear about what material has to be within our scope. It doesn’t make any allowance for certain types of material it just says, you know, this is relevant material. ... [W]here we can we’ve looked at how we can interpret that, but we can’t change what’s in the act (P61, HTA staff member).

The definition was interpreted in practice so that materials not including cells (for example serum and DNA) were exempt, even when they had started out as blood or other tissue that had then been processed to remove the cells or break down the cell walls (note that DNA is regulated elsewhere in the Act and consent is normally required for research, S.45). A tissue bank manager felt that the implications of these exemptions were “ridiculous (field notes: meeting 6)”. The definition had led to studies collecting blood samples and immediately processing them, discarding the human cells and extracting the plasma or serum, which did not require a license to store:

for those smaller 500 patient samples, small cohorts that someone in genetics may have, it makes far more sense to ... process it down to non-relevant material, so you extract the DNA you store it as DNA, therefore you don’t come under the regulation of the HTA (P12, tissue bank manager).

In the laboratories I visited a distinction between two types of material, cellular and acellular, existed, with one regulated by the HTA and the other not. This was hard to defend scientifically and had led to confusion and uncertainty when interpreting and implementing the law.

The second example of the impact of classifications relates to provisions in the Human Tissue Act (2004) about consent requirements for clinical work, audit and research. The provisions are especially strict when an individual is deceased and separate consent is needed for post-mortems, audit and research. However, clinical work, research and audit were viewed by pathologists and clinicians as fluid and overlapping in practice, and the enforced separation in the legislation had a number of implications, for example:

there’s certain questions I cannot ask because that would be research ... It’s absolutely crazy! I’m not doing anything to the tissue, I’m just looking at it again, thinking about it, comparing it to other things. I can’t (P53, pathologist).
Pathologists felt they had to refrain from asking too many questions about clinical cases for fear it would become research; clinical work naturally and easily crossed the line to research, particularly when conducting molecular testing.

*People trot out nonsense about a dividing line .... What if you find something new when you weren’t trying to find something new* (P42, pathologist)?

Another perceived outcome of the consent provisions more generally was that audits were now conducted instead of smaller research projects as consent for audit was not needed when tissue was taken from a living individual (whereas it was for research):

*where does quality assurance end and research begin? We’re allowed to use it [tissue] for audit, and I have certainly dressed-up a few things as audit that others might have said were research* (P9, pathologist).

The HTA had been known to conduct investigations when they felt that activities defined as audit or case reporting could be classified as research: “I went through six months of a full investigation to prove that what I did was a report of cases” (P53, pathologist). The distinction in the legislation between clinical work, research and audit was being policed and entrenched despite evidence that they did not exist in practice.

The final example of a classification concerns the different provisions in the Act for tissue obtained from the living and from the deceased. The Act contained an exemption to the requirement for consent for research when tissue was taken from the living, but did not have such an exemption when tissue was taken from the deceased. The practical implications for one pathologist was that it had become difficult to conduct research using post-mortem tissue, although another felt that the regulation and linked guidance had actually made rules around researching using this tissue clearer, assisting research.

Whatever individuals felt that the practical implications were, two contradictory arguments were made as to why this distinction between tissue from the living and tissue from the deceased was illogical and should be rectified. The first argument was that since the scandals that brought about the Act’s inception related to post-mortem tissue, tissue from the living should not be included in the legislation at all:

See Appendix 12 for participant details
in Scotland as you know they’ve got different legislation which only applies to tissue from the deceased .... And I think from the xxfunderxx perspective we would have seen that as quite appropriate legislation UK-wide (P55, funder representative).

Thus, tissue from the deceased should be singled out and focused upon specifically. The other, opposite, argument was that giving exclusive consideration to tissue from the deceased means that this tissue is afforded a special status:

[a]s if once you die your tissues suddenly have a magical quality that they didn’t have before .... I think tissues are tissues are tissues and they should be treated in exactly the same way (P53, pathologist).

This special status was hypothesised to have been given due to either religious reasons or an “overreaction of the Government to the Alder Hey problem (P53, pathologist)”.

In order to avoid seeing tissue from the deceased as having a special status, the legislation should treat tissue similarly no matter what the source. These two opposing arguments show how the design of the legislation has had an effect on professionals, who had questioned the decisions made by the legislator.

**Clinical trial protocols: complicated standards need central support**

Clinical trial protocols appeared to be effective tools for promoting harmonisation. Their effectiveness was linked to the actions taken by the overseeing organisations rather than the contents of the protocols themselves. Protocols were usually designed centrally by the company or project running a trial and were typically highly standardised in terms of procedures to be followed; see Figure 6-2 below for an example table of procedures (note the need for a tumour specimen, hair follicles and a skin biopsy). Clinical trial coordinators (CTCs) and research nurses working to implement protocols often found them complex and long, and typically took some time to understand them.

I mean it can be confusing, as I said for one of the commercial trials, they are so complex, the way they write things so I had to once get ... a researcher ..., to help me and he was like – this is quite simple, this is what you do. ... I am not very good at reading the protocols. It is just so long and long-winded and it is just like ‘argh’, but I don’t not do it (P30, CTC).
CTCs sometimes felt the need to summarise and simplify the protocols, producing separate documents for the local clinical centre to follow because they felt the protocols lacked clarity and straightforwardness. This was sometimes the case despite protocols evolving throughout the trials to improve clarity or to update or add procedures.

Those who wrote the protocols often supported local professionals in complying with protocols through advice, training and monitoring, an ‘education plus enforcement’ approach, for example providing a telephone hotline for querying specific points in the protocol. The companies running trials monitored local centres by visiting and inspecting them and also checked that data received from the local centres made sense.

Figure 6-2 Study schedule from company clinical trials protocol, Colham hospital
CHAPTER 6: IMPLEMENTATION AND OUTCOMES

Figure 6.2 Continued

<table>
<thead>
<tr>
<th>Blood collections</th>
<th>Screening</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Subsequent Cycles</th>
<th>Study completion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Visit no.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
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<td></td>
<td>11</td>
<td>12+</td>
<td>13+</td>
<td>14+</td>
<td>???</td>
</tr>
<tr>
<td>Day of cycle</td>
<td>-4Mo-1</td>
<td>1</td>
<td>8</td>
<td>15</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>28</td>
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<td>8</td>
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<td>22</td>
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<tr>
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<td>28</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>within 15 days</td>
</tr>
<tr>
<td>Skin biopsy</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Urine for NTX, Creatinine</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum pregnancy (WCB/Inevry other cycle)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PK analysis</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Biochemistry</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Coagulation</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac enzymes</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Angiogenesis markers</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apoptosis markers</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutational analysis</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Markers of bone metabolism</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsens</td>
<td>Continuous</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor/concomitant medications</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>Continuous</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Using forms: the disconnect between central development and local implementation

Forms were a popular mechanism through which tissue banks aimed to harmonise the collection of information on the sample or from the patient, though it did have its problems. For local sites acting as part of a federated system where central bodies provide direction, forms developed centrally (such as Rare Cancer Association – a national cancer tissue bank – sample registration forms) include redundant or useless questions, omit relevant options, or request information not routinely accessible to those completing the forms. At one collection centre for the Rare Cancer Association the need to complete the forms to obtain payment for the samples, combined with the research biomedical scientist being unable to access clinical information other than the pathology report, meant that the forms were often completed using guesswork and assumptions (for examples see the annotations on Figure 6-4 and Figure 6-5 below based on observations during fieldwork). Where patients were involved in completing forms, sometimes key details were not completed (for example details of medication) and when observing patient interviews “the answers the patients gave never seemed very exact to me (field notes: clinical trials unit)”.

See Appendix 12 for participant details
Even when defined options were given, those completing the form might still write on another non-existent option (see Figure 6-4). The high level of guesswork and variation in answers leads to questions about whether harmonisation and reliability of data can be achieved using forms, particularly when they are developed outside the organisation using them. Although forms appeared to be standardised, assumptions and potential differences occurred depending on who was completing it, and what reports it was based on.

Unlike the clinical trial example, for the Rare Cancer Association, specific training was not available but the central office answered queries about completing the forms. Monitoring was in place and the tissue bank manager scrutinised and returned incorrectly completed forms with feedback as to why they were unacceptable. Rare Cancer Association forms did evolve over time to take new researcher and legal requirements into account, illustrated by the incorporation of a consent section into the form (Figure 6-5) as a result of the implementation of the Human Tissue Act (2004) in 2006. The central office slowly amended the forms following local feedback (at least
five versions were produced between 2000 and 2010), but problems specific to local centres still arose with the new versions, see for example the comments on Figure 6-5.

Figure 6-4 Anonymised Rare Cancer Association specimen registration form (2000 version)
Figure 6-5 Anonymised Rare Cancer Association specimen registration form (2010 version)

Staff found it unclear when to create a new form, whether for each person, each set of samples or each clinical episode.

Hospital path reports rarely contained this info. Answer assumed by considering hospital treatment pathway.

Staff made assumptions based on the size of specimen in path. report. Staff were unsure what to tick if they collected normal tissue.

On occasion staff signed here after someone else completed the form.

Staff noted no code existed to denote which was normal tissue (e.g. 'N').

This info. was often not in path reports. Answer assumed 'complete' if margins mentioned. Redundant if it is a biopsy.

This info. was not always in the pathology report. Staff completing this made assumptions based on whether a first case was mentioned.

This info. was often not in path reports, despite RCP guidelines requiring it.

Databases: technical complexity and user involvement

Every tissue bank used a database of some description to store standard information about samples and participants, but the usability varied. Databases designed by an external body, without significant tissue bank involvement, appeared to be more complicated, counter-intuitive and difficult to use, and as a result adoption and implementation was difficult.
The examples of *Novelburg* and *Refport* tissue bank databases illustrated the differences that arose depending on whether user input was sought. In *Novelburg*, the database (see Figure 6-6) was bought as a package and then amended somewhat to suit their needs, with a limited amount of tissue bank input. The professional responsible for using the database described it as “cr*p”, “painful to use”, “complicated”, “tedious” and “not intuitive” (field notes: P72, tissue bank facilitator). The database appeared to be overly complicated and to make their job more difficult. Similarly *Finkleborough*’s (a local cancer tissue bank) database faced difficulties when evolving in response to new research requirements:

*There were still problems that weren’t solved with the database, for example how to track TMAs (tissue microarrays). They were just about to have a meeting with the company that supplied the database in order to work out how to create a TMA in the system, and then to follow when it is sampled* (field notes: *Finkleborough*).

In Novelburg these kinds of technical problems led to the recognition of need for employing a professional whose role it would be to maintain the database.

**Figure 6-6 Novelburg snapshot of main data entry page of database**
In *Refport* the database had been customised by the software company that supplied it with significant input from tissue bank staff, and in particular one individual who was described as conversant in both laboratory and IT ‘languages’. The database made jobs simpler by streamlining activities through automation of tasks (such as label and form printing) and barcode scanning. Classifications and ontologies, supported by selection of terms from calendars or drop-down lists, meant that data collection was standardised and searches were possible. It was a complicated system that took a long time to develop, but provided a better fit to the local context and appeared easy to use. The database had the ability to adapt to new projects built-in as data entry pages and interfaces were modifiable depending on study requirements. Local data-entry pages were designed to dispense with forms and any linked duplicity and scope for error when using a form, and *Refport* provided internal training on the database.

**Summary: nature or design factors that influence implementation**

These vignettes between them highlight five aspects of the nature and design of standards that are important when considering implementation: classifications, involving standard users in design, clarity, evolution and evidence. In one example of a database, classifications were set-up to allow it to be sensitive and responsive to practice, but in other examples such as the Human Tissue Act (2004), political decisions had created classifications that went against common sense and created artificial distinctions. Thus, it was clear that the impact of classifications should be considered carefully at the design stage.

Standards designed by external organisations (such as the Human Tissue Act (2004) and clinical trials protocols) appeared to be successful, but this seemed to be due to the influence of the organisation or its legislative support. Having tissue bank involvement during standard design increased clarity and usability, illustrated by the comparison between databases designed centrally or with local tissue bank input.

Clarity was a particular problem for long clinical trials protocols and technically complex databases, and tissue banks had identified a need to employ a person to maintain their database. The majority of the standards introduced evolved to adapt to local contexts, legal requirements, researcher requests or research techniques. A key
exception to this was the Human Tissue Act (2004), which was static and not seen as changeable or adaptable: “we can’t change what’s in the act (P61, HTA staff member)”. This could be seen as a major limitation to using law to govern tissue banking activities, which have been shown to be highly variable.

Professionals implementing the standards rarely requested or questioned the supporting evidence, and were more concerned about how the standard could work in practice. This may be because many of the professionals implementing standards such as forms and databases were clinical trial coordinators, tissue bank facilitators and biomedical scientists who were in many ways placed in a position of obligation in relation to standards. The exemption to this was the Human Tissue Act (2004) which some tissue bank managers and pathologists had questioned and had not found what they thought was a sufficient evidence base.

Companies designing lengthy or complex clinical trials protocols and forms frequently took an ‘education plus enforcement’ approach to resolving issues with implementation. Thus, successful implementation may need a combined approach involving both design elements and the actions of organisations, considered below.

The Actions of Standard Creators or External Actors

Five actions of standard creators or other external actors can encourage the implementation of a standard. Influential organisations including funders, formal networks and publishers can require implementation of a standard before funding is released, the network can be joined, or a paper published. Incentives such as money and staff can smooth the way for tissue supply chains to be established and specific standards followed. Regulators, funders or networks could impose sanctions or other mechanisms to enforce a standard. Advice and training could be provided to support implementation. Standards could be disseminated to organisations or professionals to implement them. These actions are discussed below.

See Appendix 12 for participant details
**Action 1: Funder, network or publisher requires implementation**

*To share you need to get the right carrot and the right stick. One stick is the funders (field notes: meeting 3).*

Funders had a large amount of influence over the standards that professionals implemented in the UK and elsewhere. These funder requirements were seen as a strong motivation for researchers: “there’s nothing like saying you getting the grant depends on you demonstrating your adhesion to SOPs (field notes: P71, pathologist)”. The power of funders over implementation of standards and systems was evident in a Scottish Government body who was funding the harmonisation of tissue banking across Scotland and creating national accreditation and costing schemes with supporting governance principles and standards: “I am turning the whole of NHSScotland into a single tissue bank (P65, Scottish Government representative)”. They funded relevant staff, equipment, a pilot scheme, national tissue collections and the development of shared tissue bank databases.

In the rest of the UK, funders required applicants to follow their standards on topics such as data sharing or public involvement and they each had their own individual policies which varied and lacked enforcement. Funders rarely placed very strict standards on researchers due to a lack of resources to monitor compliance: “you know I think there’s no point in putting in place very stringent systems if you’re not then going to check them (P55, funder representative)”. International funders appeared to be more strict; funders in the Republic of Ireland made it a condition of funding that a tissue bank is part of the national biobank network and “the presenter viewed this as a ‘stick’ (field notes: meeting 7)”, while French funders required that tissue banks are certified.

Another group of influential organisations was tissue bank networks. While it was not common practice for international networks such as ISBER, ESBB and P3G, other networks occasionally required that members follow a particular standard. For example, Onconet had network agreements, and was considering quality standards, which members had to commit to when joining. Onconet members saw the value of...
this practice for fostering mutual trust and maintaining or increasing the reputation of the network (see vignette A in Chapter 5).

During my research period, publishers had not yet got involved in harmonisation and had not required the implementation of standards on any great scale, yet their influence on the scientific community was undeniable and many described an academic environment with the motto “publish or perish (field notes: meeting 6)”. Professionals often felt publishers should be interested in mandating standards to ensure the publication of good quality research: “scientific journals are not as interested as they should be to the science behind the science … there’s a need for evidence-based standards there (P2, university researcher)”. A suggestion was made at an Onconet meeting that in the future “journals should not accept human tissue studies that have no information about tissue handling and quality (field notes: meeting 6)”. Professionals also felt that publishers had a role in requiring that studies recognise the contribution of tissue banks through the use of a standard identifier (see information on BRIF in Chapter 5).

Action 2: Incentives provided to implement or follow the standard

_They needed xx[...text cut...xx] for xxBigPharmaxx ... and they would allow us to use their equipment, which we couldn’t possibly afford. You know, some of the bits of kit were a million quid each. So that was mutually beneficial (P11, hospital-based researcher and surgeon)._ 

Incentives were widely used to operationalise aspects of the tissue supply chain. Incentives ranged from introducing money and resources such as equipment and staff into hospital departments, to doing favours (such as reserving samples) for individual pathologists, clinicians and surgeons. A degree of relationship management was needed to identify and negotiate these incentives (see Chapter 4). Incentives were often separate from the standard rather than built into it, and were there to induce organisations and their staff to implement and follow particular standards as part of involvement in the tissue supply chain. For example, organisations providing tissue to BigPharma were assessed for compliance with the BigPharma R&D policy:

See Appendix 12 for participant details
“evaluations of potential sources will focus on safeguarding the rights of the donor, in line with the intentions of the informed consent documentation and the other standards outlined in this R&D policy (document: *BigPharma* R&D policy).”

Incentives were not always successful. National tissue banks reimbursing money or resources to local NHS Trusts found that their payments were seen as too small or did not reach the correct department, and as a result the NHS staff were not sufficiently motivated to supply tissue and data. One example of this was the Rare Cancer Association (a national cancer tissue bank) who paid local contributing centres between £10 – £20 per set of paraffin 'blocks', which the centres did not view as a large enough sum:

> money did seem to come up quite regularly. And she did say it was for this reason that they didn’t collect paraffin blocks unless they were doing a favour to somebody in their department. She said she would only do something that would benefit the hospital (field notes: P43, research biomedical scientist).

Additionally, in this case despite the time spent obtaining consent, research nurses did not receive any of the funding, as it largely went to pathology:

> the hospital does get paid. … Not to our unit. But still it’s coming into the hospital (P59, research nurse).

Paying salaries such as research nurses or pathology assistance did not always lead to high levels of sample collection:

> individuals that were employed on our funds were employed by the hospitals or the university unit, which we did deliberately because we wanted them to be integrated into the team there and not be battling with everyone, not to have a completely different role to everyone else. But what that meant was they got involved in all the roles of the team. Would I do it differently and make them employed by us? I might (P5, tissue bank facilitator).

What type of staff to fund and where was another problem and many tissue banks, including *Canbank*, allowed this decision to be taken by local clinical centres.
CHAPTER 6: IMPLEMENTATION AND OUTCOMES

**Action 3: Implementation enforced through sanctions, licensing, inspection, self-assessment or reporting**

*We had two meetings today. The first was with researchers working on brain cancer. The tissue bank manager (P67) said during the meeting that she didn’t trust them, that there must be an audit trail, consent needs to be done well, and she threatened them with the law and said that the HTA could come and check on them any time (field notes: Novelburg University tissue bank).*

Sanctions within the Human Tissue Act (2004) and HTA licensing and inspections were often effective enforcement strategies. The Human Tissue Act (2004) contains criminal sanctions including fines and imprisonment for non-compliance. It was evident that the threat of sanctions discouraged professionals from taking part in research:

HAVEN'T YOU EVER TRIED TO MOTIVATE YOUR COLLEAGUES TO TAKE PART?

Yeah

AND THEY DON'T, THEY'RE NOT ALWAYS INTERESTED?

No, they’re not, but I think some of it that is the paperwork, the regulations ... because there is so much, there’s so much in the way of regulation, and because you do get threatened with going to jail, you know ... people do get disincentivised that way (P82, clinician).

The risk was felt to fall with pathologists, who when asked to provide tissue for research might think: “why should I risk going to prison unless you can provide me with a written bit of paper that says it is okay to do this? (P54, oncologist)”. The consultant felt this led to severe and unwarranted restrictions on the conduct of research, suggesting that the sanctions were potentially dissuasive rather than effective.

No other standard imposed sanctions as serious as these. This is not to say that no sanctions were available; one was to exclude organisations from membership of networks:

See Appendix 12 for participant details
xxBio-gov Internationalxx as an organisation ... doesn't have any power to tell anyone what to do, that’s not their role .... the most you can do is probably tell the group that they have to leave (P1, university researcher).

Another option was to exclude the group from the supply of tissue: “if it is fed back to them [the health boards] that you have been using tissue inappropriately, you would be in breach of your MTA [material transfer agreement] and you won’t get tissue again (P65, Scottish Government representative)”.

In the UK (excluding Scotland), the main organisation to use enforcement strategies in relation to tissue banks was the HTA, based on the statutory requirements in the Human Tissue Act (2004). Ethically approved research tissue banks and organisations without project-specific ethics approval required licenses to store samples: “we licence an activity and within that people can do discrete pockets of work under that licence (P61, HTA staff member)”. Some professionals complained about the cost of the licence and the geographical nature of the licensing system.

Organisations were inspected based on risk profile: “we base it on risk and we have a risk profile that is something that we can, it’s a living, breathing thing really so if adverse events occur in an establishment ... that might bring their inspection forward (P61)”.

Professionals generally reported that the HTA was friendly, helpful, constructive and approachable during inspections: “I think the whole point of inspections is to make sure that whatever you are doing wrong if you can perhaps do it better, then obviously there will always be room for improvement and I think that’s really what the take home message was (P58, research governance coordinator)”. Inspections in the form of monitor visits were used when implementing clinical trials protocols.

The HTA also required licensed organisations to complete a self-assessment report biennially, a method being considered by Onconet accreditation. Self-assessment was viewed by some as light touch “it’s self-declaration, I’m not impressed (P40, pathologist)”, or it was “felt to be insufficient as it can be a tick box exercise with users ‘pulling the wool over their own eyes’ (document: official minutes, meeting 6)”.

Thus, concern existed that alone this was insufficient for ensuring organisations follow
standards and it might not being used properly. Self-declarations were seen as useful for motivating professionals and giving direction to quality initiatives.

**Action 4: Advice and training given**

*I just then end up calling the trial centre and [ask] ... can you just specify what you really want from the sample, do you want the red cells from the bottom .... [Y]ou can call trial centres, that is your main port of call because you know if you go to them, they know the protocol back to front* (P30, clinical trials coordinator).

Many centrally designed standards or tissue banks with numerous collection sites provided advice and training. Clinical trials were a key example of when central support was provided to assist with the interpretation of the protocol, both by training at local centres and a central advice hotline (see quote above). Clinical trials coordinators could check how to interpret provisions in the protocol, thus facilitating accurate implementation. Federated and centralised tissue banks provided advice to sample collection centres, but did not always provide local training sessions, which staff mentioned would have been useful. Some tissue banks used training as a mechanism to increase motivation about the tissue banking itself, although this was not always successful:

*we’d go down and train and talk and there’d be a week where I’d get a couple of samples from between half a dozen of them and there’d be a few weeks where nothing happened and we’d go down and talk to them again and then it just didn’t embed itself in them .... I don’t understand whether we just didn’t communicate any enthusiasm or passion to them* (P5, tissue bank facilitator).

Another area where training was commonly provided was around human tissue legislation. The Human Tissue Authority (HTA) had an advice centre, gave advice during inspections and required training for ‘Designated Individuals’ under the Act. The advice and training received a mixed reaction; some tissue bank managers felt that “the HTA has been an absolute fantastic regulator to work with” (P12), providing useful, specific and timely advice. Other professionals felt that “if you go on the HTA courses they are a bit purile” (P11, hospital based researcher), or “the website and everything is all great, but I think unfortunately when you go on there you do kind of get lost in all the
information and I think it’s not streamlined enough for researchers in academia or in hospitals (P58, research governance coordinator).

Additionally, a major government funder provided guidance and training courses to researchers on regulation, and their online course was used in at least one cancer tissue bank visited. A funder representative said that materials had been developed in collaboration with the HTA and other regulators “so they are accurate (P51)”. This meant that overlap in training on regulatory issues could exist, but no-one commented on this.

**Action 5: Dissemination of standards**

*In relation to best practices in the area she [a plenary speaker] said the four most popular documents are the OECD 2007 biological resource centre guidelines, the NCI best practice for biospecimen resources, ISBER guidelines, and the Council of Europe 2006(4) recommendation. She did not mention anything from P3G or BBMRI, or the OECD guidelines on biobanks and genetic databases (field notes: meeting 6).*

Dissemination of tissue-banking standards took place at conferences, through informal and formal networks, and through tissue bank ‘role-models’. Some of these methods appeared to be more effective than others. The quote above was a typical example of what people said at at conferences and meetings that I attended, yet I found little evidence of any of the international policies mentioned being adopted into local tissue banking standards. Similarly, international initiatives on sample labelling and annotation (SPREC, REMARK, BRISQ and MIABIS, see Chapters 2 and 4) were frequently mentioned at meetings, but none were followed in the six tissue banks I visited for my research.

The dissemination that did work was through informal and formal networks and tissue bank role-models. During visits or discussions between tissue banks participants talked about the systems and standards they have in place:

*See Appendix 12 for participant details*
Having spoken to other people at different facilities, they have all got their own in-house systems for a lot of this stuff which they have just tagged on and I know a lot of them have spoken to software companies (P46, tissue bank coordinator).

Formal network meetings were used as opportunities to meet and converse informally, but in some cases tissue banks also joined the networks specifically to obtain guidance on which standards to follow:

I mean a lot of what we are doing is a bit unknown now that we are trying to centralise because no one else is going through the same processes and those that have done it are totally different in how they have been set up. ... [T]hat is one of the reasons why ... we have joined up to things like xxOnconetxx, to help us to streamline a few of our existing problems (P33, tissue bank manager).

The Wales Cancer Bank was frequently mentioned as an organisation that individuals turned to for advice: “she said that she had a role model at Wales Cancer Bank, and often called on the telephone (field notes: Novelburg University tissue bank)”. Another tissue bank manager felt that “a meeting to share experiences about different types of biobanks, for example with the Wales Cancer Bank who follow the HTA standards (field notes: P57, tissue bank manager)” would be useful. Those creating standards also discussed obtaining support from a professional body in an area relevant to the standards in the sense that the body advertised and encouraged implementation of the standard.

Several organisations producing standards had difficulty disseminating them due to the associated effort, resources and time. Bio-gov International (an international harmonisation organisation) in particular had developed useful guidance for harmonisation but did not have the time or enthusiasm to distribute them:

an employee of Bio-gov came into the room and was asked ‘how do you plan to publicise what you’ve done here?’ The response was ‘people should come to me’. After the long, difficult process of harmonisation should the organisation be expected to go to different conferences talking about it? (field notes: meeting 1).

Bio-gov produced high-profile publications describing the standards it had developed and took part in EC and other internationally funded projects, but despite this, the
standards appeared to have little impact on individual local tissue banks in the UK. Other constraints in the UK included “a ban on publications and promotions in the public sector at the moment, they’re trying to save money (P51, funder representative)”. Thus, standard creators in this sector could not disseminate. Actions such as dissemination took place differently when implementing standards within organisations, considered below.

Implementing Standards within Organisations

Features of the organisations implementing standards influenced the process of implementation. Several of these features overlapped with the ‘actions’ of external actors introduced above, while others were specifically found within those organisations intending to implement standards. Overlapping features are described briefly in this introduction and include the use of enforcement strategies, requiring that researchers follow certain standards, and training and dissemination of information about standards. Following this, six specific features of organisations implementing standards are presented.

Organisations tended to use similar enforcement strategies internally as were imposed externally, including sanctions, inspection, audit and reporting. Some major university tissue banks took responsibility for auditing and monitoring the other tissue banks in the organisation: “[w]e are sort of instigating things like training and another scoping exercise, and mini audit programs at the moment actually, outside of the tissue bank (P67, tissue bank manager)”. Sanctions for breaches of internal requirements included impounding tissue: “if there’s been any breach of the ethics you know we [the Tissue Board] have on occasion impounded tissue until the research governance issues have been sorted out (P14, departmental administrator)”.

Requesting reports on tissue banking activities was common, but not always successful, within organisations. Evidence of reluctance to provide information to central bodies or tissue banks existed in both pharmaceutical companies and universities:

See Appendix 12 for participant details
[after the organisation had conducted a survey] I asked her whether she felt she knows now how many samples are stored? She said that the study teams know, but it’s not joined up, the biobank doesn’t know what’s out there (field notes: P71, Pathologist).

One tissue bank used technology to enforce standards; the tissue bank database had options that enforced some of the rules and procedures around sample and data collection: “the database aimed at making much of the paperwork automatic, and linked to that the standard operating procedures were also updated automatically when they became outdated (field notes: Refport tissue bank)”.

Inside hospitals, research governance departments often took on the role of ‘gatekeeper’, requiring researchers to follow certain procedures in order to obtain approval and, on occasion, enforcing this through inspection or audit: “we were audited last week by the R&D office (P10, tissue bank manager)”. Obtaining approvals involved supplying documents and asking researchers to undertake training. Professionals frequently complained that these requirements were unnecessary for research solely involving use of diagnostic tissue samples, extra blood samples and/or anonymised clinical data: “the amount of trusts that just won’t release blocks, you need R&D approval, we want to see all these documents and … you are stopping a patient receiving treatment that could save their life (P68, tissue bank manager)”.

While organisations, specifically hospitals and universities, provided training on requirements of good clinical practice legislation and obtaining consent, much of the other training was around the practical elements of SOPs or standards. This included training: clinicians collecting tissue to take samples without compromising diagnosis, pathologists to take research samples post-mortem, and staff to use liquid nitrogen or dry ice for storage or transport of samples. Professionals highlighted potential gaps in this training, for example:

See Appendix 12 for participant details
I asked if they followed any rules or SOPs and P62 [Research Technician] and P63 [PhD Student] said there weren’t any, there was little training, and they were left to find out about things as they went along. The lack of rules and training on health and safety aspects seemed to me keenly felt – P63 mentioned an incident with blood that was bad and could easily happen again (field notes: Colham).

When dissemination of information on tissue banking and related standards did take place inside organisations, it was done differently from the methods outlined in action 5 above, and many different approaches existed. Tissue banks within universities did what they termed ‘campaigns’ or ‘roadshows’, for example “a campaign to make people aware of what was coming, and trying to work out pathways by which we could collect samples, so it meant lots of meetings and ... talks at seminars and ... networking locally (P67, tissue bank manager)”. The intranet was used to enable access to standards: “she accessed a page through the desktop of the computer showing what she said was an intranet she had built herself, which contained the methods for the lab (P35, lab manager)”. Tissue banking committees distributed information on standards:

* a regular *xxTissue Boardxx meeting where all those people get together, discuss the problems and the issues. ... [T]hat could range from sharing best practice across the different satellites, it could be discussing regular internal audits to make sure that we are compliant (P12, tissue bank manager).

**The features of organisations implementing standards**

Six features specific to organisations implementing the standards influenced implementation:

1. prioritisation of tissue banking and implementing related standards,
2. support and leadership of high-level professionals,
3. provision of resources to support the initiative, including technological support,
4. cooperation between relevant departments,
5. the number and location of different sites, and
6. collaboration with other organisations.

I explain these separately below.
1. Prioritisation of tissue banking and implementing related standards

Several universities, including Novelburg and Refport, had supported and funded the development of central tissue banks and related standards, in conjunction with associated NHS trusts, who both had research as an aim in their overarching strategies or visions. However, having the aim of research did not mean that, in practice, research was seen as important: “I don’t feel as though I’m working in an environment that is particularly encouraging me to do research (P9, pathologist)”. In all of the NHS trusts visited, the main priority was clinical care and anything that compromised that would not be undertaken.

Chief Executives of NHS trusts are focused on maintaining the business of their trust. To do that they need to deliver high quality healthcare so they’re interested in that. But research, in most instances, is a much lower priority (P40, pathologist).

Some professionals suggested that clinical trials were supported ahead of tissue banking projects: the “whole R&D agenda within the NHS highly values randomised controlled clinical trials (P5, tissue bank manager)

Some trusts were more likely to accept change and implement standards than others, illustrated through a comparison of hospitals in Colham and Novelburg. Novelburg NHS Trust was more successful at changing and embedding new procedures than Colham. Through collaboration with the local university, Novelburg had changed processes in the hospital so that samples from surgery were sent to pathology fresh rather than fixed in formalin, so that fresh and frozen tissue could be collected for research more easily:

it was about changing the way the hospital worked.... We didn’t want them to send tissue from theatre down in formalin any more, we wanted them to send it down fresh. ... [G]radually it gets embedded ... and now in a lot of settings the tissue just goes down automatically fresh to pathology without us getting involved at all (P67, tissue bank manager).

In Colham, all tissue arrived in pathology fixed and fresh tissue had to collected through the surgeon:
samples come here fresh for us to do things to them before we fix them, but the majority arrive [fixed]. That means that when research projects need fresh tissue, they’re usually arranged with, or run by, the surgeon (P40, pathologist).

Novelburg NHS Trust had incorporated a section for consent for research into the main surgical consent form: “they had to actually make a new consent form and that’s quite a big task to ask a big trust to do (P33, tissue bank manager)”. In Colham professionals were unsure how to achieve such a change: “she said they want a clause for research, but they have to convince a large number of doctors, surgeons and pathology services, which is not an easy job for us (field notes: P37, academic researcher)”. Finally, Novelburg University tissue bank had made a Research Tissue Bank ethics application that applied to the tissue in the NHS archives, whereas Colham had not achieved this despite agreements from pathologists and the tissue board that it was required:

*there are mechanisms whereby the diagnostic archives of a pathology archive like this one can be registered and get ethics approval in generic terms for delivering small samples without further ethics approval ... within defined limits. Does xxColhamxx have that? No (P40, pathologist).*

2. Support and leadership of high-level professionals

The success of Novelburg outlined above was partly due to the high-level support Novelburg had received for the tissue bank and related standards, and the involvement of executives from both the NHS trust and the university (see Chapter 5, vignette F). Unfortunately the support of senior staff did not guarantee success, as the example of Canbank illustrates. Canbank negotiated contracts on sample provision with senior NHS trust management, but none of the hospitals fulfilled them: “the rewards for the people on the ground in the hospitals weren’t adequate to give them the incentive to do it at the rate that their managers had basically promised it would happen (P5, tissue bank facilitator)”. Similar support was also required from middle management. For Canbank the priorities of R&D managers lay with clinical trials and this meant it was difficult to bank tissue:
the staff who are directly involved were R&D nurses, data managers, statisticians .... Their agenda was definitely being set by R&D managers, whose obsessions was randomised controlled trials, rather than us (P4, tissue bank manager).

In Novelburg support for research did not always translate to middle management:

there certainly is [support for research], definitely at higher management level, yes, there is. I’m not sure that it’s always recognised at more, in more middle management levels (P77, pathologist).

In Novelburg the tissue bank had to resolve mistrust and misunderstandings between middle managers in the NHS Trust and the University when establishing the bank: “middle management … of both institutions there’s a distrust between, one and the other, it’s almost like they’re enemies, whereas we should be partners (P76, pathologist)”. In Refport hospital, middle managers were seen as non-facilitative about new procedures because they “are not sort of dynamic, can do people, shall we say, if you come with a suggestion you’ll get a whole load of queries and problems (P52, tissue researcher)”.

Leadership by key individuals was important too. As the politics within universities and hospitals were complex to navigate for researchers aiming to obtain tissue, tissue bank managers were regularly approached to ask for advice, and as such had become leaders:

so it was often in the hands of clinicians who would collect samples and freeze them, you’d have to approach them to ask whether you could access the samples. So you’d be at his whim. And there were all sorts of political and ego issues when you do it like that. So at least the system P67 (tissue bank manager) has set-up is transparent and peer-reviewed (field notes: P80, university researcher).

The internal politics within universities and hospitals were complex, and many types of professionals, including surgeons, pathologists, lab managers, professors and PIs, were either supportive or resistant to tissue banking and linked procedures. This could encourage or discourage others from following standards. The director of Finkleborough cancer tissue bank was a surgeon who “has a lot of influence with the people he knows (P68, tissue bank manager)”. In Novelburg some surgical support

See Appendix 12 for participant details
was won through: “pathologists who will refuse to do anything for surgeons until they do tissue banking (field notes: Novelburg University tissue bank)”.

Influence could work negatively too. In Colham, one PI did not agree with consent requirements and influenced her staff:

_The professor was trying to use exemptions in Human Tissue Act [2004] to justify not getting consent, and only talking about the exemptions, something that P62 felt was going against the ‘spirit of the act’. P62 said the PI would call her regularly and have ‘tantrums’ on the phone, and the rest of the people in her office (she shares with around five others) told her that you can’t go against what the professor wants. She said she thought people were prepared to bend the rules because they were bullied or put under pressure by the professor (field notes: P62, research technician)._

### 3. Provision of resources to support the initiative, including technological support

A key resource that assisted implementation of standards was financial investment in facilities, equipment, or person hours. For example, a new high-specification computer database required the purchase of technical equipment and employment of a specialist to operate it (see the nature of the standard – database example, above). Equipment such as photocopiers in useful locations allowed professionals to copy consent forms when this was required (see Chapter 4).

Financial investment was not available in all organisations. The NHS was frequently described as an organisation with a drive to efficiency meaning insufficient resources for supporting the implementation of new standards or procedures:

_Over the last five to ten years in the NHS ... anything none-essential has to be cut because it is deemed as being inefficient. ... Because you run the system at the absolute minimum, there is zero flexibility now to do anything that’s not essential ... In general there is no drive for research at all in the NHS. In fact it is deemed to be a nuisance (P42, pathologist)._  

One solution was to include tissue banking in job descriptions:
I asked whether the biobank is currently working and if people use it? She said they are going to mandate it, it will be written into people’s job plans and they will be measured on it in terms of performance (field notes: P71, pathologist).

This would help to ensure that tissue banking projects took place – this quote shows how hard tissue banking was without dedicated staff:

So if someone wants to say we’ll employ someone to do that job, that’s fine. But this is going to be more of a problem all over the place, it’s not just here, this is gonna be everywhere. Cos banking is not built in to anyone’s job (P42, pathologist).

Including tissue banking in the job descriptions was usually not the case. On occasion, not including banking or research was seen as a good thing as it meant that it could never be taken out: “I haven’t got the research in my job plan, they can’t do that [take it out], because it’s not there for them to take (P9, pathologist)”.

Research nurses and other NHS-based research staff (such as research biomedical scientists) had been employed in hospitals to work on the tissue supply chain. In practice, research nurses undertook a variety of roles, including coordinating research projects, administration, taking blood from patients and asking for consent to take part in research: "she [the research nurse] does quite a lot, i.e. just tells them when the liver’s going to be around and who’s what’s happening and bits and pieces, just the sort of a bit of an admin co-ordinator but it’s just very loose again (P11, surgeon and researcher)”. Some research groups felt that research nurses were invaluable:

approaching patients in the surgeries they missed a lot, and only got consent from one or two people a week. So this did not last long. This was the case until one of the registrars suggested they get a CLRN [Comprehensive Local Research Network] nurse (field notes: Colham).

Research nurses did not have a standard job description or range of duties.

4. Cooperation between relevant departments

Professionals working in hospitals, universities and pharmaceutical companies all reported that relevant internal departments did not always communicate effectively, were sometimes in competition with each other, and did not always agree on
standards (see Chapter 5, vignettes). During the research period many pharmaceutical companies and universities were beginning to promote collaboration and implement harmonised standards (see Chapter 5, vignettes). But the fact that departments did not always take part in centrally distributed surveys on tissue banking suggests that this process was not yet complete.

Throughout my research, IT departments emerged as a key department that needed to be supportive as a large amount of tissue banking relied on collaboration with these departments for activities such as setting up and administering databases, or ordering and networking computers and printers:

*technology going wrong included the label printer not been networked, having cards that access the right areas of either the university or hospital so that they could walk in a more efficient route or get into the right clinic, and also P74 [Tissue bank facilitator] did not have a proper e-mail account (field notes: Novelburg University tissue bank).*

**5. The number and location of different sites**

Having a large number of offices or sites within each organisation led to increased difficulties with implementing standards. Most obviously, practical or logistical difficulties might result. Despite having numerous hospitals, some NHS trusts such as Colham only had a major pathology department in one of the hospitals, and tissue would need to be transported already fixed in formalin. This led to difficulties when implementing procedures to collect and use fresh tissue:

*samples didn’t always get put in fixative, they came fresh. Now we only have access to formalin-fixed tissues. There are problems, for example large lumps are put into fixative and the tissue doesn’t fix properly and there’s a massive difference between tissue taken fresh and preserved as far as molecular content. Pathologists can use poor quality material, but for research use it must be preserved properly (field notes: P37, university researcher).*

Further rationalisation of pathology departments was also planned for the UK, where pathology services would be shared across numerous trusts:
We are having a forced marriage as it were with another city. ... At the moment we are still separate departments. We will phase things. We will become a single department in name. We will become a single department in outlying structure (P29, pathologist).

Increased distances between hospitals and pathology departments could make it difficult to implement standards that look to control variables such as fixation time.

Internationally, when the sites were in different countries, implementing procedures was held up due to differing ethical and legal requirements of different countries:

The main issue for BigPharma [an international pharmaceutical company] was the different laws, for example the HTA and laws in other countries. The law was restricting them in other geographical areas that don’t have the same laws. When it was not up to BigPharma standards some countries changed the law but others weren’t going to change for BigPharma (field notes: P71, Pathologist).

6. Collaboration with other organisations

As Chapter 4 shows, multiple organisations were involved in the tissue banking supply chain and had to work together. Frequent interactions occurred between: different NHS trusts; hospitals and university; pharmaceutical companies and hospitals or universities; and with all organisations and their suppliers. A good example was the Scottish collaboration between health boards: “there was a letter sent out to all NHS boards in Scotland that deal with tissue, basically saying that tissue bank approval is changing in Scotland ... it is being done at NHS board level so that we can apply national governance principles and standards (P65, Scottish Government representative)”. Part of the project’s initial successes were linked to the fact the country is small and can bring efforts together: “because of the size because we have only got five million people and specifically fund R&D infrastructure in Scotland, it is much easier for us to take a central agenda and work with the NHS to get their buy in to going forward (P65)”.

In the rest of the UK the norm was differences between NHS trusts, rather than linkages and common standards, and Chapter 4 described the different pathology
practices, treatments, research governance procedures and consent forms. Some hospitals followed joint standards as part of national tissue banking projects such as the Stratified Medicines Project, funded by Cancer Research UK (see Chapter 5). Stronger connections had been formed between NHS trusts or hospitals and local universities, but these tended to be idiosyncratic. A major tension was often IT and security (see Chapter 4), for example relating to issues with accessing databases across firewalls:

_There are firewalls in place. P68 (tissue bank manager) said that the solution may be a fixed IP address. However, she said that the IT departments do not talk to each other. She said not to underestimate how long this kind of problem can take to sort out (field notes: Finkleborough cancer tissue bank)._ 

Another ongoing difficulty was access by university staff to physical hospital sites and patients (Chapter 4). Other issues related to research funding, which often did not cover the costs of pathology and storage: “[s]ervice costs of pathology and storage and using tissue in that environment can be a bit difficult and NIHR hasn’t been very keen on funding tissue storage infrastructure, but it can leave a little gap when getting tissue (P55, funder representative)”. 

**Individual and Professional Factors**

Individual factors that influenced harmonisation added a layer of complexity to the wider picture between and within organisations. These individual factors are here explored through four case studies that explore the existence of ‘research mindedness’ and altruistic tendencies; the competitive nature of the academic research environment and egos; feelings of ownership towards the tissue; and researchers resistant to standards, rules or change. 

**Case Study 1: Research mindedness and altruism**

One consultant clinician (code-named Dr L) in a _Novelburg_ hospital conducted tissue research despite pressures not to do so: “as a junior doctor, I always considered eventually that doing some kind of academic research or clinical research is part and parcel of the professionalism of being a doctor (P82, clinician)” Dr. L could be

*See Appendix 12 for participant details*
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described as research-minded, meaning that she was more likely to participate in tissue banking activities and follow related standards. This was supported by findings in other hospitals:

*for example xxxpatients with a certain diseasexxx that don’t have tumours, practically 100% of them get tissue consent because the surgeon and the pathologist are both doing a study together, so they’re passionate about it. And I get phone calls about it ..., they badger, badger, badger, if it’s [consent] not been got* (P59, research nurse).

Professionals who could not see the relevance for themselves were less likely to take part in research: “trying to persuade people oh we need to do this [collect and access tissue] for research reasons is quite difficult when they don’t see that it has any bearing on their day, on their practice (P24, trainee doctor)”.

Dr. L did not have research as part of her job plan:

*I don’t have any formal commitment to research, and I don’t get paid to do it formally, so that if I stopped tomorrow nobody would say to me, you know, why aren’t you doing that research. So, yeah, it’s self-driven really* (P82).

Dr. L described her motivations as:

*for yourself personally, and if you don’t recognise that you may as well not bother, but I must say that I’ve got so much more personally from doing clinical research in the last few years, in terms of, you know, tangible things, travel, money ... but also just the kind of respect and gratification really of being somebody who people take notice of really, it’s nice,*

*for the patient ... in a way if you’re sitting in a large hospital like this one, and you’re not giving your patients the opportunity to be involved with cutting edge innovations in treatment, then you’re being a bit negligent really,*

*for the institution ... how can you sit in a hospital which is, shares a wall with the university, and not be doing anything academic (P82)*?

Dr. L also wished to collaborate with other projects: “at least we’ve got the samples in the freezer so that we can feed, feed into those [other] projects (P82)”. Tissue bank
staff saw Dr. L as ‘research friendly’ and she acted as their gate-keeper to obtain samples from the clinics in which she was operating (field notes: Novelburg).

These motivations display altruistic tendencies, which were echoed by other professionals: “[m]ost people genuinely want to do something useful, helpful, a good thing (P41, pathologist)”. Dr. L demonstrated her altruism by fitting in research around a full-time job. Other professionals also worked overtime to do this:

This isn’t something that you get to do in your working week.... You just think well that’s that what I am, I’m a researcher, and you accept doing that [working evenings] (P7, oncologist).

For Dr. L, research-mindedness appeared to be due to the influence of training and education: “[p]eople who came before me, my predecessors in my specialty, they’re all like that, even now in other specialties, other colleagues, they all have full-time clinical jobs and they do research and shoehorn it in (P82)”. Other professionals that I interviewed felt that interest in research had recently declined, particularly in pathology trainees:

it’s a shame that more trainees aren’t interested in research. But then there are lots of, the negative aspects of research, things like the fact that it takes longer to train, so longer to a consultant post .... It puts a lot of people off (P24, trainee doctor).

In pathology, part of the blame for less interest in research was placed with the Human Tissue Act (2004) (see outcomes below).

Case Study 2: Academic competition and ‘egos’

Colham NHS Trust was an example of a hospital and university that had not harmonised tissue banking within the organisation, and researchers and research groups were left working in isolation and competition. Colham staff used words such as ‘fighting’, ‘battle’ and ‘squabble’ to refer to relations between, and within, some of the research groups within the university using human tissues. One of the reasons for this lack of collaboration was the academic environment they existed in, where publication history and building reputation was important. A trainee doctor described the need to be published:
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I want to be published partly because you need publish in order to get some kind of academic credibility. So if you want to do academia in the future then you need to have some kind of track record ... you’ve got to get several papers, and need to have the first author publication (P24).

Research collaborations led to publications where the researcher was only one of many authors and so did not satisfy the requirement for first authorship: “you’re ... lost in a massive international collaboration and then when you go back to your university they say ..., my name is name 23 on the list of publication; that’s not good enough in the traditional way that that academic researchers are being rewarded (P2, ELSI researcher)”. The push towards fast publication also led to low engagement with new standards: “[t]hey just want to do the science, they don’t want to know about the other stuff [standards on quality of the tissue samples], they want to put their blinkers on, cover their ears and get on with it and publish their paper (P5, tissue bank facilitator)”.

Collecting and distributing tissue did not meet the criteria for authorship, which meant that research groups in Colham did not have this as an incentive to collaborate:

I think the major issue with it is, it’s the altruism thing, because they all seem to manage to get the time to get a little, what’s called a tissue bank, for their own personal collection, but when ... you know ... this [tissue bank] is gonna be at a college level you know it sort of somehow never really gets to happen ... And I mean there’s issues that need to be resolved ... for example, making sure that tissue doesn’t go to competing groups ..., which I’ve had bitter experience in the past with groups fighting over, for want for a better word, ownership of a disputed collection of tissue. Which got quite acrimonious (P14, departmental administrator).

Authorship guidelines were sometimes bent to encourage surgeons at Colham to contribute tissue to tissue banking projects: “I think the only pay back that would come and we have this agreement amongst ourselves is that I think if we publish on data that we have collected as a group, then we will all be involved in that article, and I think that is probably as much as anybody really wants (P8, surgeon)”. The work of tissue banks went unrecognised, except through the acknowledgements section, but

See Appendix 12 for participant details
the use and nature of this varied and so it was not an accurate record of contribution (see Chapter 5). Professionals were concerned about building their reputations in order to build careers and so it was important to have their efforts rewarded appropriately: “an academic involved in medical genetics said in a plenary that people fight for publications like they fight for large salaries (field notes: meeting 3)”.

Problems with collaboration also arose due to clashes of ‘egos’ in Colham:

*I mentioned that I was looking into tissue banks working together and more social aspects. She said there could be different factions with different consultants that traditionally don’t get on. Ten years ago she said it was like a “war”– people couldn’t use other people’s things. She said that even now the teams don’t work together. She also told me about some liver surgeons whose groups currently don’t mingle (field notes: P23, biomedical scientist).*

In other trusts surgeons and units kept their own tissue banks despite the existence of a central bank: “the liver unit has its own biobank for ages, I’m not sure whether it’s going to become part of the main one (P76, pathologist)”. Thus, problems motivating professionals who were research-minded to contribute to central tissue banks existed, especially when the normal academic reward, publication, was not available.

**Case Study 3: Ownership in language and practice**

International and national ethical and legal standards such as the United Nations Educational, Scientific and Cultural Organisation (UNESCO) Declaration on the Human Genome and Human Rights (1997) maintained that no ownership existed in the human genome, as it was the “heritage of humanity (Article 1)”; others such as the Charter of Fundamental Rights of the European Union (2000) prohibited financial gain of the human body and its parts (Article 3(2)). Nevertheless, professionals at one international meeting still felt that collaboration was impeded due to the tendency for people to think “my syndrome ... my project, my patients, my EHR [electronic health record], my samples (field notes: meeting 7)”, which turned tissue banks into “biovaults (field notes: meeting 7)”. I use this case study to explore whether this was the case through examining the language of ownership and control in relation to samples.

*See Appendix 12 for participant details*
Principles against ownership of tissue samples had been accepted by Onconet members, who sign a network agreement that indicates their agreement that no ownership rights over a part of the human body exist once it has been removed. Regulation by the Human Tissue Authority (HTA) was viewed as supporting this: “the aim of demanding a human tissue project licence, for research tissue banks, was to stop researchers regarding tissue samples as their own property, and make sure that anything that was left over, once the project was finished, was available to anyone who could make good use of it (P40, pathologist)”. Some organisations felt they were upholding this: “local collectors may feel proprietary rights over samples, but middle-men like her organisation make sure these proprietary feelings do not happen (field notes: P4, tissue bank manager)”.

Outside this, the rhetoric around tissue banking and property was confused. The principle that human tissue could not be ‘owned’ was not always accepted. One professional first stated that property was not an option, but later used ownership-type language:

> the tissues actually belong to the xxColham NHS Trustxx. ... [T]he xxtrustxx said well the tissues come from hospital patients, you know they’re not deemed as property as such, ... we’ve all agreed that that actually is a perfectly good situation that we are happy with (P14, departmental administrator).

Professionals blamed problems with collaboration on pathologists or surgeons, who viewed the tissue as theirs: “P72 is of the opinion that the general problem was that the surgeons thought that the samples belonged to them (field notes: P72, Tissue Bank staff)”. One tissue bank manager stated:

> [p]athologists ... see it like ... they took the sample off, they stored it, it’s theirs. They may not physically own it, they can’t sell it, but they’re damned if they’re gonna give it up when they may need it (P12).

Direct evidence of ownership language existed in official documentation linked to tissue banks. BigPharma defined a “sample owner” as “[t]he person in xxBigPharmaxx, who has the authority to establish a collection of human biological samples for storage and use, and to decide what the biological samples can be used for in accordance with
CHAPTER 6: IMPLEMENTATION AND OUTCOMES

ethical approval (document: BigPharma)”. Documentation surrounding Refport
University tissue bank discussed ownership, and one of the template contracts used by
the tissue bank indicated that those depositing samples retain ownership of samples
and derivatives while they are employed by the university and able to fund storage.

The desire for control over the samples was a strong theme. One reason given for
desiring control was the law. One pathologist felt that: “we have no ownership ... but ...
according to the law we have to keep them for 30 years which means we are happy to
release them for some project, but they have to come back at some point, we have to
know where they are (P73)”. Fear of losing control was also posed by some
professionals as a reason why individuals might be resistant to standards that led to
harmonisation and potential sharing of samples:

There are instances of individuals who see the tissue within their bank as their own
tissue, or for local researchers. And therefore they know what’s gonna be done with
it and therefore they don’t need to harmonise with other people because they’re
going to be self-sufficient (P5, tissue bank facilitator).

Other pathologists or PIs wished to control who accessed the samples because they
had put time, money and effort into collecting the samples: “you want me to do a lot
of work for something, put a lot of effort in, spend a lot of my time doing something
then you ... think it’s OK for you to come and take my end product without
contributing anything (P42, pathologist)”. Funders recognised this: “there is a
possessive nature of researchers, because of the effort that they’ve put into
collections, and because it’s not so much that they feel that they own them, but they
feel that they have a right to use them, over and above anybody else, because they’ve
put the effort in (P51, funder representative)”.

Some tissue banks followed optional provisions outlined in the National Cancer
Research Institute (NCRI) template access policy on “reserving either the entire
collection or a percentage of it for a defined period of time” or access “may be limited
to ... those willing to pursue the research in collaboration with the custodian’s group
(document)”. I also identified a preference for local access that could be termed
‘localism’: “I would very much like it if those samples could go to the region as

See Appendix 12 for participant details
opposed to outside the region because of the points you get for accruing into national trials really (P82, clinician)”.

In Scotland, the tissue bank harmonisation project found that: “[s]ome [health] boards wanted to be able to reserve some tissue and some didn’t so it is acceptable for a board to reserve 20% of their stock of scarce material for local researchers but the emphasis is to make as much tissue available for researchers as possible (P65, Scottish Government representative)”. Some tissue banks only gave samples to local projects or encouraged applicants to collaborate with those collecting the samples: “we’re trying to support local researchers primarily (P67, tissue bank manager)”.

**Case Study 4: Resistant researchers**

One researcher, code-named Dr. B, who was a hospital consultant, was particularly resistant to rules or standards:

*DO YOU THINK THERE’S A LACK OF GUIDELINES ABOUT THIS AREA?*

*I doubt it, there’s probably endless guidelines.*

*YEH, BUT YOU DON’T NORMALLY ENGAGE WITH THOSE?*

*No, heavens no.*

*SO IF WERE TO SAY THERE’S A NEW NATIONAL STANDARD ON CANCER TISSUE BANKING, WHAT WOULD YOU FEEL ABOUT THAT?*

*I’d hit the delete button straightaway. You know if I get a hundred emails a day and you know there’s a new guideline on this, a new guideline on that, delete delete delete. I just can’t read all the guidelines for everything. It’s too complicated for me. There are people here who are very good at guidelines having said that, but not me, I’m terrible (P52).*

This quote speaks more of disengagement than resistance, but later comments indicated a more widespread opposition to standards:

*See Appendix 12 for participant details*
SOPs are out of control.

IN GENERAL?

In general, yeh, yeh. They’ve become, they’re meant to be a tool in order to improve standards and now they’re being seen as a sort of dogma (P52).

This level of ‘general’ resistance was rare. Resistance to specific points was quite common, especially in relation to obtaining consent. For example, one university professor allegedly, “wasted six months of his life trying to bend the rules (field notes: P62, research technician)” to avoid obtaining consent from patients.

One reason Dr. B gave for avoiding implementing standards was the potential delay to beneficial research:

most people think that the data protection act is totally unworkable, and is to the detriment of research, and therefore, choose to ignore it. I certainly do. And I’m sure that I would have the support for my patients in so doing, because everybody wants research to be done and don’t really care about … patient information, if it’s being used for good purposes (P52).

This view of bending the rules being justified as for the benefit of patients was also used by others:

they described some people as ‘loose cannons’, who may act outside the norms or law or ethics in order to achieve what they think or is a good idea. For example, you have surgeons who feel that they don’t need to get consent. They feel that the patients are coming in for free treatment so they should be willing to take part in research as well (field notes: Novelburg University tissue bank).

Furthermore, Dr. B mentioned the potential burden in terms of resources implementation might entail:

SOME PEOPLE I’VE SPOKEN TO HAVE SUGGESTED THE IDEA OF STANDARDISING THE COLLECTION OF DATA ABOUT THE SAMPLE …

Yes, might be useful. Might just be an extra burden which will diminish the return if becomes somebody’s job to fill in a lot of data which it’s very hard to get hold of and usually won’t be relevant (P52).
This concern was shared by other professionals.

As introduced in Chapter 4, professionals working to implement new standards felt that other professionals were resistant to change because of: not wanting to change techniques “there’s new technologies, new kits, but they don’t want to use them (field notes: P62, research technician)”; not feeling comfortable with working with other organisation types, “such as pharma having to work closely with academic biomedical researchers and clinicians having to work with non-clinicians (field notes: meeting 3)”; or finding it difficult to change established procedures: “I’ve done in this way for years, I don’t need to change (P5, tissue bank facilitator)”. One participant at a meeting discussing tissue bank harmonisation quoted Woodrow Wilson, “if you want to make enemies, make changes (field notes: meeting 6)”, to illustrate how hard it could be to convince individuals to accept change.

The Outcomes of Implementing Standards

As the Human Tissue Act (2004) was seen as the major standard in the area of cancer tissue banking and its implementation was extensively discussed, it is useful to use it as an example to discuss four key findings relating to outcomes of implementing standards (below). The Tissue Act was additionally an excellent example of how design elements (discussed above) directly affect the outcome: the legislative nature of the Act (with linked enforcement) had ensured that professionals took notice, and the lack of evolution had meant that the Act had become static and unable to evolve or change in response to new situations.

Standards do not always result in harmonisation, they can lead to fragmentation and diversity

The outcome of implementation was not always harmonisation, conversely it sometimes led to fragmentation or diversity rather than integration. The Human Tissue Act (2004), HTA standards, and codes of practice were the most influential standards for tissue bankers, and had been incorporated into current practice. However, implementation of these standards had not led to procedural or technical harmonisation as might be supposed; instead the contents of the standards meant
that professionals saw further divisions in their own practice, or differences between their practice and that of others. Divisions in practice arose due to the classifications imposed in the Act, which led to different types of samples having diverse rules linked to storage, collection and use, despite often being or appearing very similar in practice (see above).

As demonstrated in Chapter 5, the HTA standards contained flexible high-level principles that lacked specificity and so had been interpreted and implemented differently across tissue banks: “I know that the Human Tissue Authority has got standards under their licensing scheme, I don’t think they go into nearly enough detail mind to make sure that people harmonise practice (P51, funder representative)”.

Examples included requirements that the tissue bank developed SOPs or policies on certain topics (including consent, storage, records, equipment use, safety etc.), but with little guidance as to in-depth contents. As a result, tissue banks developed novel, unique, SOPs and databases, and each organisation interpreted the requirements differently. Consent was the main rule of the standards, but the way consent forms were designed or consent details were recorded in databases varied in practice (see Chapter 4). Thus, the Human Tissue Act (2004) and related requirements had led to the further proliferation of standards, rather than harmonisation. Little evidence existed of widespread harmonisation of specific SOPs or standards across tissue banks outside the limited information on tissue banks on the National Cancer Research Institute (NCRI) Cancer Biosample Directory.

A second example of a division was the process for gaining ethical approval of a Research Tissue Bank (RTB). Throughout the process the RTB is expected to have communicated with local hospital R&D departments, but the problem was that the departments all had different ways of dealing with the RTB applications. As a result, large research tissue banks that collected tissue from numerous hospitals (example, the Rare Cancer Association of Biobanks, a national cancer tissue bank) were dealt with differently at each hospital, which caused delays (see Chapter 4).

Further, two international harmonisation initiatives, International Organization for Standardization (ISO) standards and international tissue bank registers, had been
implemented in the UK, but their limited scope resulted in a lack of wider harmonisation. At least three UK tissue banks were accredited against ISO standard 9001:2000, a basic standard applicable to quality management systems. But because the ISO standard encouraged tissue banks to develop their own tailored quality management systems, all of the systems developed were different (see Chapter 4). Review of the website of an international register of tissue banks developed by the Public Population Project in Genomics (P3G) indicated that approximately 20 of the largest UK tissue banks were included, but this only represented a small proportion of UK tissue banks.

Some positive outcomes to the implementation of the Human Tissue Act (2004) and associated HTA standards were reported, which indicate that a small degree of harmonisation may have occurred. Organisation-level harmonisation such as central tissue banks, evident in some universities and pharmaceutical companies, was partly motivated by the desire to ensure that legislation is respected (Chapter 5). The pressure of inspections had encouraged collaboration between universities and hospitals and many had set up joint committees or boards that discussed human tissue research across the different organisations (Chapter 4). The requirements also assisted standards to improve at a general level; for example one funder representative felt that traceability had been improved as it helped researchers understand “what tissues they have where and what they are and who can use them (P55)”. These successes were linked to increased collaboration and cooperation rather than the development of more tangible harmonised SOPs and systems.

**Battle of the standards: overlap and duplication**

Different standards could include provisions that created unnecessary duplication of effort or requirements. One example from the Human Tissue Act (2004) was the geographical licensing system: “we got a geographical thing where the samples have to be in a licensed bank on a licensed premises (P40, pathologist)”. This led to the need to obtain licenses for adjacent sites, even when they were part of the same organisation: “a license is premises specific so we have to make sure it being given for that premises (P61, HTA staff member)”. Another way duplicity occurred was through numerous
courses and guidance interpreting the legislation. Training on obtaining consent, for example, was part of national regulatory training, as well as being subject to training at a hospital level (see above). This type of repetition led to the concern that the content could overlap, leading to confusion in professionals as to which requirements to follow – though many course providers worked with the HTA to develop training materials.

Internationally, a battle of the standards was taking place: “during an informal discussion an international ethics expert said that if one harmonisation organisation develops a tool, another feels it must do it to keep up (field notes: meeting 7)”. Hence, numerous overlapping and interweaving standards existed. For example, international standards on sample annotation (SPREC, REMARK, BRISQ and MIABIS) overlapped, as did best practices developed by ISBER, TuBaFrost and NCI (see Chapter 4). One concern about the existence of numerous harmonisation projects was the hope that “they are all having some discussions with each other (P55, funder representative)”, appeared on first glance to have been well-founded. But under the surface, cross-fertilisation of ideas was taking place as the members (organisational and individual) of initiatives and projects often overlapped (see Chapter 5). As a result the different harmonisation initiatives were interweaved as well as overlapping.

The dearth of an international tissue bank specific standard relevant to quality issues, such as an ISO standard, meant that the UK and other countries had started to develop accreditation or certification systems. This could mean that international harmonisation would become increasingly difficult, as exemplified by the problems with harmonisation when diverse legislation within countries must be taken into account: “in law, you can’t have a consortium of countries from Europe, Canada, or North America, Australia, etc. and say you have to do x, y and z, because Australia [would] come and say, sorry that contravenes our law, we can’t do that (P1, university researcher)”. Similarly, data and sample sharing and collaboration was reportedly difficult due to varying laws, for example: “P70 said that some countries would not allow samples out of the country and they had a research site in China that would not allow samples out, even samples that the company had sent in in the first place from other countries (field notes: P70, tissue bank manager)”.

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The international battle of the standards had little influence on practice in the UK as no tissue banks acknowledged implementing any of the best practice or labelling standards. The Onconet harmonisation initiative took the view that international standards such as ISBER or NCI could not be directly implemented into the UK and had to be specifically tailored to the national context (Chapter 5). Onconet was also making an effort not to overlap with regulatory requirements:

[t]he other thing that came up a number of times in workshop sessions was the issue of not stepping on other harmonisation or standardisation system’s toes. So they must make sure to stay away from areas already standardised, for example the Human Tissue Act, avoid duplication with existing schemes and be complimentary (field notes: meeting 6).

Within the UK, the main concern in terms of overlapping standards related to the databases, which were highly contextualised and collected varying minimum datasets (Chapter 4).

Undesirable outcomes: exclusion and marginalisation

Exclusions could be created through the implementation of standards. This occurred for example with the implementation of legislation, which by its nature contained firm classifications and limitations on scope. The implementation of the Human Tissue Act (2004) had led to the exclusion of Scotland from the majority of the law. An accreditation system had been established in Scotland to fill the gap, largely based on HTA standards, but some concerns about differences still existed, namely that tissue banking would be a lower quality and not as comprehensively regulated as in the rest of the UK:

they haven’t got a regulatory authority to implement a licensing system, but they’re doing it through the back-door, and it’s not gonna be comprehensive coverage because of course they can only regulate what’s happening in the NHS, what about all the university collections? What about you know commercial companies? So it’s an acknowledgement that something needed to be done because Scotland didn’t want to be perceived as having lower standards than the rest of the UK, ... but ... I’m not sure that it’s gonna be that effective (P51, funder representative).

See Appendix 12 for participant details
Despite these concerns, Scotland had designed and begun implementing the accreditation system, which it claimed would be comprehensive as “the NHS has responsibility for the tissue it collects ... and what they do is they control the standards in the universities and the private sector through material transfer agreements (P65, Scottish Government representative)”. The Scottish Government had particular plans and different standards, and after the initial exclusion, Scotland had moved away from the system in the rest of the UK.

Another major exclusion from the scope of the Human Tissue Act (2004) and related standards was ‘data’, apart from data about sample storage. The Data Protection Act (1998) was only very occasionally mentioned as being the relevant standard governing the use of data. Perhaps as a result of this, tissue bank SOPs focused largely on samples, and harmonisation efforts tended to focus either on samples or data, but not both (Chapter 5). As outlined in Chapter 6, professionals indicated that data was crucial for tissue research projects. In practice tissue banks were a combination of the tissue stored in liquid nitrogen tanks, freezers or drawers, and the data held in their databases (Chapter 4). Thus, this separation and exclusion of data from tissue banking standards and SOPs does make sense from the perspective of research and tissue banking.

Arguably, another consequence of the legislation was to marginalise or induce fearfulness among pathologists. The burden of the regulations had disproportionately fallen on pathologists, who did not have the means of implementing it. Professionals highlighted that pathologists were the focus of the criminal sanctions and that following the legislation was their responsibility: “but the whole consenting process takes place a very long way away from a histopathology lab (P54, oncologist)”. Consent was the main rule of the legislation, but this needed to be taken before the tissue reached pathologists and thus their potential involvement was limited (Chapter 4). Professionals wishing to tissue bank sometimes had a difficult time convincing pathologists: “I see three different pathologists ... but if you wanted somebody to act as the link for the tissue bank, I don’t know which one of those three it would be (P8, surgeon)”. Pathologists described the impact of the legislation:

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the attitude has changed from it is our duty to use human tissue to help mankind to mind your back, do your job and keep quiet. Is that surprising when you’ve got legislation that imposes criminal sanctions on research? (P40, pathologist).

Small research projects undertaken by pathologists when investigating an idea or training new doctors were described as losing out as a result of the legislation and associated system of research ethics due to requirements to complete an ethics application for each specific project: “the steps needed for ethics approval to do that ... study on fifty appendices now is just so demoralising that people just won’t bother to do it (P9, pathologist)”. A particular focus was on the length of the ethics application forms:

I mean if you just want to measure protein levels in tissue, tumour samples .... You can’t be writing 20 or 30 ethics applications every year, every time you want to do something, slightly different .... And ... it’s a criminal waste of everybody’s time to fill in these 50 page ethics forms for simple, basic research. That still is very bad and getting things through ethics takes months (P52, clinician and researcher).

A sense also existed that it was easier for larger funded research projects to deal with legal and ethical requirements than it was for smaller projects:

It has enormously inhibited the small scale projects. Now the big projects run by MRC, Wellcome and so on, it’s probably not any great effect on. But we used to run little research projects for every medical student, it was a fundamental part of training biomedical scientists in laboratories. Lots of people did those projects and not only learnt about research but got fired up to do it. ... That’s been lost. But you can’t measure what’s not there (P40, pathologist).

A more general concern was that smaller tissue banks could be excluded if a cost was associated with implementing standards. Two concerns at a cancer tissue bank harmonisation meeting were that “smaller banks may not have enough money or resources to follow similar guidelines to bigger banks” and “smaller biobanks may not be able or willing to do full harmonisation (field notes: meeting 6)”. Many of the standards were free to access, but a cost was often associated with implementation. One major example of a standard that cost money and caused difficulties was
implementing a tissue bank database; one biobanking management system (caTissue) was free, but the adaptation to local context could be costly and out of the range of smaller tissue banks due to the technical complexity (Chapter 5). The cost of certification against a standard such as ISO 9001, or purchase a HTA license, was also seen as high (Chapter 4).

*The licence fee, it’s not that expensive and you just have to organise yourself. It does mean that very small collections may not be viable if you’ve got 500 samples then yeh, paying a, what is about 6000 pound a year or something ... for a full licence is expensive (P12, tissue bank manager).*

**Professionals consider the outcome when deciding to implement a standard**

A further factor that could influence the uptake of and support for standards was a professional’s perception of the standard and the potential outcome of local implementation. Dialogue around the Human Tissue Act (2004) and related standards was split between those who found the standards complicated and limiting, and those who felt that they were not a barrier to research and some positive outcomes had arisen. Such polar opposite views existed simultaneously and made it difficult for professionals to decide whether to take part in research or not. “[T]he Government hasn’t helped itself because they’ve made it so complicated (P51, funder representative)”, “there are some areas where it gets quite difficult around what is relevant and what is not relevant material and trying to explain the information to others is not necessarily straightforward either (P46, tissue bank facilitator)”. Researchers continued to need support and explanations of the standards to ensure compliance: “I am actually doing a training session this afternoon for a group just to go over all the stuff because they had a lot of issues (P68, tissue bank manager)”.

Professionals described the regulations as an overreaction that limited research:

*I think it was an overreaction of the Government to the Alder Hey problem. I think, I remember talking to the Alder Hey parents and they xxsaidxx we don’t want that the research is stopped (P53, pathologist).*
This researcher went on to link the problems with not being able to do research due to the need to submit a long ethics application and to obtain consent. Other professionals felt that consent requirements caused issues:

*You know the tissue exists and the consent exists but they are not all in the same place. It is just very tedious and laborious. I think we have made it unnecessarily bureaucratic (P54, oncologist).*

Supporting this, particular difficulties had occurred when implementing the consent requirement within hospitals due to the paper-based nature of the system and the cost in terms of staff requesting consent (see Chapter 4). Additionally, as mentioned above, smaller tissue research projects were seen as being impeded.

Many professionals clung to negative views about the Human Tissue Act (2004), despite others explaining that the such views were a ‘myth’ that had now been dispelled:

*I think people were just in the habit of saying it’s going to be a problem, you’ve got to give us get out clauses, you’ve got to make it easier, you can’t impede research, and people just got in the habit of saying that. And I think some people just still keep saying it, especially those who, dare I say it, are potentially higher up the pecking order, aren’t at the coal face, who don’t see that there isn’t that impediment (P12, tissue bank manager).*

Initial views about the legislation stuck in some cases, and in others it appeared to be a case of wilful misunderstanding: “people think it is difficult or complicated and it is almost like they choose not to understand it or read the policies because they are all there (P68, tissue bank manager)”. One explanation provided by professionals was that others repeated the ‘myth’ as an excuse not to conduct research:

*I was very shocked … when I arrived that that [generic tissue banking] was not in place, and even worse, people were obstructing this to happen, trying to find excuses for not doing it, … people were happy to find excuses using or misinterpreting these ethical laws just not to do anything (P73, pathologist).*
Many professionals thought that legislation and the HTA had led to positive outcomes. Some felt the rules for research had become clearer in particular areas: “people think it’s more of a pain, and ethics committees freak out and go oh my god it’s a post mortem, but in fact it’s much easier … since the rules have changed and the law has changed (P42, pathologist)”. Professionals had got used to having standards in the area:

**DO YOU THINK, IT’S MADE THAT, IT’S MADE THE POSITIVE DIFFERENCE?**

*In terms of the standards, yes yes I think so and I think in terms of researchers being more supportive of standards and protocols and good practice, and not just saying it is sort of top-down imposition. Because there was a sort of top down imposition, but I think they are now seeing some benefits of that. So I think they’re much more open to that sort of approach (P55, funder representative).*

Some tissue bank managers and researchers were grateful for the Human Tissue Authority, seen as responsive and approachable; and on occasion requested HTA inspections:

*researchers have said to us, actually we want to be inspected, we want you to come and see what we’re doing, we want to show you want we’re doing well, but we also want you to tell us what you think we can do better (P61, HTA staff member).*

The Research Tissue Bank approval scheme, run together with the National Research Ethics Service, met with approval from researchers, if not always pathologists (see Chapter 4 and above).

I have used the example of the Human Tissue Act (2004) to show that the outcome of implementation was not always harmonisation, conversely it sometimes led to fragmentation or diversity rather than integration. This example also demonstrated how the outcome of implementation can be undesirable, for example leading to the marginalisation or exclusion of certain professional groups or geographical areas. Importantly, I have shown that professionals considered these potential outcomes when deciding whether to engage with, and implement, a standard.
CHAPTER 7: DISCUSSION

In this chapter the empirical findings from Chapters 4–6 are drawn together and considered in the light of relevant literature in order to address the multi-faceted question: what influences the harmonisation of cancer tissue banks in the UK? A discussion of the results is followed by potential study limitations and eight recommendations for policy and practice. The chapter ends with suggestions for future research and brief conclusions.

Tissue bank harmonisation, although widely seen as desirable, has not yet taken place on a large scale. Previous literature (see Chapter 1) has not given a full account of why harmonisation is difficult. My analysis produced a novel model of the tissue supply chain, which is important to consider before distinguishing between three components of harmonisation – drawing on Timmermans and Epstein’s thesis on standards (2010): the creation of standards, implementation of those standards, and the outcome of standard implementation. Without such clarification, it is hard to clearly identify the reasons why harmonisation is difficult to achieve. This thesis describes new and clarifies expected influences on tissue bank harmonisation in detail, from considerations of who should create standards, to what influences the decisions of professionals to implement standards.

My analysis shows that Timmermans and Epstein’s three components were a useful heuristic for considering associated challenges. I further demonstrate that standards can move backwards and forwards through the different components while they evolve to fit local contexts and respond to other influences, thus also confirming Timmermans and Epstein’s (2010) observation that in the process of creating and implementing standards the different components may blur into each other. My observations provide examples to support literature that views standards as being created in a cyclical and iterative process, and not a linear or unidirectional one (Bowker and Leigh Star 2000). I found that some key challenges to harmonisation cut across all three components. In particular, I have identified original interrelated
political, social and technical factors that make harmonisation far more challenging than it might first appear.

**Tissue supply chain**

This thesis has developed an improved understanding of the tissue supply chain. Previous literature (Chapter 2) approaches the tissue supply chain in different ways: as a process, a life-cycle, a network, or a supply or value chain. I brought this literature together and demonstrated the pros and cons of each model, before developing a synthesised provisional model (Figure 2-12) to assist with analysis and interpretation of research results. After considering this provisional model in light of my research findings, it was modified and simplified to reflect the empirical learning. The result is a new model (Figure 4-7) of the tissue banking supply chain in a UK context.

Updates to the new model as a result of my analysis included the addition of a key (optional) stage in the chain for provision of services, such as slide scanning or cell culture, to researchers, not included in previous models (Chapter 4). Other than a ‘sample processing’ step in the value chain model (Vaught et al. 2011a), the literature describing tissue banks has scant mention of providing such services, and indeed some commentators view them as potentially distracting from the objectives of a tissue bank (Grizzle, Bell and Sexton 2011). This finding that tissue banks provide services is supported by evidence that researcher demand for services such as tissue microarray production, slide scanning and cell culturing has increased significantly in recent years (Marko-Varga et al. 2012, Eiseman et al. 2003, Cole et al. 2012).

A further update to the new model was a renewed emphasis on informed consent and its management as a ‘cross-cutting process’. Dominant conceptions of the tissue supply chain (Moore et al. 2011, Vaught et al. 2011a) are based on the US context and do not feature consent as a major issue, but in the UK this emphasis is critical. Participants repeatedly mentioned that informed consent was an important concept because the Human Tissue Act (2004) and research sector standards require consent to be obtained in the majority of cases, and for it to be traceable throughout the whole tissue supply chain. However, as commentators suggest (Furness and Sullivan 2004, Liddell and Hall 2005), the aspiration for informed consent for the use of
samples is not necessarily easy to put into practice. I demonstrated empirically that strict requirements for informed consent had led to practical and resource problems within hospitals and tissue banks, which formed a barrier to collecting tissue in practice (Chapter 4).

I identified a new process and coined it ‘relationship management’ to describe a cross-cutting process within tissue banks, whereby relationships across the supply chain needed to be actively managed in order to keep the chain functioning (Chapter 4).

In terms of the inclusion of data in the tissue supply chain model, I was able to confirm empirically that data is important at all stages of the tissue bank supply chain, as data is collected, processed, stored and distributed alongside the tissue. Previous models either give limited (Shickle, Griffin and El-Arifi 2010, Vaught et al. 2011a, Gee et al. 2013) or no coverage to data (Betsou et al. 2007, Technopolis 2010, McDonald, Velasco and Ilasi 2010, Office of Biorepositories and Biospecimen Research 2010). All of the professionals I questioned on the topic felt that samples were of limited value without the accompanying data (Chapter 5), confirming previous studies and commentaries (for example Gibbons et al. 2012a and UKCRC 2011, see Chapter 1). My findings add to a developing body of literature that argues that those creating standards for tissue banks should include data associated with samples by providing professionals’ views on how and why this should happen (see Chapter 5). Creating such combined standards is a particular challenge in the UK where legal standards lead to polarisation, as the Human Tissue Act (2004) applies to tissues, and the Data Protection Act (1998) is relevant for data (Gibbons 2007).

A final reflection on the tissue supply chain is that my research provided evidence that in at least one tissue bank, the majority of the tissue was collected ‘fresh’ and immediately dispersed to the waiting researcher (Chapter 4). This had implications for the design of the tissue bank and related standards, specifically in terms of its location and the requirement for a change in routine hospital procedures (Chapter 4). These empirical findings corroborate commentary (Clotworthy 2012) and prior research (Cole et al. 2012) that suggest fresh tissue is useful for research, its timely collection may
require infrastructure changes, and an increase in the demand for fresh tissue will occur in the future.

An intriguing difference between the use of frozen stored tissue and it being distributed fresh was that in the latter case the tissue bank acts similarly to a ‘clearing house’ to ensure that appropriate legal and ethical standards are followed (Chapter 5). I suggest that this indicates a preliminary shift from a tissue bank as storing tissue to a facility that primarily enables and supports the tissue supply chain. This may have an impact on how tissue banks are established and governed; for example future tissue banks may become more of an advisory or oversight body for fresh tissue collection activities that take place in hospitals. This role change could support a move away from the ‘bank’ metaphor, especially as the term has been criticised for links to ideas of property and ownership (Alnæs 2009).

**Creation of standards**

Chapter 4 showed that the majority of professionals were ideologically committed to tissue bank harmonisation. Many of the rationales for this echoed those found in the literature review (Chapter 1), but several novel reasons emerged, including the view that harmonising tissue banks improves practice because expertise and knowledge are shared, and the desire for harmonisation *within* companies in order to ensure that employees were communicating about similar subjects in similar ways. I also identified several new challenges to these ‘pro-harmonisation’ viewpoints. Many arguments against harmonisation were specifically anti-standardisation or resistance more generally (both discussed further below). Others were hesitant because they did not trust the large organisations drafting the standards, felt that it would be impossible to reach an agreement on the contents, or were concerned that harmonisation initiatives were not communicating with each other. However, these were minority viewpoints.

Chapter 5 revealed four problems that exist in relation to the first step towards harmonisation, creating standards: what standards need to cover, what format the standards should take, who to include in the standard creation activities and the nature of the process of agreeing and producing standards.
What standards need to cover

Little agreement existed on what was to be covered by tissue banking standards, echoing the variation of suggestions presented in the literature review (Chapter 1). One exception, a common viewpoint newly demonstrated for tissue banks, was that different types of professionals agreed on the need for tissue banking standards applied to data about how samples were collected, processed and stored, also termed ‘sample annotation’. My research indicated that many standardised labelling conventions or ‘codes’ were being developed internationally to address these requests (see, for example, Betsou et al. 2010), but they were rarely implemented at the tissue bank level. A concern that arose during my study – that without such metadata the samples may be useless – was also reported by respondents in UKCRC (2011).

I show empirically that the type of organisation a professional works in affects the types of standard they are motivated to request (see Chapter 5). Professionals employed by tissue banks wanted standards that cover sample collection, processing, storage and transport, in the form of procedural standards or SOPs (standard operating procedures). This perspective aligns with literature suggesting that tissue banking SOPs could be produced (Harris et al. 2012, Yuille et al. 2008, Ravid 2008, Kiehntopf and Krawczak 2011, Vaught and Lockhart 2012), yet SOPs had not been put in place nationally. Pharmaceutical companies expressed an interest in standards linked to the collection of data, which led to the suggestion of technical standards that would outline minimum datasets. Again, while various minimum datasets have been defined internationally (Fortier et al. 2010), the Academy of Medical Sciences (2013) noted that these are still required in the UK. Finally, funding body representatives were particularly interested in online registers that would allow them to check whether a similar collection has already taken place before allocating funds (also found in UKCRC 2011), yet, though some projects have mapped the requirements for such a register (Norlin et al. 2012), nothing has yet been put in place nationally beyond outside the limited information on tissue banks on the National Cancer Research Institute (NCRI) Cancer Biosample Directory.
Some types of standards that were considered important in the literature (see Chapter 1) emerged as less important in tissue banking practice. For example, ethical issues associated with participant privacy and return of results were rarely mentioned outside conferences, despite having a large focus in literature (Budin-Ljøsne et al. 2012, Hoeyer 2012, Kaye 2012, Wallace 2011). In contrast, consent was widely discussed by professionals due to legal requirements (see politics below), and questions on ownership of human tissue also arose in practice (see social factors below). Thus, it could be argued that the importance of some issues raised in the literature or at conferences is disproportionate, in relation to practice.

What format for which standard?
My analysis indicates that when agreement existed on what the standards need to cover, the decision about an appropriate format for the standard was linked to the activity in question. The current literature lacks clarity on the types of standards appropriate for different activities (Kaye et al. 2012, Brunsson and Jacobsson 2000b). My analysis suggested that the typology of standards (procedural standards, technical standards, contractual standards and policy standards) developed in Chapter 1 is applicable, although I extend this typology by providing useful examples of each type of standard. Procedural standards such as SOPs or forms can harmonise the steps to be taken to achieve a particular aim, and are used to describe sample collection, processing, storing and transport. ‘Procedural standards’ are a feature of Timmermans and Epstein’s (2010) typology of standards, where they are described as standards that explain how processes are to be performed. Technical standards can be highly specific and often address data associated to, or about, the tissue bank, and appear as computer databases, programs and websites. Contractual standards include agreements covering the exchange of tissue and data, and thus are useful when governing relationships between organisations – vital when considering the social factors involved in the tissue supply chain. Finally, policy standards use generic terminology to explain what should or should not happen on ethical issues such as consent. Policy standards are also used when standards need to be flexible to apply across numerous organisations or within complex organisations such as universities or hospitals.
Discussions on the format for particular standards are fraught, as illustrated by the example of tissue banking standards applied to data about samples. I found that a key determinant that affects the format chosen is how flexible or specific the standard needs to be, with technical standards typically being fully standardised and policy-type standards being flexible and generic. Thus, a particular question that influences the creation of tissue banking standards is often whether full standardisation is required. Professionals I spoke to agreed on the need to standardise in the area of sample annotation so that tissue banks could accurately report how samples are treated and so this information can become searchable. Work on the criteria for sample annotation had already been conducted, resulting in technical standards including SPREC (Standard Preanalytical Coding for Biospecimens), BRISQ (Biospecimen Reporting for Improved Study Quality) codes and MIABIS (Minimum Data Set for Sharing Biobank Samples, Information and Data)(Moore et al. 2011, Betsou et al. 2010, Norlin et al. 2012). All approaches produced ‘codes’ or lists that can be incorporated into databases or websites.

Yet reasons against complete standardisation were evident. First, the more specific a standard was, the more resource-intensive and time-consuming it was to produce (a factor suggested by literature in Chapter 1, but here shown empirically). While this was suggested by prior literature (Chapter 1), my data provided evidence for this in practice and additionally confirmed the dearth of available funding for such work (Chapters 1 and 5). Second, standards lacking flexibility caused problems for procedures or processes that were variable or likely to change (Chapter 5). This finding confirms that a degree of flexibility, for example in a definition, can be pragmatic when it is likely that not everything is known at the time the standard is designed (Webster and Eriksson 2008). Third, ‘loose’ standards containing grey areas were found to be useful for allowing professionals the space to use their own discretion when conducting research (Chapter 6). This finding supports prior research (Greenhalgh et al. 2004) which showed that standards with ‘fuzzy boundaries’ enabled the implementation and adoption of innovations in the NHS. Others have commented previously that tissue researchers should be allowed to stretch rules in order to aid discovery (Hoeyer 2012).
However, it is important that nuance is added to discussion about the disadvantages of standardisation as it can sometimes facilitate rather than restrict local discretion and it can support flexibility. For example, the trend for harmonising through ‘minimum information (MI)’ conventions is recognised by genomic researchers because it allows collaboration across multiple organisations while each retains its independence (Holmes et al. 2010). Putting in place MI conventions for tissue banking in the form of sample annotation, rather than broader standardised SOPs, would counter further arguments professionals put forward against harmonisation of procedures for collecting, processing and storing samples (see Chapter 4); namely that complete standardisation of SOPs narrows the scope for creativity and limits the types and diversity of research that can take place in the future (which corroborates the arguments against standardisation in Chapter 1). If tissue banks implement MI conventions, they would be able to follow their own SOPs outlining how samples can be collected, processed or stored, and record how they chose to do this through the MI annotation.

**Who to include in the standard creation activities**

Another problem to be solved when creating standards is who should be involved. I found that creating standards in this area is highly political and varying interests are at stake for each stakeholder. The *politics* around standard creation is discussed further below, but to summarise, funders had the largest influence and presence, through initiating projects and sitting on their executive boards (see Figure 5-2). Formal tissue bank networks and universities also had a large say.

Another important decision to make when creating a standard is whether to design it centrally (for example by a funder, regulator or a pharmaceutical company executive board) and then request tissue bankers follow it, or whether to include and consult the tissue bankers (or ‘users’) in the creation process. Chapter 1 described research that showed professionals felt that their views should be represented when creating relevant standards (McLean et al. 2005, Pathological Society 2010, Gibbons and Smart 2012d). My research indicates that members of the relevant tissue banking community are normally involved in the process, but rarely generate the standards wholly
themselves, except for context-specific procedural standards such as SOPs (Chapter 5). Involvement was either through direct involvement and ability to steer the contents of the standard, for example in a working group, or less directly, i.e. through consultation. Although I did not test this directly, Holmes (2010) and Brunsson and Jacobsson (2000a) suggest that such ‘user’ involvement can improve the perceived legitimacy of the standard, encouraging implementation. I will return to involving users below, in relation to implementing standards and technical standards.

The process of agreeing and producing standards

The ‘black box’ explaining the process of standard creation in the field of tissue banking has not previously been opened. Standard creation in tissue banking has been considered solely in light of which type of organisation, or group of organisations, generates them (UKCRC 2011, Kaye et al. 2012, onCore UK 2009b, Armstrong 2010)(see Chapter 1). Separately, researchers have investigated the production of standards in similar areas such as: ‘omics research (Holmes et al. 2010), stem cells (Webster and Eriksson 2008) and tissue engineering (Hogle 2009). I consider my research results in light of their studies.

In order to understand this ‘black box’ I developed and described a new model (Figure 5-3). To summarise, this includes: finding funding and support, deciding who will work on it, mapping and discovering evidence, building consensus and creating standards. My research confirms that funding for tissue banking and specifically standard creation in the UK was unstable (Chapters 1 and 4). Although previous literature indicated that funding was not a key issue (Chapter 1), the need to find funding for standard creation emerged in my data, and thus is included in my model as a more prominent issue than had previously been recognised.

In relation to who will work on the standard, my finding that standard creation is often driven by a type of executive committee supported by working groups corroborates prior descriptions of standard creation (Webster and Eriksson 2008, Holmes et al. 2010, Hogle 2009). This ‘executive committee’ structure is a common model for standards organisations such as the International Organization for Standardization (ISO) to operate under (Tamm Hallström 2000). Similarly, my description of how the
harmonisation project maps and discovers evidence – through telephone discussions, meetings, workshops, questionnaires, document requests, focus groups – echoes reporting in other areas (Webster and Eriksson 2008, Holmes et al. 2010, Hogle 2009). Meetings and workshops were shown as particularly important in the prior literature (Holmes et al. 2010, Hogle 2009) when compared to the other evidence gathering processes I described in Chapter 5, but this could have surfaced because meetings are more tangible and easier to observe and research, and my research shows that the other methods appear equally important. Furthermore, my research revealed that in some cases, when faced with a lack of scientific evidence, those generating standards with scientific content conducted their own experiments to provide evidence. My characterisation of this extends the limited number of existing examples of this activity (Webster and Eriksson 2008, Brown et al. 2009).

I found variation on whether, and to what degree, consultation was used. Consultation varied between the broad coverage typical of standards organisations (consistent with Busch 2011 and Hogle 2009) and that limited to the scientific community (corroborating Webster and Eriksson 2008 and Holmes et al. 2010). Standards that result from the process of consensus-building are referred to as “a negotiated order” (Timmermans and Epstein 2010). My findings support the importance of negotiation, and I further consider the social factors involved in the creation of standards below.

Finally, I show that many standards evolved and moved back and forth through the stages of standard creation and implementation. I provide rare examples of standards that start small and increase in scope through successive iterations of creation and implementation. By adopting Bowker and Leigh-Star’s (2000) terminology of “living classifications”, I consider these are examples of living standards that evolve to fit into their environment. This evolution allowed tissue banking standards to adapt when new researcher or legal requirements arose (Chapter 5), hence confirming others’ view of standards having a non-linear nature (Millerand and Bowker 2009). Thus, any notion of a standard being ‘static’ should be dispelled; standards such as databases develop over time, alongside the remit of tissue banks, in order to improve their fit to context.
Implementation of standards

The implementation of tissue banking standards is influenced by a combination of three groups of factors: the impact of decisions made during the design process, the actions and features of organisations designing or requiring implementation, and the attitude of professionals working to implement the standards (see the novel summary framework provided in Table 6-1). The first two groups will be discussed initially, and the third in the section on ‘social factors’ below.

Many of the design features discussed in the section above influenced standard implementation. Involving standard users in their design emerged as particularly important. This aligns with observations in other fields; for example, innovation in the health services was found to be more successful when linkage exists between the designers, those who require it to be adopted, and those responsible for implementing it (Greenhalgh et al. 2008). Additionally, allowing the standard to evolve enables the standard to be incrementally adopted in ways that suited the local context (Chapter 6), which disconfirms literature that argues that practice must always adapt to the standard, rather than the other way around (Brunsson and Jacobsson 2000a). In tissue banking at least, implementation can be seen as a combination of the standard adapting to practice, and practice evolving to fit the standard.

Organisations can influence the implementation of standards in two different ways: the first is through the actions of external organisations (such as funders, regulators or publishers) and the second is the through the features of implementing organisations. Thus, the external actions can be distinguished from internal features.

The actions of external organisations

The five key actions of external organisations (those not directly conducting tissue banking) that emerged were: requiring implementation, providing incentives, putting in place an enforcement strategy, providing education and disseminating effectively. I found that the organisations with the most influence over tissue banks were funders, formal networks and publishers; professionals felt that because they acted as gatekeepers to funding, collaboration or publication, they were in an ideal position to
impose requirements through terms and conditions or agreements. This confirms previous research showing that funders were key oversight bodies (see Chapter 1, Gibbons and Smart 2012c) and expands previous reports on the limited initial actions of publishers in the field (Pisani and Abou-Zahr 2010). The impact of formal networks was previously hypothesised but not investigated (Meir et al. 2011).

While professionals repeatedly referred to these organisations as having the potential to take effective actions to ensure standards are implemented, this has not taken place, probably due to a lack of resources. Scotland was an exception as a government body/funder has begun its own programme to harmonise tissue banks. Funders, in particular, were called upon to provide the ‘carrot’ or ‘stick’ to encourage tissue banking standards to be followed (Chapter 6). This is also the case for other scientific endeavours: commentary on a consortium that worked to create an encyclopaedia of functional DNA elements made the point that the functioning of the consortium would have been much improved if funders had updated their standards on data sharing and had enforced their terms and conditions (Birney 2012). Potentially, the *Funders’ Vision for Human Tissue Resources* (UKCRC 2011) represents the first step to greater involvement of funders in tissue banking standards.

Having a strategy for the enforcement of standards, whether through sanctions, licensing, inspection, self-assessment or reporting, is a critical element underpinning the implementation of standards, as predicted in theoretical literature on standards (Busch 2011, Timmermans and Epstein 2010, Heimer 2008) and evidenced here in relation to tissue banking. Sanctions such as threats of jail or fines, in particular, were effective in terms of being repeatedly mentioned as a concern by professionals, but the option of providing these appeared to be limited to regulators supported by legislation. Networks, for example, reported not having the power to impose sanctions greater than deciding that an organisation should not be part of the network, while tissue banks did not give more tissue to an organisation that breached standards previously (Chapter 6). An explanation for why sanctions are effective is that they are a type of punishment, and the threat of punishment may, in the right circumstances, encourage cooperation (Nowak 2006, Holt 2006).
However, my results additionally corroborate previous findings that extreme threats of punishment could disincentivise adherence to standards. The most prominent example of this was the sanctions (fines and imprisonment) in the Human Tissue Act (2004), described by many of my participants (and prior research, Pathological Society 2010) as a disincentive to taking part in research and not proportionally reflecting the nature of the crime. Busch (2011) illustrates this type of scenario by using the example from *Les Misérables* (Hugo 1864) where a French peasant is jailed for 19 years for stealing a loaf of bread. The evidence I present, combined with that of other studies, indicates that the sanctions in the Human Tissue Act (2004) could be reconsidered to ensure that they do not unduly affect research.

I show that some external organisations combined more than one type of ‘action’ to support implementation. A popular approach which appeared to be effective was to take what I term an ‘education plus enforcement’ strategy. The types of education included training courses (face-to-face and online), telephone advice lines or guidelines. An ‘education plus enforcement’ strategy is used by organisations conducting clinical trials involving tissue collection across multiple centres, who often provide local centres with education in the form of advice and training on clinical trial protocols, and incorporate elements of enforcement in the form of reporting and monitoring (Chapter 6). This strategy is required for adherence to Clinical Trials Directive 2001/20/EC (Article 15) and Good Clinical Practice (GCP) Directive 2005/28/EC (Article 2) which require inspections to verify compliance with GCP standards and appropriate training for individuals conducting trials.

An additional method that external organisations used was provision of incentives in the form of money, personnel or equipment, to encourage the standards to be followed and the tissue supply chain to work. The practice of third parties incentivising standards to be followed through payments is common (Timmermans and Epstein 2010), but it has not previously been extensively discussed in relation to tissue banking.
The features of the implementing organisation

Features of organisations were important for supporting implementation internally. Critically, I was able to corroborate literature (onCore UK 2009b, Gibbons and Smart 2012b and 2012c, Greenhalgh et al. 2004, 2008) that suggested the right amount of support was needed in terms of: prioritisation of tissue banking; the involvement of high-level professionals; and the provision or availability of resources in terms of facilities, equipment or person hours. The NHS had deficiencies in all areas, again anticipated by the literature review (UKCRC 2011, Jackson et al. 2009), which is of concern since my research demonstrated that NHS trusts are the main site for tissue collection (Chapter 4). My data revealed that for tissue banking, NHS trusts with high-level executive support were able to change and implement new standards when necessary, but in many cases in the NHS the clear priority was clinical care (followed by clinical trials) and budgets were tight (Chapter 6). I also show that NHS management support for tissue banking varied, and in some cases did not penetrate from the highest levels through to the middle management responsible for day-to-day practice.

The study results should be considered in the wider context of the NHS currently being a “difficult and unpredictable place” in which to conduct health-related research (The Academy of Medical Sciences 2011). The model of diffusion of complex innovation in the health services (Greenhalgh et al. 2004) assists with the interpretation of my findings. The lack of prioritisation in the NHS can be seen as not having “innovation-system fit”, or alignment between organisation goals and the standard being implemented (Greenhalgh et al. 2004). Similarly, “slack resources” are not available in the NHS, and these are required for adoption of innovations (Greenhalgh et al. 2008). The need for strong leadership and good managerial relations to implement innovations in the NHS was also shown to be important (Greenhalgh et al. 2008) and inconsistent or lacking leadership can be a barrier to adoption (Department of Health 2011).

Additional internal features of implementing organisations that my study verifies enable or cause barriers for implementation are: the need for cooperation between the organisation’s departments; the number and location of different sites; and the
importance of interactions with other organisations. Two common examples of non-cooperation between groups or departments arose from my research. The first was non-communicative IT departments, a problem when tissue banking standards are technical, the second example was of research groups within organisations not collaborating and not able to agree on the need to implement standards (Chapter 6). Broader work on diffusion of innovation in service organisations shows that intra-organisational communication is one way of enhancing the potential for implementation (Greenhalgh et al. 2008), and I provide evidence to support this in the context of tissue bank harmonisation by describing a pharmaceutical company that had taken the time to build connections between research groups and departments in order to drive and support harmonisation initiatives. This evidence expands upon reports by pharmaceutical companies who have brought together departments to develop and implement standards: Pfizer established connections between tissue banking and informatics divisions in order to develop a database (McDonald, Velasco and Ilasi 2010).

A further important influence on tissue bank standard implementation was the number of sites and facilities involved, especially when some of these were abroad. Because samples decay rapidly after removal from an individual (Jackson and Banks 2010), I found that hospitals normally place the samples into formalin in surgical theatres to prevent structural change to the tissue during transport (placing samples into formalin was indicated as the norm by Riegman et al. 2006). This was more likely when surgery and pathology were located further apart, for example NHS trusts with several hospitals only had a pathology department in one of them. I showed that this leads to problems when implementing standards that require the use of fresh, unfixed, tissue in research, when professionals recommended that pathology was located close to surgery (Chapter 6). For companies with sites outside the UK, I corroborated literature describing the additional complication of navigating differing ethical and legal requirements (Wallace, Lazor and Knoppers 2009, Wolfson et al. 2010, Tassé et al. 2010).

Since I show that the tissue supply chain encompasses different types of organisations (Chapter 4), it follows that effective cooperation is required to implement a standard
across them. Literature on adopting innovations highlights that intra-organisational collaboration creates pressure for collaborators to adopt innovations (Greenhalgh et al. 2004, Department of Health 2011). In tissue banking, I show that the most popular type of collaboration was between hospitals and universities; the wider importance of this type of collaboration for cancer research has been recognised in the UK, and it underpins the network of the Experimental Cancer Medicine Centres (ECMC 2010). However, I note that for tissue banking, university-hospital collaborations were hindered by access, communication, technical and funding problems (Chapters 4 and 6), indicating that there is still work to be done to encourage smoother collaboration.

**Outcomes of implementing standards**

Perhaps counter-intuitively, the outcome of successfully implementing standards was not always harmonisation. In Chapter 6 I describe three negative consequences of implementing standards, and the first two relating to fragmentation and overlaps are new observations in relation to tissue banking. The first consequence was that generic standards such as those found in the Human Tissue Authority Research Sector Standards could create disintegration when those implementing them interpreted the provisions differently and put in place different solutions. In such cases a claim could be made that policy-level harmonisation has taken place rather than more in-depth technical or procedural harmonisation.

This description of a generic standard seen as causing fragmentation contributes another illustrative example to assist with understanding the possible outcomes of standards. Another relevant example is the European Clinical Trials Directive 2001/20/EC, where the outcome to implementation was legislative differences between EU member states and consequent obstacles to the conduct of clinical trials (European Science Foundation 2011). The model of ‘minimum harmonisation’ that European law often follows can lead to “a fragmented pattern of laws (Weatherill 2011, 851)”. In a sense, the standards themselves can create a barrier to harmonisation if they are of a policy type and implementation is a requirement.

The second way implementing standards caused problems was through overlapping with other standards, resulting in multiple layers of overlapping standards. I provide
further examples to complement those already in the standards literature (for example, Bowker and Leigh Star 2000) and show that international sample annotation standards such as SPREC overlap and one has not emerged as dominant in terms of being incorporated into practice. This not only leads to a battle of the standards that commentators assure us will not necessarily lead to the victory of the most worthy or appropriate standard (Bowker and Leigh Star 2000), but also incrementally makes harmonisation (and agreement between those who created the standards) at a country or international level less likely (Chapter 6). A process of ‘negative harmonisation’ that removes or amalgamates some of the standards could facilitate harmonisation (Enriques and Gatti 2006).

The third problem was that implementation can lead to exclusion or marginalisation – the potential for these unexpected negative consequences is a common concern (Timmermans and Epstein 2010, Dunn 2005). A standard that is developed or worked in one context may not work in others (Lampland and Leigh Star 2009). The example of the Human Tissue Act (2004) contributes towards an understanding of the types of marginalisation possible as a result of legislation, and I illustrated how implementation has led to the exclusion of Scotland and data from governance around tissue research, the marginalisation of pathologists and potentially a reduction in the number of small tissue research projects (Chapter 6). Combined with other research and commentary that highlights the exclusion of Scotland, the potential damage to smaller research projects and the perception of the law as an external threat to pathologists (McLean et al. 2005, Pathological Society 2010, Cronin et al. 2011, Furness 2006, Warlow 2005), indicates that issues of scope and treatment of smaller research projects in the legislation could be re-thought. The debate about exclusions raises the question of whether harmonisation or inclusivity is more important.

A further finding when linked to tissue banking standards was that many professionals in my study considered the potential outcome of implementing the Human Tissue Act (2004) before deciding to engage with it. At the extreme this meant that professionals stopped undertaking the activity (or did it a different way) when they had no choice but to engage, which corroborates findings from previous research (Chapter 1). This finding is also consistent with the literature suggesting that the extent to which
individuals view a novel technology or standard as an advantage or disadvantage is linked to successful adoption (Greenhalgh et al. 2004, 2008, Brunsson and Jacobsson 2000a). Thus, those designing or implementing a tissue banking standard should consider how to offer an advantage to tissue banks who adopt it (Greenhalgh et al. 2008).

**Political, social and technical complexity**

Political, social and technical complexity cut across all of the discussions above, and while acknowledging that more sources of complexity may exist, this section expands upon and explains the nature of these. Complexity exists within both the practice of tissue banking and the process of harmonisation; consequently both intertwine somewhat in the accounts below.

**Politics**

This thesis provides confirmation and new, more explicit, examples of how ‘politics’ are important during the standard creation phase for tissue banking standards, a factor previously acknowledged in tissue banking and other contexts (Bowker and Leigh Star 2000, Lampland and Leigh Star 2009, Holmes et al. 2010, Maschke and Murray 2004). I consider politics from both national and organisational perspectives; national as far as it creates legislation, and organisational in terms of the different groups that take part in projects working to harmonise. Politics locally, within organisations, also influences implementation, but is not a major focus of the analysis.

**Standard creation – national**

National political pressure was a powerful tool to create and implement standards, exemplified by my finding that the Human Tissue Act (2004) was the most influential standard in the area (Chapters 4 and 6). This influence was exemplified by new empirical evidence that the Human Tissue Act (2004) had forced differences in practice. This result is different to conclusions made by previous research which found that professionals, in particular pathologists, did not view the Human Tissue Act (2004) as having a direct influence upon them (McLean et al. 2005). The difference in my
study is likely due to the timings, my research was conducted after the legislation had taken affect and so its impact could more easily be considered.

As considered in the section on enforcement above, part of the power or legislation lies in its ability to impose strict penalties resulting in fines or imprisonment, something that other organisations such as networks were unable to do. More broadly, regulation is perceived as a type of top-down pressure that encourages diffusion of innovations (Department of Health 2011); a “following policy wind” is an incentive adoption of innovations (Greenhalgh et al. 2004 and 2008). However, the use of legislation also leads directly to negative outcomes because the nature of law as rigid, unable to evolve and difficult to amend is cause for concern about its ability to achieve harmonisation; law can create stagnation or petrification (Enriques and Gatti 2006, Tridimas 2011).

Debate in the House of Lords Grand Committee (2011) re-confirmed that the government does not intend to modify the Human Tissue Act (2004). After the legislation addressed the practice of retaining organs that culminated in the Human Tissue Act in 2004 (Whitman et al. 2008) the use of human tissue, and in particular tissue research, was no longer seen as a social problem and, as a result, is no longer high on the political agenda (Meir et al. 2011). After the public outcry has disappeared, has the law formed an inappropriate and cumbersome burden or “regulatory tombstone (Lodge and Hood 2002, 1)”? The nature of law is that it is fundamentally reactive (Busch 2011), but is it an overreaction in this case?

In my research, a particularly criticised aspect of the legislation was the classifications, which took the form of decisions about scope or definitions (Chapter 6). The criticism was not consistent – in some cases further, more in-depth, classifications were requested, and in other cases fewer (Chapter 6). Such criticism was anticipated by commentators including Parry and the Academy of Medical Sciences who described the potential detrimental impact for research of confusing or unreasonable definitions in the tissue legislation (The Academy of Medical Sciences 2011, Parry 2005), but what my research shows is that professionals have divergent views and achieving reconciliation will be an important focus for future work.
Classificatory issues have been shown to be important in other research contexts, for example the decision to include small investigator-led studies within the definition of interventional clinical trials in the Clinical Trials Directive 2001/20/EC. This inclusion had the result that smaller trials had to follow all the requirements of larger trials even though they did not have the capacity to do this (European Science Foundation 2009). A common complaint in relation to these trials, and one levelled against the Human Tissue Act (2004) in my research in terms of the treatment of smaller projects, is that a ‘one size fits all approach’ is not always suitable (European Science Foundation 2009). Classificatory decisions are important to study in relation to standards as every standard imposes a classification system that can have an impact upon individuals (Bowker and Leigh Star 2000).

National political developments in the UK have begun to draw attention to the importance of research taking place in the NHS (The Academy of Medical Sciences 2011 and 2013, Department of Health 2011, 2012 and 2013a, Department for Business, Innovation & Skills 2011 and 2012). Since my research, the importance of conducting research to improve healthcare has been embedded into the NHS constitution (Department of Health 2013b). This strong ‘policy wind’ may support tissue banking and related harmonisation going forwards.

**Standard creation – organisational**

My thesis confirms the idea that creating standards is very much “a process of negotiation among different conflicting interests (Timmermans and Epstein 2010, 191)” I show for the first time that the organisations involved in creating standards for tissue banks (Figure 5-2) were not always those with a strong direct involvement in the tissue supply chain (Figure 4-1), a disconnect partly explained by politics, and which resulted in some potential stakeholders being excluded. The organisations involved had varied and competing rationales for taking part in tissue banking harmonisation efforts, as anticipated but not enunciated by Maschke and Murray (2004). I expanded on this by describing organisational roles and rationales in detail.

Funders had the largest influence and presence in standard creation projects, often initiating projects and sitting on their executive boards. This mirrors their significant
involvement in the tissue supply chain. Funders had particular interests in not duplicating tissue collections and encouraging efficient use of the samples (Chapter 5) and funder politics were important; in Chapter 5 I introduced several examples of standard creation initiatives that ceased or changed following decisions from funders. Few examples in related literature recognise the importance of funder’s involvement in standard creation (although see Birney 2012), though they have noted the considerable influence of funders over researchers (Gibbons and Smart 2012c). Funders are rather asked to promote the standards after creation has taken place (Holmes et al. 2010). Despite their prominence, I demonstrate a lack of harmonisation across the funding sector, for example on terms and conditions or national funding schemes. Funders had little to do with later implementation, and chose to place few requirements on researchers in this regard (Chapter 6). I conclude that involvement of funders is crucial, but they lack coordination and do not have a unified approach.

In terms of the disconnect between who was involved in tissue supply but not involved in harmonisation, several organisations did not play a large part in harmonisation efforts, including: NHS hospitals, National Research Ethics Service (now the Health Research Authority), the Human Tissue Authority, contract research organisations or suppliers. Previous publications have not described the involvement of these types of organisation in similar harmonisation efforts (Webster and Eriksson 2008, Holmes et al. 2010, Hogle 2009), but in this context they are crucial as they are part of the supply chain. I noted that the pharmaceutical industry were only somewhat involved in harmonisation and its main UK involvement was in a project that did not involve the exchange of samples and which aimed to improve the availability and quality of tissue and data: STRATUM (Strategic Tissue Repository Alliance Through Unified Methods). This limited involvement is explained by the observations that pharmaceutical companies appears to only be interested in collaborations if it could receive and retain samples, and is not interested in supporting efforts linked to sample sharing unless this is linked to in-house research (Chapter 5).

I show that the extensive involvement of formal tissue banking networks (including the International Society for Biological and Environmental Repositories – ISBER) both nationally and internationally in harmonisation had both positive and negative
outcomes for harmonisation. Positive outcomes were that standards could be produced based on the extensive experience of members, and with involvement from potential users (Chapter 5). The significant negative outcome was that non-members (such as patient organisations, tissue supply intermediaries, publishers or standards organisations) were rarely involved in standard development. A disconnect also occurs here because these bodies are identified as being important for the tissue supply chain or its harmonisation (Chapters 4 and 5).

The lack of involvement of patient organisations is a major problem. In the age of what Rose and Novas (2005) term the “active biological citizen”, patients are forming communities and campaigning to support tissue banks. Commentators describe the patient as essential for the success of tissue banking (Gaffney, Madden and Thomas 2012). Patient representatives are rarely involved in wider harmonisation activities, yet I show that in some cases they have set-up independent tissue banks and harmonisation projects (Chapter 4). Some discussion had taken place on how to include the public within tissue bank governance frameworks (see for example UKBiobank Ethics and Governance Council 2009), but no agreement has been reached.

A lack of inclusion of the public in decision-making may be common to other types of standards affecting research: the International Conference on Harmonization (ICH) did not include patient organisations when writing guidelines on good clinical practice for developing interventional medicinal products, instead it allowed the pharmaceutical industry and government regulators to dominate the discussion (Maschke and Murray 2004). The balance needed between scientific ‘experts’ and members of the public or patients still needs to be resolved more generally when developing standards relating to scientific practice (Holmes et al. 2010, Winickoff and Bushey 2010).

Unlike tissue banking harmonisation projects, other scientific harmonisation projects involve publishers, journal editors (Holmes et al. 2010) or standards organisations (Timmermans and Epstein 2010, Hogle 2009, Tamm Hallström 2000) in the creation phase. One problem with the involvement of standards organisations is the massive scale at which they operate (Hogle 2009) which can itself lead to exclusion because people cannot afford to attend the meetings or take part (Busch 2011), and public
representation may be limited (Holmes et al. 2010). Despite this, my literature review (Chapter 1) and research (Chapter 4) shows that tissue banks will adopt even irrelevant standards developed by the International Organization for Standardization (ISO) in order to increase external confidence in the tissue bank. If a relevant standard could be developed by ISO this is likely to be widely adopted by tissue banks and would offer a level of international harmonisation, but it would be important to ensure that all relevant stakeholders were included.

**Social factors**

My research shows that both the functioning of the tissue supply chain and the development of related standards were heavily influenced by social factors. Tissue bank managers often undertook what I refer to as ‘relationship management’ to coordinate many individuals and organisations across the supply chain (Chapter 4), which corroborates the idea that tissue banking requires a high level of collaboration and “social manoeuvring” (see Hoeyer 2012, 211 and Meir et al. 2011). In my study I developed these ideas and catalogued how tissue bank managers and their staff used negotiation, favours, incentivising and sweet-talking to maintain the tissue supply chain (Chapter 4). I also showed how blockages occur if the cooperation between parties breaks down and to counter or prevent this, tissue banks employ staff capable of supporting and developing these connections. Collecting fresh tissue collection for researchers was a good example of the challenge of relationship management along the supply chain in a busy hospital environment as the speed in which the collection and distribution has to happen (a few hours) is particularly difficult (Chapter 4).

Individual social factors influenced how professionals implemented and followed standards along the tissue supply chain. Previous research described the altruism of patients in donating their tissue and data to tissue banks (Cragg Ross Dawson 2000, Sumner 2007) or clinical blood banks (Healy 2006), but neglected that same crucial characteristic in professionals (also noted as being rarely acknowledged in Dixon-Woods et al. 2008). I contribute towards a new understanding of how, consistently with definitions of altruism found in the literature (Healy 2006), many professionals were involved in the tissue supply chain in order to support research despite this being
outside their job description and obtaining little or no reward (Chapter 6). A need for “commitment” from tissue banking professionals was described by Gaffney et al. (2012) and Meir et al. (2011), but my study empirically illustrates how professionals often exhibit altruistic traits that reach further than ‘commitment’ for the tissue supply chain to be successful and related SOPs followed.

I describe three challenges to altruism in professionals (see Chapter 6) that form a novel conceptual understanding of the challenges for altruistic professionals involved in tissue banking and related harmonisation activities. The first was the competing requirements of the academic research environment, with the need to publish results and build reputations often outweighing the desire to share and collaborate with individuals who might be potential competitors. This aligns with literature describing barriers to data sharing, which highlights the demotivating aspects of a ‘publish or perish’ culture (Chapter 1). A general solution provided to counter this challenge in my research was to improve recognition of the contribution made by professionals to tissue banking. Examples in the literature describe the development and use of individual professional and tissue bank identifiers in projects, funding applications and publications (Cambon-Thomsen, Thorisson and Mabile 2011, Haak et al. 2012).

The second challenge was feelings of ownership in relation to tissue samples (Chapter 6). Ownership of tissue samples has a long history of discussion in the legal literature, which has been inconclusive as to who has property rights over what (Hoeyer 2012). In my research ownership feelings were expressed by professionals (whether surgeons, pathologists or researchers) collecting or holding the samples who wanted to retain control of samples, or expressed a preference for them to be used only by local researchers (which I termed ‘localism’). Tissue banks provide two types of incentives to contributors to address the desire for control: either they reserve a portion of the samples for the contributor to use, or they require that all researchers must collaborate with the originator of the samples (Chapter 6). My research indicates that the main reason underpinning the professional’s desire for control over use of the samples is a desire for ‘fairness’, or getting some return for the time and effort put into collection (Chapter 6). Commentators describing their own experiences also refer to the need for some type of “fair compromise” between collectors and users over access.
to samples (Meir et al. 2011, 280). Thus, it is clear that the interests of collectors should be recognised when considering access to the samples, a point also made in a report by the Nuffield Council on Bioethics (2011).

The final challenge to altruism was resistance to change or rules (Chapter 6). I provide examples of researchers who show little inclination to engage with standards in general, as well as those who do not agree with particular aspects, for example, consent requirements. Some empirical evidence exists describing professionals who deliberately choose not to engage with laws and guidance in the area of tissue banking (Gibbons and Smart 2012c), and researchers who feel they do not need to directly engage with human tissue legislation (McLean et al. 2005). I contribute to this research by adding details on why resistance might occur, for example because they feel that following standards is extra work and, as a result, research for the benefit of patients is slowed down (Chapter 6). I highlight that a particular problem when researchers are asked to change or follow new procedures is that they may perceive this as criticism of their existing procedures (Chapter 4 and 6). This adds to existing evidence; commentators have noted that a “territorial enforcement” of organisational rules and reluctance to change can occur in tissue banking (Meir et al. 2011, 281).

Literature suggests that resistance is more likely when voluntariness is low and that this also leads to criticism of the standard (Brunsson and Jacobsson 2000a). This could explain the criticism of the Human Tissue Act (2004), a legal requirement, I encountered. These findings contribute towards the complicated and nuanced understanding of resistance and acceptance of standards that exists in the wider literature (some examples include Timmermans 2003, Heimer 2008, Grol et al. 1998, Saario 2012, Piderit 2000, Ford, Ford and D’Amelio 2008, Foy et al. 2002).

Social factors were important when creating standards (Chapter 5); this supports claims in the literature that the process is “a social act” (Timmermans and Epstein 2010, 75). I corroborate research that shows individuals involved in designing tissue banking standards have to speak multiple ‘languages’ (in terms of technicalities and jargon) as they navigate the laboratory and IT, or the NHS and academia (Chapter 5)(Murtagh et al. 2011, Demir 2011). Professionals also reported using techniques akin
to social research as they ‘interview’ individuals for evidence to support standard development, and appear to be altruistic in manner, with energy and commitment to navigate the potentially lengthily and tedious work involved in creating a standard. Publications reporting the development of relevant standards rarely provide details on the characteristics and work of the individuals designing the standards (Fortier et al. 2010, Wallace, Lazor and Knoppers 2009), indicating that this may be a novel finding. I show that the relationship management skills important for facilitating the tissue supply chain are also crucial for coordinating people and negotiating and reaching consensus on related standards within or between organisations.

Finally, social factors influenced the implementation of standards, particularly through their dissemination through networks, role models and professionals’ peer groups. Application of social network theory demonstrates that the biomedical research community is densely connected, so news should theoretically travel fast through informal connections (Newman 2001). I confirm that an informal network of tissue banks exists in the UK, through which information on standards is disseminated (Chapter 4), anticipated in research described in Chapter 1. Additionally, I show that role models are influential for those in the tissue banking community, but the influence could be either positive (implement the standard) or negative (do not implement the standard)(Chapter 6). The importance of role models when undergoing change is highlighted in other contexts (for a summary see Greenhalgh et al. 2004).

Technical issues

I clearly demonstrate how technology is a ‘double-edged sword’ for tissue banking and harmonisation. On the one hand, technological solutions to problems such as how to locate human tissue or store data in a harmonised fashion are very useful. On the other hand, these solutions are not always straightforward to create and put into practice, and an increasing reliance of the tissue supply chain on technology leads to problems when it is unavailable or inaccessible. I outline the nature of this double-edged sword further below before focussing on the harmonisation of ‘data’, a major focus of relevant literature, and show how it is an area of confusion and complication in practice.
Technology already plays a large role in scientific practice; for example, Pickering (1995) describes scientific practice as a “dance” between humans and machines. When harmonising aspects of tissue banking, it is therefore unsurprising that technology such as online registers or computer databases were used (Chapter 5). Full automation, using machines, of the steps of sample processing and storage was one recommended way of guaranteeing the quality of the tissue (Chapter 4). UKBiobank is a high-profile example of a tissue bank that has chosen to automate (Downey and Peakman 2008), but in the smaller tissue banks included in my research it was not common. What technological solutions uniquely offer is the chance to build particular techniques or rules into the solution, ensuring implementation and compliance (Busch 2011, Timmermans and Epstein 2010). I show how this has been used in tissue bank harmonisation with examples including tissue bank databases that only accept certain data fields (Chapter 6).

The creation of technical standards is a complicated and time-consuming process (Pargman and Palme 2009) that sometimes fails (Greenhalgh et al. 2008). The main problem with developing technical standards for tissue banks is that the detailed discussion required to make the standard a good fit to a particular context takes both time and money (Chapter 5), also illustrated by the example of the National Cancer Institute cancer biomedical informatics grid in Chapter 1. Agreement is increasingly difficult to achieve as the standard gets more specific, and specificity is often a requirement for technical standards such as databases (Chapter 5). For the design of technical standards such as databases, tissue bank (user) involvement is absolutely crucial, as without this results are difficult to use or apply, making adoption and implementation difficult (Chapter 6).

The way that technology is enacted (c.f. Millerand and Bowker 2009) can cause problems for a tissue supply chain that increasingly relies on the use of technology (Chapter 4). Apparently simple operational issues, like collecting fresh tissue or data and transporting them to researchers, are in fact technically complicated. Collecting fresh tissue represents a technical challenge because it has to be labelled and transported immediately as the sample degrades quickly. Swipe cards are needed to
gain access to operating theatres in order to collect tissue, and participant consent forms (or even taking consent in some cases) require technology to scan, copy or fax the forms. Sample processing and tissue bank services use technology such as centrifuges, laser dissection microscopes or tissue microarray builders. All of these pieces of technology either enable or disable tissue banking depending on whether they are available or not. And when those pieces of technology are unavailable this causes massive hold-ups and backlogs for the tissue bank. Adding complication, I show that tissue banks often have dysfunctional relationships with the IT departments in the different organisation along the supply chain and cannot always afford to employ a member of staff with responsibility for IT.

My observations suggest that it is important not to overlook the significance of apparently mundane pieces of technological equipment and their contribution to supply chain functioning. The importance of taking account of mundane aspects that appear invisible is highlighted in other areas (Bowker and Leigh Star 2000, Woolgar and Neyland 2006). I show how this dependency of the tissue supply chain on increasingly complex technology is, in turn, making tissue banks reliant on the suppliers and IT departments for technological support or consumables (Chapter 4), which may be a novel finding in this area. This could be important for future consideration of who should be involved in harmonisation efforts.

Harmonisation of the data associated with tissue banks has been the subject of many projects and discussions internationally (see Chapters 1 and 2). My research confirms that professionals conducting research felt that high quality data must be collected along with the samples in order for them to be useful (Chapter 5). Yet I also provide detailed information about how and why it is difficult to collect data in the hospital context (for example due to the records being on paper or the time needed for patient interviews) and how desired links between tissue bank (often university-based) and hospital or cancer specific databases had not been achieved due to policies to protect patient data and resulting cybersecurity (Chapter 4). Forms were one solution to collecting data, but I show through in-depth exploration (Chapter 6), why forms can be unreliable.
Even after data is collected, I have demonstrated that tissue bank harmonisation aiming to unify databases will also be challenging due to the existence of multiple types of databases within tissue banks and hospitals (Chapter 4), already shown to be a problem for stratified medicine (The Academy of Medical Sciences 2013) and joined-up healthcare (Greenhalgh et al. 2008). Difficulties collecting data in hospitals may be solved subsequent to two policy documents that pledge to open up anonymised data collected within hospitals for research (Department for Business, Innovation & Skills 2011, 2012). However, amendments to the European Data Protection Regulation pose a threat to these movements towards sharing patient data for research (Taylor and Thompson 2014).

**Study Limitations**

This study has a number of limitations. One limitation of cancer tissue banking as a case study was that it was very broad, and as a result fine grain detail could not be collected and reported about specifics such as the exact contents of standards. As the case study progressed it became broader because cancer tissue banking was part of many professionals’ or organisations’ (for example the regulatory authority) roles and remits. Thus, future research could focus on specifics.

Elements of the research design had an impact on the results. As discussed in Chapter 3, the nature of many of the observations (the ‘go-alongs’) meant that natural practice was not always observed and the behaviour of those observed may have been modified in response to my presence, leading to uncertainty about whether the observations reflected normal practice (Mays and Pope 1995). Longer, more in-depth and less participatory observations might have allowed a more nuanced understanding of the everyday routine of tissue banking and the design and implementation of related standards. Despite this, the observations conducted provided useful information about where and how tissue banking took place, pragmatic issues and allowed under-researched support staff such as technicians a voice, contributing to a more contextualised account of tissue banking.
Chapter 7: Discussion

The main study limitations relate to sampling and which research sites or participants were, or were not, included in the study. While the major focus of the study on NHS hospitals in the UK was justifiable as they supplied the majority of the human tissue, their involvement in national or international efforts to harmonise was low. Thus, although the tissue banking supply chain was well characterised and implementation of standards considered, studying the creation of standards was difficult. Universities were frequently involved in larger harmonisation projects but these were difficult to study during the ‘go-alongs’. One solution was to attend the meetings held by harmonising organisations (meetings 1, 4 and 7), or gatherings of relevant stakeholders discussing how and what to harmonise (meeting 6). However, as noted by staff of harmonisation organisations during interviews, the main harmonisation activities took place behind the scenes of these meetings where it was impossible for me to access. Access to this sort of activity would require more long term shadowing of key individuals, but would run the risk of impeding ‘natural’ practice.

In-depth coverage of all professionals and organisations relevant to harmonisation was not attained during the study (for organisation and professional types involved, see Table A-9 and Table A-11 in Appendix 12). Notable examples included surgeons (and staff in surgery), health care managers, research governance staff, role-models like the Wales Cancer Bank, tissue supply intermediaries, contract research organisations, suppliers of goods or services for tissue banks and publishers. Only one harmonisation organisation (Bio-gov International) and one pharmaceutical company (BigPharma) were visited, leading to more limited/tentative conclusions concerning these actors. Limited access to these groups was partly because their importance only emerged during the course of the research and, despite repeated attempts, professionals did not respond or could not be located. On the other hand, conducting more observations and interviews would have generated too large a dataset to handle and analyse for a manageable PhD research study.

Sampling whist conducting ethnographic research within organisations also led to limitations in the topics covered. As discussed in Chapter 3 (data analysis), selection of deviant cases was an important step in analysing the results. However, as the research led to immersion in the field of professionals working towards harmonisation, it was
difficult to identify people that disagreed with it. It is difficult to guarantee that all potential arguments against harmonisation and standardisation were captured through the fieldwork. Furthermore, several topics identified as important in the literature review (Chapter 1) were not well-represented in the data, namely information on sanctions and enforcement and discussions on how to solve ethical dilemmas. This lack of coverage could be because few sanctions existed or because ethical issues did not arise as they were not considered widely in day-to-day practice.

**Recommendations for Policy and Practice**

My conclusions to the question of what influences the harmonisation of cancer tissue banks in the UK can be consolidated into eight recommendations for policy and practice that engage or address the factors that I identify as influences:

1. **Legislation and national schemes should be modified to better support tissue bank harmonisation**

   *Audience: Policy makers, professionals with an interest in tissue banking*

   The Human Tissue Act (2004) strongly influences tissue banking practice, but should be reconsidered and adapted in order to ensure that professions, types of research or geographical areas are not marginalised or excluded. Options suggested by my research include: reducing the severity of sanctions and reconsidering the scope of the law and the ‘one size fits all’ approach. Fragmentation caused by differential implementation of broad policy standards could be minimised by the Human Tissue Authority and the research community cooperating to produce more specific research sector standards. Further, inconsistencies in approach to tissue banks receiving ethical approval under the Research Tissue Bank (RTBs) scheme by hospital R&D departments should be remedied by intervention of the Health Research Authority. National schemes encouraging relationships between universities and hospitals for research purposes must address persisting social and technical barriers to cooperation.
2. **Influential organisations should take action to encourage harmonisation**

*Audience: Policy makers, professionals with an interest in tissue banking or designing or implementing standards*

Adherence to standards would improve if influential organisations (in particular funders, publishers and formal networks): required implementation (for example requiring data sharing before publication), enforced implementation (through sanctions, licensing, inspection or reporting), educated all involved (training courses, telephone lines or guidance) and disseminated information about the standards (via networks or conferences). Funders and formal networks should consider methods to improve enforcement, for example by introducing certification. Publishers should be further involved and require that minimal information standards are followed in relation to research reporting the use of samples and tissue banks. My research suggests that a useful strategy combines education and enforcement, as used in clinical trial management.

3. **The method of standard creation should be carefully considered**

*Audience: Professionals designing standards*

Professionals designing new standards must consider (as illustrated in the new model of standard creation, Figure 5-3): finding funding and support, who will work on the project (an executive committee structure was common), how to gather evidence and whether new experiments will need to be conducted, and how they will build consensus and finalise the standard. Of particular importance is who is involved and ensuring that all relevant interests are represented. Organisations typically underrepresented (see Figure 5-2) include: tissue supply intermediaries, contract research organisations, suppliers, patient organisations, publishers and standards organisations. Negotiation will be required as each group involved will have different priorities for the remit of the standard. The International Organization for Standardization (ISO) is influential for tissue banks and should be involved in designing standards. In the latter stages, close involvement of the end-user of the standard is critical to
ensure the standard is workable. The format of the standard should be considered, and different types are applicable depending on the remit of the standard: procedural, technical, contractual or policy. Drawbacks to some formats exist, for example, policy standards can be too generic to effect useful harmonisation.

4. **Context and outcomes should be considered when finalising the contents of standards**

*Audience: Professionals designing standards*

To ensure that the standards fit the context, professionals designing standards should be familiar with the local tissue supply chain (Figure 4-7, a model of the tissue supply chain, could be used as a guide). Amendments to the supply chain, for example to providing fresh tissue or adding services to researchers, will affect the types of standards required. As contexts can change initially, it is important for the standard to start small and evolve, for example through regular review. A flexible standard allows variation, which can be important for both tissue bank managers to maintain the supply chain and the researcher who may use new approaches to assist scientific discovery. Two design considerations avoid later negative outcomes: first, minimising overlap with similar standards, and second, eschewing confusing definitions and decisions on scope that could marginalise or exclude groups.

5. **Standardising data provides a solution for the harmonisation of tissue banks**

*Audience: Policy makers, professionals designing standards*

One route of harmonisation is standardising data about how the samples were collected, processed and stored in the form of a minimum information (MI) convention, thus allowing tissue banks flexibility of methodology and samples to be shared. Technical solutions can provide tools to support implementation of these standards through webpages or databases. However, overlapping MI standards and databases is a problem and a process of ‘negative harmonisation’ that removes or amalgamates these is required. While a focus on data can be useful, tissue banks are best considered both in terms of tissue
and data, and (especially policy and procedural) standards should aim to consider both.

6. **The social factors influencing the tissue supply chain and associated harmonisation should not be overlooked**

   *Audience: Tissue bank staff, professionals designing or implementing standards*

   Efforts should be made to recognise and facilitate the role of ‘relationship management’ in the tissue supply chain and associated standard creation, for example through negotiation, favours and incentivising. One solution is employing individuals who can develop connections and who speak the different ‘languages’ of laboratory, IT, NHS and academia. Those managing the tissue supply chain or generating related standards must be aware that the professionals involved are often acting altruistically, and that ways exist of encouraging and supporting this. Strategies include: ensuring professionals get recognition for their contributions; ensuring standards are fair and recognise the contribution of all parties involved; providing incentives such as reserving a portion of samples for the contributor; and highlighting the benefits to users of following the standards.

7. **Technological solutions for harmonisation should be used with consideration for the possible pitfalls**

   *Audience: Tissue bank staff, professionals designing or implementing standards*

   Technology could be viewed as a panacea for tissue banking harmonisation. Standards can be built into tools, for example through databases only accepting certain data formats, or sample quality procedures guaranteed by full automation of sample processing. But disadvantages to the use of technology exist, including that technical standards take time and money to develop, and relying on technology leads to both problems when it is unavailable or inaccessible and dependence on suppliers for technical support or reagents. One solution is for tissue banks or those creating standards to employ IT specialists or develop relationships with IT departments, but this is also difficult
due to lack of resources or non-cooperative IT departments. Thus, use of technology when harmonising should be viewed as a double-edged sword.

8. Implementing standards is more effective when the organisation has certain features

_Audience: Professionals implementing standards_

Organisations should support implementation via: prioritising tissue banking; involving high-level professionals; improving availability of resources in terms of facilities, equipment or person hours; encouraging cooperation within and between internal departments, especially with IT; reducing the number of sites, and especially those in different countries; and encouraging interaction with other organisations. Further, organisations could require the standard was followed, provide training, and employ enforcement strategies including sanctions, inspection and audit. For example, in the NHS further actions could be taken to support harmonisation, including: prioritising tissue banking, minimising variety between NHS Trust databases and clinical procedures, and providing resources to implement standards such as those arising from the legal requirement for informed consent.

**Future Research Possibilities**

This section describes two avenues of future research that would assist tissue bank harmonisation efforts. The first would develop a survey in order to measure the extent of occurrence of important viewpoints and findings stemming from this thesis and, as a result, provide further evidence (on a larger scale) to underpin decisions on what and how to harmonise in the UK. The second avenue would inform the development of a tool to support harmonisation activities. I outline the audience, rationale, outcome and method for each project below.

A survey could support policy makers and professionals designing standards by providing evidence of the breadth of the influences to harmonisation identified in-depth in this thesis. The survey would focus on collecting information on what and how to harmonise from professionals involved in, or influential in relation to, the
tissue supply chain. The outcome would be information that could underpin decisions on what to harmonise and support development of standards. More specifically, the survey could collect demographic indicators (including profession, organisation type and country) and information on: standards already in use; what type of standards are viewed as required at different points of the tissue supply chain and for its governance; the roles of professionals and the preferred roles of different organisation types in the harmonisation process; what type of standards are appropriate (i.e. technical, procedural, policy, contractual); and what characteristics the proposed standards should have (for example, flexible vs. standardised).

The survey would be quantitative and could be undertaken online. Distribution of the survey and dissemination of results would need to be done carefully using information from this thesis about the organisations and professional types involved in the tissue supply chain, with a focus on including those who are often under-represented, for example publishers, tissue supply intermediaries, and professionals working in laboratories. The results would update and expand previous surveys (Zika et al. 2011, Hirtzlin et al. 2003, onCore UK 2009b).

Second, the development of a tool, could be useful for tissue bank staff and professionals designing standards, as it will translate the findings of the thesis into a format usable by those developing or implementing standards in practice. Such a tool could be as simple as a check-list that professionals could use before they begin designing or implementing a standard, and throughout the process, to ensure that all factors that have the potential to influence harmonisation are considered. The factors included would relate to: the national context (for example joining networks or the equivalent of the Research Tissue Bank scheme), the local context and understanding the relevant tissue supply chains, what to harmonise, how to design the standards, and influential characteristics of their organisation (such as enforcement, education, prioritisation, support, resources and departmental cooperation). The methodological approach to tool development would be both qualitative and translational, and professionals would be observed and consulted during development.
Conclusion

This thesis clarifies and characterises the different kinds of factors that influence the harmonisation of cancer, and other, tissue banks. My in-depth study shows that a major reason why harmonisation has not taken place is because it is in reality a very complex tangle of interweaving issues. I have produced a new model of the tissue supply chain, through which I have shown that harmonisation efforts require navigation through attendant political, social and technical issues. The importance of the social aspects means that a degree of relationship management is required, especially when resistance or ownership concerns exist. Political elements underpin all activities; actors have different motivations for their own involvement, or for excluding others. Small technical problems emerged as having the potential to bring about an immediate blockage in the tissue supply chain; yet technology is also able to solve complicated harmonisation questions.

By drawing on Timmermans and Epstein’s (2010) concept of the creation and implementation phases of standards, I identified key factors that work towards and against harmonisation and those that work in both directions. By applying theories including Greenhalgh et al.’s (2004) model on diffusion of innovations in service organisations, I explained how factors such as the features of organisations implementing standards can lead to difficulties for harmonisation; for example, when there is a lack of support or leadership of high-level professionals or an organisation is distributed over numerous sites. At the same time these features enable harmonisation when leadership is present or when few sites are involved. Analysis of the findings led me to outline eight recommendations for potential strategies to assist with the harmonisation of tissue banks, and since the thesis shows that the data collected alongside the tissue samples is crucial for subsequent research, the recommendations apply to both.
APPENDICES

Appendix 1  Literature search
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Appendix 12 Characteristics of organisations, participants and meetings
Appendix 1: Literature Search

Review of literature started when I commenced my research in January 2010 and continued until the end of 2012. Studies or reports were included from 2013 onwards if these were brought to my attention by PhD supervisors or colleagues. By the time of submission in 2014 my reference management software, RefWorks, contained 716 references. The publications came from four major sources:

1. Formal searches of databases including SCOPUS, Medline and EBSCO Business Premier. I used the ‘most cited’ search functions or looked for review papers. When key papers were retrieved I considered the references used by those papers and searched for the most relevant – a process termed ‘snowballing’ (see Table A-1 for examples).

2. Academic input from individuals or projects, recommending their own or other publications related to my study (see Table A-2).

3. Attendance of training courses, which was particularly useful for methods papers and textbooks (see Table A-3).

4. Email alerts and news bulletins from numerous sources. This often led to grey literature such as policy documents (see Table A-4).

Other less formal sources included meetings and the webpages of major authors, projects, organisations or funders.

Despite the organised searches and snowballing, the majority of publications were provided to me as a result of academic input, especially at a theoretical level.

Table A-1 Examples of organised searches and ‘snowballing’

<table>
<thead>
<tr>
<th>Date</th>
<th>Search details</th>
<th>Results found</th>
<th>Snowballing</th>
</tr>
</thead>
<tbody>
<tr>
<td>July 2010</td>
<td>SCOPUS searches on harmonisation AND process, limited to social sciences/biological sciences subject areas</td>
<td>3 key results</td>
<td></td>
</tr>
<tr>
<td>Aug 2010</td>
<td>SCOPUS search for most cited articles in journal <em>Research In Organizational Behaviour</em></td>
<td>2 key</td>
<td>Yes – 1 further source found</td>
</tr>
<tr>
<td>Date</td>
<td>Search details</td>
<td>Results found</td>
<td>Snowballing</td>
</tr>
<tr>
<td>----------</td>
<td>-------------------------------------------------------------------------------</td>
<td>---------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Aug 2010</td>
<td>SCOPUS author search ‘Naomi Pfeffer’</td>
<td>2 key</td>
<td>Further 7 results</td>
</tr>
<tr>
<td>Aug 2010</td>
<td>Looked at back issues of Cell and Tissue Banking from 2008-2010</td>
<td>2 key</td>
<td></td>
</tr>
<tr>
<td>Sept 2010</td>
<td>Searched through back issues of Cancerworld</td>
<td>4 key</td>
<td></td>
</tr>
<tr>
<td>Sept 2010</td>
<td>Used SpringerLink to search for authors citing Ravid R (2008)</td>
<td>1 key</td>
<td></td>
</tr>
<tr>
<td>Oct 2010</td>
<td>Snowballed references from Timmermans S (2010)</td>
<td>5 key</td>
<td></td>
</tr>
<tr>
<td>Jan 2011</td>
<td>Looked at back issues of the Journal of Contemporary Ethnography</td>
<td>3 key</td>
<td></td>
</tr>
<tr>
<td>May 2011</td>
<td>Searched J Clin Pathol for ‘tissue bank’</td>
<td>2 key</td>
<td></td>
</tr>
<tr>
<td>June 2011</td>
<td>Searched the British Library Catalogue for ‘Biobank’ and ‘Tissue Bank’</td>
<td>20 key, incl. 1 special edition</td>
<td></td>
</tr>
<tr>
<td>July 2011</td>
<td>Searched the British Library Catalogue for ‘Human Tissue Act’</td>
<td>5 key</td>
<td></td>
</tr>
<tr>
<td>July 2011</td>
<td>SCOPUS search for ‘Human Tissue Act’</td>
<td>3 key</td>
<td></td>
</tr>
<tr>
<td>Nov 2011</td>
<td>Snowballed references from Yuille M (2009)</td>
<td>5 key, incl. 1 special edition, 1 special edition</td>
<td>Further 2 results</td>
</tr>
<tr>
<td>Mar 2012</td>
<td>SCOPUS search for human tissue supply chains, supply chains and life-cycle</td>
<td>3 key</td>
<td></td>
</tr>
<tr>
<td>Mar 2012</td>
<td>Mary Ann Liebert publishers website for tissue supply chain and tissue life cycle</td>
<td>1 key</td>
<td></td>
</tr>
<tr>
<td>Mar 2012</td>
<td>Search on EBSCO Business Premier for ‘endowment effect’ and WTA (willingness to accept) or WTP (willingness to pay)</td>
<td>4 key, 3 were reviews</td>
<td></td>
</tr>
<tr>
<td>May 2012</td>
<td>Search on Medline, google scholar, web of knowledge ISI, University of Leicester library catalogue, Ingenta connect, for cancer treatment and surgery or choice</td>
<td>5 key</td>
<td></td>
</tr>
<tr>
<td>June 2012</td>
<td>Snowballed Technopolis Report 2010</td>
<td>4 key</td>
<td></td>
</tr>
<tr>
<td>June 2012</td>
<td>Search on EBSCO Business Premier, SCOPUS and google scholar for life cycle management. In SCOPUS looked at most cited</td>
<td>3 key</td>
<td></td>
</tr>
<tr>
<td>June 2012</td>
<td>SCOPUS search for business process model (most cited)</td>
<td>3 key</td>
<td></td>
</tr>
</tbody>
</table>
### Table A-2 Academic input

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Type of papers or books</th>
<th>Dates</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhD supervisors</td>
<td>Key papers in field. Further theoretical papers, but also those on standards, science, law and ethics and tissue banking. Examples of writing also sent.</td>
<td>Jan 2010 – Dec 2013</td>
</tr>
<tr>
<td>Academic colleagues at University of Leicester</td>
<td>Theory, methods, examples of their own work. Tissue banking law and ethics. Some scientific input on nature of cancer.</td>
<td>Jan 2010 – Dec 2013</td>
</tr>
<tr>
<td>Previous project at the University of Leicester</td>
<td>Given access to the references database of a relevant project. I exported 36 references.</td>
<td>Feb – March 2011</td>
</tr>
<tr>
<td>Academic contacts outside the university</td>
<td>Examples of their own work, recommendations of useful papers e.g. on law and governance and the structure of the NHS</td>
<td>Jan 2010 – Dec 2012</td>
</tr>
</tbody>
</table>

### Table A-3 Training courses giving rise to new literature

<table>
<thead>
<tr>
<th>Dates</th>
<th>Course details</th>
<th>Type of literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>29/01/10 – 05/03/10</td>
<td>MRes in Applied Health Research Module 3: Qualitative Methods in Applied Health Research course</td>
<td>Methods papers and textbooks</td>
</tr>
<tr>
<td>22/06/10</td>
<td>Intrepid Researcher: Visual-ising Research, Pat Thomson</td>
<td>Methods papers and textbooks</td>
</tr>
<tr>
<td>23/06/10</td>
<td>Intrepid Researcher: What is Ethnography? Martyn Hammersley</td>
<td>Methods papers and textbooks</td>
</tr>
</tbody>
</table>
### Appendices

<table>
<thead>
<tr>
<th>Dates</th>
<th>Course details</th>
<th>Type of literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>05/07/10 – 08/07/10</td>
<td>4&lt;sup&gt;th&lt;/sup&gt; ESRC Research Methods Festival</td>
<td>Methods papers and textbooks</td>
</tr>
<tr>
<td>Oct – Nov 2010</td>
<td>Open University Ethnography Course (linked to other staff member)</td>
<td>Methods papers and textbooks</td>
</tr>
<tr>
<td>02/11/11 – 03/11/11</td>
<td>Introduction to Cancer: Anatomy, Biology and Treatments course, National Cancer Research Network</td>
<td>Scientific textbooks</td>
</tr>
<tr>
<td>23/01/12</td>
<td>Intrepid Researcher: Revealing Social Structures Through Social Network Analysis: Techniques, Applications, and Critique, Steve Conway</td>
<td>Methods papers and textbooks</td>
</tr>
</tbody>
</table>

### Table A-4 Email alerts and news bulletins

<table>
<thead>
<tr>
<th>Alert type</th>
<th>Details</th>
<th>Field of interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Academic</td>
<td>SCOPUS, search for ‘tissue bank’, ‘biobank’ and ‘genetic database’, arrived weekly</td>
<td>Science, technology, medicine, social science</td>
</tr>
<tr>
<td>Academic</td>
<td>Table of contents alerts from journals including Science, Journal of Medical Ethics and the Journal of Law and Policy</td>
<td>Science, law, ethics</td>
</tr>
<tr>
<td>Academic</td>
<td>Alerts from the Journal of Biopreservation and Biobanking</td>
<td>Biobanking</td>
</tr>
<tr>
<td>News</td>
<td>Bionews, weekly news digest</td>
<td>Human genetics</td>
</tr>
<tr>
<td>News</td>
<td>Becky’s Policy Pages</td>
<td>Linked to UK policy of medical research</td>
</tr>
<tr>
<td>News</td>
<td>The Association of Medical Research Charities Blog</td>
<td>Linked to UK policy of medical research</td>
</tr>
<tr>
<td>News</td>
<td>BRIF newsletters</td>
<td>Biobanking</td>
</tr>
<tr>
<td>Updates</td>
<td>Human Tissue Authority newsletters</td>
<td>UK law</td>
</tr>
<tr>
<td>Updates</td>
<td>Confederation of Cancer Biobanks – newsletters and other alerts relating to meetings etc.</td>
<td>UK cancer biobanks</td>
</tr>
<tr>
<td>Updates</td>
<td>MedSocNews – alerts relating to meetings, posts</td>
<td>Medical sociology</td>
</tr>
<tr>
<td>Updates</td>
<td>Eurograd – alerts relating to meetings, posts</td>
<td>Science and technology studies</td>
</tr>
</tbody>
</table>
Appendix 2: Ethics and Governance Process Timeline

Introduction

The University of Leicester requires that ethics review is sought for sociological research involving human subjects. My application to the University of Leicester Research Ethics Committee was for all data collection that took place outside NHS premises, including: interviews with or observations on staff from universities, funders, regulatory agencies or pharmaceutical companies; visits to tissue banks outside the NHS; and observations at meetings and conferences.

A separate NHS ethics approval was required for research that involved NHS staff or premises. Alongside this, for each trust a discussion had to be held with, and potentially application made to, trust Research Governance offices. For a timeline of the applications and outcomes see Table A-5 below.

As applications to the university and the NHS ethics committees were made independently, each evolved separately (following requirements or queries from the ethics committees), and as a result differed slightly. For the documents approved for the university application see Table A-6 and for the NHS application see Table A-7.

Table A-5 Table summarising ethics and governance procedures followed

<table>
<thead>
<tr>
<th>Date</th>
<th>Activity</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>03/04/2009</td>
<td>Project accepted for adoption onto the NIHR Portfolio</td>
<td>Recruitment data was posted every month during recruitment phase</td>
</tr>
<tr>
<td>21/05/2009</td>
<td>First approval from NHS REC ethics committee (project ref. 09/H0406/70)</td>
<td>The original PI left the project and no further research was conducted</td>
</tr>
<tr>
<td>24/03/2010</td>
<td>Approval from University of Leicester research ethics committee (project ref. jw330-ac655)</td>
<td>The timescale of the original study approved was 01/04/10 to 30/04/12</td>
</tr>
<tr>
<td>16/04/2010</td>
<td>JW received letter of access for case study 1</td>
<td>Term of access 16/04/10 to 30/04/12</td>
</tr>
<tr>
<td>12/05/2010</td>
<td>NHS REC approved a substantial amendment (no. 1, 18/03/2010). REC meeting date 19/04/2010</td>
<td>The timescale of the study approved was 01/05/10 to 30/04/12</td>
</tr>
</tbody>
</table>
### Appendices

<table>
<thead>
<tr>
<th>Date</th>
<th>Activity</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>21/06/2010</td>
<td>Yearly progress report sent to NHS REC</td>
<td></td>
</tr>
<tr>
<td>21/07/2010</td>
<td>Approval received from Research Governance (RG) department linked to Case Study 1</td>
<td>Local departments approved were pathology and cancer studies</td>
</tr>
<tr>
<td>26/08/2010</td>
<td>JW received letter of access for case study 2</td>
<td>Term of access 01/09/10 to 31/08/12</td>
</tr>
<tr>
<td>01/02/2011</td>
<td>JW received RG approval via email to enter department of surgery in case study 1</td>
<td></td>
</tr>
<tr>
<td>07/04/2011</td>
<td>Approval received from Research Governance department linked to Case Study 2</td>
<td>Local centres did not need to be identified</td>
</tr>
<tr>
<td>27/05/2011</td>
<td>Yearly progress report sent to NHS REC</td>
<td></td>
</tr>
<tr>
<td>07/11/2011</td>
<td>The RG Manager for case study 3 sent an email that Research Governance approval was not required for study</td>
<td>Due to new GAfREC rules – projects which do not recruit NHS patients are now not required to have Research Governance approval</td>
</tr>
<tr>
<td>30/03/2012</td>
<td>University of Leicester research ethics committee agrees extension of study to 31/12/12</td>
<td></td>
</tr>
<tr>
<td>05/09/2013</td>
<td>Final report and end of study report sent to NHS REC</td>
<td></td>
</tr>
</tbody>
</table>

### Documents approved

Find details below about the documents approved under each ethics application.

**Table A-6 University ethics approved documents**

<table>
<thead>
<tr>
<th>Title</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consent Form (Observation)</td>
<td>1</td>
<td>22/03/10</td>
</tr>
<tr>
<td>Consent Form (Interview)</td>
<td>2</td>
<td>04/03/10</td>
</tr>
<tr>
<td>Email Consent Form</td>
<td>1</td>
<td>10/02/10</td>
</tr>
<tr>
<td>Information Sheet</td>
<td>2</td>
<td>04/03/10</td>
</tr>
<tr>
<td>Leaflet</td>
<td>1</td>
<td>04/03/10</td>
</tr>
</tbody>
</table>
### Table A-7 NHS REC approved documents

<table>
<thead>
<tr>
<th>Title</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator CV</td>
<td>1</td>
<td>17/03/10</td>
</tr>
<tr>
<td>Protocol</td>
<td>2</td>
<td>17/03/10</td>
</tr>
<tr>
<td>Notice of Substantial Amendment (non-CTIMPs)</td>
<td>1</td>
<td>24/03/10</td>
</tr>
<tr>
<td>Covering Letter (Observation)</td>
<td>1</td>
<td>18/03/10</td>
</tr>
<tr>
<td>Interview Prompt Guide 1</td>
<td>2</td>
<td>17/03/10</td>
</tr>
<tr>
<td>Poster</td>
<td>2</td>
<td>17/03/10</td>
</tr>
<tr>
<td>Participant Email Consent Form For Telephone Interviews</td>
<td>1</td>
<td>17/03/10</td>
</tr>
<tr>
<td>Participant Consent Form: Interviews</td>
<td>5</td>
<td>17/03/10</td>
</tr>
<tr>
<td>Participant Information Sheet: Interviews</td>
<td>5</td>
<td>17/03/10</td>
</tr>
<tr>
<td>Participant Information Sheet: Observation</td>
<td>5</td>
<td>17/03/10</td>
</tr>
<tr>
<td>Covering Email (Observation)</td>
<td>1</td>
<td>18/03/10</td>
</tr>
</tbody>
</table>

The participant information sheets can be found in Appendices 3–6 and original topic guide in Appendix 6.
Appendix 3: University Ethics Participant Information Sheet

Participant Information Sheet

Project Title: A qualitative study of professional and organisational issues in tissue banking for research

Please read all of this information sheet carefully.
• You are being invited to take part in a research project.
• Before you decide to participate it is important for you to understand why the research is being done and what it will involve.
• Please take time to read the following information carefully and discuss it with others if you wish. Please ask me if anything is unclear or if you would like more information.

Purpose of the research
I am conducting a study for my PhD that is looking into professional and organisational issues related to cancer tissue banking for research.
The main aim of my research is to identify what issues can help facilitate, and what issues can act as barriers to, the harmonisation of cancer tissue banks.
To identify such issues, I want to interview people that play a role in cancer tissue banking to get a better understanding of the situation. I would also like to observe relevant meetings, events or tissue banking activities, and gather useful documents.

Why have I been chosen?
You have been chosen to participate in this research because you play a role in cancer tissue banking for research and I think you can help me with my study.
However, you do not have to take part in this research if you do not want to. If you do decide that you would like to take part, you can withdraw at any point.
If you do decide to take part, you will be given this information sheet to keep and you will be asked give consent to taking part.

Taking part
If you decide that you would like to be interviewed, I will arrange this at a time and place that is convenient for you. It may be possible that we can do the interview over the telephone. In the interview I will ask you about your opinions and experiences of cancer tissue banking for research. The interview is expected to take around 30 to 45 minutes and I would like to audio record the interview.
If I observe meetings or biobanking activities, these will be recorded through note-taking and by taking photographs.

Advantages and disadvantages of taking part
There are no significant advantages or disadvantages of taking part. An interview will take up some time but we can arrange a time and place that is convenient for yourself.
Participant Information Sheet

Confidentiality
The following actions will be taken to ensure that confidentiality is maintained:

- Audio recordings and related transcriptions will only be accessed by the research team. The audio recordings will be deleted at the end of the research.
- I will discuss data from the interviews, meetings or observations with the research team but your identity will not be revealed and the data will not be discussed with anyone else.
- No personal data will be linked to the data. Only a code such as your general job title (e.g. administrator) will be linked to the data to avoid identification. Organisation names will be similarly coded.
- Anything that you have said that might identify you will be removed or changed in the transcription.
- Quotations from the interview or meeting, or photographs from observations, may be used in the research report or resulting publications but you will not be identified.
- Confidential documents will be stored securely and not further distributed without permission.

Results of the research
If you would like to receive information on the published outcomes of the study, please give me your email address and I will send you this information after the study has finished. You can do this even if you decide not to take part.

Funding the research
This study is being organised by the University of Leicester. It is being funded by the Medical Research Council (MRC).

Contact for further information
If you would like any further information please contact myself or another member of the research team:

Jessica Wright
212a Adrian Building
Department of Health Sciences
University of Leicester
University Road, Leicester LE1 7RH
(0116) 229 7258
jw330@le.ac.uk

Professor Mary Dixon-Woods
213c Adrian Building
Department of Health Sciences
University of Leicester
University Road
Leicester LE1 7RH
(0116) 229 7262

Dr Helen Eborall
213b Adrian Building
Department of Health Sciences
University of Leicester
University Road
Leicester LE1 7RH
(0116) 229 7261

Professor Paul Burton
317 Adrian Building
Department of Health Sciences
University of Leicester
University Road
Leicester LE1 7RH
(0116) 229 7274

Thank you for taking the time to read this information sheet.

Version 2 – 04/03/10
Appendix 4: NHS REC Ethics Participant Information Sheet – Interviews

Project Title: A qualitative study of professional and organisational issues in tissue banking for research

Please read all of this information sheet carefully.
• You are being invited to take part in a research project.
• Before you decide to participate it is important for you to understand why the research is being done and what it will involve.
• Please take time to read the following information carefully and discuss it with others if you wish. Please ask me if anything is unclear or if you would like more information.

Purpose of the research
I am conducting a study for my PhD that is looking into the professional and organisational issues of cancer tissue banking for research.

The main aim of my research is to identify what issues can help facilitate and what issues can act as barriers to the harmonisation of cancer tissue banks.

To identify such issues, I want to interview people that play a role in cancer tissue banking to get a better understanding of the situation.

Why have I been chosen?
You have been chosen to participate in this research because you play a role in cancer tissue banking for research and I think you can help me with my study.

However, you do not have to take part in this research if you do not want to. If you do decide that you would like to take part, you can withdraw at any point.

If you do decide to take part, you will be given this information sheet to keep and you will be asked to complete a consent form.

Taking part
If you decide that you would like to take part in this research, I will arrange an interview at a time and place that is convenient for you. It may be possible that we can do the interview over the telephone.

In the interview I will ask you about your opinions and experiences of cancer tissue banking for research. The interview is expected to take around 30 to 45 minutes and I would like to audio record the interview.

Advantages and disadvantages of taking part
There are no significant advantages or disadvantages of taking part.

It is hoped that you will enjoy taking part in the research and the opportunity to talk about your experiences. The interview will take up some time but we can arrange a time and place that is convenient for yourself.
Participant Information Sheet (Interviews)

Confidentiality

All actions will be taken to ensure that your identity is not revealed:

- The audio recording and transcribed interview will only be accessed by the research team. Audio recordings will be deleted at the end of the research.
- I will discuss the interview data with the research team but your identity will not be revealed and the data will not be discussed with anyone else.
- No personal data will be linked to the interview data. If you agree, we would like to record your general job title (such as “consultant pathologist” or “research nurse”), but it is your choice whether it is recorded or not.
- Anything that you have said that might identify yourself will be removed or changed in the transcription.
- Quotations from the interview may be used in the research report or resulting publications but you will not be identified.

Results of the research

If you would like to receive a summary of the results of the study, please give me your email address and I will send the summary after the study has finished. You can do this even if you decide not to take part.

Funding the research

This study is being organised by the University of Leicester. It is being funded by the Medical Research Council (MRC).

Contact for further information

If you would like any further information please contact myself or another member of the research team:

Jessica Wright
2nd Floor, Adrian Building
Department of Health Sciences
University of Leicester, University Road
Leicester LE1 7RH
jw330@le.ac.uk
0116 229 7281

Supervisory Team
Department of Health Sciences
University of Leicester
University Road
Leicester LE1 7RH

Professor Mary Dixon-Woods, Supervisor md11@le.ac.uk
Dr Helen Eborall, Supervisor hce3@le.ac.uk
Professor Paul Burton, Advisor Paul.Burton@le.ac.uk

Thank you for taking the time to read this information sheet.

Participant Information Sheet (Interviews) Version 5, 17/03/10
Appendix 5: NHS REC Ethics Participant Information Sheet – Observations

Participant Information Sheet (Observation)

University of Leicester

Project Title: A qualitative study of professional and organisational issues in tissue banking for research

Please read all of this information sheet carefully.
- You are being invited to take part in a research project.
- Before you decide to participate it is important for you to understand why the research is being done and what it will involve.
- Please take time to read the following information carefully and discuss it with others if you wish. Please ask me if anything is unclear or if you would like more information.

Purpose of the research
I am conducting a study for my PhD that is looking into the professional and organisational issues of cancer tissue banking for research.

The main aim of my research is to identify what issues can help facilitate and what issues can act as barriers to the harmonisation of cancer tissue banks.

To identify such issues, I want to spend some time in cancer tissue banking settings to observe what happens.

Why have I been chosen?
Your department has been chosen to participate in this research because it plays a role in cancer tissue banking for research and I think the department and you can help me with my study.

I will be visiting your department and would like to observe what happens in your department. However, you do not have to take part in this research if you do not want to. Please send me an email if you would prefer not to take part.

Taking part
I will be spending time in your department and if I think you can help me, I will ask if you would be willing to let me observe you for example, when you do a certain procedure. Please feel free to say no if you do not want me to observe you.

If you agree to let me observe you, I will watch you do the procedure and make notes.

If there is general agreement, I may take photographs to record any procedures or the surroundings where cancer tissue banking takes place.

I will ask you for permission to observe you and to take any photographs.

Advantages and disadvantages of taking part
There are no significant advantages or disadvantages of taking part.
Participant Information Sheet (Observation)

Confidentiality
Your identity will not be revealed in the report that I write following the study. When my notes from the observation are transcribed, they will not include any personal data.
I will not intentionally photograph people’s faces or features that may identify an individual. If this happens I will use computer software to anonymise the image before any kind of publication. I will store any photographs securely.

Results of the research
If you would like to receive a summary of the results of the study, please give me your email address and I will send the summary after the study has finished. You can do this even if you decide not to take part.

Funding the research
This study is being organised by the University of Leicester. It is being funded by the Medical Research Council (MRC).

Contact for further information
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Thank you for taking the time to read this information sheet.

Participant Information Sheet (Observation) Version 5, 17/03/10
Appendix 6: Topic Guide – NHS REC Ethics Approved Version

This topic guide was approved by the NHS REC (version 2, 17/03/10).

Interview Prompt Guide 1

1. General questions
   • How long have you worked here for?
   • Can you describe to me, what your involvement is in tissue banking for research?

2. Perceptions of tissue banking for research
   • How do you feel about banking tissue for research?
   • What do you think others in the department feel about tissue banking for research?
   • Do you think there are any advantages or disadvantages of banking tissue for research in your department?
   • Is there anything that encourages or prevents people to bank tissue for research?

3. Tissue banking environment
   • Which professionals are involved in tissue banking for research?
   • Do these people work together to make sure that tissue is banked for research?
   • Is there anything that can prevent teamwork in tissue banking?

4. Practical issues
   • How much of your time is taken up in banking tissue for research?
   • What kind of training have you had in regards to tissue banking for research?
   • Are there procedures in place for you to follow regarding tissue banking for research? How do you feel about these procedures?

5. Supply chains
   • From when the tissue is requested from a patient to when it is banked and registered, if there was to be a point where the tissue would not be banked for research, when do you think this would be most likely to happen?
   • Do you think patients are routinely told about the opportunity to consent to samples being used for research?
   • During surgery or biopsy, how do the team feel about banking tissue for research?

6. Anxieties
   • What do you think about the Human Tissue Act?
   • Do you have any concerns over your involvement in tissue banking for research?
Appendix 7: Topic Guide – Preliminary Interviews

This topic guide was based on the NHS interview prompt guide and was dated 20 April 2010. It was developed after considering the results of the pilot interview and meeting attended in February 2010.

Interview Prompt Guide 2 Tissue Banks

1. General questions
   - What is your job?
   - Can you tell me a bit about your job, including how long you have been working there and what you do?
   - How would you define “tissue bank”? Do you see it as including data? If so, why?

2. Reasons for tissue banking
   - How important is banking tissues for use in research and why?
   - What would you say are the main reasons for your interest in tissue banking?
   - (If they bank cancer tissue) In your opinion, is banking cancer tissue for research different to banking other types of tissue? If so, why?

3. Process of tissue banking
   I am going to ask you some questions about tissue banking in your organisation. I’m especially interested in efforts to harmonise tissue banks by standardising things like consent and quality standards. If you can think about that as you are answering, that would be great.
   - Can you tell me about any tissue banks in your organisation?
   - What do you have to do to get tissue banking to happen successfully? What kinds of problems have to be overcome?
   - What kinds of people are involved in tissue banking?
   - What kind of teamwork is needed?
   - Can you tell me about the training you have received?
   - What role do set procedures and guidelines have when you are banking tissue? Any problems with implementing them?
   - Who uses the tissue for research both inside and outside the organisation?
   - Do issues of harmonisation ever come up? Can you tell me more about that?
4. Facilitators and Barriers
   • Have you or your organisation had particular success in banking tissue for research? If so, why do you think this is?
   • Are there people who are more or less enthusiastic about harmonisation? What concerns do people have about harmonisation?
   • Do you have three top tips for solving any problems linked to banking tissues?
   • Any top tips for promoting harmonisation?

5. Funding issues
   • What are the costs associated with tissue banking for research and how are these met?
   • How do you see the role of industry in tissue banking?
Appendix 8: Topic Guide – Final Interviews

This topic guide dated 2 February 2012 was generic (meant to be used flexibly when communicating with different types of professionals) and written for the final case study.

Interview Prompt Guide 2 Tissue Banks, CS3

1. General questions
   - Can you tell me a bit about your role, including something about how you are currently, or have previously been, involved in banking tissues for research?
   - Importance of tissue banking?

2. Tissue Banking in the Trust/University
   I am going to ask you some questions about the process of tissue banking in the Trust and associated University.
   - Do you think that tissue banking is a priority in the Trust?
   - Is tissue banking the norm in the Trust?
     - Or is it different in different departments e.g., oncology?
   - Can you give me an overview of the research tissue banking that is taking place in the Trust/University?
     - For each main tissue bank:
       - How was it set up and funded?
       - What is the range of tissue stored?
       - Any problems with particular tissue types?
       - Did the tissue bank require a change in how the hospital processes tissue?
       - What kinds of people are employed by the tissue bank?
       - Is the tissue bank flexible in terms of how the tissue is processed and stored?
       - Does the tissue bank offer processing on site?
       - How are the records of consent stored?
       - How is the tissue stored?
       - What kind of computer databases are there to support tissue banking?
       - Could you take me through a typical sample registration procedure?
APPENDICES

- Could you take me through a typical request to the tissue bank for access to samples?
- Is there any priority for local researchers to have access?
- Does everyone support the tissue bank?
- Is any tissue bank a Research Tissue Bank?
  - How does it work?
  - What was the process to apply for ethics approval like?
- Are there any Clinical Trials Units in the hospital collecting tissue?
- What kind of research takes place within the Trust/Uni using the tissue?
- How is the diagnostic archive used?
  - What are the main locations in the hospital that tissue banking takes place in?
  - What kinds of people are involved in tissue banking? E.g. pathologists, research nurses, doctors, surgeons, lawyers...
  - Does anyone have tissue banking built into their job description?
    - What kind of teamwork is needed?
    - What are the main incentives or disincentives for people to take part in tissue banking?
- Is there any particular innovation at your Trust/University that has aided the harmonisation of tissue banking?
  - Is there a pan-University or Trust Human Tissue Board or Committee? If so, how does it work?
  - Is there anything at your Trust/University that you think hinders the harmonisation of tissue banking?
  - What are the costs associated with tissue banking in the Trust and how are these met?
  - What type of training exists in relation to banking tissues for research purposes?
  - What is the role of the hospital R&D in tissue banking?
  - Does the University/Trust have any links to industry in the area of collecting, storing or using tissue?

- Do you see tissue banks as including administrative, health or lifestyle or other data about the samples? Any comments?
- Is there widespread knowledge throughout the hospitals about tissue banking?
- How is the cooperation between the NHS and the University?
- How easy is it to separate research and clinical spheres? Can you draw a line between them?
- What is the link to industry? Is there cooperation between NHS/academia and industry?
3. Standards and guidelines

- What role do set procedures and guidelines have in your tissue bank?
  - Who writes them and what documents do they draw on?
  - What kind of documents are they?
  - Any problems with implementing them?
  - How do you encourage people to follow SOPs?
  - How do you use audits?
- Can you give me an idea about what standards people banking cancer tissue for research purposes are following at this time?
- What is your view on the Human Tissue Act, do you think it has been a positive or negative development for tissue banking?
  - HTA licenses? Cost?
  - Inspections?
  - Interaction with Authority?
- What impact do you think collecting samples to different standards can have on cancer research?
  - Specifically, do you think that different ways of preparing tissue blocks/slides in different hospitals could have an impact?

4. Harmonisation and Standardisation in Cancer Tissue Banking

- Are you a member of any tissue bank networks?
- What does harmonisation mean to you? Is there a difference between that and standardisation?
- Can you tell me about any efforts you’ve been involved in to harmonise cancer tissue banks?
- Do you think that harmonisation or standardisation is required in the field of cancer tissue banking for research?
  - If so, who should harmonise?
  - If so, what areas of cancer tissue banking can/should you standardise? (E.g. should you standardise the tissue processing, or just the data you collect about the tissues?)
  - Do you think collecting samples to different standards has any impact on cancer research? E.g. different ways of preparing tissue blocks
- What mechanisms do you think would work best to enforce standardisation in this area, e.g. accreditation, law, guidelines?
- What kind of incentives would you give?
- Any structural things that need to be changed? E.g. biobank recognition/career structures
- How would you harmonise e.g. guidelines/SOP/check-list/IT tools/forms
- Are there people who, in your mind, would be resistant to standardisation, or those who would particularly support it?
- If a national standard was to be put in place, what concerns would you have?
Appendix 9: Sensitising Concepts 2010-2012

January 2010 – General study sensitising concepts

The following study areas were developed for the research protocol after an initial literature review.

1) Impact of perceptions in tissue banking

It is likely that staff perceptions of tissue banking are implicated in varying rates of registration of tissue for research purposes. Currie, Finn and Martin (2008) explored ‘networks’ within the NHS and found that professionals faced numerous barriers when trying to implement a new service into mainstream healthcare if the service is not valued or not regarded as legitimate. Our study will explore how health professionals that are directly and indirectly involved in tissue banking perceive the service and how this affects collaboration and commitment to tissue banking. Questions to be explored include:

- Is tissue banking seen as a legitimate activity in the healthcare setting?
- Is tissue banking seen as detrimental to patient care?
- What incentives are there for tissue banking?

2) Culture(s) within tissue banking

Previous ethnographic research within the NHS has identified a culture of tribalism (Bate 2000) which has contributed to a negative organisational culture in some hospitals. A tribal culture leads to professional factions aiming to win gains for their field, ward or department even if this is at the expense of the greater organisation. An example of tribal behaviour would include departments resisting sharing resources or individuals retaining samples for their own use rather than banking them for communal use. Tissue banking relies on the collective effort of multiple actors that cross organisational and professional boundaries and so it will be interesting to explore the culture(s) within the tissue banking environment and whether tribal behaviour occurs and acts as a barrier. Questions to be explored include:

- Do health professionals collaborate to ensure tissue banking occurs?
Does tribalism exist within tissue banking?
- Is tissue banking regarded as competition for resource?

3) Practical issues
There are a number of practical issues that will have an effect on tissue banking within hospitals such as resources, location and facilities, who is operating the tissue bank, and what procedures have to be followed to bank tissue. Observation in different hospitals will aid identification of these issues. Questions to be explored include:

- How are activities related to tissue banks funded and what effect does this have?
- How are human resources allocated to tissue banking? What training do they receive?
- What relationships do hospitals (or parts of hospitals) have with tissue banking organisations?
- How does the amount of knowledge a team has on tissue banking effect rates of collection?
- How much time does tissue banking take from health professionals?
- Does the location of the bank affect rates of tissue banking?
- What procedures are in place to facilitate tissue banking? Are health professionals following these procedures and do they find them easy to follow?
- Is the computer software involved in registering tissue for research effective and easy to use?

4) Supply chains
It has been argued that there is still a ‘blockage’ of human tissue from patient to researcher (Womack and Gray, 2008). Suh et al (2009) found that access to consent documentation is crucial to avoid the loss of consented samples. This research will look to identify where the disruptions within the ‘supply chain’ occur. Questions to be explored include:

- Are patients routinely informed about the opportunity to consent to samples being used for research?
- Is consent documentation easily accessible for professionals that need to verify consent?
- During surgery or biopsy, are health professionals committed to banking tissue?
- What happens to the samples after they leave the operating theatre?
- How are human tissue samples categorised? Is there ever ambivalence within the classification system?

5) *Anxieties regarding tissue banking*

There is some limited evidence that, since the human organ retention scandal and the introduction of the Human Tissue Act (2004), health professionals have become more cautious when it comes to collecting and storing human materials (Campbell et al, 2008). It will be interesting to explore whether these anxieties as well as others are present in cancer tissue banking for research. Questions to be explored include:

- What are health professionals’ views and understanding of the Human Tissue Act (2004) and how it affects their work?
- Do health professionals avoid tissue banking due to fear of violation of legislation?
- Are they wary of obtaining informed consent from patients, and if so why?

**May 2010 – General study sensitising concepts**

Table A-8 Sensitising concepts following literature review and pilot study

<p>| Harmonisation | General | What does harmonisation mean? What is harmonisation? What organisations are involved in harmonisation and why? What harmonisation documents have been produced so far? | Barriers/facilitators | What do the organisations involved in harmonisation see as barriers/facilitators to the process of tissue banking? Do these go beyond consent and access? | Coverage | How do harmonisation efforts take account of what happens at the sharp-end? Do the barriers and facilitators seen by the harmonising organisations match those seen at the sharp-end? |
| Process | What is the process of cancer tissue banking at the sharp-end? What type of scientific procedures, technologies, computer software, sample tracking systems are involved? What types of professionals are involved? How much time does it take? When and how is tissue classified? How is tissue preserved and stored, and what are the available options? What norms (e.g. laws/SOPs/standards like GCP or GLP) are followed? Are check-lists used? What are the quality control procedures? How much are the general public involved in the tissue banks? Who uses the banked tissue? What is the relationship or agreement between the bankers and the researchers? What are the access criteria/agreements? |
| Barriers/facilitators | Where and why do blockages occur in the process of tissue banking? What/who are the bottlenecks? Have centres created methods for getting over problems with banking tissue? What examples can be found about this? What are the differences between successful/less successful biobanks? |
| Cancer tissue | What is the relationship of the different professionals to the cancer tissue (e.g. does the pathologist feel a certain way about it?)? Is banking tissue for cancer research seen as any more valuable or worthwhile than banking other types of tissue? Are the types of tissue involved (e.g. surgical waste/unhealthy tissue/alien) perceived differently to healthy/normal tissue? |</p>
<table>
<thead>
<tr>
<th>Appendices</th>
<th>General</th>
<th>Funding</th>
<th>Normalisation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>The blunt end</strong></td>
<td>What is the organisational structure around cancer tissue banking?</td>
<td>What level of funding exists for the activity (and as compared to other types of tissue banking)?</td>
<td>Is the process of banking cancer tissue seen as a normal thing to do in practice? Do different people involved have different ideas about this? How could tissue banking be normalised?</td>
</tr>
<tr>
<td></td>
<td>What levels of bureaucracy exist? What are the organisational rules on tissue banking? Is it seen as a legitimate organisational goal?</td>
<td>How much does cancer tissue-banking actually cost? Is there enough funding? Are there any other kinds of incentives to bank tissue?</td>
<td></td>
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<tr>
<td></td>
<td>What is the working environment like? Where is the place where tissue is banked situated in relation to the place it is collected? How is tissue transported between them? How is the tissue bank managed?</td>
<td>How should tissue banks be funded?</td>
<td></td>
</tr>
<tr>
<td><strong>Professionals</strong></td>
<td>Motivation</td>
<td>Skills</td>
<td>Awareness/following rules</td>
</tr>
<tr>
<td></td>
<td>How are professionals motivated to take part in cancer tissue banking activities? Specifically, how does altruism and fairness come into play when professionals decide whether to bank cancer tissues? Are some professionals involved in tissue banking less committed to it than others? Is there any evidence of tribalism in relation to tissue resources? Is there any evidence of “hoarding” of tissue samples?</td>
<td>How much training have professionals received and do they give? What human resources are allocated to tissue banking? Are there perceived knowledge or skills gaps in relation to tissue-banking and research using tissues? Are some types of professionals left-out or over-involved in tissue banking and related research?</td>
<td>How much are they aware of harmonisation activities? How much do they follow them? Do professionals ever break ‘the rules’ in relation to tissue banking? If so, why and how? Does everyone break ‘the rules’? Do people prefer to follow check-lists? What effects did the organ retention scandals have on tissue banking? Are there any other anxieties relating to the rules around tissue banking, or those that help more than others?</td>
</tr>
<tr>
<td>Industry</td>
<td>General</td>
<td>What is the role of industry in cancer tissue banking? What are the views of health professionals on industry involvement? Does industry cooperate in relation to obtaining, storing or using tissue samples? Does industry follow different kinds of norms to the public sector? Do they have different types of technologies?</td>
<td></td>
</tr>
<tr>
<td>Intermediates</td>
<td>How do companies acting as intermediaries between hospitals and researchers work and what rules do they follow? Do they facilitate the tissue banking process?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Future</td>
<td>What should the future look like?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**December 2011 – Theoretical sensitising concepts**

Questions developed after initial work considering the theories potentially applicable to the emerging results.

**Altruism**
- Does it work for tissue banking?
- Does altruism help motivate people to take part in tissue banking?

**Audits**
- Have they helped concretise certain practices?
- Are they good or bad?
- What standards are they enforcing?

**Collaboration**
- What are the outcomes that motivate people to, or not to, collaborate with tissue banking?
- What are the outcomes when people do not collaborate?
- Do people find it difficult to trust others involved in tissue banking?
- Do people think about the reputation of the other people involved when making a decision whether to cooperate?
- Are people more likely to collaborate with people with a good reputation?
- Are people more likely to collaborate with people they meet regularly?
- Does being part of a network make people more likely to collaborate with others in their network?
- Are some types of people more likely to collaborate than others?
- Do people more likely to be collaborators look for similar types of people to collaborate with?
- Does the tissue banking field have a way of recognising other potential collaborators?
- In the cases above, do they often form networks or clusters?
- Are people more likely to collaborate with people in their networks?
- Do people get other benefits from being part of networks?
- What kind of punishment takes place in the field when people who said they would collaborate then do not?

Organisations
- Do organisations tend towards making their own rules about tissue banking in the absence of other rules?

Patient Safety Literature
- Consider similarity to other work in the patient safety arena.

Role and Role Strain
- Is tissue banking part of somebody's role?
- Or does it fall outside?
- Do people accept tissue research as a responsibility?
- How do people resolve conflict between clinical and research work?

Social Networks
- Who knows who?
- Which rules are they operating on (for example, are they involved with the market, a hierarchy like a hospital, the law, a network)?
- Are the rules presented as a requirement?
- To what extent is it required or to what extent is it voluntary?
- What social networks are there in the area of tissue banking?
- What are their guiding principles, rules and membership benefits?
- Are tiny tissue banks prone to failure because they not part of networks?
- Are tissue banks more likely to collect tissue because they are linked into a network?

**Social problem/social movement theory**
- Social movement theory – when does something become the focus of attention?
- What are the other priorities competing with tissue banking?
- Does tissue banking have the status of a social problem?
- Have people tried to establish it as one?
- Is there a sense of urgency?
- How is tissue banking portrayed in the media?
- What is the fall-out from the ‘scandals’ in the area in the UK?

**Sociology of standards**
- What types of standards do people follow?
- How do they feel about following these standards?
- Do they ever question the standards? Do they act upon this?
- What do they feel when they manage to comply with the standards?
- What do they feel when they do not manage to comply?
- Are the standards invisible? How can they be uncovered?
- What decisions needed to be made before the standard was put in place?
  Were any of these value-laden? Were the people making the decisions representative?
- Do the standards contain bias? For example, against people who don’t speak English
- Do some people, for example, smaller companies, have trouble following standards for some reason?
- Is someone making money out of extending, adapting or changing standards?
- Who benefits from a new or adapted standard?
- Do the standards no longer make sense?
- Has there been an emergent bias over time as the context changes?
- Are people or non-people adversely affected?
- Are the standards implemented by everyone?
- Are standards getting in the way of ‘real work’ because of the time it takes to comply with them?
- Has a particular standard failed? Have others succeeded?
- Does a particular standard create a barrier to harmonisation?
- Do coercive standards always work?
- If there is a lack of regulation are people disinclined to cooperate?
- The standardisation vs. local discretion debate – how much do standards leave to local discretion and allow differences?
- Has tacit knowledge developed and been shared and between groups that acts like a standard?
- Can you find resistance to the standards? Is some of it passive, in the mundane nature of things?

Sociology of the mundane
- What kind of mundane activities get in the way of tissue banking or harmonisation?

Supply Chain
- What decisions lie behind a piece of tissue becoming a research sample?
- Where are the weak links in the supply chain?

Trust
- Is trust seen as important for sharing samples in tissue banking?
- What are the links of trust in this area to altruism, cooperation and co-authorship for example?
Appendix 10: Examples of Analytical Memos

The excerpts below are taken from a selection of analytical memos written while undertaking the research and interpreting the resulting data.


I had the idea 31/10/11 that the problem with the HTA may not be the Act, but the implementation of the Act. Evidence e.g. P60 who talked about how it was not the Act itself but the over-zealous reaction to it? Can all the problems be brought down to how the Act was implemented?

Idea to test (Jan 2012): that people responsible for implementing it e.g. tissue managers etc. are generally quite happy with the act and understand it (they may say they understand it enough to know how to get around it). But on the ground e.g. scientists, pathologists, researchers still say they are confused about it. Could this be a meme, idea, that’s not really true? At meeting 8 someone said that this was a mindset that needs to be changed and e.g. it was passed down from the older pathologists to the new ones. Another idea is that the future rearrangement of the authority will not help. Much myth around this?

(March 2012) One idea from the observations at Trust 3 is that relying on consent, especially for fresh tissue that needs to be given to the researcher within hours, may cause problems. The piece of paper has to reach pathology (and in the case of a clause on the surgical consent form) has to be photocopied before that by someone from surgery (which is still often going on). Quite often the consent form or copy does not reach pathology with the tissue sample leading to a fascinating paper chase for the people from the tissue bank (see observation reports from Novelburg tissue bank for examples).

Flexibility

During an observation on 24 June 2011 it struck me that what a biobank needs is flexibility. The Refport University biobank is incredibly flexible, adapting the way it does things to suit the researcher. It gives individual cost assessments, it offers to
collect samples on the researcher’s behalf from surgery etc., it can store different
types of samples and process them according to the researcher’s needs. The flexibility
seems to be supported by what I will term ‘core SOPs’ for systems that underpin the
biobank.

**International standards**

People in practice rarely mention any of the big standardisation movements that are
going on e.g. BBMRI, P3G, or ISBER? Only people who are directly involved in them
mention it. When I ask them, they often look at me ‘a blank’ – as if I’m asking a really
weird question.

**Ownership**

I feel that there are still issues around this. It was interesting that P40 (Consultant
Histopathologist) who said she was involved in the discussions for the Human Tissue
Act (2004) said that part of the reasons for the licensing provisions was to stop people
feeling like they owned the tissue they were collecting.

P5 (funder representative) said that if biobanks are set up in a competitive (research)
environment like a University or a hospital, they are less likely to want to share tissues
and keep it for the organisation itself – but this is against the ethos of the biobank,
where tissue should be made available widely. She said a sea change is needed in the
way people think about this. She said that organisations like the tissue bank they were
setting up were there to be brokers to stop thinking in terms of sample ownership –
also to be a member of the cancer network she mentions, you have to renounce this
kind of thinking (see the code of conduct of the network).
Appendix 11: NVivo Coding Tree Examples

Figure A-1 NVivo structural coding tree on the Human Tissue Act (2004)
Figure A-2 NVivo analytic coding tree on the Human Tissue Act (2004)

Figure A-3 NVivo analytic coding tree on cooperation
Appendix 12: Characteristics of Organisations, Participants and Meetings

A summary of the organisations, participants and meetings included in the research project follows.

Organisations

Table A-9 provides information about the main organisations mentioned in the analytical Chapters 4–6. Less frequently mentioned organisations or organisations that have not been anonymised are introduced within the relevant text.

Table A-9 Overview of the anonymised organisations involved in the research

<table>
<thead>
<tr>
<th>Research site/organisation</th>
<th>Description</th>
<th>Mode of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colham</td>
<td>In Colham a large trust and associated university were included</td>
<td>Interview and observation</td>
</tr>
<tr>
<td>Novelburg</td>
<td>In Novelburg a medium-sized trust was studied, including one hospital and associated university</td>
<td>Interview and observation</td>
</tr>
<tr>
<td>Refport</td>
<td>In Refport a small specialist trust with a hospital and an associated university</td>
<td>Interview and observation</td>
</tr>
<tr>
<td>BigPharma</td>
<td>BigPharma is an international pharmaceutical company</td>
<td>Interview and observation</td>
</tr>
<tr>
<td>Onconet</td>
<td>Onconet is a network of cancer tissue banks</td>
<td>Interview and observation</td>
</tr>
<tr>
<td>CanBank</td>
<td>Canbank is a national (centralised) cancer tissue bank with numerous hospital collection sites</td>
<td>Interview and observation</td>
</tr>
<tr>
<td>Rare cancer association of biobanks (RAB)</td>
<td>The RAB is a national (federated) cancer tissue bank with numerous hospital collection sites</td>
<td>Interview and observation</td>
</tr>
<tr>
<td>Finkleborough cancer tissue bank</td>
<td>Finkleborough cancer tissue bank is a cancer specific (local) university-hospital collaboration</td>
<td>Interview and observation</td>
</tr>
</tbody>
</table>
### Participants

Table A-10 provides a description (by job title and professional group) of the 81 participants in my research who were either directly interviewed or observed. Participants observed in meetings were not included in the table, but may be referred to within the text, for example as a keynote speaker. Within the analytical and discussion chapters, participants are referred to by their ‘P No.’, or participant number, found in the table.

#### Table A-10 Research participant details

<table>
<thead>
<tr>
<th>Job Title</th>
<th>Professional group/s</th>
<th>Interviewed/Observed?</th>
<th>P No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>As agreed with participant</td>
<td>From profession-group categories below</td>
<td>Mode of study</td>
<td>Study No.</td>
</tr>
<tr>
<td>Reader in Molecular Biology</td>
<td>Academic Researcher</td>
<td>Observed</td>
<td>37</td>
</tr>
<tr>
<td>PhD Student</td>
<td>Academic Researcher</td>
<td>Observed</td>
<td>63</td>
</tr>
<tr>
<td>PhD Student</td>
<td>Academic Researcher</td>
<td>Observed</td>
<td>78</td>
</tr>
<tr>
<td>University Researcher</td>
<td>Academic Researcher</td>
<td>Observed</td>
<td>79</td>
</tr>
<tr>
<td>Job Title</td>
<td>Professional group/s</td>
<td>Interviewed/Observed?</td>
<td>P No.</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>---------------------------------------</td>
<td>-------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>University Researcher</td>
<td>Academic Researcher</td>
<td>Observed</td>
<td>80</td>
</tr>
<tr>
<td>University Researcher</td>
<td>Academic Researcher &amp; Harmonisation Organisation</td>
<td>Interviewed</td>
<td>6</td>
</tr>
<tr>
<td>Clinical Trials Coordinator</td>
<td>Clinical Trials Unit Staff</td>
<td>Interviewed</td>
<td>28</td>
</tr>
<tr>
<td>Clinical Research Assistant</td>
<td>Clinical Trials Unit Staff</td>
<td>Interviewed/Observed</td>
<td>30</td>
</tr>
<tr>
<td>Clinical Research Assistant</td>
<td>Clinical Trials Unit Staff</td>
<td>Observed</td>
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<tr>
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<td>Clinical Trials Unit Staff</td>
<td>Observed</td>
<td>34</td>
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<tr>
<td>Clinical Trials Research Nurse</td>
<td>Clinical Trials Unit Staff &amp; Research Nurse</td>
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<td>26</td>
</tr>
<tr>
<td>Consultant in Medical Oncology</td>
<td>Doctors &amp; Hospital based Researcher</td>
<td>Interviewed/Observed</td>
<td>7</td>
</tr>
<tr>
<td>Doctor in Oncology</td>
<td>Doctors</td>
<td>Observed</td>
<td>27</td>
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<td>Observed</td>
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<td>Funders</td>
<td>Interviewed</td>
<td>55</td>
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<tr>
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<td>61</td>
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<tr>
<td>Scottish Government Representative</td>
<td>Government Bodies</td>
<td>Interviewed</td>
<td>65</td>
</tr>
<tr>
<td>University Researcher</td>
<td>Harmonisation Organisation</td>
<td>Interviewed</td>
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<tr>
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<td>Harmonisation Organisation</td>
<td>Interviewed</td>
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</tr>
<tr>
<td>MD and Researcher</td>
<td>Hospital based Researcher</td>
<td>Interviewed/Observed</td>
<td>24</td>
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<tr>
<td>Clinical Research Fellow</td>
<td>Hospital based Researcher</td>
<td>Observed</td>
<td>25</td>
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<tr>
<td>Tissue Researcher</td>
<td>Hospital based Researcher &amp; Doctors</td>
<td>Interviewed</td>
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<tr>
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<td>Hospital based Researcher &amp; Doctors</td>
<td>Interviewed</td>
<td>54</td>
</tr>
<tr>
<td>Job Title</td>
<td>Professional group/s</td>
<td>Interviewed/Observed?</td>
<td>P No.</td>
</tr>
<tr>
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<td>-----------------------------------------</td>
<td>-----------------------</td>
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</tr>
<tr>
<td>Clinical Trial Chief Investigator</td>
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<td>Interventional Radiologist</td>
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<td>Interviewed</td>
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<td>Pathologists &amp; Hospital based Researcher</td>
<td>Interviewed</td>
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<td>Consultant Histopathologist</td>
<td>Pathologists &amp; Hospital based Researcher</td>
<td>Interviewed</td>
<td>29</td>
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<td>Pathologists &amp; Hospital based Researcher</td>
<td>Interviewed</td>
<td>42</td>
</tr>
<tr>
<td>Consultant Pathologist and Researcher</td>
<td>Pathologists &amp; Hospital based Researcher</td>
<td>Interviewed</td>
<td>53</td>
</tr>
<tr>
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<td>Pathologists &amp; Hospital based Researcher</td>
<td>Interviewed</td>
<td>73</td>
</tr>
<tr>
<td>Consultant Histopathologist</td>
<td>Pathologists &amp; Professional Body</td>
<td>Interviewed</td>
<td>40</td>
</tr>
<tr>
<td>Patient Representative</td>
<td>Patient Representative</td>
<td>Interviewed</td>
<td>66</td>
</tr>
<tr>
<td>Research Governance Coordinator</td>
<td>Research Governance</td>
<td>Interviewed</td>
<td>58</td>
</tr>
<tr>
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<td>Research Nurse</td>
<td>Interviewed</td>
<td>59</td>
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<td>Job Title</td>
<td>Professional group/s</td>
<td>Interviewed/Observed?</td>
<td>P No.</td>
</tr>
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<tr>
<td>Research Nurse</td>
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</tr>
<tr>
<td>Departmental Administrator</td>
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<td>Interviewed</td>
<td>14</td>
</tr>
<tr>
<td>Lab Manager</td>
<td>Support staff - Academic</td>
<td>Observed</td>
<td>35</td>
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<tr>
<td>Tissue Board Chairperson</td>
<td>Support staff - Academic</td>
<td>Observed</td>
<td>38</td>
</tr>
<tr>
<td>Tissue Board Secretary</td>
<td>Support staff - Academic</td>
<td>Observed</td>
<td>39</td>
</tr>
<tr>
<td>Research Technician</td>
<td>Support staff - Academic</td>
<td>Observed</td>
<td>60</td>
</tr>
<tr>
<td>Research Technician</td>
<td>Support staff - Academic</td>
<td>Observed</td>
<td>62</td>
</tr>
<tr>
<td>Biomedical Scientist</td>
<td>Support staff - Academic &amp; Support staff - Pathology</td>
<td>Observed</td>
<td>23</td>
</tr>
<tr>
<td>Laboratory Manager</td>
<td>Support staff - Pathology</td>
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<tr>
<td>Senior Biomedical Scientist</td>
<td>Support staff - Pathology</td>
<td>Observed</td>
<td>16</td>
</tr>
<tr>
<td>Senior Biomedical Scientist</td>
<td>Support staff - Pathology</td>
<td>Observed</td>
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</tr>
<tr>
<td>Advanced Biomedical Scientist</td>
<td>Support staff - Pathology</td>
<td>Observed</td>
<td>21</td>
</tr>
<tr>
<td>Biomedical Assistant</td>
<td>Support staff - Pathology</td>
<td>Observed</td>
<td>22</td>
</tr>
<tr>
<td>Office Manager</td>
<td>Support staff - Pathology</td>
<td>Observed</td>
<td>32</td>
</tr>
<tr>
<td>Research Biomedical Scientist</td>
<td>Support staff - Pathology</td>
<td>Observed</td>
<td>43</td>
</tr>
<tr>
<td>Biomedical Scientist</td>
<td>Support staff - Pathology</td>
<td>Observed</td>
<td>44</td>
</tr>
<tr>
<td>Lab Manager</td>
<td>Support staff - Pathology</td>
<td>Interviewed</td>
<td>75</td>
</tr>
<tr>
<td>Consultant Surgeon</td>
<td>Surgeons &amp; Hospital based Researcher</td>
<td>Interviewed</td>
<td>8</td>
</tr>
<tr>
<td>Tissue Bank Manager</td>
<td>Tissue Bank Staff</td>
<td>Interviewed</td>
<td>4</td>
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<tr>
<td>Tissue Bank Manager</td>
<td>Tissue Bank Staff</td>
<td>Interviewed</td>
<td>10</td>
</tr>
<tr>
<td>Tissue Bank Manager</td>
<td>Tissue Bank Staff</td>
<td>Interviewed</td>
<td>12</td>
</tr>
<tr>
<td>Clinical Research Associate</td>
<td>Tissue Bank Staff</td>
<td>Interviewed</td>
<td>13</td>
</tr>
<tr>
<td>(non-researcher)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tissue Bank Manager</td>
<td>Tissue Bank Staff</td>
<td>Interviewed</td>
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</tr>
<tr>
<td>Tissue Bank Manager</td>
<td>Tissue Bank Staff</td>
<td>Interviewed</td>
<td>41</td>
</tr>
<tr>
<td>Tissue Bank Coordinator</td>
<td>Tissue Bank Staff</td>
<td>Interviewed/Observed</td>
<td>46</td>
</tr>
<tr>
<td>Tissue Bank Manager</td>
<td>Tissue Bank Staff</td>
<td>Observed</td>
<td>47</td>
</tr>
</tbody>
</table>
Table A-11 gives an overview of the contents of the professional groups and roughly the number of professionals included in the study from each group. The numbers in this table do not add up to 81 because professionals occasionally fell into more than one professional group.

**Table A-11 Overview of professional groups consulted**

<table>
<thead>
<tr>
<th>Profession-group</th>
<th>Job roles included</th>
<th>Number of professionals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue Bank Staff</td>
<td>Tissue Bank Manager, Tissue Bank Coordinators, Tissue Bank Facilitators, Tissue Bank Scientists, Clinical Research Associate (non-researcher), Lab Manager</td>
<td>17</td>
</tr>
<tr>
<td>Hospital based Researcher</td>
<td>Clinical Trial Chief Investigator, Tissue Researcher, Consultant Clinician, Consultant Pathologist and Researcher, Designated Individual for Molecular Biology Lab, Consultant Oncology, Clinical Research Fellow, MD and Researcher,</td>
<td>13</td>
</tr>
<tr>
<td>Pathologists</td>
<td>Consultant Pathologist, Histopathologist, Trainee Histopathologist, Advanced Practitioner, Pathologist</td>
<td>12</td>
</tr>
<tr>
<td>Support staff - Pathology</td>
<td>Laboratory Manager, Senior Biomedical Scientist, Biomedical Assistant, Biomedical Scientist</td>
<td>10</td>
</tr>
</tbody>
</table>
### Appendices

#### Meetings

Meetings are referred to throughout the analytical chapters by numbers 1–8; see Table A-12 for information about each of these.

<table>
<thead>
<tr>
<th>Profession-group</th>
<th>Job roles included</th>
<th>Number of professionals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Support staff - Academic</td>
<td>Departmental Administrator, Tissue Board staff, Biomedical Scientist, Research Technician</td>
<td>7</td>
</tr>
<tr>
<td>Academic Researcher</td>
<td>Reader in Molecular Biology, University Researcher, PhD student, University Professor</td>
<td>6</td>
</tr>
<tr>
<td>Doctors</td>
<td>Consultant in Medical Oncology, Doctor in Oncology,</td>
<td>6</td>
</tr>
<tr>
<td>Clinical Trials Unit Staff</td>
<td>Clinical Trials Research Nurse, Clinical Trials Coordinator, Clinical Research Assistant</td>
<td>5</td>
</tr>
<tr>
<td>Funders</td>
<td>Funding Strategy, Funder Research Governance</td>
<td>5</td>
</tr>
<tr>
<td>Harmonisation Organisation</td>
<td>University researcher, ELSI researcher, lawyer</td>
<td>4</td>
</tr>
<tr>
<td>Research Nurse</td>
<td>Research Nurse, Clinical Trials Research Nurse</td>
<td>3</td>
</tr>
<tr>
<td>Surgeons</td>
<td>Consultant Surgeon</td>
<td>2</td>
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<tr>
<td>Government Bodies</td>
<td>Human Tissue Authority Staff Member, Scottish Government Representative</td>
<td>2</td>
</tr>
<tr>
<td>Research Governance</td>
<td>Research Governance Coordinator</td>
<td>1</td>
</tr>
<tr>
<td>Patient Representative</td>
<td>Patient Representative</td>
<td>1</td>
</tr>
<tr>
<td>Interventional Radiologist</td>
<td>Interventional Radiologist</td>
<td>1</td>
</tr>
<tr>
<td>Professional Body</td>
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</table>
### Table A-12 List of meetings and conferences observed during the research

<table>
<thead>
<tr>
<th>Meeting No.</th>
<th>Description</th>
<th>Scope and organiser</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Tissue bank network annual meeting</td>
<td>International, organised by a tissue bank network.</td>
</tr>
<tr>
<td>2</td>
<td>Meeting for those interested in collaboration in human tissue research</td>
<td>Country specific, funder organised</td>
</tr>
<tr>
<td>3</td>
<td>International meeting on harmonising data</td>
<td>International, organised by academic institution.</td>
</tr>
<tr>
<td>4</td>
<td>European project meeting</td>
<td>International, organised by European project.</td>
</tr>
<tr>
<td>5</td>
<td>Meeting on human tissue research</td>
<td>Country specific, organised by a tissue supply intermediary</td>
</tr>
<tr>
<td>6</td>
<td>Tissue bank accreditation system meeting</td>
<td>Country specific, organised by a cancer tissue bank network</td>
</tr>
<tr>
<td>7</td>
<td>Tissue bank network annual meeting</td>
<td>International, organised by tissue bank network.</td>
</tr>
<tr>
<td>8</td>
<td>Professional organisation meeting, annual conference</td>
<td>Country specific, organised by professional association</td>
</tr>
</tbody>
</table>
BIBLIOGRAPHY


European Society for Medical Oncology, 2008. *Improving Rare Cancer Care in Europe: Recommendations on Stakeholder Actions and Public Policies.* Lugano, Switzerland: European Action Against Rare Cancers. Available from: http://www.rarecancers.eu/IMG/pdf/ESMO_Rare_Cancers_RECOMMENDATIONS _FINAL.pdf [Accessed 09/09/10].


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