Ethical and Legal Considerations in Human Biobanking: Experience of the Infectious Diseases BioBank at King’s College London, UK

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1. Introduction

Since the dawn of time Homo sapiens have collected human body-parts for a variety of reasons (Lassila & Branch, 2006; Aquaron et al., 2009; Daily Telegraph, 2011). Similarly, representations of pathological lesions have been collected for educational purposes for at least three hundred years (e.g. the Hunterian Museum in Glasgow has preserved plaster casts of diseased tissues). A biobank is a generic term to describe any collection of biological materials and may take many forms, ranging from the preservation of plant seeds (e.g. the Svalbard Global Seed Vault, Norway) or, the storage of human materials for transplants (e.g. corneal biobanks). Others collect human materials for artificial insemination (sperm, eggs and embryos), for forensic investigations and animal materials to assist in the preservation of endangered species such as the Iberian lynx (Leon-Quinto et al., 2009). Some biobanks only collect a single type of sample such as DNA (genebanks), whilst others archive a wide variety of clinical materials. Until recently the modus operandi of most medical researchers was to use fresh clinical materials to test a specific hypothesis. The premise was either proven, or not, and then the process repeated to answer subsequent questions. This approach is incredibly wasteful since materials not directly needed to test each argument were discarded. In contrast, clinical biobanks can archive and distribute complete sets of materials from patients with diseases to multiple researchers thereby maximising the benefit of every donation. They can also revolutionise the understanding of very rare conditions by gradually accumulating sufficient numbers of samples –or, by the exchange of samples between multiple biobanks (networking) - to permit statistically-significant conclusions to be derived.

These advantages of biobanks were recognized by Time magazine as ‘one of the ten ideas that are changing the world right now’ (Park, 2009). This Chapter will be confined to those issues confronting biobanks which collect human materials for medical research. Such
archives can be subdivided into those which have the aim of answering one specific research question (e.g. the Multiple Sclerosis Brain bank) as opposed to systematic biobanks such as the Infectious Diseases Biobank (IDB) at King’s College London (KCL) (Williams et al., 2009), which collects clinical materials with no specific research question in mind. The growing popularity of biobanks in medical research in recent years has inevitably raised new and important ethic and legal questions regarding how they should be managed and regulated. For example, recently, the German Ethics Council has proposed that biobanks should be regulated on the basis of five ‘pillars’ including the concepts of: confidentiality; open informed consent; careful ethics review; sample quality-assurance; and, a transparency of the biobank’s goals (Deutscher Ethikrat, 2010). Here some of the most contentious ethico-legal issues facing clinical archives are considered, including: (i) the nature of the contract (i.e. informed consent) between the subject and the researcher; (ii) the concept of property or ownership rights in respect to body tissues and fluids; (iii) the duty of care of a biobank to the donor, the sample, the researcher and, society. This is contextualised against historic turning points which have led to the regulatory structures currently in force in the UK. Finally, the organization of the UK’s IDB at KCL is described and proposed as a model system for facilitating research into infectious diseases.

2. Ethical considerations in human biobanking

2.1 Novel challenges associated with biobanking

The idea of a biobank to facilitate medical research would appear to be a worthwhile and commendable activity to most people. However, the establishment of such archives raise not only many of the same ethical problems that face the medical community (particularly those involved in recruiting organ donations), but also some unique questions of their own, for example:

- How can a volunteer provide fully ‘informed consent’ when neither they nor the recruiter have any idea about the nature of future research which will be performed on the donated sample?
- Donating a sample for no pressing medical reason could be questioned since this relatively benign procedure carries an appreciable risk of adverse events (in one study the rate was 0.59% of 89,000 blood donations: of these ~15% were haematomas and 77% vaso-vagal reflex: Garozzo et al., 2010).
- Who actually owns the donated sample?
- Does a donated sample have a commercial value and can it be sold?
- What happens if research discovers that a volunteer has a potentially deadly disease?
- How can biobanks insure that they are representative of the local community?
- Should biobank samples be used for ‘trivial’ (e.g. cosmetics development) or ‘controversial’ (e.g. stem cell, cloning etc.) research?

2.2 An ethical framework

To answer such questions biobanks (and their regulators) must draw on contemporary ethical codes, attitudes and opinions to provide guidance to best practice. Whilst this approach can provide discussion points to it does not always produce definitive answers (Gillon, 1985). The earliest consideration of medical ethics was probably the Hippocratic Oath, which introduced the concepts of respecting patients as individuals and doing no
harm (Farnell, 2004). Similar sentiments are expressed in the prayer of Maimonides, originally believed to have been written by the 12th-century physician-philosopher (Friedenwald, 1917). More probably, this prayer was written by M. Herz, a physician and pupil of the Konigsberg philosopher Immanuel Kant, as print versions can only be traced back until 1793. More contemporary views on medical ethics were crystallized in a 1902 book by Dr Albert Moll on ‘Ethics of the Physician’ (Hahn, 1984). Two major ethical issues raised by biobanks revolve around consent and the ownership in human tissues. The justification for consent stems from the notion of personal sovereignty; the exclusive right an individual holds over their own person. This concept is historically rooted in liberal and political thought, as noted by JS Mills: ‘over himself, over his own body and mind, the individual is sovereign’ (Mills 1972). Equally though, Kant believed that the human ‘exists as an end in itself, not merely as a means to be used by this or that will at its discretion’ (Gregor, 1998).

Indeed, personal sovereignty now serves as the justification for the majority of articles enshrined in the Universal Declaration of Human Rights. Whilst consent is a necessary component in everyday life and medical research it is debatable how ‘informed’ consent need be. On the one extreme consent procured through misleading information (or under duress) cannot be considered valid. At the other end of the scale an individual may be informed of the risks and side effects of a medical procedure, but is not expected to comprehend the full complexities of the issues. Consent is often reduced to a subtle paternalism in regards to the unequal position of patient-subject to the researcher, as well as addressing how ‘informed’ a research project can be.

Although respecting personal sovereignty is necessary, there are also ethical principles in favour of a communal duty to society. As the aim of a biobank is to facilitate medical research (which in turn will aid the development of future treatments for the general good of society), the question arises as to whether there is an obligation to assist such endeavours. As Mills states ‘there are also many positive acts for the benefit of others that he may rightfully be compelled to perform: such as to give evidence in courts of justice; to bear his fair share in a common defence; or in any other joint work necessary to the interests of the society of which he enjoys the protection’ (Mills, 1972). Thus, respecting personal sovereignty does not negate the argument in favour of a public duty to assist such endeavours. Indeed, utilitarian arguments for the ‘greatest good for the greatest number’ (Bentham’s ‘felicific calculus’: Mitchell, 1918) and Kant’s transcendental deduction of a moral duty (Paton, 1948) may to some degree also imply an obligation to donate samples to a biobank.

Locke’s concept of property is based on the premise that an individual owns the labour of their body, which when mixed with something in nature, confers a property right in the produced object. Indeed a Lockean justification of property rights was accepted in the US case John Moore v The Regents of the University of California (1990) as a foundation for a claim on a human cell-line. Thus, Lockean justification for ownership of samples in a biobank could be constructed in a similar fashion; the labour expended in collecting, preparing and storing a biobank’s samples confers a right of ownership. Although a degree of ownership exists in relation to human samples it is better to conceive this as conditional ownership (or ‘custodianship’) rather than an absolute ownership.

2.3 Some historical precedents leading to research ethics regulation
Self-regulation of biobanks based upon general ethical principles may seem a reasonable approach to managing a few samples of blood or urine which have been willingly donated for research. However, a series of notorious cases from the 19th century up to the present...
day have so shocked the public that legislation of medical ethics and the storage of human body parts became inevitable: some of the most infamous cases are outlined below.

**Body-snatching:** The UK Murder Act of 1752 meant that the only legal source of corpses for anatomy was those of executed prisoners; however, this was insufficient to supply the demand from medical schools. Stealing a corpse was only regarded as a minor crime and thus evolved into a lucrative business. In 1827/8, the Edinburgh grave-robbers Burke and Hare realized that institutions paid more for fresh corpses and thus graduated from body-snatching to murder in order to meet this demand (Lancet, 1829; Howard & Smith, 2004). The subsequent conviction of Burke in 1829 led to the UK Anatomy Act of 1832 which stipulated that anyone practising anatomy must hold a licence and be responsible for the correct treatment of corpses. This act was repealed by the Anatomy act of 1984 which, in turn, was replaced by the Human Tissue Act of 2004 (below).

**Genocide:** In the 1930s/40s the National Socialist German Worker’s party (NSDAP) became obsessed with the ideas of social Darwinism, eugenics and the Nietzsche concept of ‘superman’ (Taha, 2005). On this basis the regime initially justified killing those with congenital defects in the T4 (Tiergarten-4) euthanasia programme (Freidlander, 1995). This was criminal programme was subsequently extended to include anyone that the NSDAP deemed ‘sub-human’ (political opponents, Russian prisoners of war, and, notably the near genocides of European Jews and Roma: Bachrach, 2004). As part of this Holocaust some victims were also subjected to non-consensual medical experiments (e.g. LD<sub>50</sub> type testing of humans exposed to hypobaric or hypothermic conditions). Additionally, the NSDAP also assembled a collection of skeletons from euthanized prisoners for the Institute of Racial Hygiene to act as a historic record (and the basis for scientific study of) extinct human ‘races’. At the end of the war the Nuremberg ‘Doctors Trial’ sentenced some of those responsible and resulted in the development of the Nuremberg code of practice for research involving humans (Table 1: US Government Printing Office, 1949). This is an important document since it has served as the basis of almost all subsequent refinements in medical ethics such as the most recent version of the Declaration of Helsinki (World Medical Association [WMA], 2009).

**Unit 731:** A less-well publicised series of medical crimes of the Second World War included those perpetrated by the Imperial Japanese Army’s Unit 731. This was euphemistically named the ‘Epidemic Prevention and Water Purification Department’ of the Kwantung Army Group in Harbin, occupied China (Alibewk & Handelman, 1999). This unit experimented on over 10,000 humans in studies involving conscious, non-anaesthetised, vivisections, weapons testing (e.g. the effects of flamethrowers, hand grenades etc. upon live humans), as well as bio-weapons research (Harris, 1994; Kristof, 1995; Barrenblat, 2004).

**Tuskegee syphilis study:** A study of 400 poor African-American men with syphilis was initiated in 1932. To induce participation, recruits were given free medical care, meals and burials and in return provided samples of blood and cerebro-spinal fluids to researchers (Roy, 1995; Crenner, 2011). At no point were the recruits informed that they had syphilis, nor were they treated for it. The 40-year study was particularly controversial because the researchers failed to treat patients even after the discovery that penicillin was an effective cure. In 2010 it was subsequently revealed that in Guatemala the same study had been extended, between 1946-1948, to include actually infecting prisoners, soldiers, and patients in a mental hospital. A total of 696 men and women were exposed to syphilis without their informed consent. As a direct result of these revelations the US Congress passed the National Research Act in 1974 and created a commission to study construct regulations governing studies which involve human participants (Prograis, 2010).
1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him/her to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonable expected; and the effects upon his health which may possibly arise from participation. The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted where there is a prior reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

Table 1. The Nuremberg code for medical research involving humans.

*Alder Hey hospital scandal:* An investigation into the retention of hearts at hospitals in Bristol UK in the early 1990s led to a public inquiry. This subsequently found that a large number of hearts were also being held by the Alder Hey Children's Hospital and
the Walton Hospital. In 2001 the Redfern Report (Royal Liverpool Hospital Children’s enquiry, 2001) was published and this led to public outcry when it was revealed that Prof van Velzen had archived organs from every child subjected to a post mortem. Around 500,000 tissue samples were being held without any realistic likelihood of them ever being used for research. These revelations led to the creation of the Human Tissue Authority and the 2004 Human Tissue Act and in the UK.

Desecration of Alaister Cooke’s remains: In 2005 it was discovered that the bones of Alaister Cooke (a distinguished BBC correspondent) and those of others had been surgically excised without permission prior to cremation by Biomedical Tissue Services Ltd. (Smit, 2008). The company then sold the treated bones for use as surgical grafts. Cooke was suffering from bone cancer when he died which would have made his tissues unsuitable for such a purpose. Reports revealed that the people involved in selling the bones altered his death certificate to hide this fact; subsequently M. Mastromarino, a former New Jersey dentist, was sentenced to between 18 and 54 years imprisonment.

The more contemporary of these cases illustrate that body-snatching is a practice which is not restricted to the dark days of the 19th century and will no doubt continue in illicit markets for the foreseeable future. Common themes linking all of these examples include: a dereliction of basic medical responsibilities by physicians; lack of compassion; complete disregard of the dignity and autonomy of the participants (and/or that of the relatives of the deceased); the storage of body parts; and, the absence of consent by the participants.

2.4 Informed consent and tissue banks

A fundamental requirement of contemporary medical ethics is that of ‘informed consent’ be provided by a participant before any study, or procedure, can be performed as discussed above (2.2). However, the phrase is fundamentally misleading (Kaye, 2004), since it implies a comprehension of the relevant facts and all possible outcomes of the research. However, how can non-medically qualified members of the public truly be considered to be fully ‘informed’? Indeed, by definition the researchers themselves can only best-guess the possibilities (‘if we knew what we were doing, it wouldn’t be called research, would it?’ Albert Einstein). This situation is exacerbated in the case of biobanks where samples may be used in future research projects that have not yet been envisioned using techniques and technologies which have yet to be developed. Indeed, one study of biobank donors found that they did not consider themselves well informed about what their samples would be used for (Hoeyer et al., 2005).

This issue was been addressed by the German Ethics Council which takes the view that: ‘if donors have been informed of the indefinite nature of the actual future applications, they will be aware that they are agreeing to an uncertainty. This uncertainty is not acceptable if it involves more than minimum health risk which is not the case with Biobanks’ (Deutscher Ethikrat, 2010). Thus ‘open’ or ‘broad’ consent to future usage of donated samples has been proposed as best practice for biobanks (Hansson et al., 2006). Similarly, the council of Europe’s biobanking recommendation acknowledges the conflict between the traditional informed consent and the needs of population genetic databases, and as a result stated that consent need not be specific, but it must be as specific as possible with regard to unforeseen uses (Council of Europe, 2006).

Such proposals are not without their critics who see equivalence between the broadening of consent and the dilution of ethics which may result in increased public distrust (Hofmann, 2009). Though others have noted that actually the reverse may be true (Lipworth et al., 2009). Some commentators have gone further, suggesting that for genebanks and for population databases, informed consent should be abandoned altogether (Kaye, 2004). Furthermore, in countries such as the UK where free healthcare is provided to all by the state, there is debate as to whether there is an automatic moral obligation upon patients to automatically donate...
any excess clinical material taken for diagnostic purposes to medical research: *i.e.* the introduction of an ‘opt-out’ as opposed to the current ‘opt-in’ system. Such ‘opt-out’ genebanks are already in operation in Europe (*e.g.* the Vanderbilt DNA databank) and have driven the development of new approaches to the governance as well as innovative public education and communications strategies (Pulley *et al*., 2010).

### 2.5 Inclusivity of biobanks

There are many problems facing researchers in gaining the public’s confidence in donating samples to biobanks. In the case of donations to genebanks public refusal to consent (revealed by a questionnaire) was explained by a lack of personal relevance of the contribution and feelings of discomfort related to the possibility that the DNA would be used for purposes other than the original study (Melas *et al*., 2010). The underlying concerns revolved around issues of integrity, privacy, suspiciousness, and insecurity. Interestingly though despite concerns about privacy another study of 4,569 US participants revealed that 60% would be willing to participate (Kafam *et al*., 2009). However, the same study noted that ethnic minorities, women and those without a College degree, were concerned that the government could gain access to their personal information. Such concerns may be translated into an unwillingness not to engage with biobanks. Indeed, there are well acknowledged problems in recruiting sufficient organ donations from ethnic minorities resulting in a higher mortality amongst these communities from diseases necessitating transplants (Bratton *et al*., 2011; Salim *et al*., 2010). In the USA educational schemes have been introduced and appear to have partially resolved this problem (Callender *et al*., 2010).

In industrialized nations the ethical points of reference for regulating medical research have inevitably been drawn from classical western moral philosophies and Judeo-Christian religious traditions. Relatively recently, the UK population has transformed from a predominantly Caucasian European Christian admix into a diverse multi-cultural/ethnic society as a result of immigration. Whilst more recent migrants from Eastern Europe share many of the cultural and religious traditions of the former, others from Africa, the Indian sub-continent and Asia often do not. Research biobanks (like organ donation schemes) need to be representative of their communities, consequently they must: (i) appreciate the cultural and religious sensitivities of ethnic minorities; (ii) understand historic negative perceptions of Western medical research, and, (iii) use this information to insure that ethnic minorities become fully engaged in such research projects.

An example of such cultural differences include Chinese tradition where self-determination is not a recognized phenomenon (Bowman & Hui, 2010), meaning that the family -rather than the patient- receive clinical information and make decisions to coordinate treatment. In Judaism, bodies are buried undisturbed and quickly after death as a matter of respect. Discussion within the Jewish faith about whether it is permissible to harvest organs for transplant from brain-dead persons is ongoing (Bresnahan & Mahler, 2000). Similarly, amongst Hindus and Sikhs the individual is caste-bound in its decision, and there is the concept of purification by death/rebirth axis: organ donation or contribution to a biobank might be seen to interfere with. In a systematic review of the opinions of twenty-eight major religions only one, Shintoism, was noted to be completely antagonistic to the idea of organ or tissue donation after death (United Network for Organ Sharing [UNOS], 2000). This is based on the concept that the cadaver is impure and dangerous, and injuring it is a serious crime as it damages the ‘*itai*’ (the relationship between the dead and the bereaved).

Many ethnic minorities resident in industrialized nations also have perceptions of ‘scientific imperialism’ or ‘bio-colonialism’ (Emerson *et al*., 2011) or scientific racism (*e.g.* the Tuskegee study 2.3 above). Not surprisingly there can be considerable distrust of western medical
research. A recent example of this was the reticence of the Indonesian government to share samples of the H5N1 influenza virus with the international scientific community (Gelling, 2007). One suggestion to restore public faith is the proposal to establish a tissue trust to serve the interests of the common good (Emerson et al., 2011) and would act by involving tissue donors and community members in research governance. These issues are of considerable importance to the current ‘opt-in’ model for biobanking in the UK. Indeed, for biobanks to be effective they must collect tissues from all of the community. Failure to do this may mean that downstream medical research using a biobanks samples may effectively result in further examples of scientific racism in that some research may be race-specific. These concerns are also a persuasive argument for locating biobanks in ethnically-diverse regions of a country.

Extending this concept of inclusivity further is the idea of harmonizing legal and ethical permissions internationally. This is important as a major ambition of biobanks world-wide is to establish networks for the international exchange of important clinical samples (Pearson, 2004). Whilst differences in national laws may complicate this process it has been suggested that if all countries simply abide by the Helsinki Declaration (WMA, 2009) any additional regulation would be counterproductive (Hansson, 2011). In contrast, others have argued in favour of a greater harmonization of ethics legislation between nations (Chalmers, 2011). Harmonization of biobank regulation is an important future goal since a survey of 126 European biobanks noted that most had currently only a very limited networking activity, and just a half having policies for cross-border sharing of samples (Zika et al., 2011).

### 3. UK regulations and statutory bodies

In the UK there are three major governmental bodies which regulate medical research. Regulation of research ethics is by one of two types of review bodies: universities (e.g. the King’s College London’s College Research Ethics Committee) and the government’s National Research Ethics Service (NRES, 2007). Whilst there is some overlap between these two bodies (e.g. human studies not involving NHS patients can be considered by both, investigations using NHS patient samples can only be considered by the latter), most medical researchers use the NRES’s local research ethics committees (LREC) scheme. LRECs have evolved over recent years so that now specialized committees exist which are trained in issues arising from biobanking.

Storage of human tissues is regulated by a different body, the Human Tissue Authority (HTA) and premises keeping human tissues for research are required to hold a specific type of HTA licence and are subject to periodic inspections. The definition of tissues by the HTA differs considerably from the biological meaning (a collection of the same kind of cells with a common structure and function: e.g. muscle, skin and bone). For the HTA, a tissue is considered to be a mixture of different cells acting with common purpose (e.g. such as cells of the immune system). Thus, blood is considered a tissue under the HTA act, though so too are faeces and urine since they also contain a mix of immunological cells. Conversely, a cell-line derived within a week of isolation from the body is not considered a tissue on the basis of its homogeneity. Similarly, hair – not containing cellular architecture - is not regarded by the HTA as a tissue. Confusingly, if tissue architecture architecture is immediately disrupted the resultant biochemical mix is not considered a tissue by the authority (e.g. DNA extracted from a human tissue).

Anyone who collects, stores, uses, discloses or destroys identifiable personal information about living individuals, must also comply with the UK’s 1998 Data Protection Act (DPA) and the Common Law duty of confidence. For the deceased, researchers must comply with the latter only. Anonymised personal information (as most frequently collected by biobanks)
whether concerning the living or the deceased, falls outside the scope of these legal requirements. The DPA applies to ‘personal data’, which are data that relate to a living individual who can be identified either from those data alone or from those data taken in conjunction with other information that is available to the person who controls the data. When gathering identifiable personal information researchers should aim at all times to ensure that its processing is defensible as both ‘fair and lawful’. This requires as much transparency as possible about the uses to which data will be put and any risks that might be involved. The net effect of the DPA act is that centres which recruit and anonymise human data and clinical materials prior to submitting them to a biobank are subject to the provisions of the DPA, thus such personal information must be kept secure at all times. Dependent on the nature of the human samples being archived the Health and Safety Executive (HSE) will often need to be consulted by biobanks, particularly if this includes the use of clinical materials from patients infected with dangerous human pathogens (e.g. the IDB below).

4. The KCL infectious diseases biobank as a model system

4.1 Vision

Biological resource collections such as the Multicenter AIDS Cohort Study (Kingsley et al., 1987) and the Sidney blood bank cohort (Oelrichs et al., 1998) have helped drive important advances in the understanding of the pathogenesis of human immunodeficiency virus (HIV). In 2005 there were many biobanks in the UK dedicated to the collection of brains or cancer biopsies, but no equivalent facility for the collection of materials for HIV, or indeed any other infectious diseases, research. Even within Europe only three other biobanks held stocks of publicly-accessible material for HIV research, the Spanish HIV biobank (Garcia-Merino et al., 2009, 2010), the Sapienza University HIV biobank in Italy, and the Picardie biobank which holds only sera from infected subjects (Chaigneau et al., 2007). A consultation exercise with researchers at KCL indicated that an infectious diseases tissue bank facility would be welcomed by many. This led to the establishment of a group of clinicians and scientists to develop what has now become the KCL IDB. The central issue of the IDB was to collect materials which are of significant value to researchers. For example, around this time many pathology departments were (and still are) rebranding themselves as biobanks to attract research funding. The problem with this approach is that such pathological collections are plentiful and the types of samples preserved do not always coincide with the requirements of researchers (e.g. materials suitable for molecular biology studies).

It was therefore established early on that the IDB would not be a genebank, but rather an archive of a broad range of clinical materials which would enable a spectrum of proteomic and genomic studies to be performed (e.g. containing live lymphocytes, RNA, DNA, plasma, sera, cerebro-spinal fluids etc.). These would be prepared and stored to a high-standard and fully documented in terms of sample tracking and processing details. The initial patient cohorts selected for study were those infected with pathogens that were of significance to the local community and also to local researchers. These were patients infected with HIV, hepatitis B virus or, with bacteraemia (especially methicillin-resistant Staphylococcus aureus). In the case of the major sample collection from HIV-infected subjects it was further decided to selectively recruit those with particularly interesting clinical histories. For example, those initially recruited were HIV-1 clade B infected individuals who either progressed to disease unusually quickly (rapid progressors) or, very slowly (long-term non-progressors) as these extremes are most likely to yield important answers to the determinants of pathogenesis. Importantly, none of these patients were to be receiving medication so that the natural history of the infection and disease processes could be studied.
4.2 Location and setting
The IDB is uniquely located for purpose as the local population in Lambeth and Southwark is large (~4 million) and extremely diverse. Indeed, after English the second most common spoken language is Yaruba (African) and then Portuguese (Lambeth census, 2001). This community also suffers from some of the highest rates for HIV infections, the viral hepatitides and sexually-transmitted infections in Europe. The prevalence of UK HIV infections is highest within this area and over 10% of all UK HIV cases are treated by local clinics. This is exemplified by the facts that amongst pregnant women attending St Thomas’ Hospital to deliver their babies around 1% are infected with HIV and 2% with hepatitis B (Health Protection Agency, 2008). The IDB is embedded within the KCL Department of Infectious Diseases which is affiliated to King’s Health Partners and Guy’s And St Thomas’ NHS Foundation Trust. The latter hosts an Academic Health Science Centre (AHSC) and also an NHS National Institute of Health Research (NIHR) comprehensive BioMedical Research Centre (cBRC). The latter offer considerable advantages since it has established two clinical research facilities (CRFs) that effectively comprise of two wards and resources in which to conduct clinical trials.

4.3 Ethical permissions for the IDB
The prerequisites for the IDB’s ethics included the concept of the dignity and autonomy of the volunteers yet also acknowledged the uncertain future research uses of biobank samples. Thus, the patient’s information sheets and consent forms were designed to make it absolutely clear about the uncertainty of future usage. They also make it transparent that their samples would probably be used for genetic research and, the possibility that they would be used both for academic or commercial research purposes anywhere in the world. It is also made clear to participants that their healthcare would be unaffected by their decision to donate a sample, that they could withdraw from the biobank project at any time (and also demand that previously donated samples be destroyed) in line with most recommendations (Gertz, 2008) and that all samples would be anonymised. An additional safeguard was that should a downstream third-party researcher make a finding that was pertinent to the health care of the volunteer, this information would be passed back up through the management chain via the biobank to the clinicians at the tissue collection centre (TCC) who could then break the code and advise patients accordingly (since codes linking the patient’s NHS number and the biobank code are only held at TCCs). These core principles were consequently remarkably similar to those proposed by the German Research Ethics Council some four years later (Deutscher Ethikrat, 2010).

The timing of the establishment of the IDB was far from ideal since the HTA act was just being implemented. Like any such legislation it is the interpretation which sets the precedents, a process which can take some time. Currently the IDB has ethical permission from the Southampton and South West Hampshire Research Ethics Committee (B) which extends until 2014 (reference # 09/H0504/39) to collect research samples (blood, urine and faeces) and (any) residual diagnostic samples from patients (adults, children and infants) with any infectious or inflammatory disease who are attending a routine clinical appointment.

The IDB cannot recruit from patients who are prisoners or those who are incapable of providing informed consent (other than children where the parent/guardian can consent for them). There are also restrictions for researchers and IDB samples cannot be used for ‘trivial’ or ‘controversial’ research projects such as those involving: fertility, reproduction, stem cells, cosmetics or animals. The IDB can establish TCCs at any NHS location in England, Wales or Northern Ireland with the co-operation with a local medical Consultant. Local NHS R&D
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Offices have to be informed that a TCC is being established but can play no other role in the process. The IDB governance committee is also enabled (through devolved ethics powers) to act as an LREC and provide ethical opinions upon studies wishing to access IDB samples. The IDB stores samples under the authority of an HTA research license held by the Guy’s Hospital campus (reference # 12521). This not only covers the storage of materials by the IDB, but also those researchers who remove IDB samples to other sites for the duration of their ethical permission. A diagram of the IDBs operations is provided (Figure 1).

**Fig. 1. Management of the IDB.**

**4.4 Governance**

The IDB has a Governance Committee comprising of scientists, doctors, representatives of funding bodies and of the patients. This Committee is responsible for managing the IDB, strategy decisions, ensuring that it conforms to current legislative requirements and also to local Medical school regulations. The IDB is regularly audited by the internal KCL Medical School representatives and by the HTA (–four times in 2010) and the results of these checks are passed back to the Governance Committee. Researchers wishing to access the IDB’s samples submit a simple two-page application detailing what they propose to do and, the type and numbers of samples required. These details are scrutinized by the IDB’s Governance Committee for scientific validity and also for any ethical dimensions. If successful, researchers sign a materials transfer agreement (MTA) and the samples are released.
Staff involved in recruiting volunteers must all have completed ‘in house’ courses on 'consent taking', 'good clinical practice' and phlebotomy. Copies of these certificates are held by the IDB. Members of the IDB staff are also encouraged to undertake an academic module in ethics, philosophy and religion (a three year ‘Associate of KCL’ course). The Governance Committee has also established a clear policy on charging researchers to access the IDB’s material; they may either agree to pay a fixed rate for the individual samples or contribute funds towards the salaries of IDB staff, to offset the processing and storage costs incurred by the IDB. Researchers are encouraged to approach the IDB early on during the preparation of grants so that projected costs can be included in their applications.

4.5 Quality control
The IDB utilizes standardized operating procedures (SOPs) based upon EEC standards (ISO guideline 34, # 17025:2005) and works within the UNE-EN-ISO 9001:2000 guidelines to facilitate future inter-biobank networking capabilities. Samples are continuously tracked from the time of venepuncture, the time of courier collection from the TCCs, through to freezing at the IDB, with a target of processing >75% of samples within four hours of the bleed. All materials from patients with infections are processed in negative-pressure category III laboratory and stored in locked -80 °C freezers. All of the freezers are: on a protected hospital electricity supply; alarmed to the IDB’s staff mobile telephones; and, checked daily for temperature fluctuations. None of the released samples from the collections have undergone a freeze-thaw cycle. Purified DNA samples are tested for the concentration of DNA and, by polymerase chain reaction (PCR) amplification of the housekeeping gene β-globin, for the absence of PCR inhibitors prior to release. In-house assessment of viral RNA viability has also revealed that viral RNA and sequences can be recovered from all plasmas of HIV patients so far tested (for those with viral loads of >350 copies per ml). Similarly, an independent analysis of human genomic RNA integrity has demonstrated that all of 104 samples were of high-quality (mean RNA integrity values of 9.3, on a scale where 1=degraded and 10=completely intact RNA) and were successfully used to generate DNA for transcriptome analysis (Kozlakidis et al., 2011). Ultimately, the IDB aims to have all of its procedures, SOPs and operations validated by the International Standards Organisation.

In addition to merely maintaining the samples under the IDB’s custodianship we have also sought to enhance their research value. For example, for the core cohort of HIV infected patients approximately 33.3% of samples have been genotyped for their HLA class I and II alleles and their plasma viruses have had their Gag genes sequenced. The Gag region is important as protein products of this reading frame are believed to be important determinants in viral escape from the innate and adaptive arms of the immune system (Deml et al., 2005). To date, several hundreds of full-length Gag genes have been cloned and sequenced (and the latter data deposited in Genebank: accession numbers FN597659-FN600533). These cloned Gag genes are available to researchers by arrangement. The intention is to obtain equivalent data for the complete HIV cohort. The other type of quality control that the IDB is actively involved in is monitoring that the samples being collected are those which are of (a) most clinical significance and (b) representative of the local community. Initial analyses of the first 200 HIV patient volunteers indicated that it was collecting a population greatly enriched for those with unusual rates of disease progression and that the ethnicity of the volunteers matches well with that of the local community (Kozlakidis et al., In Press).
4.6 Transparency
Given the multiplicity of studies that any individual sample may be used in, the Governance committee decided that logistically it would be impossible to provide individual volunteers with research feedback on their individual samples, despite reports that this is the preference of potential volunteers (Meulkamp et al., 2010). However, the IDB does attempt to provide feedback in the types of studies performed and these data are displayed on the IDB’s website (http://www.kcl.ac.uk/schools/medicine/research/diid/centres/pii/biobank/index.html). The IDB has also publicised its mission and was reviewed in Nature Medicine (Towie, 2006), has published in Retrovirology (Williams et al., 2009), Biopreservation and Biobanking (Kozlakidis et al., 2011) and has made presentations to national and international meetings (e.g. the 2010 Biobanking Conference; the European Virology Congress in 2008 & 2010, Nuremberg and Como). The IDB director has served on the feasibility study of Biobanking in Northern Ireland (NI) for the NI NHS R&D committee (2008), the KCL College Research ethics committee and associated sub-committees (2010-) and, is chair of the IDB Governance and ethics committees. The IDB has also consulted with patient representatives and has, as a consequence, increased its electronic footprint by establishing KCL IDB sites on the social networking sites ‘Facebook’ and ‘Linkedin’.

4.7 Growth of the IDB
Since sample collection was initiated in January 2007 there has been a logarithmic growth in the number of patient visits to TCCs as well as the numbers of studies approved to access IDB samples (Figure 2). Indeed, currently the IDB is processing over three litres of peripheral venous blood per week. These examples of growth have also been matched by the expansion of the IDB into new categories of diseases. These now include those with hepatitis C virus or papillomavirus virus infections and patients with inflammatory diseases (including: as diabetes, Crohn’s disease, ulcerative colitis, systemic lupus erythematosus, and, pre-multiple sclerosis syndrome). Some of the currently approved studies are listed (Table 2), and a steady stream of research publications is starting to ensue (Nath et al., 2006, 2007; Alvarez et al., 2008; Thorborn et al., 2010). In addition, publications arising from the contract research work of the IDB are expected to increase significantly (4.8 below).

Fig. 2. Year-on-year growth of the IDB’s HIV sample collection. Gray bars indicate the recruitment of new patients in total, whereas black bars indicate the number of donations per year.
T-Regulatory cells in HIV infection
Ps20 studies in HIV infections
The roles of vpu and tetherin HIV/AIDS pathogenesis
The control of inflammation in immunity and autoimmunity
Naive B cell responses in older people
Gene expression signatures of HIV-1 infection in vivo and in vitro
ccess and study residual clinical samples made available during routine joint surgery.
Genetic variations in IL28B on the natural history of hepatitis B and C and their treatment response.
Non-infectious co-morbidities in HIV infection
Renal function and bone homeostasis in patients starting HAART
Defining the function of CD161+ CD8+ T cell subsets in HIV infection and their response to therapy
Investigating the effect of Maraviroc on Microbial Translocation in HIV infected individuals who are receiving antiretroviral therapy
The metabolic impact of Darunavir/ritonavir maintenance monotherapy after successful viral suppression with standard Atripla in HIV-1-infected patients

Table 2. Some of the types of studies currently accessing the IDB.

4.8 The IDB as a contract service
The IDB’s skill and expertise is also being currently utilized to provide research support for clinical studies performed locally, these are often intervention studies and hence require independent ethical permissions from LRECs other than that of the IDB. The largest of these is currently the KCL Human Immune Response Dynamics (HIRD) study. This ground-breaking longitudinal study is investigating the response in humans to vaccination with the H1N1 (‘swine flu’) influenza vaccine using a protocol was approved by the Brent LREC (09/H0717/88). Briefly, the study involves the IDB collecting and archiving of peripheral venous blood samples from overnight fasted volunteers at the CRFs. Two pre-vaccination samples are harvested and, after vaccination (with PandremixTM H1N1 vaccine: GlaxoSmithKline Biologicals Ltd), a further four samples are collected until six weeks post vaccination. To date over 170 volunteers have completed the course of bleeds and vaccination.

5. Conclusions
This Chapter has summarized the development of some key ethical concepts which specifically impinge upon the newly emerging discipline of human tissue biobanking in terms of classical notions as well as historical turning points which have resulted in current UK legislation. In particular, this paper highlights the fundamental dilemma between the rights of the individual and their duty to the society and describes in practical terms how the KCL Infectious Diseases Biobank is regulated and managed. Whilst, the essential ethical
keystone to any biobank is the principle of informed consent, the effective functioning of a biobank necessitate that there should be as few restrictions as possible. A major challenge not mentioned above is that of the education of the general public about biobanks as one study reported strong evidence that more people are likely to embrace the idea of biobank research if they are informed (Gaskell & Gottweis, 2011). Interestingly, they proposed the use of social networking sites to promote the concept.

Now that the IDB has been established for several years most of the governance and ethics issues have been established, nevertheless new challenges are arising. Most pressing for the immediate future is improving the IDB’s IT and data processing capabilities. This arises from the facts that the IDB’s MTA which requires researchers to feedback raw experimental data and with some of the initial studies drawing to a close the quantity of information is becoming overwhelming. Ultimately though this will eventually permit the IDB to amass a detailed database on the patient volunteers and subsequently permit the multivariate analyses on these cohorts to identify important pathogenic markers.

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This innovative book integrates the disciplines of biomedical science, biomedical engineering, biotechnology, physiological engineering, and hospital management technology. Herein, Biomedical science covers topics on disease pathways, models and treatment mechanisms, and the roles of red palm oil and phytomedicinal plants in reducing HIV and diabetes complications by enhancing antioxidant activity. Biomedical engineering covers topics of biomaterials (biodegradable polymers and magnetic nanomaterials), coronary stents, contact lenses, modelling of flows through tubes of varying cross-section, heart rate variability analysis of diabetic neuropathy, and EEG analysis in brain function assessment. Biotechnology covers the topics of hydrophobic interaction chromatography, protein scaffolds engineering, liposomes for construction of vaccines, induced pluripotent stem cells to fix genetic diseases by regenerative approaches, polymeric drug conjugates for improving the efficacy of anticancer drugs, and genetic modification of animals for agricultural use. Physiological engineering deals with mathematical modelling of physiological (cardiac, lung ventilation, glucose regulation) systems and formulation of indices for medical assessment (such as cardiac contractility, lung disease status, and diabetes risk). Finally, Hospital management science and technology involves the application of both biomedical engineering and industrial engineering for cost-effective operation of a hospital.

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