

# **Disclosure or discourse?**

**A critical examination of consent in research using  
surplus clinical tissue**

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# Abstract

Patient tissue samples are a valuable resource for medical research, and can therefore be used to contribute to the well-being of people in the future. It is common when using tissue for research to seek the consent of the person it came from. Conventionally, this requires that they are given a description of the proposed research project so that they can make an informed decision about whether to consent to this use.

However, advances in technology mean it is feasible to store tissue samples in good condition for long periods. Alongside this, research techniques are continually being developed, and research results are revealing new areas for investigation. Because of these factors, a sample collected today could conceivably be used throughout the next several decades, for multiple experiments, none of which might have been thought of when the patient's consent was first sought. If full disclosure of the proposed research is necessary to support this consent, then uncertainty over future use makes this difficult to achieve when the sample is first collected.

I have described and evaluated the most prominent approaches to working around this difficulty with disclosure. Each of these approaches presents its own moral and practical difficulties, from undermining donor autonomy to placing excessive administrative burdens upon researchers. Nonetheless, the statutory requirements for consent to future unspecified use of surplus clinical tissue range across this spectrum of approaches to consent, potentially complicating international research collaborations. Publication of results, sharing research

material, establishment of further collaborations, and funding of follow-up work could all be adversely affected if there are varying consent requirements in each of the jurisdictions where the work is being conducted. A more consistent approach to the ethics of research using human tissue is required.

In order to develop such an approach, I have identified and discussed the ethical values that are most prominent when considering the use of surplus clinical tissue for future unspecified research. These values include support for the autonomy and dignity of individual donors, protection of their privacy, and respect for the concerns of minority groups within the wider community. I have also discussed the public good that can arise from this type of research, whether patients have a duty to contribute their tissue to research, and the role of consent in supporting these values.

I conclude that it is possible to support the values that I have identified, and that the key to this support is communication between those who plan and conduct research, and the community as a whole. By using a discourse between the parties concerned to identify points of concern, a standard approach to using tissue for research can be negotiated. Individual patients should still be asked for a broad consent to use of their tissue in research, which will be supported by a disclosure of how projects will be approved and how their interests will be supported. They can then make an informed decision as to whether they wish to opt in to this system.

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*In memory of Esme and Gytha.*

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# **1. Introduction**

## **1.1. The role of research in medical care**

Medical care is informed by a body of knowledge about human biology that has accumulated over time. An important source of this knowledge is the practice of systematic research carried out upon people, either upon their bodies or upon portions of tissue removed from their bodies. The goals of this type of research are to characterise the underlying function of the myriad systems that make up the human body and identify any differences between healthy and diseased systems that could be relevant to disease and healing. Researchers then use these differences to make and test predictions about how to manipulate the diseased system in ways that could eventually be used by medical practitioners to prevent or treat disease.

Improved medical care benefits current patients, by providing relief or remedy for diseases or injuries they suffer, and future patients, by enabling earlier diagnosis, limiting the impact of poor health on their lives and improving the likelihood of a cure. It also benefits the community, by reducing the likelihood that community members will require medical care in the future, by facilitating

participation in community life by all members, and by reducing expenditure of community resources on health care, enabling the provision of other community goods instead. Research contributes to these goods as well as producing economic benefits to the community as a whole and providing a satisfying occupation for those individual community members who flourish when performing and communicating research.

## **1.2. The use of tissue in research**

As an example of how research into human biology can improve the treatment of disease, I will briefly discuss the etiology of gastric ulcers. These are lesions that develop in the stomach lining of some people, which are often extremely painful due to the effects of stomach acid on the ulcerated tissue. In addition to the pain, gastric ulcers may also lead to serious, possibly life-threatening, complications such as internal bleeding and perforation of the stomach wall. It was previously thought that ulcers were caused by stress and diet, and treatments included lifestyle and diet changes along with antacid treatment. These treatments were difficult for patients to adhere to, and rarely produced more clinical benefit than temporary relief from the pain. However, a study of tissue samples taken from the stomachs of patients revealed an association between the presence of *Helicobacter pylori*, a species of bacteria, and gastric ulcers. This discovery started a sequence of research studies that led to the confirmation that infection with *H. pylori* is the underlying cause in many cases of gastric ulcers (Marshall, 1995). Furthermore, this research indicated that patients with confirmed gastric ulcers should be tested for the presence of *H. pylori* as part of their diagnosis. The outcome of this test gives doctors a clearer

indication when prescribing treatments of what approach is likely to succeed in relieving the patient's condition. Patients with ulcers caused by *H. pylori* can be treated with a course of antibiotics, which, in many cases, results in a permanent cure (Suzuki *et al.*, 2007), healing the ulcers and thus relieving the pain and preventing the development of more serious complications. The discoveries of the utility of the diagnostic test and the treatment with antibiotics were built upon that first observation: that the bacteria in question were present in samples of tissue from patients who already had the disease.

Research studies of the type just described can lead to important discoveries about how human body systems work, and how they change during the onset and progress of disease or the healing of injury. In order to carry out work of this type, researchers need access to collections of tissue that has been removed from patients with the disorders in question. "Tissue" in this context could refer to a wide range of types of sample: from a small number cells scraped from the inside of a person's cheek, or a vial containing a few millilitres of blood, to a surgically-removed tumour, or an entire organ. Tissue could come from a deceased person, having been removed at a post-mortem examination. It might be collected from a research participant, as part of the research project that they have agreed to take part in. Or it might be surplus clinical tissue; that is, tissue that has been removed from the body of a patient as part of the normal clinical process of diagnosing, treating or monitoring a health issue, and is no longer needed for these purposes. The collection and use of tissue from each of these sources raises diverse and characteristic ethical questions. For the rest of this thesis, I will limit the scope of my discussion to the issues that arise from the collection, storage and use of surplus clinical tissue for research.

### **1.3. Ethical issues**

When considering possible research use of this tissue, it is important to remember that it has come from people, who have personal interests as well as interests that come from being part of a community. Their personal interests include respect for their autonomy and dignity, protection from harms that might result from breaches of their privacy, support for their own current health care needs, and recognition of their personhood. They may also be members of minority groups within the community who have specific interests due to their minority status, such as respect for their cultural beliefs, or protection from stereotyping or exploitation (Maschke, 2005). In addition, as members of the wider community, they also share in the interests that are held by the community as a whole.

The research process, while supporting communal interests through potential benefits to personal and public health, may also risk undermining some of the aforementioned personal interests. Because of these risks, most jurisdictions require ethical oversight of research conducted upon human tissue, but the extent of this oversight varies significantly from one jurisdiction to another (reviewed in Gefenas *et al.*, 2012; Maschke, 2005; Salvaterra *et al.*, 2008). Regulations pertaining to the use of human tissue for research are often derived from those used for human participant research. They seek to support the autonomy of the tissue donor, and mandate informed consent as the means by which this support is to be achieved.

#### **1.4. Criteria for informed consent**

In any context, in order to recognize a genuine informed consent which supports as far as possible the interests of the person whose consent is sought, several criteria have been specified which should be met before the procedure in question can go ahead (Beauchamp & Childress, 2009 pp120-121). These criteria cover the consenting person's understanding of the situation, their ability to make a reasonable and authentic decision based on that understanding, and the voluntariness of their expressed choice. A fourth criterion, without which no consent could be characterised as "informed", is adequate disclosure of the procedure that is proposed, including any relevant risks or impositions. In human participant research, this disclosure requires giving the candidate participant an explanation, at their level of understanding, of the research question that the tissue will help to answer and the risks that they may be exposed to as a result of their participation, and asking them if they will participate.

#### **1.5. Problems with disclosure in research using tissue**

However, the realities of present-day research into human biology mean that the level of disclosure described above is difficult, if not impossible, to achieve when considering whether to donate surplus tissue for research. Modern technology permits the preservation and storage of tissue samples for longer and longer periods, and developments in methodology mean that research questions that were impossible to address ten or twenty years ago may well be feasible now or in the future. This means that a sample that is collected today in order to contribute to a study that is under way now may well be able to also help

answer research questions five years, or fifteen years, or fifty years in the future, but there is presently no way to predict the exact research question to be asked or the techniques that could be used. Without these predictions, it is not possible to inform the tissue donor fully under the protocol described above, so consent to use their tissue cannot be sought except in the broadest sense. If we believe that these sorts of research details are instrumental to a fully informed consent, then this inability to provide specific information to donors presents a problem for ethical use of surplus clinical tissue for research. A variety of approaches to resolving this have been suggested and discussed (Caulfield & Kaye, 2009; Hansson *et al.*, 2006; Knoppers, 2005; Lipworth *et al.*, 2009; Wendler, 2006), but the issue remains controversial.

## **1.6. Diversity of regulation**

As well as within the bioethical literature, there are diverse approaches across jurisdictions to finding a balance between donor and community interests when considering informed consent. They range from the one extreme of permitting any research upon de-identified human tissue, with no ethical oversight (Office for Human Research Protections, 2008), through to the other extreme of only permitting tissue to be used for a particular research project if the donor has consented to that specific use, either at the time of tissue collection or in response to a later approach (Council of Europe, 2006), with a variety of consent protocols lying between these two extremes. This diversity in enacted regulation is difficult to justify in ethical terms: if donors in one particular jurisdiction have a particular interest, donors living in other jurisdictions will share that interest. In addition, with the international nature of many research

collaborations nowadays, conflicting regulation of the same activities performed by different members of the team complicates the conduct of the project as a whole (Borisch, 2007). Researchers in such collaborations may be tempted to assign ethically-proscribed procedures to their colleagues working in jurisdictions where such activities are permitted, but this does not absolve them of responsibility as far as the decision to conduct the research is concerned, and it may lead to complications regarding publication of the results, establishment of further collaborations, and funding of follow-up work. A more universalisable approach to the ethics of research using human tissue is required.

### **1.7. Scope of this work**

In this thesis, I will be considering the role of consent as it applies to research using tissue that has been removed from patients as part of a routine clinical procedure which is carried out to diagnose, treat or monitor an issue they are experiencing with their health. Examples of tissue of this type include the portion of a blood sample which remains after completing a measurement of an anaemic patient's iron levels, a tumour which has been surgically removed as part of cancer treatment, or an inflamed appendix which has been surgically removed to prevent a more serious condition developing. These types of tissue sample will be referred to as surplus clinical tissue.

Once the needs of the patient that were to be served by removing the tissue have been met, the tissue could reasonably be discarded as medical waste. If the tissue were not to be discarded, it could be stored, with the intention of either using it for a specific research project, or adding it to a research collection that

is being assembled to facilitate future, as-yet unspecified, research projects. These latter scenarios represent a research use for the tissue, but the patient themselves would not undergo any experimental intervention. All of the medication that they would receive and the procedures they would undergo prior to the removal of the tissue are those that would be prescribed for their condition under routine clinical practice.

Although the patients that the tissue comes from are not research participants, in the sense that they are not personally subjected to any interventions that would not be part of their expected clinical care, much of the ethical analysis I will make of using surplus clinical tissue will refer to the ethics applying to human participant research. The ethical principles most often applied to the use of surplus clinical tissue have evolved from the ethics of human participant research, so comparing and contrasting these two scenarios will serve to illustrate what these two situations have in common and where they differ in an ethically significant way. I will make these comparisons throughout the thesis.

## **1.8. Structure of the thesis**

In order to illustrate the types of ethical questions that arise when considering the use of surplus clinical tissue for research, I will begin by presenting a short, fictional narrative. This narrative will present the journey of one tissue sample from one patient, beginning with the first request to use the tissue, and following it through several types of research use, highlighting points of ethical concern along the way. I will use this narrative to illustrate my analysis throughout the rest of the thesis.

I will then describe a sample of the regulatory instruments that have been enacted in various jurisdictions in response to concerns about the use of human tissue in general, and some of the official guidelines that have arisen from these instruments. This account focuses on the provisions within these documents for consent by tissue donors, and, in particular, consent in the absence of disclosure. I will highlight the extent of the variation in approaches to consent that these instruments prescribe. In order to begin addressing this variation, I will identify and discuss some key values and interests that arise when considering the use of surplus clinical tissue for research, and I will examine the roles of consent and the difficulties in implementing it in this context. Finally, I will propose a way forward, which will permit maximal support of the ethical values which are of concern when using surplus clinical tissue for research.

## 2. An illustrative narrative

The types of research that any individual piece of tissue may be used for are diverse. It would be reasonable to expect that the motivation driving the original collection of the tissue would be to study some aspect of human biology related to the patient's diagnosis, but research has a tendency to spin webs of follow-up questions out of observations made while seeking to answer the initial question. This could lead to a sample of tissue becoming useful for characterising biological phenomena that are not obviously related to the patient's original diagnosis. Similarly, the types of analytical techniques that could initially be applied to a sample could be predicted based on the likely research question and the analytical techniques available at the time, but the pace of technological development makes it almost inevitable that research techniques that could be applied to the sample in some hypothetical future may not be feasible or even conceivable when the tissue is first removed from the patient.

In order to illustrate these points, I will present an account of a fictional patient, the route a piece of tissue removed from her body takes from the clinic to the research lab, and the various paths it might take from there onwards. While the narrative itself is fictional, the events within it are either based upon extant

research or intended to be plausible extensions of current knowledge and practice.

This narrative is intended to demonstrate the sorts of research questions that may arise from study of human tissue, and some of the ethical questions that could arise at each stage. In order to do ethical research using human tissue, particularly surplus clinical tissue, these ethical questions will need to be addressed. I will not be addressing all of the questions raised throughout the narrative in this thesis, instead focusing on those that concern the information available to the patient and the interests supported by this information.

I will return to this story at various points throughout the rest of this thesis, and use it to illustrate the ethics- and research-related points that arise.

## **2.1. The tale of the gallbladder**

Mrs Brown has been experiencing intermittent abdominal pain for several months, and, after investigation, she is diagnosed with gallstones. Mrs Brown asks the specialist, Dr Black, why these stones might have formed, and is told that there are a wide range of risk factors, including older age, higher body mass index, and family history, among other factors (Portincasa *et al.*, 2006). They try conservative treatment (dietary management and palliative medication), but Mrs Brown finds these measures to be burdensome and only partially effective. As the next step Dr Black recommends surgical removal of the gallbladder, to which Mrs Brown agrees.

While he is seeing Mrs Brown, Dr Black attends a seminar presented by Professor White, who is studying specific characteristics of those gallbladders which produce gallstones, and comparing them to the characteristics of

gallbladders which do not. Professor White hopes that her team's discoveries will one day help doctors screen patients for a tendency to produce gallstones. If they can identify such patients, Professor White speculates, doctors may be able to start conservative treatment earlier, when it is more likely to be effective. In order to be certain about her findings to date, Professor White would like to study more gallbladders from patients with gallstones. Dr Black, once he is reassured that the study has received approval from Professor White's institutional ethics committee (IEC), agrees to help by asking his patients to donate their gallbladders for research.

During a pre-operative consultation, Dr Black asks Mrs Brown if she will consent to her gallbladder being given to Professor White for use in research into how gallstones form, so that the information can be used to help future patients like her. He tells Mrs Brown that the gallbladder will be given a unique identification code, and only he and his secretary will know which code corresponds to which patient. He states that he will also need to tell Professor White some of Mrs Brown's medical information, but that no-one will be told her name, address, or other personal information. He also tells her that if she does not consent to the use of the gallbladder in research, it will be disposed of as medical waste. Dr Black gives Mrs Brown a form to sign which contains two statements: one, that she consents to the surgical procedure, and two, that she consents to donate the gallbladder (along with some medical information that has had Mrs Brown's personally-identifying details removed) to Professor White for research. Mrs Brown signs the form indicating her consent to both the surgery and the donation. The surgery is successful in relieving Mrs Brown's condition, although she now needs to be careful of her diet.

*What has Mrs Brown consented to? What does she think she has consented to?*

*What does she think will happen to her tissue after Professor White is finished with it?*

*What should she have been told?*

Meanwhile, in a research institute across town, Professor White is approached by her long-term collaborator, Dr Green. Dr Green is studying another human organ whose cells produce an essential hormone. He has discovered that some cells found in gallbladders also produce this hormone, and wants to examine this finding in more detail<sup>1</sup>. He is planning a series of experiments which will start with taking a few cells from normal and gallstone-producing gallbladders, and using these to develop cell lines which he can then manipulate in various ways and measure the resulting effect on hormone production. Knowing that Professor White occasionally received freshly-removed gallbladders from Dr Black and his colleagues at the hospital, Dr Green asks Professor White if he might take some of these cells from the next gallbladder she receives. He will also need some advice from Professor White on gallbladder biology in order to help the experiment succeed. Professor White agrees, but points out that the patients who donated the gallbladders in her collection only consented to her studying the tissue, not anyone else, when they donated it. She assembles the relevant documentation and they apply to their IEC for advice on how to proceed. The IEC decides that given Professor White's close involvement with Dr Green's research in general, and the proposed study in particular, the original

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<sup>1</sup> Based on Coad *et al.* (2009)

consents also apply to this situation, and gives permission for Dr Green to use Mrs Brown's gallbladder for his study as well.

*Is this permission appropriate?*

*Should Mrs Brown have been approached? How is she affected?*

*Should Mrs Brown have been asked to consent to this scenario (research by a different researcher) at the outset? If so, should this have been a separate clause, or just part of the overall consent? Had she already consented to this?*

Professor White's research into the causes of gallstones gives some information as to how they form, but doesn't reveal any therapeutic targets, and the funding eventually runs out. She publishes the findings she has in case they are useful to others working in the field and turns her attention to higher-priority research questions. The gallbladders are stored in a freezer in her laboratory. However, Dr Green's research into hormone secretion by gallbladder cells looks much more promising. He creates and characterises several interesting cell lines from various gallbladders, including that taken from Mrs Brown, and publishes papers detailing the results.

*What are the practical/material differences between cultured cells and primary tissue samples?*

*Is an ethical boundary being crossed here? If so, why is this a boundary? What are its regulatory implications?*

*Should the possibility of work on derived cell lines have been discussed at the outset?*

Other researchers interested in the hormone Dr Green is studying contact him and ask for samples of the cells so that they can validate his findings and study the characteristics of the cells using techniques that can only be performed in their labs<sup>2</sup>. As these investigations can provide information that Dr Green does not have the resources to gather, he is happy to do this, but checks with his institutional ethics committee first.

*Does he need to do this?*

*What should the committee rule?*

They rule that he must get the consent of the original tissue donors before he can make the cells available to any other researchers.

Dr Green, with Professor White's help, gets in touch with Dr Black, who approaches Mrs Brown and attempts to explain the situation. As he is not completely familiar with Dr Green's research, he is unable to satisfactorily answer Mrs Brown's questions about what Dr Green is studying, how the cells relate to the original gallbladder, and why Dr Green wants to send the cells to other researchers. Mrs Brown does not feel as though she understands the situation well enough to make a decision, so she declines to give permission for Dr Green to send the cells from her gallbladder to other researchers.

*Was asking Mrs Brown for consent necessary in this situation? Would it have supported any interests that were not supported by the original consent?*

*Should the possibility of research in other labs have been discussed at the outset?*

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<sup>2</sup> Based on Conrad *et al.* (2008)

*Is there any difference between working on these cells in Dr Green's lab, or sending them to another lab (possibly in another country)? What if a researcher from the other lab visited Dr Green and performed the same experiments in his lab?*

*What if it had been (a piece of) the original tissue that was to be sent? Is this more likely to be permissible, or less?*

*Are there interests in addition to Dr Green's that are threatened by Mrs Brown's dissent?*

Mrs Brown also asks Dr Black what happened to the gallbladder after Professor White had finished with it, and is told that it is in a freezer in Professor White's lab. Mrs Brown decides that she is comfortable with this, because she believes that Professor White is still studying how gallstones form.

*Is this consistent with her previous decision?*

*Should she be kept up-to-date with Professor White's research activities? What difference might this make?*

*Are donors' interests supported by distinctions between who is working with tissue they have donated, and what research questions they are working on?*

Professor White's group is joined by a new researcher, Ms Gray, who brings new skills to the team. In particular, Ms Gray knows a great deal about genetic analysis, and Professor White believes that this presents an opportunity for a new line of research into the formation of gallstones. She asks Ms Gray to compare the genetic material of tissue from the different gallbladders and see if there are any patterns which might explain why some people are more prone to

gallstones than others. Ms Gray discovers the sequence of a gene that works differently in people who are prone to gallstones, and she and Professor White publish a paper describing this finding. The sequence is also published (without any information which might identify the donor) on an internet database that, while intended for use by researchers, is also open for anyone to access.

*Is this another moral boundary? Why? What are the implications of studying genetic data?*

*Was this new project within the scope of the original consent?*

*Should Mrs Brown have been asked if she was happy with genetic information being studied?*

*Are Mrs Brown's interests compromised if this information is used by other research groups?*

The general news media also pick up the story, and Mrs Brown's daughter reads about it during a break in studying for her Biology 101 exam. She realises that some of her mother's genetic information is now available on the internet for anyone to read, and that there is a chance that this could also be her own genetic information.

*What are the implications of genetic research for the interests of the tissue donor's relatives?*

*Can these be managed at the time of the original consent?*

Professor Rose, a researcher studying a debilitating muscle wasting condition, uses some genetic data from his results to search the genetic databases and finds

that the sequence that Professor White published is high among the results<sup>3</sup>. He contacts Professor White and asks for information about the donor from which her sequence came. Professor White only has information about Mrs Brown's gallstone history, which is of little use to Professor Rose, but she becomes concerned about a possible link between the two conditions. Professor Rose doesn't think there is a link, as the protein encoded by the gene in question is involved in many different processes in different tissues, and the characteristics of the gene he has identified in his patients are different from those in Mrs Brown and other gallstone patients.

*Should Professor White be concerned? Should she attempt to contact Mrs Brown, or her children?*

Over the following years, Mrs Brown develops dementia and becomes unable to make many decisions on her own behalf. Another researcher contacts Professor White wanting to collaborate on another study of the gallbladders in her collection, so she approaches Dr Black again. Dr Black tells Professor White that he can't in good conscience ask Mrs Brown for additional consent, due to her condition.

*Should the possibility of loss of competence have been considered when the gallbladder was first solicited?*

*Could Dr Black approach Mrs Brown's family instead?*

*Can Professor White just go ahead with the new study anyway? What else might she need to consider?*

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<sup>3</sup> Based on Cardani *et al.* (2008)

The preceding narrative illustrates some of the ethical questions that may be raised when considering patient consent to use of surplus clinical tissue for research. I am unable in this thesis to address all of these questions. Instead, I will explore the underlying ethical conflicts that arise in these situations, and attempt to identify the role that patient consent can play in creating or resolving them.



### 3. Approaches to consent

As we have seen from the story of Mrs Brown's gallbladder in chapter 2, there are a variety of ethical questions that arise when using surplus clinical tissue in research. Throughout the world, regulatory bodies have attempted to provide guidance towards answering these questions when they are encountered in a real-world setting.

The use of human tissue is regulated in many jurisdictions (Salvaterra *et al.*, 2008). The legislation enacted in these jurisdictions typically covers the circumstances under which tissue may be collected and retained, the persons who are authorised to carry out these activities, and the uses to which the tissue may be put. Most of these regulations make at least some mention of consent on the part of the person from whom the tissue has come. Legislation tends to be general in its approach to ethical issues, so the central governments of the jurisdictions in question have delegated administration of the day-to-day practicalities of enforcing the legislation. The bodies so empowered typically publish guidelines which provide a more detailed explanation of the steps researchers are required to take in order to comply with the legislation, often with some ethical rationale for the approach prescribed.

However, the application of consent varies widely across jurisdictions, to the point where a practice which may be entirely legal in one country may be forbidden in another. For example, some jurisdictions require explicit consent from the patient before their tissue is used for research (opt-in), while others permit research use as long as the patient has not explicitly refused consent (opt-out). A second example of this type of inter-jurisdictional inconsistency pertains to ethical oversight of research using human tissue; such oversight is mandatory in some jurisdictions, but is only required under specific circumstances in others. At first glance this seems ethically unsupportable - surely if a tissue donor in New Zealand or the United Kingdom has a particular interest, then their counterparts in the United States or in Iceland would also have this interest. Assuming the relevant interest is universal in this way, if the relevant legislation in each nation does not support that interest, then it would seem that someone somewhere must be acting unethically - either by failing to uphold donor interests, or by excessively regulating the use of tissue. If all of the variant approaches to consent found in legislation are to be regarded as ethical, then a closer look at the particular circumstances of research in each jurisdiction is necessary.

On a more practical level, modern biomedical research relies more and more upon collaborations between different research groups, who may be based in different countries. International collaborations of these types may be hindered if the applicable legislation in each researcher's home nation is in conflict with that governing the activities of their research peers.

In order to illustrate this diversity of regulation, I will describe the legislation and regulatory guidelines from various countries which cover the use of human

tissue in that jurisdiction, focussing on individual instruments which illustrate the variety of approaches to consent to be found in such documents. I will also categorise the approaches to consent that emerge from these instruments, and review some of the discussion of these approaches that exists within the research ethics literature.

### **3.1. Examples of human tissue regulation**

In this section I will describe the approach taken to regulation of collection and use of human tissue in a few selected jurisdictions, namely New Zealand, Iceland, Estonia, the United Kingdom, and the United States of America. I selected these jurisdictions because they illustrate the range of approaches discussed in the literature on the ethics of using human tissue for research.

#### **3.1.1. New Zealand**

In New Zealand, the two main pieces of legislation relevant to research using surplus clinical tissue are the Human Tissue Act 2008 and the Code of Health and Disability Services Consumer's Rights. These Acts appear to require donor consent in most circumstances. There are also various government documents which provide more detail regarding the obligations of practitioners and researchers with respect to using this tissue for secondary purposes such as research.

##### **4.1.1.1 New Zealand Human Tissue Act 2008**

This legislation covers the use, for research or other purposes, of tissue from people who have died. The tissue in question may have been collected post mortem or while the person in question was alive. The Act requires evidence of

donor's consent, or consent of a family member, before tissue may be used for research. In either case, another family member can present an “informed objection”, which must take into account the values held by the deceased and the deceased's immediate family. The introductory sections of the Act explicitly state that the intent of the legislation is to support the autonomy of the donor, as well as their dignity and the cultural values held by the donor and their family (section 3).

#### **4.1.1.2 Code of Health and Disability Services Consumers' Rights (1996)**

The Code was created in compliance with the Health and Disability Commissioner Act 1994, which was enacted in response to recommendations made by the Cartwright Inquiry in 1988. It codifies and explicitly states the rights that consumers of health and disability services in New Zealand have with respect to their health care. The current version of the Code was enacted in 2004.

With respect to health service consumers's rights regarding the use of tissue in research: Right 7 (9) states

“Every consumer has the right to make a decision about the return or disposal of any body parts or bodily substances removed or obtained in the course of a health care procedure.”

With respect to secondary use such as research, Right 7 (10) states:

“No body part or bodily substance removed or obtained in the course of a health care procedure may be stored, preserved, or used otherwise than -

(a) with the informed consent of the consumer; or

(b) for the purposes of research that has received the approval of an ethics committee.”

It appears from this that patient consent is not required by the Code as long as the research has been ethically approved. However, it is possible that an ethics committee could require documented consent as a condition of approval.

Right 7 (10) was originally worded

“Any body parts or bodily substances removed or obtained in the course of a service [health care procedure] may be stored, preserved, or utilised only with the informed consent of the consumer.” (Health and Disability Commissioner, 2009)

and amended to its present form in 2003. The wording of this right has stimulated some comment each time the Code was reviewed (in 1999, 2004 and 2009). Supporters of the current wording do so because of the facilitation it offers research and public health initiatives; opponents express concern that it will undermine informed consent.

There is also no explicit statement about de-identification of tissue or patient records used in research in the present version of the Code (Health and Disability Commissioner, 1996). However, it is possible that an ethics committee could also make this a condition of approval. In addition, Right 9 also explicitly extends all of the rights in the Code to situations where the consumer is participating (or being asked to participate) in research. This includes Right 1 (2), the right to respect for their privacy. De-identification is frequently offered in the literature as a way to achieve this.

#### **4.1.1.3 New Zealand Standard: Non-therapeutic use of human tissue (NZS 8135:2009)**

A Standard is a document of best practice in a specific area, which is compiled by experts in the relevant field, under the oversight of a government body empowered by the Standards Act 1988 (Standards New Zealand, 2011-2012). NZS 8135:2009 was created to facilitate compliance with the Human Tissue Act (2008), and covers tissue from living and deceased people which is intended to be used for non-therapeutic purposes, including research. It does not cover embryos, nor does it cover tissue which is to be used for therapeutic purposes, but it does cover cell lines derived from human tissue. It specifies acceptable practice with respect to collection, storage, non-therapeutic use, and disposal of human tissue, including ethical issues.

Before tissue is collected, informed consent to the proposed use is required, from either the donor or their family (section 2.2). Donors have the right to consent to use in future unspecified research, subject to specific Ministry guidelines (described below).

Once consent is given, donated tissue must be stored, used, and disposed of in a manner which is sensitive to the donor's or their family's cultural values (sections 2.3-2.5). Tissue may only be used for the purpose for which it was collected, or for a legally-approved alternative purpose (section 3.9). Records must be kept at every stage (section 3.8).

#### **4.1.1.4 Ministry of Health Guidelines on the Use of Human Tissue for Future Unspecified Research Purposes (2007)**

Following a period of public consultation, these guidelines (New Zealand Ministry of Health, 2007) were created to cover the situation where tissue is solicited from a donor, and it is anticipated that some of this tissue may be

stored and used for as-yet undecided projects in the future. These guidelines permit seeking the consent of the donor to use the tissue in such research at the time of the initial tissue donation (Part 1), as long as the donor has been given as much information as is available regarding matters such as likely research areas, who could be studying the tissue and where (including research conducted outside New Zealand), where and for how long the tissue will be stored, how their confidentiality will be protected, and what ethical oversight procedures will apply (Part 2).

The guidelines also state that consent to unspecified research must be separate from consent to specified research and consent to sample collection, and suggests that donors be offered multiple, tiered, consent options. The options they suggest include broad consent to any future unspecified research on linked samples, consent to unspecified research only if the sample is unlinked, or consent to specified research only (Part 3).

### **3.1.2. Iceland**

Iceland is included in this discussion because it was the first nation in the world to create a national biobank. This was set up, amid some controversy, in 1998, in order to support genetic research by scientists from all over the world. The Icelandic population has genetic features which facilitate certain types of research, making a comprehensive biobank a valuable resource. To facilitate the establishment and administration of biobanks in Iceland, the Biobanks Act was passed.

#### **4.1.1.5 Biobanks Act, No. 110/2000 (Iceland, 2000)**

This legislation distinguishes between samples collected from volunteers for research (research samples) and those that are surplus tissue from samples collected from patients for clinical purposes (clinical samples) (section III).

Samples may be collected from research volunteers and lodged in the biobank only with the volunteer's informed consent. These could be samples taken from a participant enrolled in a cohort study, for example.

Clinical samples may be lodged in a biobank used for research unless the patient opts out, as long as the patient has been informed of this when the sample was collected. The patient may revoke this “assumed consent” at any time, and the sample will be destroyed. This is an example of an opt-out or presumed consent model.

The distinction between samples from research volunteers and from patients is noteworthy, as is the differing treatment of these groups with respect to consent. On the one hand, they reflect the practicalities of the two scenarios; on the other, there is a disparity in choice and therefore power held by each of the two groups. A research volunteer has no reason to submit to sample collection beyond their willingness to contribute to a research project, so the sample could only be collected with their consent and co-operation. A patient, on the other hand, has personal interests in permitting tissue to be taken from their body for the purposes of diagnosing or treating a current health issue, so the tissue is likely to be removed from the patient-donor in any case, and once it has been, the patient-donor has minimal control over the disposition of any surplus material. Unless they know that they can object and have the means to do so, the

sample taken from their body will, under this regulation, be used for research no matter what their preferences may be.

### **3.1.3. Estonia**

Estonia is included because, like Iceland, it also has a national biobank, which was set up shortly after the Icelandic biobank was established. Estonia and Iceland were the first two nations to enact legislation to cover the operation of these resources (Kaye *et al.*, 2004).

#### **4.1.1.6 Human Genes Research Act 2000 (Estonia, 2000)**

This legislation requires the “specific knowledge and voluntary consent” (section 9) of the donor in writing before tissue and personal data can be collected. This consent must be full and unconditional. The Act explicitly requires that donor privacy is protected (section 8), and the donor can require that their records and sample be destroyed at any time (section 10).

Unlike the Icelandic legislation, this Act makes no distinction between samples from research volunteers and samples from patients, and it requires that donors are asked explicitly to opt in to permitting their tissue to be used for research. The “unconditional” consent requirement sounds like permission to use the sample for any research project permitted under the management of the biobank, without returning to the donor to ask permission to use the sample for specific projects.

### **3.1.4. United Kingdom**

#### **4.1.1.7 Human Tissue Act 2004; Human Tissue (Scotland) Act 2006**

The provisions of these two Acts are essentially the same. They require the consent of the donor or (if the donor has died) their designated representative or a close family member before tissue may be used for research.

The wording of the legislation is fairly general, but emphasises donor consent (section 1). The 2004 Act covers tissue from both the living and the dead; however, when the 2006 Act was drafted, there was no inclusion of wording equivalent to that which in the 2004 Act covers the use of tissue from the living (Furness, 2006). The 2006 Act also uses the term “authorisation” where the 2004 Act has “consent”, but the practical relevance of this distinction is unclear.

#### **4.1.1.8 UK Human Tissue Authority (Human Tissue Authority, 2009)**

This body was established under the UK Human Tissue Act 2004 and is responsible for ensuring compliance with the provisions of the Act. They have published several documents detailing the steps researchers should take in order to comply. Their Code of Practice: Consent (2006) clarifies and expands consent requirements from the Act, and states that consent is always required for use of tissue from the living in research, although it may not be required for some other purposes such as training or auditing. This consent requirement is, however, waived if the tissue donor cannot be identified by the researcher. The Code of Practice permits linking of tissue to donor identity via a code held by a third party, but notes that gaining donor consent is “best practice”. They also point out that consent is not a single act but a continuing process.

### **3.1.5. United States of America**

#### **4.1.1.9 Office of Human Research Protections: Guidance on Research Involving Coded Private Information or Biological Specimens**

Office of Human Research Protections guidelines (Office for Human Research Protections, 2008) state that research on de-identified human tissue or medical information is “not human subjects research” (page 1), and is therefore not subject to ethical review.

This seems to permit any research to be performed upon a tissue sample without further consultation, as long as there is no information included with the sample that permits the researcher to personally identify the tissue donor. The regulations regarding the nature of this personally-identifying information are detailed and specific (U.S. Department of Health and Human Services, 2003 footnote 15). The emphasis on privacy may reflect a belief that the most significant source of harm to tissue donors is through a breach of their privacy, and that once that source of harm is removed, individual consent to the use of their tissue is not required. This seems to be at odds with the practice in other jurisdictions, where donor consent is paramount whether the donor is identifiable or not.

### **3.2. Getting down to specifics: guidelines**

The legislation and regulations listed above describe general principles of how human tissue should be regarded, and how the use of tissue taken for therapeutic purposes in research and other secondary purposes should be managed. Several different bodies have considered the ethics of this situation and published

guidelines that discuss in more detail the ethical justifications for the legislated principles, and the means by which these principles may be upheld in practice.

#### **4.1.1.10 German National Ethics Council - Biobanks for research: opinion (2004)**

This document (German National Ethics Council, 2004) places donor self-determination at the centre of policy regarding the storage and use of human tissue for research. Specifically, it states that donors should be permitted to consent to any use, even if the specific use is currently unknown, and that donors should be able to permit storage for any length of time (p13). This position contrasts with that of other groups discussed in this chapter (such as the UK Medical Research Council), who require that donors be given information about proposed research use of tissue samples before their consent to that research can be considered valid, and who seek to limit the length of time for which tissue may be stored.

The Council states that harm to donors can be prevented by coding samples or by removing donor information entirely. Once this has been done, consent for the sample to be used in research is not required, and these samples may also be transferred to other laboratories, including those in other countries, without ethical review. Donors of samples that have not been anonymised may revoke their consent to the research use of the tissue at any time. However, the Council would still permit research use of this tissue as long as it is anonymised. Like the US Office for Human Research protections, these positions indicate that the Council feels that the only source of harm to individual donors is via a breach of their privacy.

#### **4.1.1.11 Medical Research Council - Human tissue and biological samples for use in research: operational and ethical guidelines (2001) (UK)**

The position on consent taken by the Medical Research Council (MRC), as set out in this document (Medical Research Council, 2001), is that the tissue donor's informed consent is required when samples are taken for use in research, and also, wherever practicable, when surplus clinical tissue is used for research. This latter consent should be sought each time a tissue sample is to be used in a new research project, if practical, except where the tissue sample is anonymised. All research using human tissue may only occur if the benefits to society outweigh the risks of harm to the tissue donors, and must be approved by an ethics committee before it can proceed. Donors have the right to be told research results that may have clinical significance to them, but they also have the right to have such information withheld from them if that is their preference.

Tissue samples must be treated with respect, and regarded as a gift from the donors to the researchers, to frame research participation as altruistic. Research data and donor's medical information are to be kept confidential by the researchers. Stored tissue should be administered by institutions, not individuals, and these institutions should be considered to be custodians of the tissue. Old collections of tissue should be regularly reviewed, and disposed of if no longer of value to research. There may be no financial gain for any party directly from the tissue, but it is permissible to profit from any intellectual property that arises from the research.

#### **4.1.1.12 Nuffield Human Tissue Report (1995) (UK)**

This document (Nuffield Council on Bioethics, 2011) differs from the others examined in this chapter by noting that avoidance or limitation of harm is the

fundamental principle to consider when using human tissue for research, including respect for dignity and bodily integrity. According to this report, consent to donation is important, but it is not the primary principle (page 5). An assessment of the benefit to society of research compared to the risk to donors is also relevant to the issue, and public interest in ethical, scientifically sound research will typically outweigh individual concerns. The report notes that it is unlikely to be feasible to limit the types of research that may be performed using a specific tissue sample, or the duration of storage of the sample.

The report also states that consent to treatment is consent to ethical research using tissue removed in the course of that treatment. This is at odds with the NZ Ministry of Health guidelines described above, which require that storage and secondary use be consented separately from the primary consent, which is to the procedure of tissue removal. However, the Nuffield Council does recommend that the process of requesting the patient's consent to treatment includes discussion of secondary use.

### **3.3. Comparing and contrasting regulatory instruments**

The predominant principles addressed in all of these documents are those of donor consent, protection of donor privacy, and support of research using human tissue.

With respect to donor consent, the documents described above vary widely in regard to what donors should be asked to consent to and under what circumstances. Some mandate a one-time consent to any research use of tissue (German National Ethics Council, 2004), while others require that the donor be re-contacted for each new research project that their tissue might be used for

(Medical Research Council, 2001). An alternative option is to present the donor with “tiered” consent options, containing statements of consent to either a specific research project or to research in general, and ask them to choose which option they prefer (New Zealand Ministry of Health, 2007). The authors of the various documents justify their approaches to consent in terms of supporting the principle of autonomy. A third position regarding donor consent is that it is not required if the researchers are unable to identify the tissue donors (as specified in (Office for Human Research Protections, 2008) and (Human Tissue Authority, 2009)). The requirement for ethical review of research using de-identified tissue also varies; review is required under the UK Human Tissue Act (2004), but research subject to the guidelines issued by the US Office for Human Research Protection is exempt from review if any human tissue samples to be studied have been de-identified.

De-identification - that is, removal of identifying information, so that researchers cannot link the tissue or associated medical records to a specific patient - is also specified as a means of protecting donors from harm arising from breaches of their privacy (Office for Human Research Protections, 2008) and (Human Tissue Authority, 2009). The term anonymisation is also used, apparently with equivalent intended meaning. However, there are practical constraints to removal of information from a record or sample which prevent it from being made fully anonymous, such that it is never possible to determine which patient it originally came from, and this makes the term anonymisation a less accurate description of the outcome, if not the process, of removing patient information from tissue samples or medical records which are to be used in research. I will discuss the above-mentioned constraints in Chapter 4. For the

purposes of the current discussion, I will simply state my intent to, from this point onwards, use the term de-identification for any data amendment procedure which seeks to support donor privacy by removing information about them from a record or sample.

De-identification of a sample may be carried out at the time it is collected, or at some later date. De-identification is also sometimes presented as an alternative to withdrawing the tissue entirely from research use (German National Ethics Council, 2004).

### **3.4. Conclusions**

The documents discussed all acknowledge the value of donated human tissue to medical research, and the need to balance the ethical principles they highlight against the benefit to society that this research is expected to bring. However, finding this balance requires negotiating the tension between these two points. Many commentators have approached this negotiation by examining the ethical principles involved more detail, and I will review their arguments in detail in the next chapter.

## **4. What's at stake? Values and interests in research using surplus clinical tissue**

### **4.1. Introduction: typology of consent**

Towards the end of the previous chapter, I alluded to multiple approaches to consent when researchers seek to use surplus clinical tissue for research. These approaches can be broken down into four broad categories: specific, broad, tiered, or no consent.

#### **4.1.1. Specific consent**

Patients are asked for consent to research use of tissue for one specific project (Hansson *et al.*, 2006). They may be told details of the project such as: who will be performing the research, where the research will be conducted, the techniques that will be used, the reason why the researchers are taking this approach, how the research results will be disseminated, and who is expected to benefit. The consent given by the patient to this research is not intended to also permit the use of the tissue for other research projects, and the patient must be

contacted for a new consent if this is contemplated. This is the form of consent advocated by the Medical Research Council (2001).

If Mrs Brown had been asked for a specific consent, she could have been told that Professor White and her team, based in a laboratory at the local university research facility, would be conducting a research project which is intended to identify physiological factors that pre-dispose patients to forming gallstones, by using biochemical techniques A and B. The results are hoped to help patients who might otherwise develop gallstones in the future, and would be published in medical journals and presented at conferences. Such a consent would not have permitted Dr Green's study; for that to proceed, Mrs Brown would need to have been re-contacted and asked for another consent. It may also have prohibited Ms Grey's study, even though it was being conducted in Professor White's lab, on the grounds that it used different techniques to the original research project.

#### **4.1.2. Broad consent**

Patients are asked for consent to use the tissue for research, but are not given details of the research projects themselves (Knoppers, 2005). This approach is intended to permit the tissue to be stored and released to any research project that satisfies criteria set by the curators of the facility where the tissue is stored. Patients could still be told where the tissue will be stored, for how long, and how the research projects will be chosen, but they will not have any input into which projects the tissue they have donated will be used for. The guidelines issued by the German National Ethics Council (2004) advocate a consent of this nature.

A broad consent in Mrs Brown's case would most likely have permitted all of the research projects described in the narrative, subject to approval from an independent review body. There would have been no need to re-contact Mrs Brown herself.

#### **4.1.3. Tiered consent**

Patients are presented with a list of options for research use of their tissue, which typically range from one specific project to research use in general, with one or more points in between which are intended to highlight ethical boundaries that the patient is able to specify that the researchers do not cross (Salvaterra *et al.*, 2008). These boundaries may include research which collects genetic data, or which is performed in another location, perhaps even another country, or which seeks to build knowledge in areas other than that covered by the specific project already contemplated. Even if the patient consents to one of the more permissive options, there may still be a requirement for an independent review body to give the final approval for tissue to be used. This is the method preferred by the New Zealand Ministry of Health (2007).

A tiered consent in Mrs Brown's case would have ranged from consent to Professor White's original project at one end to consent to any research at the other. In between, the tiers may have reasonably included consent to use in other projects conducted by members of Professor White's team, which would have permitted Ms Grey's genetic study, and possibly also Dr Green's.

Additional tiers might permit any research conducted within Mrs Brown's country of residence, or any research into gallbladder pathology no matter where in the world it is conducted. As with broad consent, approval to use the

tissue in any project other than Professor White's original study could come from independent review.

#### **4.1.4. No consent**

The tissue is stored and used for research without first asking for any consent from the patients from whom the tissue came (Gefenas *et al.*, 2012). This approach may include a requirement for de-identification of the tissue sample and associated records, as specified by the United States Office for Human Research Protections guidelines (2008). Researcher access to de-identified tissue may also be subject to approval by an independent ethics committee, as in the United Kingdom (Human Tissue Authority, 2009). In addition, patients may be presumed to have consented to research use of the tissue unless and until they make it known that they do not consent, as with the Icelandic Biobanks Act (Iceland, 2000). Describing this last option as "no consent" may seem inaccurate, as it does allow for some patient input. However, the patient's dissent is only registered after the tissue has already been designated for research, a process that the patient must then expend effort to reverse.

In Mrs Brown's case, the gallbladder could have been stored and released for research without her consent, or knowledge. Her interests could have been supported to some extent by de-identification and ethical review, if these provisions were required in the jurisdiction where she is being treated. If her consent was assumed and made subject to an explicit opt-out, then she would need to have been informed by Dr Black that the gallbladder would be used for research and how she could go about registering her dissent.

The approaches to consent described above illustrate the overall spread of options enshrined in regulation of research use of tissue, and discussed in the literature. They all have the same goal - to maximise support for, and minimise undermining of, all of the conflicting interests that are affected when using human tissue for research. However, the approaches themselves are widely variable, and in some cases somewhat contradictory with respect to each other. This diversity creates practical difficulties when conducting research, particularly when research is carried out by teams with members based in different jurisdictions (Kaye, 2006). It also reveals the tensions between the various principles that underlie the regulation of research using surplus clinical tissue. For example, Salvaterra *et al.* (2008) assert that “Broad consent is not truly informed consent, but rather is a generic authorization that sacrifices the right of the donor to self- determination in favour of research interests.” (p311). However Hansson *et al.* (2006) argue that “Acceptance of broad consent and future consent implies a greater concern for autonomy than if such consents are prohibited.” (p267). Yet both broad and specific consents are presented (although by different authors) as ethical approaches to the tension between individual and public interests that research use of tissue creates.

Contradictions like these may arise sometimes because different commentators are viewing the value from different perspectives, and sometimes because different commentators place different priorities on the values under discussion. In an attempt to smooth over these contradictions and to begin a discussion of the best way to approach the ethics of using surplus clinical tissue for research, I will use this chapter to identify and characterise the values and interests that are at stake, with particular reference to their role in this context.

Research use of surplus clinical tissue has features that distinguish it from other applications of the previously mentioned values and interests, such as in human participant research or medical treatment, and I will highlight these differences throughout the discussion. Once the relevance of each value or interest to research using human tissue is discussed in that context, it may be possible to balance them against each other and reveal the best way forward when seeking consent for use of surplus clinical tissue in research.

## **4.2. Autonomy**

In the introduction to this chapter, I have presented the principle of autonomy as an example of the tensions within the discussion of informed consent to research use of surplus clinical tissue. Autonomy is used in bioethics to refer to the ability of a moral agent to make choices about the conduct of their lives (Christman, 2011), in terms of the freedom a person has to make and enact decisions, and their capacity to do so. Some accounts of autonomy focus on the qualities of the person making the decision (an “autonomous person”); others are more concerned with the context and nature of each individual decision (an “autonomous decision”) (Faden & Beauchamp, 1986 p235). In the context of using surplus clinical tissue for research, both of these accounts are relevant. However, the previously highlighted difficulties with achieving adequate disclosure in this situation shift my focus onto the resources available to the person being asked for consent, as distinct from their abilities to use these resources. Therefore it is more appropriate, when discussing consent to use surplus clinical tissue for research, to consider the autonomy of the decision-maker in the context of the decision to be made.

In the context of biomedical ethics, one of the most influential accounts of autonomy is presented by Beauchamp and Childress (2009). They argue that autonomy represents the freedom of a capable moral agent to conduct her life on her own terms, with adequate understanding and without interference from others (p99). For Mrs Brown, in the context of a decision to permit Professor White to use the gallbladder for research, an autonomous decision would require knowledge that the research use is a possibility and of the likely consequences for herself if it were to go ahead, along with an ability to understand the implications of this information. Mrs Brown must also feel free to make and express her decision without undue influence from other parties such as Dr Black.

The above-described account of autonomy has attracted criticism, particularly claims that it is fundamentally individualistic and therefore insufficiently sensitive to the network of inter-personal relationships which create our communities and shape our identities (Nedelsky, 1989), and that it privileges reasoned approaches to personal decision-making over emotional approaches (Corrigan, 2003; Dodds, 2000). As a result, this account is said to be unable to accurately reflect the true nature of much human decision-making, particularly when the decision to be made concerns abstract factors such as the interests of the community as a whole, as well as the decision-maker's own more concrete individual interests, values and feelings (Corrigan, 2003; Dodds, 2000). In the context of Mrs Brown's decision to consent to donating tissue for research, she would be considered autonomous if she were free to make the decision in the light of her own values and experiences. Even if her understanding of some of the material consequences of tissue donation was considered insufficient, she

could still potentially recognise that, while her understanding of some aspects of the situation (such as the details of the techniques to be used) was limited, this limited understanding was not material to her decision. She may, however, choose to accept assurances that permitting research will not adversely affect her interests, and express an autonomous preference to donate or not on those grounds.

However, the individualistic account of autonomy seems to dominate current biomedical and research ethics discussion (O'Neill, 2002 p34). Approaches to consent which require patients to make decisions regarding all research projects for which their tissue may be used, either before each research project begins (specific consent) or by contemplating contingencies presented by the researchers or their oversight bodies (tiered consent) could most easily be justified in terms of an individualistic account of autonomy. On the other hand, broad and blanket consent proposals could be justified in terms of a community-oriented account of autonomy, situating the patient within a society which values medical research for the benefits it can bring and for its own sake. In addition, these approaches to consent differ from the specific and tiered approaches in that they are more clearly supportive of community interests such as the benefits of conducting research.

A more community-oriented account of autonomy may also more closely reflect the reality of donating tissue to research. Donating surplus tissue, like participating in research in general, is rarely expected to immediately (or ever) materially benefit the donor. Because of the timelines involved in research, particularly basic research, it is also unlikely that work on tissue from the present patient will produce knowledge that can be used to help other patients

currently living with the same diagnosis. Rather, investigation of human biology is predicted to benefit individuals who may become ill in the future, either by preventing illness or by facilitating diagnosis or cure. When patients are asked for consent to use surplus tissue for research, they are not only making an assessment of concrete information, such as the direct benefits and harms to them in the context of their own values, but also evaluating more abstract concepts, such as the place of research in their own value system, and their empathy with the suffering of unknown people who may never touch their own lives.

In conclusion, either account of autonomy could be used to justify selecting one of the approaches to consent described above, and to rule out the others. The lack of agreement on what autonomy actually is has become an obstacle to its usefulness in resolving this question. However, autonomy is not the only principle that is important when establishing an ethical approach to consent to use surplus clinical tissue, and some discussion of the other principles at stake may shed more light on how to proceed.

### **4.3. Dignity**

Dignity is explicitly invoked in the New Zealand Human Tissue Act 2008, almost in the same breath as autonomy (section 3.a.i), but with little guidance as to how the two differ. This is problematic because dignity is a controversial value. At one extreme of the discussion, Macklin characterises dignity as a “useless concept” (2003), a simple restatement of principles such as respect for persons or respect for autonomy. Schopenhauer called dignity a “shibboleth of all thoughtless philosophers” (Schopenhauer, 2007 p51). However, it is also

lauded as a “guiding principle in medical ethics” (Killmister, 2010). Foster (2011) goes further, concluding that “...there is nothing more fundamental than dignity” (p177).

This diversity arises from confusion over what is even meant by dignity, a confusion which is highlighted and unpacked in some detail by Schroeder (2008). She points out that dignity as discussed in the literature is perceived simultaneously as two mutually contradictory ideals. In the first of two examples (“riddles”) of this contradiction, she cites the appeals to human dignity made in the debate surrounding assisted suicide: both in support of (prevention of a drawn-out, dependent existence beyond the point at which life remains bearable) and against (the taking of life, in any circumstances, being a violation of the patient’s intrinsic humanity). In the second “riddle”, she notes that most people, when asked to describe someone who exemplifies dignity, will name an individual person famous for their “poise” or “serenity” in the face of adversity; yet, multiple documents of national and international law and convention state that all human beings have dignity, with no reference to their character or demeanour. In the first “riddle”, Schroeder presents arguments that dignity could be regarded as either violable or inviolable, depending on the definition of dignity used by the side of the debate invoking it; in the second “riddle”, she claims that dignity is perceived as either a universal property of all human beings or a special characteristic of an exceptional few, again, depending on how dignity is perceived by the invoker. Because of these contradictory ideas of dignity, she questions the usefulness of the concept in ethical discourse.

In the context of the regulatory instruments reviewed in Chapter 3, it would seem that dignity is regarded as a universal property of human beings that, in

certain circumstances, can still be taken from them, and therefore needs to be protected. In order to see how to support dignity in human tissue research, we will need to come up with a definition of the concept that fits the situation. Schroeder (2008) has identified four conceptions of dignity, which I will examine in turn.

Schroeder's first conception is Kantian dignity (2008, p232): this is an intrinsic and inviolable property of human beings, which as a consequence requires that they be treated as an end in themselves, never just as a means to another person's ends. This idea is similar to the expression of respect for persons alluded to above, in Macklin's dismissal of dignity and in my earlier enumeration of relevant values found in the Code of Patient Rights. As such, it is an attractively concise definition of dignity in the context of research using human tissue. However, the limitation of taking a purely Kantian approach to dignity is that he defined such a property as being possessed only by rational beings; beings who can reason and can therefore understand the moral law and choose to act in a manner consistent with it (Jacobson, 2012 pp13-14). The requirement of rationality here excludes many of the categories of individuals we would intuitively seek to protect under this concept. Human individuals who are children, who are unconscious, or who have intellectual disabilities would not be categorised by Kant as rational and would therefore not engender this respect. However, modern conventions on human rights, such as the United Nations Convention on the Rights of the Child (1989) and Convention on the Rights of Persons with Disabilities (2006) do include these categories of individuals. Furthermore, the group of patients from whom tissue may be solicited for research may also include these individuals. The existence of

instruments such as the conventions cited above, in combination with an intuition that we should still respect individuals who, under a Kantian account, would not be regarded as possessing dignity means that defining dignity solely as a property of rational beings does not explain why it should be respected in all cases of using human tissue for research.

The second conception of dignity in Schroeder's account is aristocratic dignity (2008, p233). This is the dignity perceived within an individual of high rank within society, and appears to be derived from that rank. By this conception, only a few select individuals within a society could be said to possess dignity. However, the New Zealand Human Tissue Act seems to assume that dignity is a property of all human beings, not just a select few. Therefore, aristocratic dignity as a concept is of little use in this discussion.

Third, comportment dignity (Schroeder, 2008 p233) is derived from an individual's compliance with societal conventions regarding appropriate behaviour, particularly in the face of adversity. By this definition, only individuals who behave in conventional ways could be regarded as possessing dignity. This seems to place the responsibility for respecting a person's dignity upon the person themselves, by presenting dignity (and the consequent favourable regard of other members of society) as a reward that follows spontaneously from the act of behaving in a fashion acceptable to society at large. Legislating a respect for dignity on the part of third parties is inconsistent with this idea of dignity.

Schroeder's final conception of dignity is meritorious dignity (2008, p234), which she describes and evaluates in terms of the teachings of Aristotle. She concludes that dignity in this account is a virtue of the individual possessing it,

which derives in turn from Aristotle's "cardinal virtues" and a sense of self-worth. As with comportment dignity, this conception seems at odds with a necessity via legislation for protection from third-party interference. If dignity is a property of a virtuous individual, then only their lack of virtue can erode it.

With these four concepts of dignity, Schroeder illustrates that dignity can be a useful concept, if one only recognises which concept is referred to in any given debate. Killmister (2010) takes the discussion further by re-unifying some of the strands of Schroeder's argument and by applying them to biomedical ethics in particular, and concludes that dignity (in a medical context) is an "inherent capacity for upholding one's principles". In the context of research using human tissue, this capacity could be supported in the same way that autonomy could be supported, by providing the person from whom the tissue has come the information that their tissue could be useful for research, which gives them the opportunity to consider this information in the context of their values and to permit or decline to permit this use to be made of it.

However, Killmister's definition of dignity is vulnerable to the same objection as is a strictly Kantian conception of dignity, in that not all of those whom we would seek to protect under this value have such an "inherent capacity", either for deciding what their principles are or for upholding them. In fact, when formulated in this way, dignity sounds little different from autonomy. Yet dignity is repeatedly invoked as a value that is distinct from autonomy. Perhaps the only articulation of dignity that we can take from this is that it is a property of human beings that, in the absence of autonomy, nevertheless confers moral value. It is this moral value which limits what we are permitted to do to other human beings, and, to some extent, to tissue taken from them or to their dead

bodies. In the context of medical ethics, this formulation expresses our intuition that non-autonomous patients should still be treated with respect; in the context of using human tissue for research, it may justify placing some of the decision to permit secondary use of tissue upon the person from whom that tissue was removed, despite the limited degree of the material harm that this use would expose them to. Therefore, respect for the dignity of the tissue donor requires that researchers seek consent in some form, from the donor or from their representative, if they wish to use surplus clinical tissue for research.

#### **4.4. Privacy**

The New Zealand Code of Health and Disability Consumers' Rights (1996) requires that patient privacy be safeguarded. Privacy of research participants is also a frequent topic of discussion in the research ethics literature (Cook & Hoas, 2013; Kaufman et al., 2009; Rothstein, 2010). Protection of privacy is frequently linked to informed consent in regulatory instruments and guidelines, in the sense that participants must be told a minimum of information about what will happen to their medical records and research results, and who will have access to this material (for example, New Zealand Privacy Act 1993, part 2). This information about privacy is presented to candidate participants as part of the process of gaining informed consent. Privacy is a prominent, separate issue in discussion of the ethics of using tissue for research; requirements that privacy be protected appear in all of the legislation and regulatory guidelines covered in the previous chapter. It seems important, therefore, to take a closer look at this specific point of research ethics, and to situate it in the context of research using surplus clinical tissue.

Privacy, in a general sense of the term, is regarded as a universal human right.

Article 12 of the Universal Declaration of Human Rights states

“No one shall be subjected to arbitrary interference with his privacy, family, home or correspondence, nor to attacks upon his honour and reputation. Everyone has the right to the protection of the law against such interference or attacks.”

(United Nations, 1948)

Theoretical discussions of privacy cover a broad range of concepts, from the freedom to express one's authentic self, to the right to make decisions on one's own behalf (decisional privacy), to the right to limit other people's access to information about ourselves (informational privacy) (Wacks, 2010). Thomson (1975) argues that privacy is in fact a bundle of other rights, mostly to do with freedom from interference with ourselves or our property. Rachels (1975) responds by noting that Thomson's account doesn't capture everything that we seem to mean when we invoke a right to privacy. He also points out that our control over the information others know about us permits us to control our relationships with them. There are some categories of information about ourselves that we are socialised to keep within close, even intimate, relationships, and sharing this type of information with someone who is a more distant acquaintance can change the nature of our relationship with them. Conversely, we maintain close relationships in part by sharing personal information, and those relationships may suffer if we are unable or unwilling to do so (pp329-330). Scanlon (1975) offers accounts of thwarted attempts to intrude into another person's “conventional zone of privacy” as additional violations of privacy, even though no information has been gained – in this case

it is the (attempted) intrusion that is the harm, rather than any consequences of personal information becoming known to the wrong people.

Privacy supports autonomy by permitting us to control who we have social relationships with, and the nature of those relationships (Rachels, 1975), which in turn supports our well-being. The information about us that is known to others is key to managing our interactions with other people, both in the present and in anticipated futures.

When discussing the use of human tissue for research, privacy means the control by a person (or trusted authority on their behalf) of dissemination of certain types of information about themselves. These types of information include medical information (symptoms, test results and prognoses, for example), but may also include lifestyle information that a patient would not normally choose to disclose, were it not a necessary part of helping their doctor to support their interests in improved health. Some of this medical information is regarded as private because it could potentially be used against the patient by a third party - for example, the real or perceived likelihood that life or health insurance would be declined or made more expensive if the insurance companies learned that the applicant had earlier in her life been diagnosed with breast cancer (Stewart *et al.*, 2001). However, much of the information disclosed in a medical setting is regarded as private not because its disclosure would be harmful, but simply because most members of society feel that certain topics are “personal”, and inappropriate for discussion outside close relationships.

#### **4.1.1.13 How is privacy protected?**

The predominant approach to preventing unauthorised dissemination of information about a patient by third parties who are given access to their medical information is to withhold information that would permit their identity to be readily ascertained. This procedural approach is variously referred to as de-identification or anonymisation; as previously stated, I will use the term de-identification in this discussion. A de-identified record would permit a researcher access to information about a patient's diagnosis, treatment and outcome, but the researcher should not, in theory, be able to match that medical information to the person it is about. In practice this separation of medical record and patient identity is not always so complete (Sweeney, 1997). This is especially true of small populations, in which there are fewer people who might be the individual referred to by a specific record. In the US, the HIPAA Privacy Rule (U.S. Department of Health and Human Services, 2003) specifies eighteen pieces of information about a patient which must be removed from a record if it is to be regarded as de-identified. Other jurisdictions are not so prescriptive, but still require that it be difficult if not impossible to determine from which individual patient a tissue sample came.

In order to facilitate some activities, such as withdrawing tissue samples from research, it may also be necessary to create an identifier which is unique to each sample but also arbitrary, which can be used to connect research findings to the original donor. The link between an identifier and the donor would be known to a third party but not to the researchers, supporting the privacy of the donors by limiting the researchers' access to their personally-identifying information, but still retaining a connection between the sample and the patient from whom it

came. Records and samples bearing such identifiers are usually referred to as “pseudonymised” or “coded”. If it becomes necessary to identify which sample was contributed by which donor (for example, if the donor wishes their tissue withdrawn from the study), then an independent party can use the code to identify to the researchers which sample is affected. Similarly, if the research protocol allows for clinically significant research results to be communicated to tissue donors, then the identifier can be used to permit the researchers to specify the patient who is to receive the information, without knowing the patient’s identity.

In the context of research using surplus clinical tissue, the tissue samples have frequently been collected and associated patient records created before any question of secondary use has been raised. In these cases, privacy is frequently managed by removing specific items of personally identifying information from tissue samples and medical records before they are released to researchers. The specific pieces of information that must be removed may be defined in law. This process of removing information from a record after the information has been collected is frequently called “de-identification”. Some jurisdictions, such as the USA, require that certain criteria be met before a record may be regarded as de-identified (U.S. Department of Health and Human Services, 2003). Either the record must be examined by an expert in appropriate statistical methods who can conclude that it is no longer possible to identify the individual to whom the record pertains, or a set of specific pieces of demographic and clinical information must have been redacted from the record. This information includes details such as the patient's full date of birth, the full zip code of their residence, or their Social Security number. If the second method is used, the entity

releasing the information must also have no knowledge that the remaining information could be used to identify the person from whom the record came. Once either of these conditions is met, the records can legally be regarded as de-identified, and it is no longer subject to statutory restrictions upon the use of medical information (U.S. Department of Health and Human Services, 2003 footnote 15).

Most other jurisdictions, such as New Zealand (Privacy Act, 1993) or the United Kingdom (2013), don't have such detailed rules regarding the privacy of medical information, but do require that either patient consent or approval from an ethics committee (or both) be a condition of releasing medical information to researchers. When seeking such consent or approval, the researchers need to specify what information will be sought and why, and who will have access to it. Legislation such as that cited above requires that all private information, including medical information, may only be collected for a legitimate purpose, by duly qualified organisations, and must be kept secure.

#### **4.1.1.14 How effective are these measures?**

The goal of the approaches described above is to protect the privacy of the patients from whom tissue samples have come. However, the effectiveness of these approaches in supporting this goal is unclear. The exact information that should be removed from medical records before they are released to researchers, the effectiveness of this removal in preventing disclosure of the identity of the donor, and the implications for later research use of the samples or records are the subject of much discussion (for example, Kaufman *et al.*, 2009; Rothstein, 2010). The risk of inadvertent or malicious re-identification of de-identified samples is also salient (Horner, 1998; Sweeney, 1997). There are multiple

examples in the literature of re-identification of donors, using clinical, demographic or research data, alone or in combination, to which the authors had legitimate access. For example, Homer *et al.* (2008) were able to use DNA analysis to determine the presence of DNA from one specific individual in mixtures of DNA samples from up to 184 donors. Sweeney (1997) demonstrated the limitations of the de-identification protocols of the time by using voter record information in combination with “de-identified” medical information to identify the medical record of the then-governor of Massachusetts. The specific information that Sweeney used in that demonstration would now be removed from medical records, but she and colleagues have since shown that seemingly-innocuous information such as the locations and dates of clinic visits could also be used to re-identify patient records (Malin & Sweeney, 2004), and they have used demographic data in a similar way to the 1997 study to identify contributors to the Personal Genome Project by name (Sweeney *et al.*, 2013). These re-identification demonstrations were facilitated by modern computational techniques, which are advancing rapidly, such that re-identification in this way will become easier and easier in the future.

It may seem from these demonstrations that current measures to protect privacy are ineffective, and are likely to become even less effective in the future. So can patient privacy be protected at all? Certainly those with access to medical records and other sensitive information must continue to make best use of the procedural and technological safeguards at their disposal now and in the future. It may be that these safeguards are not one hundred percent effective at preserving privacy, but this does not mean that they are entirely without use, as

they may provide protection against carelessness, or deter those who lack the resources or inclination to breach them. In addition to technological safeguards, those who manage collection, storage and transmission of sensitive information should consider which details from the patient's demographic and medical data are relevant to the end use of the data, and only collect the data that they need. A culture of respect for privacy within organisations that are in the business of processing personal information could help prevent some breaches, particularly those arising from carelessness.

Aside from these moral considerations, from the point of view of research it is prudentially important to show due regard for the privacy concerns of the wider community in order to support the trust of potential donors that their concerns will be taken seriously. If donors fear that their privacy will not be taken seriously, they may decline to donate tissue samples, hindering research. Concerns for privacy are closely linked with donor consent. In the narrative in chapter 2, potential privacy concerns were addressed by telling Mrs Brown what information would be shared with the researchers, what information would not be shared, and the measures that would be taken to prevent her identity from being linked to the records given to the researchers. This information would have enhanced her ability to assess the impact consenting to donation of tissue could have had on her interests.

#### **4.1.1.15 Tensions between privacy and research**

We have seen in the previous section that simply removing personal identifiers from donor information may not be an effective way to prevent information from their samples from being linked back to them. It may also make it more difficult to support certain donor interests, such as their ability to withdraw

consent in the future. If a tissue sample is to be removed from a study at donor request, then it must be possible to uniquely identify that sample and link it to the donor. This requires that sample identifiers, even if these convey no other information in themselves, must be linked to patient information, which provides a route for compromising patient anonymity.

Linking samples to patient information can also support another donor interest: that of being informed about the results of the research projects in which their samples are being used. This may be for a number of reasons, from individual curiosity about the progress of the project, to enhancement of their sense of participation in the research, to findings that may be directly relevant to themselves or members of their family. Depending on the nature of the information, it may be possible to communicate with the donors via a broadcast method, such as publishing research progress in a newsletter that is sent to all donors in a study. However, for information of more personal relevance, a broadcast approach may not be suitable. If research findings of personal relevance (for example, the results of validated clinical tests) are to be returned to donors, it must be possible to link the sample to the donor, which, as previously stated, also provides a route for compromising their privacy.

In addition, some aspects of conducting research may also become difficult if large amounts of patient information are permanently removed from tissue samples or clinical records. Research results may need to be considered in context with the overall clinical picture, and factors such as time since diagnosis, medications prescribed, and co-morbid diagnoses may influence interpretation of research data. In some cases, withholding this information from

the researchers may compromise the quality of their conclusions and therefore diminish the value of the research results.

#### **4.5. Community values and group harms**

Communities are rarely monolithic. While broader values may apply universally across the entire community, the relative importance of these values and the specifics of how to support them may vary from individual to individual. Within any society, there will be distinct communities with their own characteristic values and priorities, and their own history within the wider community, a history which may place their values at odds with those of the wider community's. These groups may be distinguished from the wider community by race, sexuality, or disability, to name just a few points of difference.

In New Zealand, the harm that can arise when one group is singled out for study is demonstrated by the “warrior gene” controversy (Crampton & Parkin, 2007; Gillett & Tamatea, 2012; Merriman & Cameron, 2007; Wensley & King, 2008). The controversy arose when a genetic variant that was considered to be associated with risk taking and aggressive behaviour in specific individuals was found to be present at higher frequencies in Māori men. This finding was reported at a scientific conference and picked up by mainstream media, who erroneously linked the information to alleged higher rates of criminal and violent behaviour in Māori men. The ensuing reporting resulted in great offence to Māori (Anon. 2006, 2009; Stokes, 2007) due in part to its reinforcement of negative stereotypes about Māori people as individuals and as a group.

In the United States of America, a similar controversy arose surrounding research performed using samples collected from the Havasupai, a tribe of

Native Americans who live in the Grand Canyon (Caplan & Moreno, 2011; Santos, 2008). The Havasupai people struggled with diabetes, and gave permission for scientists to collect blood samples from individual members of the tribe in order to study why they were so devastated by the disease. However, the samples were also used (without donor permission) for studies of mental illness and the tribe's genealogy. When the Havasupai elders discovered that these latter studies had taken place, they were outraged, and sued the university where the studies took place. These studies not only revealed potentially stigmatizing information about the individuals who were studied, but they also threatened the identity of all tribe members, by challenging their traditional stories about the origin of the Havasupai people.

Both of these cases demonstrate the harm that can be caused to a group by indiscriminate application of broader procedures. In order to safeguard the reputation of research and support the values of all members of the community, it is important to be aware of the variations in values within the community and to account for them when determining how human tissue, including surplus clinical tissue, may be used. An example of a situation where the values of the community to be studied were treated with sensitivity can be found in Durie's account (2004) of a study of child nutrition which involved a large number of Māori children. The researchers leading this study wanted to analyze blood samples from the participants, but this was initially resisted by community leaders because of "... a Māori world-view that people are vulnerable if their body parts, including fluids, fall into the malicious hands", and because "[t]here was a lack of trust in the ability of the researchers to safeguard human property." (p1141). These objections were taken seriously by the researchers,

who took advice from Māori community leaders and made some modifications to the research protocols. The execution of these modifications satisfied the community representatives that their beliefs and the samples from their children were being treated with respect. The relationship between the researchers and the Māori community was strengthened, and the research project was a success.

The conduct of the child nutrition study demonstrates that it is possible to discover the world-view and values of a group within a wider community and to conduct the research with sensitivity to this information. Awareness of the potential for conflict is the first step, and communication between donor, community, and research team is the next. A requirement for consent to use tissue for research provides a checkpoint that ensures that this communication is initiated, if it has not already. This will facilitate and demonstrate respect for the donors and their beliefs, and will also support research by enhancing the relationships between researchers and all groups within the community.

#### **4.6. Trust**

Trust is fundamental to, and originates from, relationships between people (Baier, 1986). According to Cohen and Dienhart (2013):

“Trust is said to be an attitude, inclination, or willingness to act and accept certain risks (the disposition), given a set of beliefs or expectations about the trusted party (the epistemic states)—beliefs or expectations that the risks of a trusting action will not materialize, and by extension, that the risks are justified by the potential benefit.

Trust enables us to legitimately acquire goods that we cannot create for ourselves, and commission services that we cannot conduct ourselves, because we lack the knowledge or the means to do so. We trust the supermarket to sell us a bag of rice that is safe to eat, because we want to eat rice but we don't live in a climate that permits us to grow our own. We trust the mechanic who services our car to ensure that it will be safe to drive, because we need a vehicle in order to travel to work but we don't have the knowledge to keep it in good repair ourselves. Trust is so central to human existence that most of the time we are not even aware that we are trusting, or that we are seeking another's trust – we simply interact, as we carry out our daily routines. These interactions would be impossible without the trust that they imply.

There are some circumstances, however, where we may be more conscious that our trust is being sought. In these situations, we might do well to consider more carefully whether to place our trust. When the circumstances are unfamiliar to us, or when the consequences of misplaced trust might be more damaging than usual to our interests or those of others, we may consider more carefully whether we are prepared to trust. Depending upon the need for the good that is offered in exchange for our trust, we may decline to participate any further in the transaction. Recalling the illustrative narrative in Chapter 2: Mrs Brown could have refused consent to removal of her gallbladder, based perhaps upon her perception of the relevance of Dr Black's advice to her circumstances, or on her assessment of his surgical competence, or some other factor that she may even struggle to articulate. However, she found her gallbladder condition so disabling that she was prepared to trust his judgment and skill in diagnosis and treatment, as well as trusting his good will towards her best interests.

Mrs Brown might also have refused consent to donate the gallbladder to research, because she may have seen little benefit to herself to do so. This lack of benefit, by itself, has little to do with her trust or otherwise in Dr Black or Professor White, but, if that perceived lack of benefit is coupled with concern that donating will expose her to harm, then it is rational for her not to trust.

When trusting other people to have our interests at heart, it is important to consider the context of their advice. For Mrs Brown, donating the excised gallbladder for research was a separate question to that of whether surgery was the best course of action for her condition. Let us stipulate for the sake of the argument that Dr Black was qualified to advise her in that decision, as he is a doctor who specializes in disorders of the gallbladder, and that he had developed a rapport with Mrs Brown as part of establishing a therapeutic relationship between them. In this case, it would be reasonable for Mrs Brown to take his advice regarding the surgery. However, it's possible that Mrs Brown's trust in Dr Black as a medical practitioner also contributes to her trust in his judgment of her best interests regarding secondary use of the tissue. As many consent decisions regarding donation of tissue will be made in a therapeutic context, it is important that the patient's trust in their practitioner does not unduly sway their decision to consent to research use of the tissue. If misfortune or misconduct leads to the research attracting controversy, conflation of the two consents may adversely affect the trust of individual patients, or the community, in the practice of healthcare as well.

Trust is needed because life is uncertain – if we were certain about the competence or motives of others, we would be able to predict their actions and use that information to help us decide what to do in any given situation (O'Neill,

2002 p.13). Discussing the use of tissue in research with candidate donors will expose the uncertainty that emerges from the difficulties with disclosure that arise when tissue can be stored for long periods before use. The likelihood that new research questions will arise and that new technologies will be developed expands the likely uses that can be found for a stored sample of tissue, but it also expands the uncertainty regarding whether or not a patient would be wise to consent to such use in the first place. If the patient is able to trust that the research will be conducted within an ethical context that supports their interests, they may be more inclined to permit the use of their tissue for research.

Seeking the trust of another implies a duty to be trustworthy, to a degree that is proportional to the degree of trust that we seek. Depending upon the situation, we might demonstrate our trustworthiness in various ways. The creation and public dissemination of codes of conduct for practitioners seeking trust is one way to start demonstrating trustworthiness, as it demonstrates that said practitioners are aware that there is general concern about the implications of their activities and that they take these concerns seriously. The existence of third-party bodies responsible for monitoring practitioner activity could also support trust by providing a visible means for detection of misconduct, and for punishing any misconduct that occurs. An established history of good conduct will also contribute to public trust, as will openness about their activities.

Openness not only permits the trusted party's activities to be monitored by anyone who cares to do so, but also signals by its presence that the trusted party is not doing anything that the community would object to.

When seeking to use tissue for research, doctors and researchers are asking patients to expose themselves to some potential undermining of their interests.

For example, as discussed earlier, donor privacy and cultural values may be at stake. Patients could protect themselves from this undermining of their interests by refusing to permit the use of tissue, but this would undermine other interests, including any interests that the patient herself has in contributing to research. If it is possible for them to trust that their interests will be protected, then they are more likely to permit research use of their tissue. This permission in turn supports the interests of the researchers in being able to conduct a project, and the interests of the community in the good that could arise from the knowledge that may be gained from the research.

#### **4.7. Public good**

The literature about scientific research into human biology and medical science regularly invokes a “public good” that arises from this activity (for example Allen & McNamara, 2011; Schaefer *et al.*, 2009). In addition, regulations and legislation that govern research activities acknowledge the necessity of medical research, particularly inasmuch as it supports the welfare of everyone. From the Declaration of Helsinki:

“The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.” (World Medical Association, 2013)

From the New Zealand Human Tissue Act ("Human Tissue Act," 2008):

“The purpose of this Act is to help to ensure that collection or use of human tissue occurs only with proper recognition of, and respect for [...] the public good associated with collection or use of human tissue (whether for health practitioner education, the investigation of offences, research, transplantation or other therapeutic purposes, or for other lawful purposes)” (part 1 section 3a (iv))

In an economic sense, the term “public good” or “common good” is used to refer to the benefits that members of a community enjoy as a consequence of an activity or the presence of a resource that all may access by virtue of their membership of the community (Gibbons, 2011). Clean air is a commonly offered example of such a good. Provision or improvement of such a good has the potential to benefit all community members, whether or not they regard it as beneficial, and consumption of the good by one person has little if any effect on access to it by another. Public goods can be contrasted with private interests - those interests held by individuals that are not necessarily held in common with other individuals in the same community. Provision of public goods may require some sacrifice by individual community members, if the provision of a benefit regarded as a public good, such as national defence, is in conflict with the private interests of some or all community members. Those individuals who are exposed to risk by performing military service are making some personal sacrifices for the benefit of everyone (p1381).

Callon and Bowker (1994) note that scientific knowledge in general possesses several of the characteristics of a public good. In the absence of economic and regulatory gatekeeping, the knowledge produced by research is available to all

members of the community, it is infeasible to prevent individuals from consuming it, and consumption by one does not prevent consumption by others. These are all features of a public good. In addition, public use of scientific knowledge, rather than depleting it, can in fact enhance its value by demonstrating its accuracy and by stimulating the creation of more knowledge (p401).

When invoked in the discussion of medical research, the public good mostly arises from the body of knowledge that is created by research which uses either samples of tissue removed from people, or their bodies and experiences. The knowledge which results can then be used to direct further research and ultimately (it is hoped) improve medical care. There may be intellectual and economic goods that also arise from research which benefit the community as a whole. However the term “public good” in this discussion is intended to refer to the development of knowledge about human biology that is hoped, ultimately if not immediately, to improve the health of the population by informing measures that prevent sickness or facilitate cure.

Not all research into human biology yields directly medically applicable results - much of this activity is basic research, which seeks to elucidate the foundational mechanisms of human biology without the aim of uncovering information that is directly relevant to a specific medical problem. However, even these basic discoveries may ultimately lead to improvements in diagnosis or therapy once their implications are recognised and followed through to clinical applications. In this way, even basic research is able to contribute to the public good.

In the context of the tale of Mrs Brown presented in Chapter 2, the public good that was hoped to arise from the initial research using her excised gallbladder was knowledge that would help community members to remain free from gallstones, or to allow their doctors to help them quickly relieve themselves of any stones that might form, before they cause further health issues. This good would potentially be available to anyone who could reasonably benefit from it, and use of medical knowledge if not the resources required to put that knowledge to use) by one person would not preclude its use by any other. Examples of public goods that specifically arose from investigations using samples of tissue from patients include the discovery of imatinib, a chemotherapeutic agent used for treatment of chronic myeloid leukaemia (Deininger *et al.*, 2005; Deininger *et al.*, 2000), and the knowledge that the bacterium *Helicobacter pylori* has a causal relationship with various gastric disorders including ulcers, gastritis and certain types of cancer (Marshall, 1995; Parsonnet *et al.*, 1991).

#### **4.8. Duty**

We have seen in the previous section that medical research is widely regarded as a public good, and that access by researchers to samples of human tissue has the potential to contribute substantially to that good. I also noted that, in general, support of a public good may, in some cases, be dependent on individual community members compromising their personal interests. This leads to the question of whether patients who have had tissue removed in a therapeutic setting should in fact be required to permit use of any surplus material for research - whether they have a duty to acquiesce when this request

is made of them, or indeed whether it might be permissible to simply use tissue removed for therapeutic purposes for research without consulting the patient at all.

The idea that patients have a duty to participate in research is not new. A variety of arguments have been presented that support this view (Chan & Harris, 2009; Evans, 2004; Harris, 2005; Schaefer *et al.*, 2009), and these have naturally attracted counter-arguments (Brassington, 2007; Perna, 2006; Shapshay & Pimple, 2007). Some, but not all, of these arguments and counter-arguments are also relevant to the use of surplus clinical tissue in research.

The arguments in favour of research being a duty typically appear in two forms: an argument from reciprocity, and an argument from beneficence.

#### **4.8.1. Argument from reciprocity**

Evans (2004) begins his examination of a duty to participate in research by drawing an analogy with income tax - a means by which all income-earners in a community contribute a share of the money that is needed to support the common goods that are administered by their government. As he is discussing participation in research, which may impose limitations upon the liberty of the participant, this seems a reasonable analogy. He then continues his discussion by presenting a series of objections to his analogy between research participation and income tax, and attempting to refute those objections. Some of these objections are not relevant to the discussion of the duty to permit use of tissue, but others are, and I will discuss them in turn.

The first objection is to the fundamental relevance of the income tax analogy.

The objection is that one's body is very different to one's money, and that one ought not to equate them when making a moral argument (Sandel, 2012)

In the specific context of a duty to permit use of tissue for research, there are two substantial differences between money and tissue. One is that money is fungible - any one taxpayer's money is equivalent to, and could be substituted for, any other taxpayer's. It doesn't matter who contributed the money that pays for education, the police force, or servicing the national debt, only that they do contribute. Tissue, however, is much less likely to be interchangeable in this way. A liver biopsy could not be used for a study that required a particular type of skin tumour; a project that required cerebrospinal fluid from patients diagnosed with Huntington's disease would have no use for blood samples from people with diabetes. Mrs Brown may be swayed by arguments that she has a duty to contribute to the public good by consenting to research use of her gallbladder, but that is of little use if the most immediately pressing projects are investigations into the aetiology of Parkinson's disease or a new type of treatment for asthma. The "public" good which she supports is in fact the good of the community of patients who currently, or may in the future, find themselves diagnosed with gallstones. However, with the use of biobanks the chances of a gallbladder that was collected this week being used to contribute to a project next year are increased. The presence of a reasonable number of gallbladders in a biobank may also stimulate the initiation of a project using them. In addition, the possibility of unrelated lines of enquiry developing from the original study (such as that conducted by Dr Green in Chapter 2) may make a sample of tissue more broadly useful. These latter points may somewhat

diminish the dis-analogy between tissue and money, by making tissue samples more consistently usable, which strengthens the application of Evans' analogy to research using surplus clinical tissue, and therefore strengthens the argument that donation of tissue to research is a duty.

The other difference between money and tissue is that by paying one's taxes, one may be contributing money to the provision and upkeep of public goods from which one derives benefit. However, one is also unable to spend that money in other, preferable, ways, such as paying the electricity bill, or buying a better computer. A sample of tissue, however, would be of little use to the patient - in fact, they may well be significantly better off now that it has been removed - but it may be of substantial non-pecuniary value to a researcher, in that it supports the continuation of a research project in which the researcher is personally invested. And by extension, this could also support the interests of future patients with a diagnosis related to that of the donor.

The second objection from Evans is that participation in research carries with it a risk of harm. He answers this by downplaying the actual risks to research participants, noting that an ethical research project would be designed to carry minimal risk to its participants, and to provide a means of managing any adverse events that did occur. He also notes that any risk that does occur could well also occur during clinical treatment. This objection may also apply to the use of surplus tissue for research, but as the research is performed upon a disembodied piece of tissue, the clinical risks that Evans is contemplating do not apply. However, the risks I discussed earlier such as breach of privacy or stigmatization of minority groups do apply to tissue research, and must

therefore be adequately managed if an argument in favour of a duty to donate tissue for research is not to succumb to this objection.

The last of Evans' objections that I will discuss here rests on the observation that the people who will be subjected to the negative aspects of participating in research - some risk, perhaps, and some curtailment of their freedom - will be the more vulnerable members of the population, those who don't have any choice about using the public health system. The objection that follows is that there are many shocking examples throughout history where vulnerable people have been exploited and neglected, if not tortured and murdered, in the name of research, where their participation was far from voluntary. If we take the step of requiring that people participate in research as a condition of receiving medical care, are we not taking a step towards similar transgressions? Indeed, instruments such as the Nuremberg Code (U.S. Department of Health and Human Services, 1947) and the Belmont Report (The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979), both founding documents of contemporary research ethics, were published in response to such episodes in history.

Evans responds to this objection by pointing out that the fundamental assumptions behind these atrocities were completely at odds with those behind contemporary research, and to regulate research activities with the goal of preventing recurrences of such activity is to assume equivalent malice on the part of today's and tomorrow's researchers, many of whom are also the practitioners we trust with our medical care. Similar transgressions have occurred in the name of research using human tissue, but using these as a reason

to further limit the use of tissue in research would assume similar malice on the part of researchers and biobank administrators.

Codified procedures for the management of participation in research, including the use of surplus clinical tissue, are certainly necessary, but not for their power to prevent misconduct. Instead, they set out expectations for researchers and for potential participants and donors, enhancing transparency and trust, and thereby supporting the interests the community has in the efficient conduct of research into human biology and disease.

Evans closes his discussion of patient duty to participate in research with a strongly worded conclusion that this duty does exist, grounded in reciprocity with other patients who were also research participants. He presents seven objections to such a duty, and shows that all of them fail. Similarly, those of his objections that I have applied to using tissue in research also fail, which leads to the conclusion that there is a patient duty to permit the use of surplus clinical tissue for research. However, there are a few additional issues that are not covered by Evans' arguments, and I will discuss these now.

#### **4.1.1.16 Reciprocity and free riding**

The above discussion of Evans' (2004) paper uses reciprocity to justify assigning patients a duty to contribute to medical research. The care received by today's patients depends upon research participation by past patients, so it is perhaps only fair that today's patients support the care of future patients by participating in research in their turn. Patients who undergo removal of tissue in the course of their clinical care have an opportunity to contribute to this support by permitting research use of the tissue. Anyone who does not donate tissue will

be gaining benefits that others have paid for, but without contributing themselves. This is commonly termed free riding (Hardin, 2013)

There could be many reasons why an individual patient would decline to make a contribution that the majority would be willing to make themselves, and some of these reasons weaken attempts to characterise these patients as free riders.

For example, it may be that research use of their tissue would expose them to greater risk of re-identification than most other people. If they have unusual combinations of personal and/or clinical characteristics, that may make it easier than usual to re-identify them from their medical records. If they have been diagnosed with a very rare medical condition, or if they are of an ethnic background that makes up only a tiny proportion of the patient population, there will be fewer individuals who could be the patient who donated the sample, making it easier to rule others out based on other information linked to the sample<sup>4</sup>. Patients in this position may be justified in feeling that their unusually high risk of re-identification overrides any duty they may have to donate tissue.

Alternatively, it may be that their re-identification risk is similar to anyone else's, but that re-identification could have more profound consequences for them than it would for others. A possible example of this is a woman who has left an abusive relationship and is hiding her location from the abuser, knowing that if he can locate her, he may seek to cause her further harm. For any other person, the harm they might face as a result of an inadvertent disclosure of their location might be minor, so the concern they feel for keeping this information private would be small and their willingness to participate in research would not

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<sup>4</sup> It should also be noted here that individuals from minority groups who do donate samples will be making a substantial contribution to the potential welfare of other members of the same minority group, so the overall good arising from their donation could be greater.

be much affected by this risk. But for this particular woman, the disclosure could be life threatening, so she would feel much more strongly that it should be kept private, and would have greater reason to decline to participate in activities, such as research, that exposed her to risk of disclosure.

Patients who face a higher probability of re-identification, or who would reasonably expect more severe consequences if re-identification were to occur, have better reasons than most of the population to decline to contribute tissue for research. As a result, the label of free rider is less appropriate when applied to members of these groups.

At the other end of the spectrum, there will be patients who decline to contribute simply because they do not want to. Without a more compelling reason to decline, these people clearly are free riders. The issue of free riding is a concern when considering the provision of public goods. It may be possible to take steps to reduce or even eliminate free riding, which might enhance the public good, but these steps would come at the cost of other ethical goods. For example, we could eliminate free riders in the provision of surplus clinical tissue to medical research by placing such tissue in biobanks without asking for patient consent (for example, by following the United States OHRP guidelines described in Chapter 3). However, controversies such as those following the Alder Hey scandal (Hall, 2001), in which tissues from deceased infants were stored without parental knowledge or consent, erode public trust in healthcare and in research in general. In addition, storing tissue and medical data without donor consultation, much less consent, may expose specific individuals to unacceptable levels of risk. In such a case, even if the public good is increased by increased availability of tissue for research, it may be decreased overall by

such a policy. Free riding may be undesirable, but the community may have to tolerate a limited amount of free riding in order to prevent undermining of other goods.

#### **4.8.2. Argument from beneficence**

A second justification of a duty to participate in research rests upon beneficence and non-maleficence, and specifically the assertion that there is a duty to participate in research because this would prevent harm to or support the welfare of other members of the community.

Much of the discussion of beneficence as a justification for imposing a duty to participate in research is based upon Singer's pond analogy (Singer, 1972). He says:

“...if it is in our power to prevent something very bad from happening, without thereby sacrificing anything morally significant, we ought, morally, to do it. An application of this principle would be as follows: if I am walking past a shallow pond and see a child drowning in it, I ought to wade in and pull the child out. This will mean getting my clothes muddy, but this is insignificant, while the death of the child would presumably be a very bad thing.” ( p231)

If one were to apply this analogy to research using human tissue, then the drowning child would be the current or future patients who would remain bereft of a cure if research were not conducted into their condition, and the rescuer would be the patient who is being asked to donate their tissue to research. The muddy clothes would be the harms that might accrue to the donor, such as

violations of their privacy or stigmatisation of any minority groups with whom they identify. I discussed these harms earlier in this chapter, where I concluded that they are potentially real concerns for patients and their advocates, and that an ethical approach to research would provide guidelines for managing these concerns. These guidelines must include some form of donor consent, in addition to other measures for the support of privacy and the improvement of communication, in both directions, between researchers and the public.

In discussing this formulation, Singer goes on to say:

“...the principle takes, firstly, no account of proximity or distance. It makes no moral difference whether the person I can help is a neighbor's child ten yards from me or a Bengali whose name I shall never know, ten thousand miles away.” (p 232)

We might feel more inclined to help members of our community. We might feel that people with a shared experience of disease are members of our community. Singer mentions the “global village” - forty-odd years on, this is even more salient. Even those diagnosed with rare conditions now can and do reach more and more people “like them” through the Internet (Chung, 2013). However, Harris (2005) criticises the idea of helping people only because they are “like” us:

“This is surely close to claiming that research should be confined to others who are “black like me” or “English like me” or “God fearing like me”?” (p246)

When helping people through our participation in research, we can't help but help people who are like us, at least as far as they share a similar experience of disease. In Chapter 2, Mrs Brown's donation of her excised gallbladder was solicited by researchers who sought to study a disease of the gallbladder, not of the heart, or the skin, or any other part of the body. Her donation was encouraged by presenting the possibility that it could help researchers find out how gallstones form, thus helping other patients who have, or might acquire, gallstones. Granted, researchers in other fields did make discoveries using Mrs Brown's gallbladder, leading to potential benefits to patients with other diagnoses, just as Singer's rescuer might, once he is standing in the pond, happen to notice a lost wedding ring lying on the bottom, pick it up and hand it in to the police, who can then return it to the grateful owner. This was an unforeseen benefit of the decision to rescue the child, which nonetheless increased the net good in the world. However, the request that was made of Mrs Brown (or that would be made of any other patient undergoing removal of tissue for therapeutic or diagnostic reasons) was that they donate their surplus tissue because it might facilitate research into conditions related to their own diagnoses. The patient's motivation to donate can therefore only be regarded in the light of helping others like them, at least in the sense of a shared experience of disease.

Singer also notes:

“Secondly, the principle makes no distinction between cases in which I am the only person who could possibly do anything and cases in which I am just one among millions in the same position.” (p232)

As Shapshay and Pimple (2007) point out, Singer's pond analogy is too simple to fully represent the scenario where a moral agent could perform an act of rescue by participating in research. With Brassington (2007), they note that the sources of distress in the world are many and varied, as are the opportunities to alleviate some distress. If someone has a duty to rescue, they might just as effectively discharge that duty by donating money to charity. Returning to the pond analogy, there may be many people nearby, any of whom are capable of rescuing the drowning child. Similarly, a patient being asked to donate tissue to research, if their condition is relatively common, may be one of many potential donors of tissue to a particular research project. Even if one individual declines to contribute, there may well be many others who are willing to agree, and who can contribute a sample that is so similar to that from the original patient that it makes no material difference to the immediate research outcome from which patient it came. However, banking more tissue samples may improve the quality of a research project's results, or permit additional projects to be undertaken in the future, so the presence of other potential contributors does not completely eliminate any one individual's duty to donate.

In the case of relatively commonly diagnosed disorders, the duty of any one person to consent to donate tissue to research becomes defeasible on the grounds that another patient will surely be along soon to make an equivalent contribution. Under those circumstances, why should this patient expose herself to even the minor risk of some of her personally identifiable information being inappropriately revealed? However, the larger size of the patient population also makes it more difficult to re-identify the donor of any individual sample, reducing this risk, and reducing the argument for defeasibility. In the case of

more rare disorders, the risk of re-identification is greater, because there are fewer people that any given sample could have come from. However, the contribution of any one sample to the welfare of patients with that disorder is correspondingly greater, because there are fewer people who are in a position to make that contribution. So the ratio of benefit to others to harm to donor is approximately the same as in the example of the commonly diagnosed disorder; only the magnitudes of the benefits and the harms to an individual donor are different when comparing the rare disorder to the more common one.

From the above, it appears that, while arguments could be made that patients do have a duty to contribute tissue taken from their bodies to research, this duty is at least somewhat defeasible. An individual patient's unique circumstances may mean, for example, that research use of their tissue presents a more substantial than usual risk of harm to them, or to groups with which they can be identified. The existence of other patients who could contribute equally well may also reduce the need for any one patient to contribute. In addition, there are multiple ways any individual could contribute directly or indirectly to the support of medical research. They could donate money to charities which fund research into specific conditions, or they could inspire the next generation of researchers by pursuing a career as a science teacher. In general, the range of opportunities to help others is unlimited, but this is not taken to mean that any one citizen is morally obliged to pursue all of these opportunities to their full extent. It is possible to argue that patients do have a duty to contribute tissue to research, and that in most cases the impact upon their interests will be minor. However, the existence of this duty does not justify using the tissue without the patient's consent.

## **4.9. Conclusion**

In this chapter I have identified and discussed several values and interests which are relevant to the ethical conduct of research using surplus clinical tissue. Some of these, such as autonomy, dignity and privacy, apply directly to the patient from whom the tissue comes. Others, such as cultural values and public good, are more relevant to the community as a whole. While research using surplus clinical tissue is not conducted upon the body of the patient, it is still possible for this research to undermine their interests. In addition, any perception that research is conducted without consideration for the concerns of those who contribute to it will undermine the interests of the community. Donor consent seems to be necessary, if not sufficient, to protect these interests. Therefore effort must be made to seek consent from patients when research use of their tissue is contemplated. The precise form of that consent will depend upon what ethical work the consent is required to do, which I will explore in the following chapter.

## **5. The role of informed consent in research use of tissue**

### **5.1. Introduction**

It is clear from the survey of the legislative instruments and regulatory guidelines in Chapter 3 that the informed consent of tissue donors to use of their surplus clinical tissue is regarded as a prominent feature of the ethical use of human tissue in research. From the discussion in Chapter 4, it seems that some form of donor consent to this use is also required in order to support each of the values and interests that I have identified as relevant to research use of surplus clinical tissue. However, incomplete information regarding future uses of the tissue presents a challenge for achieving informed consent in its most rigorous form.

The survey in Chapter 3 of the statutory or recommended procedures for achieving consent to research use of tissue demonstrates that protocols for achieving the required consent vary widely among jurisdictions. It is tempting to speculate, therefore, that some of these procedures either may be insufficiently rigorous to fully support the interests for which they are put in

place, or are restricting the use of tissue to a degree which is out of proportion to the extent of the interests of the tissue donors. This also assumes that the interests that consent is intended to protect are perceived consistently from one jurisdiction to another. Consistent perception in this sense refers to an agreement on both (a) what the interest consists of, and (b) its importance relative to the other values at play when seeking to use tissue for secondary purposes.

In order to explore these tensions further, I will examine more closely the role that informed consent plays in general, in the context of human participant research, and in research using surplus clinical tissue. I will also discuss the interactions between informed consent and other prominent ethical features of research involving the use of surplus clinical tissue.

In order to compare the diverse procedures proposed for achieving informed consent in research using human tissue, it is important first of all to be clear what is meant by this term in a wider ethical context. Informed consent is a foundational procedure in ethical clinical care and human participant research, and a legal requirement in many jurisdictions. It is a process which is intended to make otherwise impermissible intrusions permissible, by ensuring that the person being asked for consent understands what will be done to them in order to carry out a proposed procedure, that they are willing to permit these actions to be done, and that this permission is documented (also discussed in Beauchamp & Childress, 2009 pp117-120; Eyal, 2012; Manson & O'Neill, 2007 p27; U.S. Department of Health and Human Services, 1947). In general, this process is intended to support the interests of the consenting party by enabling them to fully participate in decisions that may have a lasting impact upon their

well-being. I will return to this question of the purpose of informed consent later in this chapter.

## **5.2. The power of informed consent**

There are certain interactions that could be either permissible or impermissible, and the only distinction between these states is the consent of all of the involved parties. (Hurd, 1996). For example, if Alice takes \$10 from Bob's wallet, she may be committing the impermissible act of stealing from him. If, however, Bob has already consented to Alice taking the money, by giving his permission, then the situation changes - it may be that the money is a gift or a loan, or it may be that Alice is to use the money to run an errand for Bob. However, he may have wished to be the one to open the wallet and remove the money himself (perhaps because he did not wish Alice to have knowledge of or access to other items in his wallet) so he would not have consented to Alice helping herself. The overall act of transferring the money from Alice to Bob may be made permissible by Bob's consent. However, the circumstances of the transfer also affect Bob's interests, for example, in preserving his privacy. Details of these circumstances are therefore part of the consent that Bob gave, and the transaction would therefore only be permissible if it takes place under these circumstances. Alice taking Bob's money by helping herself to his wallet may be consistent with the outcome Bob sought, but is not the means of achieving that outcome that Bob agreed to.

In a healthcare setting, practitioners commit a range of intrusions upon their patients which would be impermissible in any other context. Removing someone's clothing, touching their body, injecting them with drugs or cutting

their flesh are all acts which, if performed in any other setting, would be potential grounds for criminal charges. There are several features of the clinical encounter that make these acts permissible, but the fundamental feature is that the patient has given their consent to be subjected to them.

Consent may be the only feature of these (or any) interactions that converts them from impermissible to permissible<sup>5</sup>. In chapter 4, I identified a set of values that seem to be important when considering research use of human tissue. The process of gaining informed consent from tissue donors seems to be intended to at least partly support these values. If informed consent is to accomplish this support in a meaningful way, then it is important to be able to clearly recognise whether it is feasible to achieve an acceptable standard of informed consent in the context of donation of surplus clinical tissue for research. To this end, I will briefly discuss an influential set of criteria presented by Beauchamp and Childress (2009 pp120-135), which they argue must be met in order to completely achieve informed consent. These criteria are: competence and voluntariness on the part of the consenting party; disclosure of information, recommendation of a plan, and understanding of the material presented in the disclosure and recommendation; and decision and authorisation by the consenting party to a particular course of action. These criteria are intended to apply broadly to any situation where consent is required, such as in a clinical setting, and some or all of them may be relevant when discussing consent to the use of surplus clinical tissue for research.

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<sup>5</sup> There may be some interactions where even consent cannot make an act permissible: for example, it may be conceivable on some very basic level for Carol to consent to Dave cutting off and eating part of her body, even if this results in her death. However, most people's intuition is that this act is still wrong, even if Carol is fully capable of making the decision to consent.

#### **4.1.1.17 Criteria for informed consent**

I will begin this discussion of the criteria of informed consent by briefly describing each one in a general context, thinking about how each might be applied in the majority of the situations where a formal, documented consent is sought. In a later section, I will focus particularly on the criterion of disclosure and its significance to the ethics of consent to use surplus clinical tissue.

Disclosure is the term used for the process of imparting relevant information to the consentor (Beauchamp and Childress 2009, p121). The extent of the information given, the means by which it is presented and the language used can all affect whether or not the consent is genuine. Disclosure relies upon the person seeking consent having an understanding of what information the consentor would need in order to make a decision, and it also relies upon the discloser having this information available to them. This latter aspect of disclosure can be problematic in research using tissue, as I have mentioned earlier, and will be the focus of much of the rest of this section. In a clinical setting, a disclosure may also include the practitioner's recommendation of a course of action.

Comprehension is the ability of the consentor to make sense of the information given in the disclosure and recommendation (Beauchamp and Childress 2009, p127). It is dependent upon the language and terminology used, particularly in settings where very technical information is to be imparted. In order to maximise comprehension, the person making the disclosure must use terminology that is at a level appropriate to the consentor's educational background, and must engage the consentor in a conversation so that they can assess whether the consentor is understanding what they are being told.

Comprehension can also be impaired by the consentor's inability to accept the information they have been given, and by false beliefs they might hold about their circumstances (Beauchamp and Childress 2009, p131).

Competence is the ability of the consentor to use the information that they have been given, in combination with their own values and wishes, to make a decision. Some people who might undergo a clinical or research procedure may not be competent, and in these cases a decision may need to be made on their behalf. People who are (or are likely to be) incompetent include children, unconscious or intoxicated patients, or individuals with disorders such as dementia. If a patient is temporarily incompetent, and the decision is not urgent, then it may be feasible to wait until they are competent. If the patient is not expected to become competent, or if a decision must be made before they can become competent, then these decisions are made by surrogate decision makers. They can use a variety of resources to inform this decision, including any advance directives the patient may have made in anticipation of their becoming incompetent, what the person who is the subject of the decision would most likely have decided had they been competent, and what course of action would be in the patient's best interests.

Voluntariness is the absence of inappropriate influence by another individual over the expressed preference of the consenting person (Beauchamp and Childress 2009, p132). An inappropriate influence might take the form of threats, either of causing harm or withholding benefit. Offering an unrelated benefit (such as a bribe) can also be an inappropriate influence, as can deliberately limiting or framing any information disclosed. In reality, most of our decisions are made within a context of some sort of external influence, and

the point at which this influence becomes inappropriate is difficult to define in abstract terms.

Beauchamp and Childress close their list of requirements for informed consent with (1) the act by the consenting party of making a decision and (2) their authorisation of the decision. These two elements of consent seem self-evident, particularly in a clinical setting – how else is a decision to be enacted, if it is not made by the patient or their representative and then communicated to the practitioners entrusted with the patient’s care? However, they also highlight the importance of two-way communication when establishing consent. Certainly the practitioner must impart information to the patient, but they must also listen to the patient’s questions, identify and correct any misconceptions, and respond to the patient’s expressed values. The whole conversation must occur in a setting where the patient is, as far as possible, free to consider and to question before they express consent or refusal.

### **5.3. Disclosure**

I described earlier how achieving adequate disclosure can be problematic when seeking consent for future research use of surplus clinical tissue. This is an example of a situation where the person seeking the consent may not have full information about the proposed research available to them, which limits the disclosure they can make to the potential donor. To see how this might affect a consent for future research use of surplus clinical tissue, I will examine how disclosure is approached in more clear-cut situations, and whether these approaches can be reasonably adapted in order to compensate for the limited information available.

The “informed” term in the phrase “informed consent” emphasises the claim that a consenting party cannot give a valid consent to something they know nothing about. Thus, an “informed” consent, by definition, requires that some information must be disclosed to a patient, candidate research participant, or anticipated tissue donor (Nuffield Council on Bioethics, 2011; U.S. Department of Health and Human Services, 1947).

There is substantial room for uncertainty as to the extent of the disclosure required in order to adequately inform a patient or participant. The specific information imparted will depend upon the procedure and the circumstances, but it is reasonable for the person from whom consent is sought to be told the reason for the procedure, the expected benefits to them (if a therapeutic procedure is proposed), a reasonable account of any likely harms, and their rights with respect to refusing or withdrawing consent in the future. Quite what “expected” and “reasonable” mean here has transformed over time (Eyal, 2012; Faden & Beauchamp, 1986 pp30-34 ). Initially, the information imparted was expected to conform to that which would be made by any competent member of the profession making the disclosure, known as the “professional standard” or the “professional practice standard”. The professional standard relies upon the assumption that a trained professional is in the best position, by virtue of both their expertise and their duty to care for the patient, to identify the information that is most relevant to the patient’s decision regarding consent. It permits an objective identification of what information to impart, simply by finding out from other professionals what they have told patients in the past (Brock, 2008 p608).

However, the professional standard of disclosure has attracted criticism on several grounds (Faden & Beauchamp, 1986 p31). The notion that all practitioners would agree on what information is reasonable to impart has been challenged, as has the assumption that practitioners are in fact adequately qualified to recognise the best interests of the patient and impart advice accordingly. It also lacks any internal mechanism for ongoing reflection upon past practice, and therefore permits uncritical practitioners to impart inadequate disclosure simply on the grounds that all of their predecessors made similar disclosures. Relying on the judgement of practitioners also assumes that they hold no personal interests in the outcome of the consent, and are therefore unbiased when determining the content and tone of the disclosure. More fundamentally, the professional standard of disclosure is held to undermine the autonomy of the patient, on the grounds that, while a decision regarding which of several treatments is appropriate to offer is in the hands of the practitioner, the ultimate decision regarding whether or not to undergo any of those treatments is up to the patient.

The professional standard was eventually superseded by a “reasonable patient standard”, in which the disclosure is expected to consist of information that a generic reasonable patient contemplating the decision in question would regard as significant (Faden & Beauchamp, 1986 p32). This standard is vulnerable to similar objections to those raised to the professional standard, particularly that it requires assuming exactly who a “reasonable” patient is and what information they would want to know (Faden & Beauchamp, 1986 pp32-33).

In response to these objections a third standard for disclosure is often discussed. This standard requires that the individual interests and values of the specific

individual being asked for consent are used to inform the disclosure. This is known as a “subjective standard” (Faden & Beauchamp, 1986 pp33-34). The subjective patient standard requires reflection by the practitioner upon the facts of the individual case, including the outcomes of conversations with the patient about their clinical and personal circumstances, and is therefore more likely to result in disclosures that more closely match the information the patient would need to make an adequately informed decision. By requiring the practitioner to make a reasonable effort to elicit the particular patient’s concerns, a subjective patient standard also facilitates the making of choices that most patients would not consider, but that individual patients would still be entitled to make if they are aware of the option. This still leaves open the question of what level of effort the practitioner is to make to constitute an adequate disclosure that is “reasonable” under these circumstances. Faden & Beauchamp (1986, p33-34) have objected that a subjective patient standard places an excessive burden upon the practitioner to anticipate patient interests, and makes them vulnerable to later charges of inadequate disclosure in the event of an unsatisfactory outcome.

In the context of human participant research, the information that must be imparted to the participant includes the nature of the research project, the interventions the participant will be subjected to, and any meaningful risks to them that could reasonably be predicted. For example, if it had been proposed that Mrs Brown take part in a study which compares the effects of a new pain relief medication with an established one, she would need to be told, among other things, the likely side effects of the medication, how the efficacy and side effects would be monitored, how often she would need to take the medication, and when she would be expected to attend a clinic for follow-up. Because

human participant research is performed directly upon the body of the participant, it is essential that such risks and impositions are documented and communicated to candidate participants in order to support their right to determine whether participation could be contrary to their best interests. In research that is to be performed upon the body of the participant (as distinct from research performed upon tissue), this communication is more likely to be feasible. The process of scientific and ethical review of proposed research that is typical of the present research environment requires that human participant research protocols are planned and documented before participant recruitment can even begin.

In contrast, it is possible to collect and store tissue with the general intent of using it for research, but without having made any specific decisions about the nature of the experimental procedures to be performed. If these procedures have not yet been decided, then they cannot be communicated to donors at the time the tissue is removed from their bodies.

### **5.3.1. Disclosure in research using surplus clinical tissue**

Disclosure is the element of informed consent that features most prominently in discussions of the ethics of using surplus clinical tissue in research. This is because it is difficult (and maybe impossible) to raise the disclosure of information about likely use of tissue in research to a level which could be definitively stated to conform to a standard that supports fully informed consent (Lipworth *et al.*, 2006), particularly by a subjective patient (or participant) standard of disclosure. This is because developments in storage technology and methods for analysis could extend both the length of time a sample of tissue

may be stored, and the types of research for which it may be used, far beyond the likely predictive capabilities of the researchers drawing up the consent form. Disclosure of likely outcomes of interventions in human participant research are often a delicate exercise in expressing probabilities in a way that maximises participant comprehension. By contrast, attempts to describe to a patient all of the ways in which their tissue could conceivably be used in research, particularly if it is proposed that the tissue is to be stored and used for as-yet unspecified research, would be more an exercise in outright speculation. In addition, it is not certain how adequately the patient's interests would be supported by such an exhaustive account of likely uses, nor how substantially they would be undermined by its absence. Given the relatively low level of harm a tissue donor would be exposed to, and weighing this harm against competing interests such as the public good of research, a disclosure that focuses on how sample use is managed may be sufficient when soliciting tissue for research. This disclosure may not be able to cover all the uses to which the tissue could be put, but it should be able to inform the donor of the procedures in place to decide how tissue in general is permitted to be used and how any concerns raised by the wider community will be addressed.

#### **5.4. Goods supported by informed consent**

As we have seen in Chapter 3, there has been much discussion of how the procedures for achieving informed consent may be modified in order to take into account the limitations imposed by the nature of research using human tissue. These discussions all pre-suppose that informed consent is necessary in order to conduct ethical human tissue research. In order to assess the value of

these alternatives, it will be necessary to look more closely at the reasons why informed consent is so central to ethical clinical or research practice.

#### **5.4.1. Protection from harm**

Most accounts agree that the prominence of informed consent in therapeutic or research settings arose from the outcomes of the Nuremberg trials (Beauchamp & Childress, 2009, p117; Manson & O'Neill, 2007, p4; Faden & Beauchamp, 1986, p156) as a response to the atrocities perpetrated in the name of research upon vulnerable and unwilling prisoners. This prominence was further developed through later documents such as the Helsinki Declaration (World Medical Association, 1964) to its position as a fundamental principle in the ethics of medical practice and human participant research. In this context, consent (and informed consent in particular) was intended to minimise harm to participants (Beauchamp & Childress, 2009, p118).

As already stated, direct material harm to the research participant arising from use of tissue taken from their body is limited. As the tissue in question is removed during a therapeutic procedure intended for their clinical benefit (for example: a blood draw, a liver biopsy, or surgical removal of a diseased gallbladder or a tumour), considerations of risk of harm arising from this procedure are covered by the process of gaining their informed consent to the procedure, and are not connected to any proposed use of the excised tissue for research. Similarly, any therapeutic benefits of removal of this tissue would apply whether or not the removed tissue is later used for research, as the procedure would not be carried out at all if it were not expected to ultimately enhance the patient's state of health. Therefore, the types of direct harms or

benefits typically covered by informed consent to such procedures are out of the scope of any conversation with the patient regarding the later fate of the tissues so excised. In considering the decision to permit secondary use, however, it may be necessary to consider more abstract (and possibly more complex) benefits and harms to the patient, such as those ensuing from breach of donor privacy, or undermining of the autonomy or dignity of the donor or of groups with which they are identified.

#### **5.4.2. Support for autonomy**

More recently, the most widely held justification for informed consent in a clinical or research setting has become that of protecting the “autonomous choice” of the individual who is to undergo an intervention (Beauchamp & Childress, 2009, p118). I discussed autonomy in some detail in Chapter 4, so will not repeat that analysis here. Briefly, autonomy is the principle that competent individuals have a right to determine the course of their lives, where the exercise of that right does not unduly hinder the exercise of the same right by other competent individuals. Informed consent supports autonomy by placing the decision about whether to permit an intervention under the control of the person who is to receive that intervention.

O'Neill (2003) disputes the place of autonomy as a justification for requiring informed consent on the grounds that there are many and diverse conceptions of autonomy, with differing levels of ethical importance. Eyal (2012) agrees that grounding informed consent solely in autonomy is difficult, offering the example of a patient who needs to consent in order for an urgent procedure to go ahead. For most patients, this would have been a formality, but in the

example the patient has misunderstood a critical fact of his situation, and declines. Eyal agrees that this patient has acted autonomously, but questions whether the autonomy has been supported by the informed consent procedure.

### **5.4.3. Protection from paternalism**

I have already discussed the role of consent in protecting the consenting party from material harm. This account of protection as a purpose for informed consent invokes protection of vulnerable parties (such as patients or research participants) against harm that results as a consequence of deliberate wrongdoing by physicians or researchers (such as the Nuremberg atrocities already alluded to). Consent is also tasked with protecting a vulnerable party against harms that may be caused by the physicians' or researchers' (possibly incorrect) assumptions regarding decisions that best support the vulnerable party's welfare. Assumptions of this nature are regarded as paternalistic; paternalism is unethical when it does not take account of all of the dimensions of a person's well-being and disregards the autonomy of the vulnerable party in decisions concerning their welfare. Paternalistic decision-making may result in consequences which unintentionally undermine the well-being of the person the decision is being made for. Attention to the elements of informed consent can therefore protect patients against adverse consequences of decisions founded upon paternalistic assumptions. In addition, paying attention to paternalism plays a moral role, by placing respect for the autonomy of the person the decision is about at the centre of the decision-making process.

Paradoxically, by insisting upon informed donor consent when research use of tissue is contemplated, ethicists may also be guilty of wrongful paternalism. If a

patient is unlikely to be harmed by research use of their tissue, and is of a disposition where they have little or no concern for its fate, then requiring them to pay attention to a complex and uncertain disclosure and make a concrete sign of authorisation to the use of the tissue may be a greater burden upon them than is justified by the risk posed by using their tissue for research to their welfare. For example, if Mrs Brown had found her surgery so traumatic (perhaps for reasons unrelated to her diagnosis) that she developed mental health issues as a result, she may be re-traumatised (and therefore harmed) if reminded of the experience by a later request to consent to research use of the gallbladder. Similarly, if patients have already considered the issue in the absence of disclosure but in the context of their personal values, and decided that they are comfortable with research use of their excised tissue, then requiring them to second-guess that decision questions their autonomy.

#### **5.4.4. Promotion of trust**

Of the purposes for informed consent on Eyal's list, one that seems particularly interesting within a discussion of the ethics of using surplus clinical tissue for research is promotion of trust. Manson and O'Neill (2007, ch7) also present an extensive discussion of the role of some sort of consent (perhaps not necessarily a fully informed consent) in supporting trust. They see trust as particularly relevant in situations where public goods are to be provided, and where the criteria for a fully informed consent cannot be adequately met (p154). Both of these conditions apply to research using surplus clinical tissue, as (a) it is an endeavour intended to produce public goods, and (b) it is very difficult to fully disclose to patients all of the likely uses researchers may find for their tissue sample, for reasons I have discussed elsewhere.

For the former condition (public good): research into human biology is conducted in order to elicit knowledge about the functioning of the body and its systems that will benefit future patients and the community in which they live. It is unlikely, and certainly not expected, that research upon Mrs Brown's excised gallbladder will yield any information that will prevent her developing additional disease, but it's still possible that new screening methods or treatments can facilitate the diagnosis or management of patients in the future. The good that comes from research is primarily directed towards the community, of which the patient is a member, rather than purely towards the individual patient from whom the tissue came. As such, the patient may still benefit through her membership of the community, although this would be contingent on the nature of the good and the means by which it is distributed. For example, Mrs Brown is not expected to suffer further from gallstones now that her gallbladder has been removed. However, an overall reduction in gallbladder disease in her community should lead to a reduction in the use of community resources for the care of future gallbladder patients, permitting those resources to become available for other purposes, for example subsidised influenza vaccination. However, Mrs Brown is not expected to directly benefit from gallbladder research.

For the latter condition (inadequate compliance with consent criteria), I have discussed the difficulty of adequate disclosure in research using surplus clinical tissue above. If we accept that disclosure may never be sufficient to support a truly informed consent in this situation, then it is clear that informed consent cannot support the other justifications for its use in cases where it is proposed that research using surplus clinical tissue is to be conducted. However, the

intuition that informed consent is important in human tissue research still exists, and must be addressed if the tension between individual interests and the public good in research is to be relaxed.

Research using surplus clinical tissue is intended to support the public good, and it is difficult to achieve a high level of disclosure when seeking consent from patients to use their excised tissue for research. These are the two features that Manson and O'Neill note are common to situations where consent can support trust. Therefore, it may be appropriate to focus mostly on trust as a motivation for seeking consent to use a patient's tissue in research, and to use that motivation as a foundation for a discussion of suitable informed consent procedures.

From the preceding discussion, it emerges that there are several moral problems with requiring consent to do the bulk of the work of supporting donor interests when considering the research use of surplus clinical tissue. Because it is difficult to make an adequate disclosure of the uses to which the tissue may be put, the use of consent to support autonomy and prevent harm becomes questionable. In addition to these moral problems, there are some practical issues which arise when attempting to comply with a requirement for informed consent when seeking to use surplus clinical tissue for research.

## **5.5. Goods undermined by informed consent**

As we have seen in the previous section, there are several ethical goods which informed consent is capable of supporting. However, a narrow focus on consent as a procedure can undermine other goods, particularly in research. Two of the situations where uncritical use of informed consent can create difficulties are in

the creation of bias in research outcomes, and in requiring linkage of a donor's personally identifying information to their tissue sample.

### **5.5.1. Consent bias**

One potential hindrance of research by a requirement for informed consent arises from the observation that the consent process itself can introduce a bias into the set of samples that are studied for a particular research project. This "consent bias" is widely reported in observational research, and several studies have concluded that the distribution of clinically relevant factors in the population of individuals who consent to participate in research is not the same as the distribution of those factors in the population as a whole. If true, this means that research results will not be as readily generalisable, as they may fail to account for clinical factors that happen to be associated with patients who are particularly reluctant to consent to participate in research.

There are a number of examples of consent bias described in the literature. For example, Al-Shahi *et al.* (2005) approached general practitioners treating a group of patients diagnosed with a particular intracranial vascular malformation, and asked them if they felt it appropriate to contact each of their patients directly regarding the study. If their general practitioner agreed, each of the patients were contacted directly and asked for their consent to examine their medical records and send them annual questionnaires about their condition. The authors also received ethical approval to study all of the patients in the diagnosed cohort (including those who did not explicitly consent to receiving questionnaires, and those who were screened out in the initial approach to the general practitioners) via questionnaires to be completed by their general

practitioner, and “medical record surveillance”. Patients who explicitly refused consent to either of the above study methods would be omitted from the study. Most patients explicitly consented, and the remainder of the cohort did not respond. The authors found that the explicitly consenting patients were demographically similar to the cohort as a whole, but their clinical situation at presentation and at each follow-up contact was substantially better than that of the cohort as a whole. In addition, a prognostic variable was found to be clearly associated with poor patient outcomes if the entire cohort (consenters plus non-responders) was studied; this association was not apparent if only the consenters were studied. This illustrates the potential for valuable research findings to be missed if explicit consent is required from an entire study cohort.

In another example of consent bias, Buckley *et al.* (2007) sent questionnaires to a cohort of patients who had already been recruited for a cross-sectional study of ischaemic heart disease, and included forms requesting consent to study their medical records. Most patients responded and consented to further study, some returned the questionnaire and declined to consent to further study, while a substantial proportion did not respond at all. The authors studied the medical information already collected for the earlier study, and found that there was an association between consent to study of medical records and positive prognostic variables. In this study, many of the patients approached did not indicate whether they consented or chose not to consent to participate in the project, and these patients were classified as non-consenting.

Damery *et al.* (2011) carried out a study on patients diagnosed with iron-deficiency anaemia, and also found that a substantial proportion of the patients approached for additional study did not respond. They compared the

demographic data of the patients who consented with that of the patients who did not respond or did not consent, and found notable differences which may have clinical relevance. As with the Buckley study, this finding may indicate that a means of approach that requires the patient to make a decision one way or the other will lead to a more representative study cohort.

In each of the examples given above, the entire cohort included a group of patients who did not explicitly refuse consent. Including these types of patients in future studies may improve the degree to which the patients who were finally enrolled in the study reflect the overall population, improving the quality of the research data. This raises the question of whether it would be acceptable to use an absence of dissent from a patient as permission to go ahead with certain types of study, such as examination of medical records or study of surplus clinical tissue. To qualify for this departure from informed consent norms, these studies would need to present a significant likelihood of enhancing the public good, coupled with low risk of harm to patients (most likely to occur through breach of privacy).

Consent bias is difficult to measure in an ethical fashion because it requires studying information about people who may not have explicitly consented, and, in some cases, may have explicitly refused consent. However, the studies described did receive ethical approval for some form of study of patient information regardless of patient consent, either by avoiding direct contact with the patients, by studying patient data in aggregate form, or by examining information that had been collected under previous consents. This was justified by recognition of the community interest in establishing the extent of any bias introduced by a requirement for informed consent.

The cases described above are examples of observational research, a research methodology which gathers data by observing participants but not subjecting them to experimental interventions. Because most study populations naturally exhibit substantial variability, which can introduce bias into the collected data, it is important when designing an observational study to be conscious of this issue (Meininger, 2006). The less bias there is (from any source) in the study population, the more robust the study data will be, leading to more reliable conclusions.

Research using surplus clinical tissue is also observational research; it typically uses samples of opportunity (rather than samples that have been explicitly solicited), and the individuals from whom the samples have come have not been subjected to any interventions other than those that are specifically indicated for their own clinical condition. Thus, consent bias, especially where restrictive consent protocols are used and where limited numbers of samples can be collected, could have a profound effect on the usefulness of the results of studies using human tissue. However, the extent of the effect of consent bias in research is controversial (Rothstein and Shoben, 2013), and it may be possible to ameliorate its effects by careful experimental design. This is an area worthy of additional discussion, but the specifics of research design are beyond the scope of the present work. However, it should be noted that accounting for consent bias, on top of all the other possible sources of bias, may be disproportionately burdensome upon research. The additional work that this could involve may include recruiting more participants (which may undermine attempts to minimise harm to donors), or spending more resources on selecting candidates to approach. It may be, on balance, that the ethical costs of

simplifying or eliminating consent requirements for some types of research are much less than the logistical costs of designing or executing scientifically valid studies that also approach consent more stringently.

### **5.5.2. Linking samples to donors**

In chapter 4, I summarised some of the approaches to consent that have been presented by various authors as solutions to the problem of adequate disclosure in research using surplus clinical tissue. Some of these solutions require preserving a connection between the donor's personally identifying information and their sample. This approach is intended to promote ethical goods such as autonomy, but it may undermine others, particularly the interests that donors have in preserving their privacy, and the enhancement of public good that comes from efficient use of research resources. In order to address this tension, I will consider the goods that are being promoted and discuss whether they are significant enough to justify the risks that they create. The goods that are promoted by linking samples to donors are: withdrawing consent, facilitating specific or tiered consent, and communicating results of individual significance.

#### **4.1.1.18 Withdrawing consent**

Withdrawing from a research study, for any reason or no reason, is regarded as a fundamental right of research participants (Edwards, 2005; McConnell, 2010), but is more controversial when considering research on tissue (Edwards, 2005; Eriksson & Helgesson, 2005; Holm, 2011). In human participant research, withdrawal of a participant may be straightforward or complex, depending upon the nature of the study interventions, but it is always clear to the researchers who the participant is who wishes to withdraw. In addition, given the embodied

nature of human participant research, the harms the participant could suffer if they continue the study may be substantial (again, depending on the study), so facilitating withdrawal supports participant welfare.

In research using tissue, withdrawal is only feasible if there is a link between the identity of the donor requesting withdrawal and the piece of tissue in question. Such a link can feasibly be created at the time the sample is collected, but it provides a greater opportunity for negligent or malicious re-identification of patient information, as I discussed in chapter 4. In this case, is the ability to withdraw a tissue sample from research of sufficient value to justify exposing the patient to other harms? If the initial consent had not been contingent on later being able to withdraw that consent, then one justification for linking the donor's identity to the sample is removed. In addition, if the likely harms of donating tissue are minimal, and if removing any link between the donor and the sample substantially diminishes those harms, then there is little need to present withdrawal of consent as an option.

#### **4.1.1.19 Additional consent**

Another reason for linking the donor's identity to the sample is to enable consent to use the tissue in additional studies to be sought, if this had not been done when the sample was first collected. As with the discussion of withdrawal, this linking carries some risks of breach of donor privacy, which can only be justified if re-contacting for consent enhances donor autonomy to an extent that outweighs the additional risk to privacy.

#### **4.1.1.20 Communicating results**

A third reason for retaining links between a donor's sample and their identity is to permit communication of clinically significant information to them (as distinct from research results that might be of interest to the patient population in general). Return of results to tissue donors is a controversial topic (Forsberg *et al.*, 2009; Ossorio, 2006; Ravitsky & Wilfond, 2006). In these situations, care is needed to ensure that the information that is to be communicated to donors is genuinely clinically significant. The types of tests done on tissue in a research laboratory are not always the same tests that would be done in a clinical setting, and their validity for diagnosis may not yet have been proved. It would be misleading to permit donors to believe that they may hear something of importance to their own health if they agree to donate tissue for research. This phenomenon is termed the therapeutic misconception (Appelbaum *et al.*, 1982), and is widely discussed in human participant research. There may be times when it is appropriate to offer tissue donors research results specific to themselves, but this should not be used to induce them to consent, and the above-mentioned privacy issues that arise when linking contact information with tissue samples should be considered.

The situations above also require extensive record keeping and administration. This record keeping will require provision of additional money to fund staff and resources, money that will then not be available to spend on this or other research projects. The expenditure is justified only if the ethical constraints are also justified.

## **5.6. Other ethical requirements in human tissue research**

As discussed earlier, informed consent as a foundational value has its origins in early documents such as the Nuremberg Code (Vollman & Winau, 1996).

However, informed consent is not the only item specified in such documents, and, by itself, it is not sufficient to render research ethical (Emanuel *et al.*, 2000). To illustrate this, I will discuss the previously cited paper, in which the authors identify and examine seven requirements for ethical human participant research, of which informed consent is just one. These requirements may also be relevant to research using human tissue.

The first requirement Emanuel *et al.* (2000) list is value. By this, they mean that the research that is proposed must be intended to answer a question that is either directly relevant to future patients or develops foundational knowledge that is expected to lead to advances in patient care in the future. In order to do so, the research should not aimlessly repeat earlier work, but should, at minimum, either validate and support the results and conclusions of previous investigations, or demonstrate their limitations. In an ideal world, new research would build on earlier research results by extending them in a meaningful way, but this is not always possible. Whatever the results of the research, they must be disseminated so that other researchers can use them to identify potentially productive directions for their own work. Pointless or aimless research undermines non-maleficence by exposing participants to harm without concomitant benefit to the community, and disrespects participants by demonstrating disregard for their time and goodwill.

Like human participant research in general, research using human tissue must also be valuable. This is not solely to protect the donor from undue harm, but because each tissue sample is finite, so can only be used for a limited number of studies. While data pertaining to the tissue, once collected, could potentially be stored and disseminated without limit, the opportunities for collecting the data itself are limited by the quantity and prior handling and storage of tissue that is available. In addition, processing the tissue in order to collect one type of data, such as the quantity of a particular drug metabolite present in the tissue, may render it unsuitable for use in procedures to collect other types of data, such as the sequence of a particular gene or the distribution of a hormone receptor. In this way, the tissue samples themselves would eventually be consumed, and their future value limited to that of the data already collected from them.

Valueless research would waste the tissue, undermining the public good by diminishing the effectiveness of other projects which might have made use of the tissue. Wasting tissue would also disrespect the donor's generosity, and may make them or others reluctant to consent to research use of tissue samples in the future.

The second requirement for ethical research is validity. A research question may be valuable, but, unless experiments must be designed in such a way that they are capable of answering the research question, the research cannot be ethical. In human participant research, the participants must be selected without bias; there must be a sufficient number of them to produce meaningful results, but not so many that more people than necessary are exposed to risk of harm. The research experiments themselves should use appropriate techniques and be conducted accurately, and the results interpreted honestly (Freedman, 1987).

Research that is not valid will expose participants to undue risk of harm, waste their time and goodwill, and undermine future research by consuming resources such as money and researcher's time that could have been put to better use. The issue of consent bias discussed above can also compromise the validity of research, and must be considered when designing the ethical and experimental protocols to be used in a study.

In the context of research using human tissue, invalid research will, as for value, waste samples, undermining work that might have made better use of the samples, and demonstrating disrespect for the donor. This may also undermine the public good by reducing levels of tissue donation in the future, hindering research.

Ethical research must also use fair methods for selecting research participants. This is for two reasons: firstly, to prevent any one group being exposed to undue risk of harm through participation in research; and secondly, to ensure that research results are generalisable to as much of the population as possible. It may be tempting to select research participants because they are in a location that is convenient for the researcher to access, or because they are unlikely to ask questions about their treatment, but, unless the participants represent a group expected to benefit from the research findings, this may be wrongfully exploitative. The use of prisoners for research is controversial for this reason – they make a convenient sample group because their environment is constant and they are easy to access, but they also have less control over their activities and choices than the population in general (Gostin, 2007; Kalmbach & Lyons, 2003). Similarly, if members of groups who are expected to be included amongst those offered interventions informed by the findings of the research are

not also included amongst those recruited for the study, they may experience variations in the effects of the intervention that were not predicted by the study results.

It may also be tempting to select tissue samples for research based on convenience, especially if they are already present in the research facility. In fact, it may be tempting to design a study around an existing collection. If the tissue was originally collected with this type of general use in mind, with samples selected appropriately and ethical considerations managed carefully, research designed this way may not be exploitative. For example, if the tissue collection is a biobank containing samples specifically collected for all types of gallbladder research, then it would be acceptable to use these samples to investigate an hypothesis of how gallstones form. However, if this approach to research design is contemplated, the expected results must still be generalisable. If they are not, the validity of the research may be compromised, and the potential value of the samples would not be fully realised. Therefore fair sample selection is still important in research using human tissue, but the balance of reasons for this is slightly different to that for human participant research.

The fourth criterion Emanuel and colleagues list is a favourable risk-benefit ratio. In studies where research is performed upon the body of the participant, the risk of direct physical harm is particularly salient and could be substantial. Studies of this type may involve, for example, administering drugs to participants or varying the details of a surgical procedure that they are to undergo. To mitigate this, researchers are required to present candidate participants with detailed information about the risks their participation could entail before consent can be given, to select only those participants who face the

least risk of harm, and to justify the risk in terms of the benefit to the community that the research could provide. The lengths to which researchers must go to satisfy these conditions is proportionate to the risk they are asking participants to take.

In human tissue research, the risks to the tissue donors from use of their samples in a given study are much fewer than the risks that research participants undergoing a direct physical intervention would be exposed to. When using surplus clinical tissue, the tissue would be removed from the donor's body whether it were to be used in research or not, and the risks of the removal procedure are balanced against the expected therapeutic benefits to the patient. The only relevant risks to discuss in terms of using the sample for research are those arising directly from the research itself. As with human participant research, any such risks to tissue donors must be proportionate to the expected benefit of the research to the public good (Gauld, 2001).

Emanuel *et al.* (2000) next list independent review as an important feature of ethical research. Researchers have legitimate interests in the successful conduct of the investigation, but these may come into conflict with the interests of participants. For an example of this in human participant research, see the account of early AIDS drug trials given by Arras (1990). On that occasion, the researchers' and future patients' interests in objective data regarding the medication being studied came into conflict with the participants' interests in a treatment for a life-threatening condition, threatening the validity of the study data. The Institute of Medical Ethics Working Party on the Ethical Implications of AIDS (1992) present an approach to such conflicts where the research design takes these interests into account.

The conflict described illustrates the types of concerns that can be identified and mitigated by ethical review. Such review is a common feature of research carried out throughout the world (Gauld, 2001), and is frequently a condition of funding and conducting the project, and of publishing the results. It is typically performed by a committee of volunteers who each bring specific expertise in areas such as ethics, medicine, research methodology, cultural issues, and law, as well as community representatives and lay members of the public. The review itself usually consists of reading and critiquing proposed research projects, with a view to identifying areas of ethical concern. An unaffiliated third party, overseeing the research at all stages from design onwards, could moderate any conflicts, reducing the risk of harm to the participants and maximising the benefit to the community arising from their contribution. Independent review also provides a means by which the community in general can observe the conduct of research and respond to issues, creating accountability and assuring present and future participants that their interests will be upheld.

The risks of harm to donors of tissue used for research have already been discussed. Independent review bodies can oversee the management of these risks as they do for human participant trials. The use of human tissue samples for research has been the subject of significant public controversy over the years, often as a result of misconduct by individuals or small groups (Burton & Wells, 2002; Jones & Galvin, 2002). Controversy of this nature can lead to reduced goodwill on the part of the public towards research as an activity, which may lead to fewer tissue samples being made available for research. The public accountability arising from independent review can support a culture of

respect for donors amongst researchers, reassuring the public and ensuring that researchers continue to have access to sufficient samples to work with.

Sixth on Emanuel *et al.*'s list is informed consent. They note that informed consent is widely discussed in the research ethics literature. As informed consent is substantially discussed elsewhere in this thesis, I will limit my comments here to noting that they do acknowledge the importance of informed consent in human participant research, but that they point out that it is a "procedural requirement" aimed at achieving objectives which may also be achieved in other ways.

The final requirement Emanuel *et al.* discuss is respect for "enrolled subjects" - in other words, for the participants in the research. This respect must be manifested at all stages, from initial approach, throughout the conduct of the experiment, to analysis and dissemination of results. The requirement for respect also applies to individuals who decline to participate, on the grounds that some information about them is already available to the researchers, information that may need to be kept confidential. Respect for participants includes providing the means for them to change their mind and withdraw from the research, and requires support for their welfare at all stages of the project.

As with the other requirements listed in this paper, respect is substantially focussed upon the welfare of the research participants, a concern which is substantially diminished when the research is performed upon tissue which has been separated from the body of the participant. There is still a concern for the privacy of the donor, however, as well as their cultural or spiritual connection to the excised tissue, and a policy of respect for participants may require that these issues be addressed.

The requirements listed by Emanuel *et al.* apply most directly to research using human participants. With some modifications, however, they can also encompass issues related to using excised tissue in research. They argue that informed consent is but one of several conditions which must be met if human participant research is to be ethical; most of these conditions also apply to research using surplus clinical tissue. If research using human tissue is to be ethical then all of the applicable requirements must be met. Informed consent may be able to contribute to ethical human tissue research, but we must not lose sight of other important concerns when considering how best to manage the issues.

### **5.7. Is informed consent needed in human tissue research?**

Given the difficulties with informed consent described earlier, it is tempting to wonder whether it should simply be abandoned in cases where the risk of harm to the donor's interests is minimal. However, a consent process is still capable of supporting some important values in research using surplus clinical tissue.

First of all, the act of simply asking a potential tissue donor if they will consent to research use of tissue which will be (or has been) removed from the body for clinical reasons demonstrates to them and to the wider community that the feelings and opinions of the patients who contribute to such research are of significance to researchers. This reinforces the principle of respect for the personhood or dignity of others when conducting research, a principle which was discussed by Emanuel *et al.* (2000) in their account of other values which should be upheld in ethical research.

As a consequence of demonstrating respect for patients as people as well as potential tissue donors, asking for consent also supports trust. Manson and O'Neill (2007, ch7) discuss the relevance of informed consent to supporting trust, particularly in situations where public goods are to be provided and where it is not possible to adequately satisfy all of the formal criteria for informed consent. Research using human tissue fulfills both of these criteria, so may well benefit from enhanced trust in the research process. A culture of trust supports research by ensuring that resources such as tissue samples are more likely to be available for research use in the future, which enhances the ability of research to support the public good by expanding our knowledge of human health and disease.

It seems therefore that there is certainly still a place for informed consent in use of surplus clinical tissue in research. The roles for informed consent of supporting trust and demonstrating respect for research participants are important enough that some attention must be given to the question of asking patients if they will permit tissue that has been removed from their bodies. However, the minimal harm that can come to donors through research use of their tissue, and the logistical and ethical issues that emerge when requiring stringent consent to using surplus clinical tissue suggest that a simpler approach to consent would be more appropriate.

## 6. Conclusion

Research into human biology is essential to provide medicine with robust, evidence-based approaches to preventing and treating disease. This basic research needs samples of tissue from patients, so that researchers can study the differences between diseased and healthy tissue and identify investigative approaches that have the potential to lead to improvements in health care. The tissue itself can come from a variety of sources, including tissue that has been removed from patients for diagnostic or therapeutic purposes, as part of the normal course of investigating and treating health issues. There is an extensive literature discussing ethical issues pertaining to the use of human tissue - including surplus clinical tissue - in research, which I have drawn on throughout this thesis. A dominant issue that emerges is the seeking of informed consent from donors for the use of their tissue. This emphasis on consent to research using surplus clinical tissue comes from the ethics of human participant research, where it has a clear role to play in supporting the interests of research participants.

However, it is not straightforward to apply models of informed consent from human participant research to the use of surplus clinical tissue. The term

“informed” emphasizes the claim that consent is not valid unless the person who is being asked to consent has had sufficient information disclosed to them that is relevant to their interests and values. For human participant research, which is performed upon the body of a volunteer, this disclosure must include details of the research project such as its purpose and rationale, the things the participant will be asked to do, the risks they face as a result, and how those risks will be managed, so that the candidate participant can decide whether to participate. Contemporary ethical practice of human participant research requires that such details are established before participant recruitment can begin. It is therefore reasonable to expect this information to be available for communication to participants when they are being recruited.

In the case of research that will be performed upon tissue, the details of the project may well be available when the tissue is collected. However, it is now becoming more and more feasible to store tissue samples for long periods of time before they are used in in a very wide range of research types, and there may not even be a specific research project in mind when a sample is collected. In this case, information about the research project is simply not available at the time the tissue is collected, making it impossible to disclose to the same degree as in human participant research at the time the tissue is collected.

Various approaches have been devised to manage consent to use of tissue when future projects are unknown, and these have informed the regulation of tissue research in various jurisdictions. This has resulted in diverse, and sometime incompatible regulation, which complicates management of international collaborations and potentially leads to inconsistent support of ethical values between jurisdictions. Given this picture, I have identified a set of values that

seem most important in research using human tissue, and considered the role that consent plays in supporting these values.

On an individual level, informed consent is said to be the primary means of supporting autonomy. However, there is still some debate over the nature and value of autonomy, which poses a problem for specifying an approach to consent which supports autonomy. Dignity is another value that is often invoked in discussions of research. It is similarly difficult to define satisfactorily, which makes using it to determine how to manage consent also problematic. However, respect for both autonomy and dignity provide a reason to require some form of consent from tissue donors, even if this consent is a very general one.

Research which uses human tissue often also requires access to sensitive information about the donor, or may result in the discovery of information which the donor may prefer not become widely known. Because of this, the interest that tissue donors have in protection of their privacy is widely discussed. Breach of privacy is the most substantial harm that individual tissue donors face as a consequence of their donation, but technological and procedural means of preventing such breaches, while important, also look vulnerable to failure. As these risks are so salient, patients who are approached to donate tissue should be informed, and allowed to decide if they wish to be exposed to such risks. Therefore, consent, informed in this way, is required.

Some members of the community may not share the values of others, perhaps even the values of the majority, regarding the significance of pieces of tissue taken from their bodies. They may regard the material itself as a treasure that must be treated with respect, or as a source of personal vulnerability. A more permissive approach to collection, storage and use of tissue might be acceptable

to the majority of the community, but it could undermine the values of specific groups within it. Consultation with these groups can demonstrate good faith on the part of researchers and reveal ways to permit the use of tissue samples that still respects the beliefs and concerns of all community members.

Research performed upon tissue from members of minority groups could also potentially harm all members of that group, even those who were not part of the research cohort. These group harms arise, for example, when research results lead to uncritical generalisations about an identifiable group within society that stigmatises the group as a whole, or reinforce negative stereotypes about the group. Consultation regarding the nature and goals of proposed research projects can identify such points of concern before offence is caused, and make a space for discussion of how to manage them. It also demonstrates respect for the autonomy of the group (as distinct from personal autonomy) over the uses that are made of tissue when conducting research into issues of particular concern to the minority in question.

Research that is intended to facilitate medical care supports the interests of the community and of individuals within it in furthering the aims of preventing and treating disease and injury. Thus, it can be regarded as a public good. However, this good can be undermined by too strict a requirement for consent, by introducing bias into the research and diminishing the usefulness of the results. In studies of the magnitude of consent bias, it was found that a substantial proportion of the population did not indicate a preference either way when asked for consent to have their medical records examined. Where studies do not require the patient's active co-operation, and present a low risk of harm, asking for consent and honoring only explicit refusal may be an ethical compromise

between producing high-quality research and respecting patient and participant autonomy.

As research is a public good, a case can be made that members of the community have at least some duty to contribute to research, and submitting to use of their tissue is one way to accomplish this. However, I have argued that this duty is not absolute, and should therefore not override the need for some sort of consent on the part of the donor. In addition, as research is a public good, it would be reasonable for some level of public involvement in deciding which research should take priority. Concern for the values of specific groups within the wider community could also find some resolution through public involvement in managing research. This involvement could be carried out at a government or a grass roots level, and could support broad priorities or specific initiatives. They could also cover issues such as the details of managing international collaborations in which differing values or procedures may conflict with the local consensus. However, the details of consultations of this type are beyond the scope of the present work. Discourse about research in general, and about specific initiatives and projects in particular has the potential to contribute substantially to supporting the good of the community and the values of minority groups within it.

It seems from the above points that open channels of communication between researchers, tissue donors in general, and specific interest groups are key to foregrounding the concerns of community members. In this way, potential sources of harm and disharmony can be identified and managed, and a space found for potential compromise. Communication of this nature also demonstrates respect for the concerns on each side, and supports trust.

Requiring some form of consent provides a justification and a mechanism by which this communication can take place.

But I have already argued that requiring “informed consent” by individual donors creates problems for research, in that it is unachievable in practice, especially when the nature of future research activities is unknown. Attempts to approximate individual informed consent can undermine the benefits of research, hence undermining the public good. Instead, individual donors should be asked to make a more general consent to opt in to a system whose parameters have been defined in consultation with representatives of the wider community. The parameters of the system would include ongoing consultation on the topics raised above. Tissue donors would be informed, in so far as they are informed about the system that is in place to decide which research projects using donated human tissue are authorised to proceed, but the scientific details of particular uses would not be necessary for that disclosure. In this way, more detailed consent would be situated not in the individual but in the community. Patients who do not wish to participate on these terms remain free to withhold their consent to donate their tissue, preserving a degree of individual autonomy. The consent given by the individual would be to participation in a communal consent to research, a consent that is informed by community discussion.

### **6.1. The tale of the gall bladder, redux**

How would these conclusions look in practice? To illustrate this, I will return to the story of Mrs Brown and her gallbladder. Let us assume that, by the time she meets with Dr Black, a community biobank has been established and that it

operates according to the principles I've arrived at in the conclusion. This biobank would be a facility that interacts closely with medical practitioners, researchers, and community representatives. There would be a mechanism for on-going consultation between all of these groups in order to ensure that all of the values I've discussed are supported as far as possible, and that the policies are responsive to new ethical and practical issues as they arise. In addition, the biobank would have a program of communicating updates on its activities and results from researchers using biobank tissue to interested community members, particularly those who have contributed samples.

The biobank management would include a team of trustees who are tasked with considering applications from researchers for collections of tissue samples.

These applications would be processed and the tissue allocated according to a policy that has been established through public and researcher consultation, in order to identify and manage points of concern such as those described throughout this work. The terms of reference under which the trustees operate would be established through discourse with researchers, patients and the community in general. They would cover the interests of tissue donors in being treated with respect and protected from harm, of researchers in making valid research findings and fulfilling their obligations to their colleagues locally and internationally, and of the wider community in occupying a space in which these interests are upheld.

Under this system, researchers such as Professor White would apply to the biobank trustees for use of the tissue samples, and would be required to adhere to any conditions the biobank requires. This could include communicating information about their research findings to the biobank, limiting use of the

samples to specified projects, and returning un-needed or withdrawn material to the biobank for respectful disposal. Depending on the outcome of the public consultation, it may be possible for Dr Green's and Ms Gray's projects to proceed without further authorisation; this would depend on the community's feelings regarding the types of research that these two scenarios represent.

During Mrs Brown's conversation with Dr Black, she would be told that her gallbladder could be useful for research into human biology, and that the biobank facility could store it and allocate it to one or more research groups according to the policy mentioned above. Dr Black could advise Mrs Brown that more information about how this system works is available, and tell her where to find it. He could also address specific issues such as privacy by describing briefly how they would be managed. Mrs Brown would be free to decline, under the terms presented, to donate the gallbladder; if so, it would be discarded after her clinical needs had been met. However, if she chose to donate it, it would be in the knowledge that it would be available for any researcher approved by the biobank to use. Mrs Brown's interests would be supported by the procedures followed by the biobank trustees, and she would not be required or permitted to make any further decisions regarding the use of the gallbladder, except perhaps in future to withdraw any as-yet unused tissue from the biobank. If she is curious about the types of work researchers are doing on gallbladders in general, she would have access to general information about the research findings to date through the biobank's science communication program. If she eventually becomes incompetent or dies, the tissue could still be used for research as long as this is within the overall terms specified during the community consultation.

The system of consent I've outlined is, like that in the original narrative, somewhat dependent upon disclosure, in the sense that the original donor still needs to be informed about the possibility of research use of the excised tissue, the implications for their interests, and how these implications will be managed. The details of managing donor interests, however, would be established via a continuous discourse between researchers and the community in general, which is intended to articulate fairly the concerns that arise from the use of human tissue for research, and arrive at a solution which supports everyone's interests as much as possible.

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