

Human Tissues Working Party Response to the Nuffield Council on Bioethics public consultation on Human Bodies in Medicine & Research (13th July 2010)

Please note: the following responses, unless otherwise stated, deal exclusively with the use of donated human tissues or organs for research. We are very happy for our responses to be quoted or otherwise made public.

Signatories:

Dr Margaret Clotworthy, Safer Medicines Trust (Chair, Working Party)
Jeffrey Anthony, Individual, London
Kathy Archibald, Safer Medicines Campaign
Dolores Baldasare, International Institute for the Advancement of Medicine, USA
Dr Delphine Behr-Roussel, PelviPharm, Orsay, France
Dr Kelly Berube, Cardiff University
Dr Tony Brown, Asterand
Dr David Bunton, Biopta
Dr Bob Coleman, Safer Medicines Trust
Dr Ann Cooreman, Tissue Solutions
Prof Ann Dickinson, University of Newcastle
Peter Fishman, Individual, New York, USA
Prof Chris Foster, Liverpool University
Wendy Fulcher, tissue bank patient representative & founder, Brain Tumour Research Campaign
Dr Kirstin Goldring, University College London
Dr Russell Higbee, VaxDesign
Dr Morag McFarlane, Tissue Solutions
Mr Anup Patel (surgeon), St Mary's Hospital, Imperial College London
Prof Barbara Pierscionek, University of Ulster
Dr Rivka Ravid, BrainBank Consultants, Amsterdam, the Netherlands
Dr Paul Rooney, NHS Blood and Transplant Tissue Services
Ian Scoular, Alcyomics
Dr Heidi Sowter, University of Derby
Prof Gerry Thomas, Imperial College London & Wales Cancer Bank
Jacki Trafford, Abcellute Tissue Bank
Dr Bridget Wilkins, Guy's and St Thomas' Hospitals NHS Foundation Trust, London
Dr Amanda Woodrooffe, Asterand
Dr Karen Wright, Lancaster University

1. Are there any additional types of human bodily material that could raise ethical concerns?

When a potential donor's family is being asked about organ donation for transplant, or when a member of the public is joining the organ donor register, the possibility of donating tissues that would be removed *solely* for use in research (i.e. not for transplant) e.g. large bowel, bladder, dorsal root ganglia, prostate, ought also to be considered, as these are also extremely valuable for research but may raise additional ethical concerns as they would not have been removed otherwise.

2. Should any particular type(s) of human bodily material be singled out as 'special' in some way?

Certain tissues, such as those with a reproductive function, may be widely considered as 'special' in some way. The perception of other tissues as special, such as heart, brain or eyes, may be dependent on cultural or religious factors.

Unlike post mortem tissues, tissue residual to surgery (and not required for diagnostic or therapeutic purposes) & which would otherwise be incinerated, could be considered as special in that patients may readily accept a system of presumed consent for the use of such tissue for research. Indeed, many patients are surprised and disappointed that this is not already the case.

Patient testimony:

'My key personal interest is from the viewpoint of brain tumour patients, but my involvement on Imperial's Tissue Management Committee broadens the interest too. I believe that tissues from a live patient as opposed to tissues collected post mortem raise different issues: where brain tumours (and other rare cancers) are concerned, there is a strong likelihood that research cannot be undertaken at all until after death as many of them are inoperable and therefore cannot be researched until after the patient has died. This means that this class of donor is usually in the post mortem donor group. There are therefore several issues, emotional as well as medical: most people would agree to (& indeed encourage) donation of waste tissue collected during surgery, but when parents or carers are faced with the death of a child or other loved one, sometime heart overrules head and they aren't able to think rationally.

I would also like to add another dimension: there is a movement advocating the right of patients to retain ownership of their tissue & have some of it kept in tissue banks for their own use, for genetic information &/ or other research uses in the future (Axler *et al*, *Pathobiology*, 2008;75(6):323-9).

Personally, I don't have a problem with tissues being passed on to intermediaries. The consensus of the recent British Neuro-Oncology Society conference in Glasgow (<http://www.gla.ac.uk/cvso/bnos2010/>) was that we are most definitely not where we should be in terms of tissue collection and something must certainly be done as a matter of urgency to improve the situation. I

would definitely volunteer to participate in any activity that might accelerate a better process of consent collection in order to improve access too tissue for research.'

3. Are there significant differences between providing human bodily material during life and after death?

Post mortem donation cannot physically harm the donor, while donation during life could potentially harm the donor, except where the tissue being donated is residual to surgery & not required for diagnostic or therapeutic purposes. Yet paradoxically, it is post mortem donation that is more ethically sensitive.

Despite this, the regulations governing the handling and consent processes are equally cumbersome whether the tissue concerned comes from a woman having a breast tumour removed and a researcher wishes to use some of the discarded material for research, or whether the tissue has been removed from a child who has died. The absence of parental consent for the removal and retention of organs from children who died at the Alder Hey Children's Hospital & Bristol Royal Infirmary was of course the scandal which ultimately led to the Human Tissue Act (2004) & the establishment of the Human Tissue Authority, with a remit to regulate the removal, storage use and disposal of human bodies, organs and tissues.

4. What do you consider the costs, risks or benefits (to the individual concerned, their relatives or others close to them) of providing bodily material? Please distinguish between different kinds of bodily material if appropriate.

a) Costs: There should be no costs incurred by donors, relatives or relevant others

b) Risks:

Physical: In the case of live donation, there are generally tangible physical risks, but these are generally small, as it is difficult to imagine ethical approval being sought or granted, or patients or volunteers being willing to participate, in significantly risky procedures purely for the purposes of research. In the case of donation after death, physical risks do not occur.

Non-physical: Risks other than physical can apply in the case of both live and post mortem donation, where research can lead to the discovery for example of a genetic defect or an associated susceptibility to a disease for which there is no present cure; in this case, it could be argued that it would be better not to know, and in addition, it may have a serious negative influence on the availability for example of life insurance for the donor or their relatives. Further guidance would be welcome on how much information which is potentially clinically relevant to the donor should be fed back via the donor's medical professional. The situation would be particularly difficult were sensitive information, such as the existence of a communicable disease, to be

identified, with implications not only for the donor but their spouse or other relatives.

c) Benefits: Apart from the positive feelings gained from a truly altruistic gesture, donation for research may have a long-term positive and tangible impact, where the donor or a family member can benefit directly from the research based on the tissue donated.

Another possible benefit is the flip-side to the risk discussed above, wherein the presence or likelihood of developing a serious condition may be uncovered. If clinically relevant information which could lead to early intervention or altered treatment is discovered during research using donated tissues, there may be a strong moral case for feeding this back through the appropriate medical personnel – more guidance on this would be welcomed. A positive example of this occurred in the US recently. VaxDesign uses immune cells harvested from blood donations to develop and produce miniature human immune system constructs. During the course of detailed analysis and processing of one of their donor's samples, unusual abnormalities were uncovered in a person who otherwise appeared to be perfectly healthy. VaxDesign scientists collaborated with the donor's medical team at a hospital to discover that they had detected a form of leukaemia several years before it would otherwise have come to doctors' attention. Following successful treatment, the donor requested that he be allowed to make a testimonial, which may be found as part of a short video clip here: http://www.youtube.com/watch?v=1wNWv_a-upc.

5. What do you consider the costs, risks or benefits (to the individual concerned, their relatives, or others close to them) of participating in a first-in-human clinical trial?

N/A

6. Are there any additional purposes for which human bodily material may be provided that raise ethical concerns for the person providing the material?

Apart from the generation of mixed-species animals or embryos, as described above, one respondent mentioned that they would be uncomfortable about cosmetic uses, except where this was to correct a problem with a serious negative impact on the potential recipient's quality of life.

7. Would you be willing to provide bodily material for some purposes but not for others? How would you prioritise purposes?

Willingness to donate any particular bodily material would be affected by

- a) whether it involved live or post mortem donation
- b) the use to which it was to be put (e.g. life-saving research versus weapons research)

- c) who would benefit (e.g. a potential donor may be more willing if the research to be carried out might benefit the donor or relatives)
- d) the likely risks associated with donation.

Thus many people would be willing to donate post mortem any bodily material for medically acceptable purposes. However, in the case of live donation, people would be reluctant to donate anything that caused them personal risk or serious discomfort, unless for the direct benefit of a family member or close friend – a scenario which is unlikely to occur in a purely research setting.

8. Would your willingness to participate in a first-in-human trial be affected by the purpose of the medicine being tested? How would you prioritise purposes?*

N/A

9. Are there any other values you think should be taken into consideration?

Another value that should be considered is confidentiality, which is not only a legal but also an ethical concept. It is important to respect individuals' right to privacy and to keep confidential matters that donors may not wish to disclose and that are not medically necessary to disclose. Further guidance on the disclosure of information which may be extremely important for close relatives to know (such as the presence of an infectious disease, or a high genetic risk factor for a certain disease) would be welcomed.

'Maximising health and welfare' could also be separated or expanded to encompass beneficence, which is doing good, and non-maleficence, which is avoidance of harm. It may also be necessary to assess risk and make a just risk/benefit analysis to ensure that the good that the act of donation may bring exceeds any harm or risk of harm of taking the tissue or organ. As discussed above, the physical risk to a post mortem donor is non-existent, whereas it may be very different for a live donor to consider.

It may be worth noting that where consent is generic, or even where a specific research project is in mind, it is not entirely clear how meaningful a concept 'informed consent' is, as the details of the project involved may be very complex and difficult to understand, particularly where the donor is not familiar with medical research. In most cases, patients are anxious that their tissues should 'go to a good home' and be used for some potentially useful purpose which may benefit others, understanding that the benefits from such research are often revealed on a long time scale and so may not see the benefits themselves.

10. How should these values be prioritised, or balanced against each other? Is there one value that should always take precedence over the others?

The rights of the donor as an individual should always take precedence over the benefits which society may gain by experimenting on a person or their tissues. However, as discussed above, more guidance may be required on balancing the rights of the individual with those of relatives, in particular where potentially clinically relevant information relating to them is inferred from discoveries made using donated tissue.

11. Do you think that it is in any way better, morally speaking, to provide human bodily material or volunteer for free, rather than for some form of compensation? Does the type or purpose of bodily material or medicine being tested make a difference?

Consensus was not obtained among the Human Tissues Working Party members on whether it is morally better to provide tissues for free rather than for some form of compensation. It was agreed, however, that at least the donor should not be out-of-pocket as a result of their donation, so some form of compensation may be appropriate, and there is no doubt that compensation, whatever combination of expenses, time and inconvenience this may encompass, can stimulate donation (or indeed participation in research generally). One would not expect people to donate tissues for research at significant personal risk, and so compensation proportionate to risk may not be a valid measure, but it may be reasonable to offer some compensation based on discomfort or time taken.

The provision of material benefits, and the extent thereof, in exchange for the provision of tissues is controversial and agreement was not reached among the Human Tissues Working Party on the extent to which this is appropriate, if at all. However, it may be possible to reward and engage donors or their families in other ways. For example, hospital newsletters informing patients in lay terms of discoveries made using tissues donated at the hospital may be a way of making donors feel appreciated and that they are not simply passive but also making a real contribution to research to defeat their disease or condition. In the US, the IIAM, also mentioned below in Q14, has an online 'virtual memorial' where donors' families can submit photos or stories relating to their loved ones, and runs a support group where donor families can make contact with others going through the same bereavement process. Donor family testimonials indicate that families often find some solace in the knowledge that their loved one's organs or tissues are being used in important research.

12. Can there be a moral duty to provide human bodily material, either during life or after death? If so, could you give examples of when such a duty might arise?

There is a strong case for making it the default position to provide human bodily material after death, since others' need is then greater than the donor's; thus there is an opportunity to embrace the values of reciprocity and solidarity. There is also a strong case for making donation the default position for residual surgical tissues, since the vast majority of patients would prefer their waste tissues to benefit others rather than to be incinerated. In such cases, it is of course important that an opt-out is provided so that those for whom the body or body parts have religious or other significance are not ethically disenfranchised.

We do not agree that there is a moral duty to provide human bodily material during life, except perhaps in cases where the potential donor would not experience significant risk or discomfort by doing so (for example blood donation).

John Harris, writing in the *Journal of Medical Ethics*, makes a powerful argument that, as moral agents and members of society, who benefit from the existence of the social practice of medical research, we do have a duty to contribute/participate. He says: 'it is crucial that the powerful moral reasons for conducting science research are not drowned by the powerful reasons we have for protecting research subjects.' (Harris, *Scientific research is a moral duty*, *J Med Ethics* 2005; **31**:242-248).

13. Can there be a moral duty to participate in first-in-human trials? If so, could you give examples of when such a duty might arise?

N/A

14. Is it right always to try to meet demand? Are some 'needs' or 'demands' more pressing than others?

Clearly, uses of tissues for diagnosis and treatment and organs for transplant must take precedence over the needs of researchers. However, we are surprised by the assertion made in the introductory paragraph to Section 4 of the Nuffield document that states that 'supplies of tissue for research... are usually adequate.'

Case Studies:

The following are examples of the difficulties experienced by some of the Human Tissues Working Party members trying to obtain tissues for research, and/or the clinical data which must accompany specimens in order to make the best use of tissue and obtain the most valuable results.

Disclaimer: Please note: the views expressed within the case studies are not necessarily those of all of the respondents.

Case study A:

A US perspective from a former clinical research coordinator:

The UK has the opportunity to rationalise the regulation of research without compromising ethical accountability

'As a clinical research coordinator in oncology in the US, I frequently walked prospective clinical trial participants through the *consent to participate in research* process. There was often a separate consent form for tissue collection and it was often not signed by the patient. Because of procedures designed to comply to the utmost with the guidelines of the Health Insurance Portability and Accountability Act of 1996 (HIPAA), we were limited in our ability to convey to patients the great benefit their tissue could have had to future sufferers of their illness. HIPAA has heightened awareness about the sensitivity of personal health information, which is an unquestionably good thing. However, an unintended consequence has been paranoia-inducing consent-process language. Understandably, many patients opted not to sign these threatening, incomprehensible documents.

It is vital to create regulations that shield research subjects from abuse of their personal information. However, we need to be realistic about the true risks; this involves honest dialogue with patients. I am encouraged to see that the UK is considering rational policies that could foster a new way of thinking regarding the consent-process, tissue collection, and tissue use. Unlike the American approach, which generates major regulatory hurdles for scientists in an attempt to account for a universe of unlikely contingencies, the UK approach to policy-making can be based on evidence. By fostering education and breaking down bureaucracy, Great Britain's legislation can demonstrate to the scientific community around the world that a balance can be struck between providing individuals with the respect and protection they deserve and providing scientists the material to fuel the medical advancements that will help us all.'

Case study B:

A consultant histopathologist's perspective (Dr Bridget Wilkins):

The burden of regulation, even in relation to ethically straightforward specimens archived after diagnosis or residual to surgery, is making it impossible for smaller facilities to contribute tissues to research efforts, and for clinical trainees and technical staff to conduct or participate actively in research

'I have been involved in research and supervision of clinical/laboratory trainees engaging in research since the mid-1980s. Until about 1995 in any large teaching hospital histopathology department you would have found almost all clinical trainees and a substantial number of laboratory technical staff involved in tissue-based research using surplus diagnostic tissues. Now there is almost none of this type of research, which was highly suited to the limited time available for trainees to complete a small but informative research project.

The main constraints pre-HTA (2004) were increasing requirements to account to Research Ethics Committees for use of accompanying patient data, or in cases where extra tissue was being obtained at the time of surgery/biopsy specifically for research. After Bristol and Alder Hey, “simple” tissue-based research studies within Pathology departments ceased almost completely because post mortem holdings came to be considered almost illegal and many pathologists rightly feared that holdings of surplus tissue from the living would become regarded in the same light.

Now that the Human Tissue Act is fully implemented, much of this sort of research using anonymised surplus tissues could resume. However, there is widespread uncertainty and misunderstanding about the status of tissues stored from September 2006 onwards in the many hospitals where generic consent for research storage of “surplus” tissue is not obtained. Also, the Human Tissue Authority has shifted ground in this area (particularly re. licensing and use of diagnostic archives as *de facto* tissue banks – see below), further reducing confidence among potential researchers. As time passes, it is increasingly unsatisfactory to confine research use of archived diagnostic tissues to those obtained before September 2006. In theory, if used anonymously for basic research requiring minimal access to patient information, this is not a constraint under the HTA (2004). However, many potential researchers lack confidence that this will remain the case and fear retrospective criticism. Most would be much happier if consent were in place but pathologists rarely have any control over the consent-taking policies and procedures within Trusts (even less in GP-led areas such as skin biopsy) and many Trusts have been unwilling and/or slow to adopt appropriate consent policies. Compounding this, some of the simple consent procedures started before the HTA (2004) came into being (e.g., tick-boxes on surgical consent forms, not supported by adequate training for consent takers and information for patients) are not compliant with the legal requirements of the Act.

Legislators have been naïve in their assessment of the challenges involved in the apparently simple task of obtaining patients’ consent for tissue research storage and establishing procedures to govern the subsequent handling of tissues stored with and without accompanying consent. Many Trusts have been unwilling to update pre-existing consent policies and procedures to take these requirements into account. In academic hospitals with established departmental links to formal tissue banks in partner universities there is little understanding of what is appropriate in terms of informing and consent-taking for the diagnostic archive compared with the detailed procedures needed to support a tissue bank of material obtained and stored under optimal, standardised conditions. At the London teaching hospital where I work, after more than 3 years’ work on this theme, we are still only at a stage of launching a limited pilot of such consent-taking in a single, highly motivated department. Inertia and aversion to the potential risk of having a target (to operate the policy and obtain consent) which the organisation may then be identified as not meeting adequately, has turned this issue into a major bureaucratic hurdle.

Current constraints make participation in some research activities impossible. Last July, the Human Tissue Authority changed its approach to research use of diagnostic tissue archives and made it mandatory for any archive from which tissue is contributed to research to be licensed. They envisage extension of post mortem licences, which are held by almost all Trusts, to encompass this activity without a significant burden on Trusts resulting. However, this requirement means that there must be a suitably qualified designated person in each Trust to manage this activity under the authority of the local Designated Individual (DI). Requirements in this area are quite different from the skills of the DI and designated persons operating PM services. There must also be procedures in place to track the consent status of individual specimens and to monitor their use and ultimate disposal. Busy pathology staff in smaller hospitals, with no or little direct personal interest in tissue-based research, have little motivation to take on these tasks and their Trusts generally have no specific resources to support them.

A specific example: colleagues and myself in London wish to establish from our diagnostic archives a virtual tissue bank for haematological (blood, bone marrow, spleen, lymph node etc) diseases in London and the South East. This would potentially involve several major London teaching hospitals and 10-20 partner hospitals with whom we have networking arrangements for diagnostic activity in this specialist field of pathology. However, under the Human Tissue Authority's revised guidance, unless a hospital is prepared to extend its PM licence to become additionally a research licence, that hospital cannot participate. Colleagues from smaller hospitals, initially very keen to participate, now feel unable to do so, because there is insufficient support (time and IT infrastructure, in particular) for this to be feasible. In the teaching hospitals, licensing arrangements mostly exist already through extension of either university tissue bank licences or post mortem licences. However, a high proportion – over 50% in some instances – of specimens originate from patients in smaller partner hospitals and are inaccessible for research purposes. Currently, this initiative has stalled because the bureaucratic burden is too great for most potential collaborators who, in other regards, would be very pleased to be able to contribute indirectly to national and international research using the pooled resource of our virtual tissue collection.

It would be helpful if the Department of Health provided all Trusts with guidance and templates for incorporating a simple level of generic consent for research storage of tissue into surgical/biopsy consent processes, and for managing “surplus” tissue as a research resource for the public good. Aim for an “NHS Tissue Bank” with uniform standards and procedures. Realistically defined levels of compliance with this should be made a target for NHS Trusts.

I would like to add that hospital-based archived diagnostic specimens are not the only collections of potentially immense scientific value which may remain effectively locked up; there is also concern that collections of great potential value are stored inaccessibly in the archives of companies conducting clinical trials. Not only are these collections less, or completely, inaccessible to

researchers unconnected with the companies in question, but the tissues are also unavailable to benefit the donors should new diagnostic applications become available.'

Case study C:

A tissue-broker:

Confusion over legitimate cost-recovery for tissue banks, the relationship between tissue banks and for-profit companies in tissue sourcing and distribution and over-zealous NHS R&D managers is driving us to work with US suppliers

'a) We contacted the * Tissue Bank to see if they could provide fresh tumour tissues for an ongoing project we have and we were told that they could only work with us if there was some sort of research collaboration or we donated a piece of equipment in return for the tissues. They would not charge us a cost recovery fee for the tissue. They said that they had reservations that there seemed to be a lot of work for little tangible benefit to the tissue bank, other than the payments which would be received – and this sits uncomfortably with their undertaking not to charge researchers for tissue freely given by patients. While the door is not closed neither of us could see how we might persuade the tissue bank access committee that it was in the interests of the Bank to participate in this particular project. We are currently working with 2 NHS trusts in the UK to provide these tissues.

b) We were talking to a clinician in a hospital in England who was keen to help us with a project needing FFPE (formalin fixed paraffin embedded) lupus biopsies. He had archival material he was able to share. However, when we spoke to his R&D department about getting an agreement in place we were told that they could not be seen to sell tissues. This is a common response; they seem to mix up not being allowed to sell organs for transplant with providing tissues for research on a cost recovery basis.

c) * Biobank - despite repeated approaches they will not supply us with any tissue as they do not want to work with "middle men" despite the fact that they will know exactly where the tissue is going and we will have a Material Transfer Agreement (MTA) in place with the client. The reply is usually 'the client can come to us directly'. However, in our experience, clients do not want the hassle; they want tissue as quickly as possible without having to deal with NHS trusts and getting agreements in place with them. To this end we have found that many of our clients send us a "wish list" and ask us to let them know what is available and from where to save them time and allow them to focus on what they are good at. This is often the case with Contract Research Organisations (CROs).

d) The brain banks in the UK would not work with us as they want the MTA to be directly between them and the client. The client also has to submit a project application for review before they can get the samples. We are working with a number of specialist brain banks in the USA as a result.'

Case study D:

**A pathologist-researcher (Prof Chris Foster, University of Liverpool)
Lack of interest and motivation among custodians of tissue collections,
coupled with disorganisation & fear of privacy laws is driving me to
work with US collaborators instead**

Despite high-profile publications in the field of biomarker discovery in prostate cancer, leading directly to a means of detecting which patients need to be treated immediately and which could be kept under observation – findings with significant implications for patient care and quality of life, Prof Foster continually experiences difficulties in obtaining access to the large quantities of samples and associated relevant clinical data he needs in order to conduct his research, due to an apparent lack of interest in participating on the part of some tissue banks. As a result, his focus is shifting to neurological studies using samples and funding provided by the US military.

Case study E:

**A tissue banker's perspective (Prof Gerry Thomas, Imperial College
London & Wales Cancer Bank)
Bureaucracy and increasing pressures on staff time, coupled with a
drought in pathology department funding is driving pathology-based
research & research services into decline**

'Tissue banks have a responsibility to distribute tissues freely donated by patients, not only to the projects which we believe to be of the highest quality and most likely to benefit patients in the long term, but also in as close accordance as possible with patients' wishes. In some cases it is the patients who donate to the tissue banks that request we deal directly with the end users, rather than dealing with intermediaries such as tissue brokers.

The major problem with accessing tissue from operative specimens is the amount of bureaucracy and the lack of support for pathology in all of this. However it also has to be said that even when funds are available to help pathology, bringing pathologists to the table to discuss their distribution is difficult due to the competing pressures on their time.

The discipline is under enormous pressure and seems to be in terminal decline. This will not be improved in the coming years due to the increasing pressure to save money in University and Hospital departments alike - support staff in all areas will be cut, and I am afraid tissue banking is likely to slip further down everyone's agenda, despite its importance for the academic and pharmaceutical research sectors. Patients' wishes for the use of their material in research are less likely rather than more likely to be met in the future, I fear.'

Case study F:

**An academic researcher's perspective (Dr Neil Chapman, University of
Sheffield)**

Lack of understanding amongst frontline staff of the importance of biopsy samples in medical research, as well as lack of time, hampers potential donor recruitment

'I run a research group investigating the mechanism of human birth/reason(s) for premature birth. In one sense my group is in an advantageous position because, in theory, we should be able to access a ready supply of non-post mortem uterine biopsy material from women undergoing elective sections, emergency sections or hysterectomies for benign reasons. However, in my experience, for this to work both midwives and clinical staff at all grades must be on-board with the research.

I costed in a clinician's time on a recent grant but to no avail. Regrettably, the supply of tissue remained intermittent at best and is now non-existent meaning my group has had to source cells from a collaborating lab instead. Moreover, attempts at educating midwives were not as successful as one would have wished: all the research documentation that was placed in the midwives' station was always removed. I suspect this was not done deliberately, but it did make finding consent forms and study-related literature difficult. This, in my view, illustrates the low priority placed on the research itself. In hindsight, perhaps a more robust solution would have been to employ a full time midwife on the project: her presence in all ante-natal clinics and labour wards would perhaps have ensured that the study received the priority it deserved since she would be supernumerary. This is an avenue being considered in future applications.

Obtaining consent etc. is presently a very time consuming process, which has been used as reason why tissue will not be obtained; for example, even though an LREC (Local Research Ethics Committee) has approved the project, clinical staff have decided they still will not obtain tissue. Whilst that is their right, it is frustrating to observe this since similar procedures are performed in collaborators' University NHS Trusts without any problems whatsoever: perhaps there is a problem with interpretation of clinical governance?

Essentially, I don't believe patients would not consent to providing a small uterine biopsy. Indeed, when they were approached, the vast majority were happy to donate a small piece of uterine tissue. The point, however, is that many women are not being approached at all and are therefore not aware of the study. Consequently, an integral part of any research planning process must be to ensure that all ward-based staff understand that such biopsy specimens are vital for research and that women must be given the choice to opt in or out of a study (hence the reason to perhaps included a senior midwife/nurse on a future study). Clearly, any solution must incorporate a process of educating clinical, nursing and midwifery staff in the importance of human biopsies for research and ensuring there is a mutually cooperative relationship between those parties and academics leading such studies involving patient tissue.'

Further factors limiting the availability of human tissues for medical research are:

- Some biomaterials are not commonly removed through surgery, limiting the 'ease of access' for research purposes.
- Access to some normal / non-diseased tissues can be challenging as these would typically have to be sourced from post-mortem donors or from non-heartbeating (multiorgan) donors. For instance, some tissues required for the FDA tissue cross reactivity panel (therapeutic antibody testing) are challenging to access, in particular thymus. In addition, access to "fresh" diseased tissues for functional studies is also difficult, including normal and diseased brain, pancreas from diabetics and lungs from asthmatics. Preserved brain tissue from donors with psychiatric conditions (e.g. depression, schizophrenia) is also very difficult to source in numbers that would lead to performance of studies with adequate statistical power.
- Some diseases are very rare and thus difficult to access. There is growing demand for focus on development of treatment for rare conditions (see links) and access to human tissues from these patient groups may slow the pace of research.
(http://www.boston.com/business/healthcare/articles/2010/06/16/pfizer_to_launch_rare_disease_research_group_in_cambridge/;
<http://news.bbc.co.uk/1/hi/wales/8531045.stm>;
<http://www.xconomy.com/boston/2010/04/12/cooking-with-the-genzyme-recipe-new-players-funding-rare-disease-drugs-in-boston/3/>
- Improvements in medical care have led to the extraction of smaller tumors. This is an excellent development from the perspective of patient care, which is, after all, what medical research is all about. From a research perspective, as the volume of sample available per donor has been reduced, it means that more patients are needed to opt into research in order for there to be an adequate supply of such tissues for research.

Referring to tissues residual to surgery

We would like to see it become standard practice for patients to be asked for their generic & enduring consent for their residual tissues to be used in research. This would make available vast quantities of tissue for research which has great potential to benefit patients, through drug safety testing, drug target identification or better understanding of disease processes which can lead to better disease management, for example. We believe that there is a case to be made for the introduction of presumed consent to better facilitate life-saving & life-enhancing research using this valuable tissue which is otherwise all too often incinerated. This would need to be preceded by an extensive information campaign, to make people aware that they could opt out if they wished and the establishment of processes to ensure that such wishes are complied with fully.

Meanwhile, it may be that the most straightforward way of obtaining generic & enduring consent for most people would be to allow or to encourage GPs or nurses to ask patients when they attend the GP for a routine appointment whether they would be willing to consent for residual tissues to be used in research, should the need for them to have surgery ever arise in the future. The information campaign would include measures to ensure that patients understand that this consent could be withdrawn at any time. Another way of reducing the bureaucratic burden, whilst still facilitating explicit consent taking, may be to alter the consent process so that once consent has been given, it is allowed to stand for all subsequent procedures. This would be on the clear understanding that the patient may at any time in the future withdraw their consent for their residual surgical tissues to be used in research. An alternative strategy, which is being tested at the NHS Greater Glasgow & Clyde NHS Trust, is to ensure that patients receive information about tissue-based research in the post alongside other information to prepare them for surgery. Patients are then consented during the admissions procedure.

The more generic the consent process, the more research studies should be facilitated by this surplus tissue collection. However, in conjunction with the introduction of more generic consent processes, it may be that more people would be willing to donate their residual tissues to research if it was also standard to allow people to opt out of a small number of potentially controversial areas of research. These areas may include areas of reproductive research, or where donated material would be incorporated into animals, such as with the creation of mixed-species embryos or xenograft mice. This would allow more potential donors to participate with peace of mind, whilst facilitating the broadest range of research. The International Institute for the Advancement of Medicine (IIAM), which is responsible for the nation-wide collection & distribution of organs (& whole bodies) for non-transplant purposes in the US (www.iiam.org) operates across many states with different regulations, some of which give donors' families the opportunity to withhold their relatives' tissues from certain applications.

It seems clear, for example from the case studies above, that no progress will be made unless frontline staff, including time-pressured midwives, research nurses, surgeons and pathologists are not only made aware of the vital role of human tissue samples in medical research, but also have their contributions to the medical research process officially recognised and facilitated as part of their normal work. A Research Nurses Workshop to educate research nurses about the importance of human tissues in research and to promote best practice in consent-taking has been mooted in the Working Party, and we are currently seeking a small amount of funding to make this possible. More broadly, a surgeon-researcher member of the Working Party has suggested that a roadshow or workshop showing the process map for how successful teams move from patient consent to actually getting the tissue once removed promptly to the pathologist, with agreed protocols in place for sampling & reporting before surplus tissue is banked or made available directly to researchers would be helpful. Such a workshop may be more effective than simply making the information available online, because it would enable all

the various stakeholders & participants to link together & illuminate the problems from various perspectives.

Some access challenges may be able to be addressed through outreach to patients / patient groups on the importance of being able to access tissues to advance medical research and thus help encourage more patients to opt into research programmes. Furthermore, 'patient power' was a key factor in making the Wales Cancer Bank such a success, and Prof Chris Foster of Liverpool University, for example, has begun a programme of speaking to patient groups with the aim of educating patients about the importance of their donated tissues in research, in order not only to improve participation rates but also to engage patients in the process of ensuring that politicians also recognise the importance of facilitating human tissue-based research.

Referring to tissues donated post-mortem:

It is vital to ensure that the extremely high quality, and therefore enormously valuable, tissues which could be made available from transplant donors whose organs are unsuitable for transplant are not simply incinerated. In order to facilitate this whilst maintaining the highest possible ethical standards are in place, it has been found that a number of steps must be implemented by stakeholders. (Please note: the system in Scotland is slightly different to the rest of the UK, as Scotland operates under the HTA (Scotland) 2006 whereas the rest of the UK operates under the HTA (2004), and it is the latter system to which the following information relates.)

NHS Blood & Transplant Organ Donation & Transplantation now operates using a single consent form which incorporates consent for organs to be used in research, should they prove unsuitable for transplantation, and so the research option is now one which should be routinely discussed. While it is enormously helpful for Donor Transplant Coordinators to have as much information as possible, explained in lay terms, concerning proposed research projects, or more generally concerning the work of approved tissue banks with whom they collaborate and who hold NHS REC approval, nothing is possible without the understanding & goodwill of the surgeons, who, time permitting, are needed to remove any organs and tissues which are being donated in the knowledge that they cannot be used for transplant but only for research.

Close coordination to ensure that Donor Transplant Coordinators are aware of tissue needs, and particularly 24/7 availability, of the tissue bank or of the researchers who needs the fresh tissue, is another key factor, as organs are inevitably removed late in the day or at night after regular surgery has already been carried out, and fresh tissues often have a very limited window of usability. Both tissue providers and tissue researchers need to have a frank discussion and understanding of both researchers' needs and the inherent limitations of what it is possible to provide. This is necessary to prevent, for example, providers processing tissues in ways which make them unsuitable for the majority of users, reducing the potential benefit to be obtained from their retrieval, but equally so that researchers do not place so many

complicated constraints on handling and processing, or restrictions on their availability to receive tissue, that it is rarely possible to provide them with what they need.

15. Should different forms of incentive, compensation or recognition be used to encourage people to provide different forms of bodily material?

As discussed above in Q11, the provision of material benefits, and the extent thereof, in exchange for the provision of tissues is controversial and agreement was not reached within the Human Tissues Working Party on the extent to which this is appropriate, if at all. As discussed, other forms of recognition (such as IIAM's virtual memorial) may also be appreciated. The level at which 'incentive' may override other factors in influencing a potential participant's judgements will vary depending on the person's circumstances. It is not clear to what extent people need to be protected versus to what extent individuals should be, and have the right to be, trusted to make their own decisions and weigh up risks and benefits for themselves (or those they are legally responsible for). However, it is not expected that potential donors of tissue purely for research purposes would ever be asked to participate in a process which carried any reasonable risk of substantial harm or discomfort.

16. Are there forms of incentive that are unethical in themselves, even if they are effective? Does it make any difference if the incentive is offered by family or friends, rather than on an 'official' basis?

As discussed above, some Human Tissues Working Party participants believe that the provision of any kind of financial incentive is inherently unethical, while others believe that it is only fair to offer some kind of reward or compensation, at the very least to the extent that the donor is not out of pocket in any way.

17. Is there any kind of incentive that would make you *less* likely to agree to provide material or participate in a trial? Why?*

An interesting article published in *Science Daily* last year indicates that potential clinical trial volunteers are more wary of participating in trials that pay more, as they perceive it to be a flag for raised risk (<http://www.sciencedaily.com/releases/2009/12/091206112521.htm>, : Human Guinea Pigs Wary of High-Paying Medical Trials). In fact, clinical trial payments are permitted to factor in time, inconvenience and expenses but not risk. Although these points relate to participation in clinical trials, it may be that providing very high levels of incentive for participation in human tissue donation might also make people wary of taking part.

18. Is there a difference between indirect compensation (such as free treatment or funeral expenses) and direct financial compensation?

N/A

19. Is there a difference between compensation for economic losses (such as travelling expenses and actual lost earnings) and compensation/payment for other factors such as time, discomfort or inconvenience?

N/A

20. Are you aware of any developments (scientific or policy) which may replace or significantly reduce the current demand for any particular form of bodily material? How effective do you think they will be?

At some time in the future, the availability of cultured stem cells, and a better understanding of the control of their phenotypic expression may to some extent replace the requirement for donated bodily materials for research.

21. In your opinion are there any forms of encouragement or incentive to provide bodily material that invalidate a person's consent?

As discussed previously, some Human Tissues Working Party respondents feel that any financial or other form of reward, or one which is sufficiently excessive, may induce a potential donor to take substantial risks they would not otherwise consider, and so could amount to coercion that would invalidate a person's consent. There is a broad interpretation within the Human Tissues Working Party of what level of compensation might be appropriate or fair.

22. How can coercion within the family be distinguished from the voluntary acceptance of some form of duty to help another family member?

It may not be possible to ever be assured of this with any great certainty, but it should be tested rigorously by appropriately trained members of medical staff. It should be explained to the potential donor that relatives may be told that certain tests for suitability were failed, for example, if the person did not wish to donate but felt under undue pressure to do so. This scenario is unlikely in terms of human tissue-based research, but it is possible for example that family members may wish to undergo genetic testing for a disease they are at high risk of, and may desire other members of the family to participate, or that other family members may find out information likely to apply to themselves as an indirect result.

23. Are there circumstances in which it is ethically acceptable to use human bodily material for additional purposes for which explicit consent was not given?

Unless the original consent specifically excluded additional uses, we believe that it would be appropriate to use donated material for additional non-consented uses, as long as these uses were given appropriate ethical approval. Ideally, the original consent should be sufficiently generic to make further clarification unnecessary.

24. Is there a difference between making a decision on behalf of yourself and making a decision on behalf of somebody else: for example for your child, or for an adult who lacks the capacity to make the decision for themselves?

As long as the individual is in an appropriate position as representative/ decision taker in other life aspects, then there is no difference between making a decision for self and for others. In both cases, however, it is important that the relevant medical team should be under no obligation to proceed if they feel the donation may be inappropriate.

25. What part should family members play in deciding whether bodily material may be used after death (a) where the deceased person's wishes are known and (b) where they are unknown? Should family members have any right of veto?

- a) Where the donor was of sound mind, and intentions clear, his/her decision should be accepted and taken as final, without necessitating further consent from relatives. If however a family member intervened with strong objections, it is difficult to imagine that it would be appropriate to continue.
- b) Where the individual's intentions were not clear, the family or others in an appropriate qualifying relationship should have the right of veto.

26. To whom, if anyone, should a dead body or its parts belong?

The concept of ownership may be better replaced with the concept of stewardship, as regards donated bodily material, such that material is always in the hands of an ethically approved steward, and that a steward should only pass material to a third party if that party agrees to act in accordance with the requirements of the steward.

27. Should the laws in the UK permit a person to sell their bodily material for all or any purposes?

Some respondents feel that under no circumstances should an actual or prospective donor be permitted to sell bodily material, except where that material is normal 'rejected' waste material, eg hair, nails, faeces etc. Others

feel that, again, it should be up to the individual whether they wish to part with some tissue samples in exchange for some reward. In either case, research should not be carried out if it would require human tissue samples needing to be removed exclusively for research purposes (i.e. not because they were being removed anyway as part of treatment), if doing so would risk seriously compromising the health and safety of prospective donors.

28. Should companies who benefit commercially from others' willingness to donate human bodily material share the proceeds of those gains in any way? If so, how?

The most important issue for donors appears to be that their tissues should be put to good use, rather than who precisely makes use of them, although this may be worthy of further research. In most cases, it would be very difficult to try to trace back whose tissue contribution, if any, made a defining contribution to a commercially successful venture, and how to fairly apportion proceeds in that case. Also, if this were to be attempted, it could constitute payment for donors to provide tissue, which some respondents would find repugnant.

Pharmaceutical companies, amongst others, may profit from discoveries made using tissues donated by the public. Most donors appear to be comfortable with this, as they recognise that a variety of organisations, and types of organisation, are required to bring the fruits of discoveries made during the course of research including the use of their tissues to the stage where they can actually benefit patients. However, a potentially relevant document to consider relating to this point is the Health Select Committee inquiry into the influence of the pharmaceutical industry (2005), which recommended that such companies be subject to specific regulation to ensure that any obligations to the public, on whom their profits depend, are fulfilled

(<http://www.publications.parliament.uk/pa/cm200405/cmselect/cmhealth/42/42.pdf>).

Although the Human Tissue Authority does not provide an opinion on whether it should be possible to charge for human tissues themselves, it seems fair that companies should be permitted to charge a fee for work associated with the supply of human tissues, eg retrieval, processing, transport, 'transformation', additional characterisation, etc. There may also be a case for allowing tissue banks funded by the NHS to do more than simply recoup costs when providing tissues to researchers. This could, for instance, provide vital extra funding to support pathology services, to invest in development, or even to recoup some of the costs associated with patient care. It is crucial that academic researchers in particular are not, however, priced out of access to human tissues for their research, so if public tissue banks were to begin charging above the level of recouping costs, this would probably need to be introduced in a stratified manner.

This issue is worthy of further discussion as there appears to be some confusion over whether & to what extent public tissue banks, which provide an absolutely essential service to research, may charge for tissue, and how

much & whether it is appropriate for it to be sold on to other tissue providers or intermediaries (even with MTAs or other appropriate agreements & ethical assurances in place), or how much public repositories should be allowed to charge above the mere recoup of costs.

Relevant examples of this confusion may be found in Q14, Case Study C, examples a-c, and further clarification would be welcome. Another example, from the same tissue broker, follows:

'We carried out a piece of work for a UK client to identify a clinician willing to provide a certain type of fresh tissue that is not easy to obtain. We found someone keen to work with them on this and both sides were happy to collaborate until the hospital R&D people got involved. They placed a seriously high price tag on the tissue (way over what the client was paying from another commercial supplier) but also wanted a tie in to future royalties of any compound developed using these tissues! As you can imagine, the client walked.'

29. What degree of control should a person providing bodily material (either during life or after death) have over its future use? If your answer would depend on the nature or purpose of the bodily material, please say so and explain why.

Beyond the right to withdraw consent at some future time, and as long as the donor's opt-out clauses are respected regarding specific types of research they may originally have identified at the time of consent, the donor probably should not have any rights over the nature of the use to which the donated bodily material is put, as long as any intended use is appropriately ethically approved. In cases where consent has been withdrawn, this should ideally not be retrospective, so that any work performed using the material prior to withdrawal of consent should be allowed to stand, and be regarded as fully consented. Such non-retrospective nature of consent withdrawal should, however, be made explicit to donors at the time that consent is obtained.

30. Are there any other issues, connected with our Terms of Reference, that you would like to draw to our attention?

Routine access to non-transplantable tissues from transplant donors (both heartbeating and non-heartbeating) for research purposes is essential if human bodily material is to continue to make a significant contribution to the advance in human healthcare.