MRC Centre for Transplantation, King's College London, NIHR Biomedical Research Centre at Guy's and St. Thomas' NHS Foundation Trust and King's College London - Transplant Theme

MRC Centre for Transplantation
Response to Nuffield Council on Bioethics Consultation Paper

Give and Take?
Human Bodies in Medicine and Research

The key aims of the MRC Centre for Transplantation at King's College London are to improve the health of transplant recipients by high quality research on the inflammatory and immune responses; to facilitate the application of biological technologies including genetics, therapeutics, imaging and stem cells; to sustain progress through recruitment and training; and to promote dialogue with the public about transplant research.

Our Centre welcomes the opportunity to respond to this consultation paper on human bodies in medicine and research. Advances in biomedical science and biotechnology mean that human bodies and parts thereof may be used in an ever increasing range of clinical and research applications and, as a result, demand for the donation of such material has increased considerably. Basic scientific inquiry and clinical transplant research have yielded significant advances in our understanding of transplant biology and its clinical therapeutic applications.

Organ transplants represent the best, most cost-effective treatment for patients with end stage organ failure. Numerous lives have been saved. However long term survival rates of transplant organs are problematic; a 50/50 chance of graft loss within 9 years for deceased donor organs and harmful immunosuppressive (anti-rejection) drug regimens that dampen immune responses causing complications which include malignancy and infection related deaths. These complications, in particular graft failures from whatever cause, place extra pressure on transplant waiting lists. Ultimately, they contribute to the ever increasing discrepancy between the demand for organs for transplants and their supply. Simply making tissues/organs available for transplantation does not adequately address this fundamental problem. One of the key research aims in transplantation research is to optimise the quality and suitability of donor organs and improve the longevity of organ transplants. In our view the importance of conducting research on donated bodily material in order to improve understanding of transplant biology and, above all, improve clinical transplant outcomes, cannot be overstated.

We understand that the intention of this consultation paper is to explore the ways in which society might appropriately respond to the demands for bodily material and in particular to consider what limits there should be, if any, on the promotion of donation or volunteering, including examination of whether the use of inducements are, or can ever be, legitimate; the role of consent; ownership and control of donated materials; the role of those acting as intermediaries between donors and recipients; and cultural and international perspectives.

The remit of this consultation paper is broad and encompasses issues related to the uses of donated human material that are currently regulated by three different authorities. We realise that these authorities appear to have adopted different approaches to the matter of donation and volunteering, perhaps in response to different demands and governing statutes, and appreciate that the intention of the working party is to consider whether the existing regulatory differences can be justified. We have chosen to respond primarily with reference to issues that affect the donation of organs and tissues for transplantation and, where relevant, how these may have particular import for transplantation research applications. We would be happy to expand upon any of the points made in this response.

General Comments and Response to Selected Consultation Questions

Section 1: Nature of human bodily material and first-in-human trials

The use of living whole organ donors has increased considerably over recent years. Although we agree that 'historically' organs have been obtained after death, it is interesting to note that Joseph Murray's team in Boston performed the first successful renal transplant between identical twins.[1]

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

Yes.

(1) The Face

The face has now been designated as an organ. To date only one full face transplant and very few partial face transplants have taken place worldwide. While whole and partial organs are included in the different types of human bodily material set out in the consultation document we consider that the face may raise additional ethical concerns, in particular those relating to personal identity.

(2) Composite transplants

For example hand or limb transplants.

(3) Transplant biopsy specimens

As a matter of routine, and for important clinical purposes, 'time zero' biopsy specimens are obtained from donated organs at the time donation prior to transplantation. Who, if anyone, is entitled to agree or refuse to such a procedure taking place? And to whom does the material to be biopsied, the kidney say, correctly belong?

(4) Donated material that is 'surplus to requirement'

Donated material may be 'surplus to requirement' for clinical transplantation purposes (eg. blood, serum, spleen tissue, lymph nodes). In this event should it be retained for some reason or another, research or future clinical purposes say, or should it be returned to the donor, or should it be disposed of?

Clinical transplantation encompasses far more than the simple transfer of donated material from donor A to recipient B. In our view identifying these additional types of human bodily material

[1] Murray JE, Merrill JP, Harrison JH "Renal homotransplantations in identical twins" *Surgical Forum* 1955; 6: 432.

raises important questions about what 'appropriate consent' to 'transplantation' set out in sections 2 and 3 of the Human Tissue Act 2004 actually means. We will consider this further below, in particular in our response to question 23.

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

In the context of transplantation, in all but exceptional circumstances no.

While we appreciate that certain types of body parts, perhaps most obviously the heart, evoke emotional responses we consider that it is unhelpful to consider that any type(s) of human bodily material donated for the purposes of transplantation be singled out as 'special' in some way. One possible exception is the (as yet theoretical) transplantation of germ cells which has clear implications for possible future progeny and personal/genetic identity.

While we do not think there is an absolute ethical difference between particular type(s) of human bodily material, we do appreciate that different people may attach 'special sensitivity' to different types of treatments of certain organs, for example the retention of organs for display or undergraduate medical education perhaps. We would like to acknowledge that tissues/organs donated for transplantation do differ and require different treatment pre-, peri-, and post-transplant. Further, different research applications may also require tissue/organs to be treated or processed differently. These differences need not mean (or require) the ascription of 'special' status, but they do emphasise that tissues/organs donated for clinical transplantation or research may have features that are unique (or peculiar) to them that may mean (or require) that they are treated differently.

Question 3: Are there significant differences between providing human bodily material during life and after death

We consider that there are significant, morally relevant, differences between *providing* human bodily material during life and after death. These differences relate most obviously to risks incurred and obtaining valid consent. Living donation entails risk, including, in specific instances, the risk of death. In contrast to the deceased, living donors may be harmed and incur potential loss of earnings by providing bodily material.

It follows from this that there are also significant differences, in particular for professionals involved, in *obtaining* human bodily material during life and after death. The process of obtaining human bodily material, a kidney for transplant say, from a living donor may cause their death.

Demonstrating that living organ donation is, or may be, harmful provides a powerful argument against it. Other things being equal, inflicting harm on persons is wrong. The difficulty however with importing this kind of justification to the context of living donor organ donation and transplantation is that is does not take account of other morally relevant reasons, in particular individual autonomy, which may have contributed to an individual's decision, and motivation, to donate. Nor does it adequately capture the real, or actual, circumstances in which an individual may be prepared to volunteer to incur, or risk, harm to themselves in order to benefit, or rescue, another and consider the overall benefit mutually advantageous regardless of the harm which may or may not be caused to self. We fully support living-donor transplant programmes however

we do think that the considerations we have set out in response to question 3 should prompt careful consideration of the principles and processes which underpin the provision of deceased donor organs/tissues for transplantation.

Question 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.

The costs, risks or benefits to an individual in providing bodily material are likely to vary enormously depending on which body part they are providing and to whom they are providing it. Living donor kidney donation for example is associated with a mortality risk of 1 in 3000.[2] Living donor liver donation carries a far greater mortality risk of, in some cases, up to 1 in 100.[3] Beyond empirical differences, the current models and evolving landscape of living donor transplantation highlight the good deal of variety in the sorts of values and importance that individuals place on costs, risks and benefits associated with providing bodily material. As seen in our response to question 3 we consider that the circumstances in which an individual may be prepared to provide bodily material and risk the possibility of incurring harm in so doing are likely to vary considerably.

In the context of deceased donation where an individual has chosen to become a deceased organ donor in the event of their death, and this is clearly documented, we consider that it is wrong to allow family members to invoke a veto to organ transplantation and where possible this should be discouraged. In our view the wishes of the individual providing bodily material should be respected and, in all but exceptional circumstances, outweigh possible costs and risks to their relatives or others close to them.

Question 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?

The costs, risks or benefits of participating in a first-in-human clinical trial are likely to vary enormously. Assessment of risk will include understanding when a study is scientifically feasible, regulatorily possible and ethically appropriate. It will also be necessary to understand how the risk benefit ratio competes with genuine scientific/clinical uncertainty in this context (cf. TGN 1412 study, Northwick Park Hospital).

We appreciate that in this consultation, the working party are interested in exploring whether meaningful parallels can be drawn between those who provide bodily material for medical treatment and research, and those who provide their bodies on a temporary basis for experimentation with no expectation of personal health benefit. While not participation in a 'first-in-human' trial *per se* we consider that there are aspects of 'non-directed altruistic living donation' that may provide meaningful parallels here. The good societal effects of their donations notwithstanding, so-called 'altruistic living donors' undertake a substantial medical risk with no expectation of individual personal health benefit. It may be interesting to examine *whether or not* individuals who come forward as 'altruistic' living donors share goals in common with those who participate in a first-in-human clinical trial. We acknowledge that the motivation

[2] E. M. Johnson, M. J. Remucal, K. J. Gillingham, *et al* 'Complications and risks of living donor nephrectomy' *Transplantation* 64(8) (1997), 1124-8.

[3] Estimates vary. See for example R. M. Ghobrial, C. E. Freise, J. F. Trotter, *et al* 'Donor morbidity after living donation for liver transplantation' *Gastroenterology* 135(2) (2008), 468-76.

to participate in first-in-human clinical trials is likely to vary considerably from pro-social (eg. participation in a biobank) to participation that is motivated only upon the level of 'compensation' payment provided, which in many cases is likely to be far greater than the compensation received by an altruistic living donor say. We consider that our responsibility in this setting includes presenting information regarding the risks and benefits of participation as accurately as possible in an accessible way regardless of an individual's motivation to participate.

We consider that further meaningful parallels may be usefully drawn with 'translational research' and we hope to draw the working party's attention to aspects of translational research in the field of transplantation throughout our consultation response. Translational research may require individual patients to provide their bodies on a temporary (or possibly permanent) basis for experimentation with the possible outcome that there may or may not be personal health benefit. In our view in the setting of translational research it is important to identify and communicate with patients and to be able to adequately account for 'therapeutic misconceptions' (eg. new treatment is better treatment) and misconceptions that may be inversely proportional (eg. research participation guinea pig).

Current regulatory guidelines from the Medicines and Healthcare Products Regulatory Agency[4] and declarations, for example the Declaration of Helsinki, [5] provide important models for research in the context of novel drug treatments and innovative techniques used for instance by surgeons. However, they do not capture or adequately account for the innovation that translational research (for instance biomarker projects currently underway at the MRC Centre for Transplantation) presents. We will provide further detail on translational research in the field of transplantation in our response to question 20.

Section 2: Purposes of providing bodily material/volunteering in a trial

(1) Classifying treatments

Classifying treatments using donated bodily material may be helpful. However, donations for transplantation often overlap in the categories listed. For instance, a kidney transplant may be life-saving, life-prolonging and life-enhancing. Further, these classifications are not really about the *purposes* of the donations but rather about their results.

(2) Directed and non-directed organs/tissues

It is not clear how the issue of 'directing' or 'not directing' organs for transplants provides guidance on their purposefulness *per se* other than to perhaps frame the legitimacy of the purpose in the context of societal responsibility and the interest of the common good, or some relationship or another. Interestingly, in the context of organ donation for transplantation two parallel donation/allocation regimes have evolved and are in operation, with an 'impartial justice' rationale governing deceased donation and, for the most part, an autonomy driven rational underpinning living donation. This is so even though at the present time a model of consent forms the basis upon which *all* individuals agree (or refuse) to donate. The recent Department

[4] www.mhra.gov.uk
[5] www.wma.net/e/ethicsunit/**helsinki**.htm

of Health Public Policy framework document *Requested Allocation of a Deceased Donor Organ* [6] takes account of and to some extent addresses this issue. This policy framework says that 'the fundamental principle of all deceased organ donation is that it must be unconditional'. But if we continue to accede to a model of 'appropriate consent'[7] or 'authorisation'[8] both afforded primacy in the Human Tissue Act 2004 and the Human Tissue (Scotland) 2006 respectively, as the basis upon which deceased donor organs become available for transplantation, then we must provide good reasons as to why such authorisation does not allow for the possibility of donors placing restrictions or conditions (which may include directing their donated bodily material is some way or another) upon such authorisation before their death.

Whether organs for transplants may be directed or not (or controlled in any way) might usefully be considered in conjunction with section 5: the role of consent, and/or section 6: ownership and control.

(3) Immediate and future uses

We agree with the assertion 'material provided for a specified use may also turn out later to have a value for research purposes that could not be predicted at the time the material was provided'. However, it does not follow that this will be true in all instances. Not all future uses are, or need be, 'hence unspecified'. Further, future purposes may have clinical as well as research value, for instance, in the context of transplantation future testing for donor specific antibodies. A category which captures 'future specified clinical and research' purposes may be useful.

(4) Existing and processed form

Donated tissues and organs for transplants are used in their 'existing form' insofar as the material transplanted is the same material that was donated. However, donated tissues/organs are often the subject of a good range of procedures, which may or may not be part of a clinical research project, prior to transplantation including, but not limited to, preservation techniques and bench preparation. The purpose of these interventions is to optimise the donor tissue/organ for transplantation. While we do not consider that this amounts to 'transforming' the donated material in any way it may, for some individuals, raise ethical concerns which relate to the timing/purpose of such interventions. This has particular import in the context of deceased donation.

As we have already highlighted in our response one of the key research aims in transplantation research is to optimise the quality and suitability of donor organs and improve the longevity of organ transplants. New translational research in the field of protein therapeutics has considerable potential to improve the quality and suitability of organs for transplants. For instance, using proteins to 'coat' a donor kidney say, will offer more robust protection from the recipient immune system. If the potential of this innovative area of work is to be realised it requires that research is conducted on deceased donors and/or their donor organs. The same is true of

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[6] *Requested allocation of a deceased donor organ*
www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_114800

[7] The law protects individuals' rights to control the use of their bodies for medical purposes. See generally Herring J "Crimes against the Dead" in eds Brooks-Gordon B, Ebtehaj F, Herring J, Johnson M, Richards M *Death Rites and Rights* (Hart Publishing 2008) pp.219-239. It is by virtue of this right that the Human Tissue Act 2004 empowers an individual to appropriately say 'yes' or 'no' to (consent or refuse) organ donation. See section 3 Human Tissue Act 2004.

[8] The Human Tissue (Scotland) Act 2006 uses the term 'authorisation'.

translating innovative organ preservation techniques. Such research, subject to necessary scientific and
ethical review and oversight, need not conflict with organ donation, and could usefully be co-ordinated with organ procurement teams.

(5) Commercial and non-commercial uses

Referring to 'whole organs donated after death' as being 'used non-commercially within the health system' usefully reinforces the position that organs for transplants are donated voluntarily and freely in the NHS. However, transplantation provides a net financial gain for the NHS. A considerable amount of money in this country is saved through organ donation and transplantation. Further, hospitals are in receipt of 'payment' from a Department of Health/ NHS funding source (usually a Primary Care Trust, although this is of course likely to change in light of the NHS healthcare reforms recently proposed by the Secretary of State for Health Andrew Lansley) when a deceased or living donor organ is transplanted.

Section 3: Ethical Values at Stake

The ethical values stated appeal to the virtue of saving life through organ transplantation. The NHS exists for the common good. Identifying ways in which we might maximise health and welfare is a legitimate and worthy goal.

Question 9: Are there any other values that you think should be taken into consideration?

(i) Professional Values

The MRC Centre for Transplantation is part of a Comprehensive Biomedical Research Centre and an Academic Health Science Centre. A significant proportion of staff working at or collaborating with our Centre have professional responsibilities, including a good number with clinical responsibilities. We think it would be useful for professional values, including for example the principle of 'do no harm', and responsibility, to be taken into consideration. These responsibilities become particularly relevant in the setting of living donor transplantation where greater risks are incurred.

(ii) Societal Values

The value of life is, in most circumstances, accorded the highest value that society, and morality, recognises. Transplants save lives. Scientific innovation has made it possible for the enterprise of clinical transplantation to save the lives of thousands. That future knowledge acquired from scientific advances in the field of transplant immunobiology might solve the complications, and challenges, which remain outstanding in the field of organ transplantation, highlights the importance and justification of supporting their continued pursuit. If, for instance, advances in biotechnology are able to overcome the problem of organ shortage, the purpose of science and the contribution that it makes, not only to the enterprise of clinical transplantation, but also to associated matters which have profound social, political, and economic importance, will be clear.

The shared aim of medicine, science and society should be benefiting society and humanity as a whole. Society has legitimate concerns over the protection of deceased donors and the use of their organs as transplants. But we consider a balance must be struck between these concerns and the many benefits that research will bring. If we focus exclusively on the rights of deceased

individuals and their relatives we may lose sight of those individual rights which constitutes the common good. We all benefit from biomedical research. It is both of benefit to patients, and research subjects, and in their (and all of our) interests to be in a society which pursues, and actively accepts, the benefits of research. It is imperative that society takes on the responsibility for supporting, and engaging with science.

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

It is not clear that there could ever be a straight forward way in which the competing values set out in this section can be prioritised. Different people hold different values and beliefs about organ transplantation. Individual circumstances differ and it is not clear that one persons set of values will be relevant for another. However, we do support the view that rights and comparable interests should be considered on equal terms. We also take the view that since the value of life is, in most circumstances, accorded the highest value that morality recognises there should be just reasons for limiting or curtailing the ways in which we might appropriately save life.

While not wanting to detract from the virtue of the ethical values listed it is not clear that they only compete with each other in isolation. As we have highlighted above professional responsibilities and societal values require consideration. Further, while not ethical values *per se*, other factors, for instance coercion and exploitation, may impact on the donation process and the effective delivery of transplant services. Deciphering whether an act (a donation for transplantation in this case) is the result of coercion or altruistic voluntariness is not always straightforward and may be notoriously difficult in the clinical setting.

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

In our view this question is essentially asking whether it is better, morally speaking, for altruism (according the definition set out in section 3 of the consultation document) to form the basis for providing human bodily material or volunteering in a first-in-human trial rather than some form or another of compensation. We contend that in the context of organ donation and transplantation the definition of altruism set out in section 3 does not adequately capture all acts of altruism and that compensation, of some form or another, does not necessarily lessen or debase acts of altruism or benevolence, just as the act of altruism of a fireman who saves a child from a towering inferno is not lessened or debased because he is remunerated to undertake such duties. In almost all instances donating an organ is acting to save a life or prevent human suffering; it is necessarily altruistic whether compensated or not.

The types and purposes of bodily material or medicine being tested will inevitably differ. Whether the type or purpose of bodily material or medicine being tested *makes a difference* regarding the legitimacy of compensation raises a broad range of questions including, but not limited to, the following:

(a) Should different risks or possible harms require different compensation?
(b) Should risks/possible harms be stratified?

As seen in our response to question 3, living donation entails risk, including, in specific instances, the risk of death. In contrast to the deceased, living donors may be harmed and incur potential loss of earnings by providing bodily material. However, this possibility of harm remains unchanged regardless of whether the donor organs are given freely, compensated for, bought, sold or wasted. On this basis it follows that any scheme of compensation based upon risk stratification will be arbitrary. This does not, in our view, mean that compensation is illegitimate, but it does highlight that decisions regarding the type(s), or perhaps amounts, of compensation that may be given for different types and purposes of bodily material or medicine being tested will be notoriously difficult and are unlikely to ever be consistent. It may be that the only way of navigating this issue is by responding to the various demands that different types or purposes of bodily material or medicine being tested pose.

We support the reimbursement of costs incurred and losses attributable to the transplant donation process. We take the view that such reimbursement should be the responsibility of the health services and that information regarding reimbursement should be made available and accessible to all potential living donors. Any system set up to provide such reimbursement should be open and transparent and have appropriate safeguards in place that as far as is possible exclude the possibility of inducement, exploitation of donors, or profit to intermediaries. In our view the type of bodily material or the purpose for which it is donated makes no difference in this regard.

Question 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?

As we made clear at the outset of our response to this consultation, it is generally acknowledged that advances in biomedical science and biotechnology mean that human bodies and parts thereof may be used in an ever increasing range of clinical and research applications and that, as a result, demand for the donation of such material has increased considerably. This demand has come about to provide the means for the pursuit of knowledge and treatment that benefits society and humanity as a whole.

As seen in our response to question 9, we consider that the shared aim of medicine, science and society should be benefiting society and humanity as a whole. We all benefit from biomedical research. It is both of benefit to patients, and research subjects, and in their (and all of our) interests to be in a society which pursues, and actively accepts, the benefits of research.

It is imperative that society takes on the responsibility for supporting, and engaging with science. While we do not consider that this straightforwardly translates into a ‘moral duty to provide human bodily material’ either during life or after death, we do think if society wishes to uphold a system of donation based upon a model of consent and individual wishes then there is a responsibility incumbent on society to ensure that individuals are equipped with the appropriate means to *decide whether or not* they wish to donate organs/tissues for transplantation and research purposes. One such means that has been discussed in this arena is the mechanism of ‘mandated choice’, but there may be others. In our view this has particular import to deceased donation.

Question 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?
See response to question 12.

Section 4: Responding to Demand

Question 14: Is it right always to try and meet demand? Are some 'needs' or 'demands' more pressing than others?
There are good reasons to support the view that it is right always to try and meet the demands of a clinical service and to achieve the aims of an ethically sound research agenda, particularly when the moral imperative is to save life. It is straight forward to agree on aiming to achieve this end goal. Matters are more complicated when we take account of the means by which we might legitimately achieve this goal. At the present time the UK system of tissue/organ donation is based upon altruism and the good will of others.

We support the view of NHS Blood and Transplant (NHSBT) and the British Transplantation Society (BTS) that the clinical needs of some individuals waiting on the transplant list are more urgent and pressing than others. We support the view that deceased donor organ allocation schemes must give priority to patients in desperately urgent clinical need. Patients registered on the NHS Blood and Transplant (NHSBT) 'Urgent Heart Scheme' or 'Super Urgent Liver List' should always take priority.

Question 15: Should different forms of incentive, compensation or recognition be used to encourage people to provide different forms of bodily material or to participate in a first-in-human trial?
As seen in our response to question 11, we support the reimbursement of costs incurred and losses attributable to the transplant donation process/procedure and this includes loss of earnings due to time off work. As we have made clear we do not consider that donating different forms of bodily material for transplantation requires different forms of reimbursement. However, we acknowledge that claims for expenses incurred and compensation for lost earnings may differ in amount and that this may depend in part on which tissue/organ is donated. For example a living kidney donor may require more time off work following the donation procedure than say a bone marrow donor.

As far as we are aware different forms of compensation and recognition do currently exist and are given to those who provide bodily material. It is not clear to us whether these different forms of compensation and recognition 'encourage' or 'have encouraged' people to donate. However we would like to acknowledge that different forms of recognition may engender a sense of 'belonging' and some people may accord high importance to this, in the same way perhaps as people can often feel affiliated to a club or charity say.

As seen in our response to question 5 we acknowledge that participation in first-in-human clinical trials may be motivated only upon the level of 'compensation' payment provided.

Question16: Are there forms of incentives 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?

Consistent with the view of the BTS, we believe there are forms of incentives that, regardless of whether one takes the view that such incentives are 'unethical in themselves', may have the effect of coercing or exploiting an individual's good will to donate bodily material for transplantation. In our view coercing or exploiting an individual's good will in this context, no matter whether the good effect of organ donation is achieved, is unethical. We believe this is so regardless of whether such a state of affairs came about through family or friends or an 'official' basis, however we acknowledge that in the context of family/friends such a state of affairs may come about covertly and as we acknowledged in our response to question 10, deciphering whether an act (a donation for transplantation in this case) is the result of coercion or altruistic voluntariness is not always straightforward and may be notoriously difficult in the clinical setting.

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

Yes. In our view there are clear differences between indirect compensation and direct financial compensation. However it is not clear that these differences are morally relevant.

Question 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?

We do not consider that there is a morally relevant difference between *compensation* for economic losses (such as travelling expenses and actual loss of earnings) and other factors such as time, discomfort or inconvenience which are consistent with losses attributable to the transplant donation process.

Question 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 or for first-in-human volunteers? How effective do you think they will be?

(1) Scientific developments:
There are a number of exciting new developments in the field of transplantation research. We would like to highlight three key aspects of research that we consider have the potential to be highly effective in reducing the current demand for bodily material for transplantation and one further key research area, xenotransplantation, which has the potential to replace the demand for human bodily material for transplantation.

(a) Deceased donor organ optimisation and preservation
As we have already outlined, new translational research in the field of protein therapeutics has considerable potential to improve the quality and suitability of organs for transplants. For instance, using proteins to 'coat' a donor kidney say, will offer more robust protection from the recipient immune system. If the potential of this innovative area of work is to be realised it requires that research is conducted on deceased donors and/or their donor organs. The same is true of translating innovative organ preservation

techniques. Such research, subject to necessary scientific and ethical review and oversight, need not conflict with organ donation, and could usefully be co-ordinated with organ procurement teams.

Other advances include the use of extracorporeal membrane oxygenation (ECMO) in deceased donors to improve organ preservation.

(b) Immunological transplant tolerance

Transplant tolerance can be regarded generally, as a state of unresponsiveness to non-self antigens in the absence of ongoing (immunosuppression) therapy. Ideally, a state of immunological tolerance, or unresponsiveness, would be induced in recipients of allogeneic organ transplants preventing rejection of the transplant, without the need for life-long pharmacologic immunosuppression with its hazardous and potentially life-threatening side effects. Importantly, the state of tolerance must exist in the context of general immune competence, including normal immune responses to pathogens, and cancer risks no greater than the general population. This state of immune tolerance would completely prevent destructive immune responses against the transplant organ, but would not interfere with the normal immune responses against environmental pathogens and tumour cells. Donor specific tolerance, if achievable would completely transform the routine clinical practice of transplantation.

A multi-centre research study led from the MRC Centre for Transplantation at King's, has recently identified an immunological signature for transplant tolerance. [9] This research is now approaching a stage of translation into new strategies for tolerance induction in vivo. The goal is to develop, and apply, durable and antigen-specific tolerogenic therapies that lead to permanent graft acceptance in the absence of life-long therapy and deleterious side-effects.

The demand for donor organs would decrease if a state of tolerance and minimal use of immunosuppressive drugs with toxic side effects led to prolonged graft survival, with fewer patients returning to the transplant waiting list.

(c) Genome wide association studies and genetic biomarker led therapy

Ascertainment of genetic variation has already had a major impact in clinical transplantation. For example, genotype testing and tissue type matching of potential organ donors and transplant recipients currently forms an essential part of almost all organ allocation schemes

Human genome analysis has the potential not only to widen the number of genetic biomarkers on which patient outcome can be modeled, but may also lead to changes in clinical practice and patient management that will overcome important limitations of current therapy. For instance, by identifying biomarkers associated with those transplants

[9] Sagoo P, Perucha E, Sawitzki B, Tomiuk S, Stephens DA, Miqueu P, Chapman S, Craciun L, Sergeant R, Brouard S, Rovis F, Jimenez E, Ballow A, Giral M, Rebollo-Mesa I, Le Moine A, Braudeau C, Hilton R, Gerstmayer B, Bourcier K, Sharif A, Krajewska M, Lord GM, Newell K, Seyfert-Margolis V, Warrens A, Janssen U, Volk H, Soulillou J, Hernandez-Fuentes M, Lechler RI, "Development of a cross-platform biomarker signature to detect renal transplant tolerance in humans" *J Clin Invest* doi:10.1172/JCI39922

likely to succeed without long-term immunosuppressive treatment, drug toxicity and adverse side effects can be minimised. Another example might include the achievement of longer graft survival though individualised patient management. These strategies, if implemented, have considerable potential to reduce pressure on transplant waiting lists as a result of graft failures. Human genome studies will hopefully also give new insight into the mechanisms of transplant acceptance, rejection and tissue damage.

Several organ donor and recipient genetic biomarkers that associate with transplant outcome and with drug-free long-term renal transplant survival have already been identified. These include complement genes[10] whose expression in kidney transplants has a potent influence on outcome. The next step in scientific investigation is to find out if typing of these candidate genetic loci offers significant benefit to patient management, and to establish whether the presence of genetic biomarkers associated with excellent outcome (a) enables assignment of less intense anti-rejection therapy at the time of transplantation, and (b) identifies patients who are able to tolerate early withdrawal of anti-rejection therapy. A study currently underway, which is being led form the MRC Centre for transplantation, aims to define the genetic basis of the interaction between donor and recipient DNA that determine early and late renal transplant dysfunction.

(d) Xenotransplantation

Xenotransplantation involves the transplantation of organs or tissue from one species to another. An example of a xenotransplant is porcine heart valve transplants (colloquially known as 'valve replacements'), which are quite common and successful. The single most compelling rationale for xenotransplantation is the shortage of organs available for clinical transplantation. However in addition to organ availability xenografts may have a number of benefits over their allogeneic counterparts. For example the transplantation of tissues or organs from genetically engineered animals producing desired gene products, either constitutively or under regulation, would be uniquely possible for xenotransplants. However, because the antigenic differences recognizable by the immune system of a recipient of a different species are greater than those within a species, the immunological barriers to xenotransplantation present a more complex problem than those encountered for allotransplantation. Further, concerns over infectious risks have precluded translation of this work into the clinical domain. Most experimental work has remained in the laboratory, in the pre-clinical realm, however advances in scientific knowledge are sufficiently impressive that it seems likely that renewed clinical efforts will be forthcoming in the near future.

(2) Policy developments

There have been a number of recent policy developments. Although not policy *per se* we would like to highlight reports from the Organ Donation Taskforce and two policy framework documents that have been published in the last year by the Department of Health (DoH).

[10] The complement system consists of a set of proteins that, when activated, generate important effectors of the innate and adaptive immune response. The complement system may be activated at several stages during renal transplantation and can contribute to tissue injury that may influence the long-term outcome of the allograft.

(a) *Reports from the Organ Donation Taskforce (ODTF)*

In 2006 an Organ Donation Taskforce was established by the Secretary of State for Health. Its task was to identify barriers to organ donation and to recommend actions needed to increase deceased donor organ donation and procurement within the current legal framework in the UK. Their first report 'Organs for Transplants', published in January 2008, identified that a failure to resolve the problems resulting from the lack of a structured and systematic approach to organ donation, and to a lesser extent, organ transplantation, has let down both the public, transplant healthcare professionals, and most of all, those needing transplants.[11]

The report provides a comprehensive summary of the main issues affecting organ donation in the UK. A set of fourteen recommendations detailed in the report will, the taskforce believes, help achieve a 50% increase in organ donation after death in the UK within 5 years if they are systematically implemented. A programme of work to implement these recommendations is underway and, as far as we are aware, there has been a 19% increase in organ donation since the taskforce's first report was published. However, as we highlighted at the outset of our response to this consultation, simply increasing the overall number of donations will not solve all the issues facing transplantation, in particular problems associated with poor long term graft survival.

The taskforce subsequently undertook to conduct a systematic review of the potential impact of an "opt-out" system of deceased organ donation. Several expert working groups were set up by the taskforce, and their second independent report was published in November 2008.[12] By the end of a thorough and transparent process a clear consensus was reached. The taskforce rejected the idea of an 'opt-out' system. The main reasons for this rejection were scepticism about the extent to which an 'opt-out' system might improve the supply of donor organs, and faith that putting in place the measures they recommended in their report 'Organs for Transplant', will result in a 50% increase in deceased donor organ availability by 2013. In our view there is no compelling evidence that a simple change in the legislation to an 'opt-out' system of organ donation will solve the problem of organ shortage in the UK. However, as we made clear in our response to question 12, if society wishes to uphold a system of donation based upon a model of consent and individual wishes then there is a responsibility incumbent on society to ensure that individuals are equipped with the appropriate means to *decide whether or not* they wish to donate organs/tissues for transplantation and research purposes. In our view this has particular import to deceased donation.

(b) *Legal issues relevant to non-heartbeating organ donation*

In November 2009 the DoH published clear and helpful guidelines addressing legal issues relevant to non-heartbeating donation and the ways in which donation in that setting may be facilitated.[13] This document we believe has proved to be highly effective

[11] Organs for transplants: A Report from the Organ Donation Taskforce. UK Government Department of Health Publication January 2008. The Taskforce's 14 recommendations are detailed in this report.
http://www.dh.gov.uk/en/Healthcare/Secondarycare/Transplantation/Organdonation/index.htm

[12] The potential impact of an opt-out system for organ donation in the UK: An Independent Report from the Organ Donation Taskforce. UK Government Department of Health Publication November 2008.
http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_090312

[13] *Legal issues relevant to non-heartbeating organ donation*

for clinicians involved in the deceased organ donation process. Further, since the number of non-heartbeating organ donors has increased considerably in recent years it may be effective in helping to satisfy the current demand for organ donors. Unfortunately, the document does not give any guidance on issues related to *research* on deceased donors and their organs.

(c) Requested allocation of a deceased donor organ

In our response to section 2, we outlined issues related to directed and non-directed organs for transplants. We made reference to a recent DoH policy framework document *Requested allocation of a deceased donor organ* [14] published in March of this year. We do not consider that this document, which in our view is effectively a concession to personal feeling in situations which occur only rarely, is likely to significantly reduce the demand for organs. However, we do think that it usefully highlights the conflict between concepts of consent and autonomy considered central to donation, and equitable impartial justice inherent in the practice of deceased donor organ allocation. We hope the document will prompt careful consideration of the principles and processes which underpin the provision of deceased organs/tissues for transplantation. In our view if society wishes to uphold a system of donation for transplantation based upon a model of consent and individual wishes then there is a responsibility incumbent on society to ensure that individuals are equipped with the appropriate means to *decide whether or not* they wish to donate organs/tissues for transplantation and this we believe should extend to donation for research purposes too.

Section 5: The Role of Consent

Question 21: In your opinion are there any forms of encouragement or incentive to provide bodily material or participate in first-in-human research that could invalidate a person's consent?

As seen in our response to question 16 we believe there are forms of incentives that, regardless of whether one takes the view that such incentives are 'unethical in themselves', may have the resultant effect of coercing or exploiting an individual's good will to donate bodily material for transplantation. In this event we believe that an individual's consent to donation will be invalidated.

Question23: Are there circumstances in which it is ethically acceptable to use human bodily material for additional purposes for which explicit consent was not given?

There are almost certainly additional purposes for which using the human bodily material donated for transplantation may be of considerable value for both clinical and research purposes. We appreciate that Part 1 and Schedule 1 of the Human Tissue Act 2004 makes it clear that consent must be obtained for any scheduled purpose, including research. However, we would like to highlight that for the scheduled purpose of transplantation, our practical experience suggests that it is not always clear to those involved in organ donation and transplantation whether an individual's 'appropriate consent', set out in sections 2 and 3 of the Human Tissue

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http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_108825

[14] *Requested allocation of a deceased donor organ*
www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_114800

Act 2004, to deceased organ donation extends to consent to any 'additional purposes'. There is much ambiguity surrounding who should seek consent for the use of human bodily material for additional purposes, when it should be sought, and, in particular, the implications if consent obtained by a 3rd party and accepted by a clinician/pathologist/researcher in good faith turns out to have been obtained inappropriately. We are even aware of specific instances where, possibly as a result of this ambiguity, principal research investigators have 'missed out' on the opportunity to contribute to important collaborative research that has already been in receipt of local research ethics approval. This is at best disappointing.

The practical difficulties that have been encountered may relate to a more general misunderstanding of those perhaps not familiar with operational issues which are an integral part of delivering an organ donation and clinical transplantation service. As we have already explained clinical transplantation encompasses far more than the simple transfer of donated material from donor A to recipient B. In our view 'appropriate consent' to 'transplantation' set out in sections 2 and 3 of the Human Tissue Act 2004 should encompass a generic consent to all aspects of transplantation which will almost certainly involve purposes beyond procuring the organ to be transplanted from donor A and performing the operation of transplanting it into recipient B.

It would be useful to clarify the meaning and application of the term 'appropriate consent' in this context and in particular whether it extends to consent to the use of donor tissue/organs for all clinical and research applications which may include future unknown ('secondary') purposes. In our view unless consent is generic and applies to all conceivable types of clinical and research applications (that have been approved by an appropriate ethics committee) that could be carried out on donated organs and tissues, then any consent will be meaningless and researchers will need to re-visit patients' relatives to acquire consent for procedures that were not previously envisaged. This may prove practicably impossible.

Question 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?

As seen in our response to question 4, in the context of deceased donation where an individual has chosen to become a deceased organ donor in the event of their death, and this is clearly documented, we consider that it is wrong to allow family members to invoke a veto to organ transplantation and where possible this should be discouraged. In our view the wishes of the individual providing bodily material should be respected and, in all but exceptional circumstances, outweigh possible costs and risks to their relatives or others close to them.

Matters differ when the deceased's wishes are unknown and in this event we accept that there may be circumstances in which family members (or others close to the deceased) have a legitimate right of veto. We think these circumstances could (and ideally should) be avoided by ensuring that individuals are equipped with the appropriate means to *decide whether or not* they wish to donate organs/tissues for transplantation.

Section 6: Ownership and Control

Question 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 and purpose of the bodily material, please say so and explain why.

In our view it is not clear that a person's 'degree of control' over future uses of their bodily material (either during life or after death) necessarily requires that material to be the subject of property or ownership. A model of consent may, quite legitimately, provide the basis upon which an individual may exert a degree of control over contemporaneous and future uses of 'their' bodily material and this may, for the individuals concerned, depend on the nature of the material provided and the intended purpose(s) of its use. For example at the present time an individual is entitled to withhold, and a good number do withhold, certain body material from donation for transplantation, their eyes say.

However, from a purely practical point of view it may prove difficult to uphold an individual's every wish in this regard, and it is unlikely that the process of informed consent, however detailed, is ever likely to capture all possible future clinical and research uses of donated bodily material. For this reason, as we set out in our response to question 23, in our view consent should be generic and apply to all conceivable types of clinical and research applications (provided that any research applications have been approved by an appropriate ethics committee) that could be carried out on donated organs and tissues to advance the study of the biological and clinical problems of tissue and organ transplantation.

Section 7: Any other issues

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

(1) Terms of reference - general

At the outset the consultation document language is framed in terms of 'give and take' and 'transactions'. While we do not oppose these terms *per se* we would like to highlight that they may be seen, by some, as pre-empting a conclusion. Is for instance the phrase 'give and take' endorsing or making an appeal to some sort of justice or solidarity? In like vein, although the glossary makes clear that the term 'transactions' used in this document is intended as an 'umbrella concept', considering the ethical, legal and social implications framed in these terms to some extent assumes, first, that 'contractual arrangements' are possible or even desirable in such a setting and second, that the discussion inherently rests upon the legitimacy of considering the human body and bodily material as 'property' to be 'exchanged' under the terms of such a 'contract' or 'transaction'. Mindful that (rightly or wrongly) use of the term 'the gift of life' is commonplace in the setting of organ donation and transplantation, it is not entirely clear that the term 'transactions' provides a useful starting point for discussion.

(2) International perspectives and cross border collaborative transplantation research

Transplantation plays an important role in cross border and, in particular, the European research agenda. Cross-border collaboration is an integral part of this. For example seven European institutions collaborated in the multi-centre research study we previously mentioned led from the MRC Centre for Transplantation at King's, which has identified a signature for transplant tolerance. This research, recently published in the *Journal of Clinical Investigation*, demonstrates

the importance of cross-border collaboration.[15] It is highly likely that future opportunities to build upon existing cross-border European collaborative links will arise. There may be instances where cross European clinical trials, which may require the donation of human bodily material, will offer major benefits, and, although likely to be difficult to implement, where possible should be supported and facilitated by the regulation and governance framework.

In our view standardising information submitted to ethics committees may help bring about greater consistency in the ethics review process in this setting. There may even be instances where Member States should consider developing centralised research ethics committees with the requisite expertise to provide a comprehensive review of more complex clinical trials using advanced therapies (for example gene therapies and novel cell-based therapies). A key area of work in this regard relevant to transplantation is the standardisation and validation of immune biomarkers to predict and monitor transplant outcome. Another pertinent example is investigation into the treatment of the deceased organ donor to enhance organ preservation.

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July 2010

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Addendum

We would like to acknowledge that Dr. Antonia J Cronin, in her capacity at chairperson of the British Transplantation Society (BTS) ethics committee, was also responsible for preparing and drafting the BTS response to the Nuffield Council on Bioethics consultation paper 'Give and take? Human bodies in medicine and research'. There are clearly aspects of the BTS response and this response from the MRC Centre for Transplantation where both organisations converge on their views, and where appropriate this has been acknowledged.

[15] See note 9.