

## **Report of the UKDEC/NRES workshop on ethics of transplantation research, held on 10 November 2010.**

### **1. Introduction**

- 1.1. The UK Donation Ethics Committee was established in January 2010 to be an independent source of advice on ethical matters in organ donation and transplantation. Following a short consultation exercise UKDEC identified transplantation research as an area for early consideration.
- 1.2. This report has been prepared following the UKDEC/NRES workshop on ethics of transplantation research, held on 10 November 2010, and has been agreed by participants as an accurate record. UKDEC are invited to consider the recommendations and initiate appropriate action directly or with stakeholders.

### **2. Principal recommendations**

- 2.1. The workshop proved to be a forum for a great deal of detailed discussion, and provided a rich source of information about issues in transplantation research and some options for how they might be overcome. Sections 7-12 of this document provide a report of the discussion and detailed recommendations.
- 2.2. Four areas were identified repeatedly as requiring urgent attention, and should be prioritised for action.
- 2.3. **Donor consent (see section 7):** there was a strong view that the consent form for transplantation should include a short section seeking general consent for research. (The current form only seeks consent for research in event of the organs being unsuitable for transplantation). Ideally this consent, sought routinely, would mean that in most cases specific additional consent for the planned research from donor families at a very distressing time would be unnecessary.
- 2.4. **Research Ethics Committee allocation process (see section 12).** The allocation process often results in transplantation proposals being diverted to RECs with specialist expertise in patients without capacity. This is inappropriate as donors are dead, not incapacitated. This should be addressed, which will enable researchers to build relationships with the appropriate REC.
- 2.5. **Human Tissue Act licensing requirements (see section 12).** There was a strong view that the Human Tissue Act is not working as it was originally intended. Organs and associated tissue taken for transplantation are specifically exempt from licensing requirements. However, samples taken for research may only be taken if the operating theatre at the donor hospital holds a research licence. Donors may be in any hospital, but not many hospital operating theatres hold a research licence. So this is preventing research from taking place if it involves taking additional samples (eg of blood) in

addition to those taken routinely for transplantation. At least one UK research team has had to withdraw from an international collaboration as a result. Options for re-interpretation of the law or for changing the law should be pursued as a matter of urgency.

- 2.6. **Organ Donor Register (see sections 7, 10, 11)** – the need for detailed discussion with relatives at what is a very distressing time would be reduced considerably if more was known about the donor's views with respect to research. Options for expanding the information collected in the organ donor register should be explored, including whether the donor considered 1) participating in research and 2) accepting other interventions (such as heparinisation) administered when they were close to death for the benefit of the recipients of transplanted organs which they might donate.

### **3. Background**

- 3.1. Transplantation research has a number of unique features. These include:
- Research on the deceased (organ donors)
  - Unpredictability – organ donors may be in any hospital so all institutions would have to give R&D approval for a research project, although only a few will ultimately take part. Similarly, it cannot be predicted accurately which potential recipients will be offered which organs.
  - Time constraints – once a donor is available there is very little time to make decisions about participating in research, as the organs have to be retrieved and transplanted in a matter of hours.
- 3.2. Respondents had reported multiple problems in getting research studies approved, including lack of understanding by Research Ethics Committees, contradictory requirements being set by different parts of the system (RECs, Human Tissue Authority, insurers), and problems associated with licensing requirements under the Human Tissue Act. In some cases, projects had taken more than three years to be fully approved, and in one case researchers had to withdraw from a planned international study as legal obstacles could not be overcome.
- 3.3. UKDEC established a small sub-group under the chairmanship of Professor Anthony Warrens. Membership in annex 1. A joint UKDEC/NRES workshop was planned to bring together researchers, members of research ethics committees, clinicians involved in organ donation and transplantation and representatives from regulatory and governance organisations. The aims were:
- To identify the barriers to transplantation research, both ethical and technical; and
  - To make recommendations to address the issues raised.

### **4. Workshop format**

- 4.1. An open invitation was issued to anyone interested in transplantation research. 65 people attended the day. A full list is given at Annex 2.

Expertise included transplantation researchers, other clinicians, members of research ethics committees, specialist nurses for organ donation, representatives from NHS Blood and Transplant, the Human Tissue Authority and from the UK Donation Ethics Committee.

- 4.2. The day was originally planned in four sessions. The first was a series of short introductory talks on key topics – two stories from researchers, then factual presentations from a legal expert, then from representatives of the Human Tissue Authority, the National Research Ethics Service, Trust Research and Development, and lastly from donor and recipient perspectives. After this session the plan was to move into discussion groups, with each group considering a different ‘scenario’ that illustrated some of the complex issues. After a feedback session and lunch, the groups were to move on to consider a second scenario before coming back to plenary to summarise progress and agree conclusions.
- 4.3. In the event the opening session provoked a great deal of interesting debate and was extended for the whole morning. A single session in discussion groups was held in the afternoon before the final plenary.
- 4.4. Notes were made during discussions and collated to enable some ‘real time’ collation and feedback of the main conclusions. Notetakers in each group provided a more detailed record for the secretariat.

## 5. Opening presentations:

- 5.1. The key issues identified in the opening presentations from researchers are outlined below. Full details are given in the attached presentations (Annex 3).
- 5.2. **Chris Watson**, from Cambridge, opened by describing the challenges he had faced in getting approval for a normothermic recirculation study. This is an established technique in Spain, France, parts of Italy and parts of the US. It involves taking a donor after cardiac death and connecting them to an extracorporeal membrane oxygenator (ECMO) and pump – in essence a cardiopulmonary bypass machine. Full details are in the presentation attached at Annex 3 Key issues arising:
  - The Research Ethics Committees allocation process resulted in the protocol being considered by a committee with specialist expertise in assessing studies on subjects who cannot consent for themselves. Research on such subjects is normally subject to the requirements of the Mental Capacity Act (MCA), but the MCA does not apply to the dead. In these circumstances, the relevant legislation is the Human Tissue Act. The study also involves recipients, who can consent for themselves, and for whom the issues are arguably more complex. This is where the ethical debate was focused
  - Insurers took a different view from the REC about the best way to seek consent from the recipients. Ultimately this resulted in higher insurance premiums.
  - Seeking consent from the donors needed to be seen in context. Donor families have been through a long and detailed consent form for

donation at a very stressful time. Research consent forms are often long and complex but a shorter, 2-page form was agreed to be appropriate by the REC at this time. Consent would be taken by Specialist Nurses for Organ Donation (SN-ODs), but these are employed by NHS Blood and Transplant (NHSBT). A formal request had to be made to NHS Blood and Transplant to ask the SN-ODs to seek consent for the research study.

- The overall timescale for completing all stages of the approval process was 3 years.

5.3. **Professor Marlene Rose** (Imperial College), then described her experiences when she was asked to take part in an international study to evaluate the efficacy of an 'Endothelial Cell Cross-Match Kit' in heart transplant recipients. The study was to recruit only dead donors, and required that an additional 80mls of blood be taken from the donor. The blood would be sent to the tissue typing lab of the recipient hospital, and analysed by the laboratory team according to the research protocol. The retrieval team would therefore be asked to take a further 80mls of blood in addition to the usual amount taken for tissue typing and other routine testing.

5.4. Issues arising:

- The Research Ethics Committee (REC) advised that consent from donor families should not be sought, as this would be unduly upsetting. [But is consent legally required under the Human Tissue Act?]. Clinicians in collaborating hospitals in the UK were uncomfortable with the lack of consent, but collaborators in the US and New Zealand do not seek consent.
- The Human Tissue Act requires that the site from where the blood originates must be licensed for research, but, as already noted, very few hospitals have the operating theatre licensed for research and this legal requirement made the project impractical.
- The possibility of calling the project 'service development' rather than research was investigated, which would have meant a research licence would not be required in the donor hospital. Definitions were not clear and researchers throughout the collaboration were uncomfortable. Professor Rose's group had to withdraw from the study.

## **6. Technical presentations and group discussion**

6.1. Technical presentations stimulated a lot of discussion, particularly in the light of the initial stories from researchers. This continued through into the group discussion sessions in the afternoon, where groups worked through a series of scenarios. Groups were asked to identify where they had a consensus, where there was disagreement, where further information was required and what recommendations they had for action by UKDEC or others.

6.2. Although each group focused on an individual scenario (Annex 4), there was a great deal of overlap between groups, so the comments

and recommendations have been grouped into themes to avoid repetition.

## **7. Donor Consent**

### 7.1. Technical points:

- The Human Tissue Act requires that consent be sought for use of donor tissue for research. Responsibility for giving consent remains with the donor until the tissue or organ has been transplanted into the recipient.
- Research Ethics Committees (RECs) consider what is ethically appropriate in the given context. In some circumstances a REC may advise that requiring detailed consent from donor families would cause them undue distress. (The legal requirement for consent in some form remains, and this can lead to confusion.)
- The organ donation consent process in England includes a general question asking whether, if organs are found to be unsuitable for transplantation, they could be used for research. This does not include consenting to research being performed on organs that are to be transplanted.
- The authorisation process in Scotland has a simpler formulation for consent for research.

Comment:

- 7.2. A number of researchers were unaware that the requirement for consent from the donor remained until the point of transplantation. A number of participants described a model of assuming that the organ became the recipient's once it was in the recipient's hospital or theatre, and at that point they regarded the need to obtain consent as having moved from donor to recipient. There was agreement that the continuing requirement for donor consent not only complicated the research process, but also risked placing donor families under considerable additional stress, and adding extra time to the process. A number of ideas were discussed, including considering whether there might be an alternative legal custodian of the organ in the time from retrieval to transplantation. (Human Tissue Authority or coroner).
- 7.3. There was a clear consensus that the standard consent for donation documentation should have a general consent to research section, with more detailed information available if families requested it. There was some discussion about whether more detailed consent might be appropriate in some circumstances, such as if the research procedure would be happening while the organs were still in situ. After retrieval a more detailed consent process was thought unlikely to be required. Participants reported that talking to patients reveals that, when being asked to consent for 'research', many relatives do not appreciate that the purpose of the research is to improve transplant outcome; they think the research has nothing to do with transplantation. Any addition to the organ consent form about research must emphasise that it is transplant related research approved by an ethical committee.

- 7.4. In discussion there had been at least one experience of a REC advising that seeking consent from relatives to take more samples for research could be distressing, and the general consent for research element of the form should be the source of consent for that research project. However the REC did not understand that the general consent clause is to seek permission to use tissues and organs that *cannot be used for transplantation* in research.
- 7.5. It was noted that respect for the donor is independent of consideration of their family. It was thought it might be useful to have more information about protocols for handling material during research, to consider whether there were appropriate safeguards for preserving dignity and respect for the donor.
- 7.6. When working with donor families it is important to ensure they understand that using an organ for research may mean an organ that would otherwise have been considered unsuitable for donation is now transplanted, or contributes to the longer term success of the transplantation programme. Careful consideration needs to be given to the language used, which can be offputting for a lay person. A leaflet explaining how donated organs are used might be useful. Information for donor families on outcomes should be considered –results of the research programme, or perhaps why organs might not have been used. This should be incorporated into the usual follow-up arrangements so information remains available if and when donor families wish to have it.
- 7.7. Donor families should still feel they have the right to refuse to give permission for research, and should have this decision respected.
- 7.8. Recommendations for action:
- A general clause in the consent forms, asking for permission to undertake transplant related research, should be incorporated, with a view to this being the main source of consent for research on retrieved organs prior to transplantation. This will need to encompass organs that will be transplanted, and those that are unsuitable for transplantation, and blood and tissue samples. It should include an assurance that all research will be approved by a REC.
  - Every case is different and researchers and those working with donor families need to tailor discussions to the needs of the donor family, but a general guideline for donor consent might be:
    - If the research intervention is to happen while the organs are still in the donor (such as use of ECMO), or where organs are to be used solely for research, then specific consent should be sought.
    - If the intervention is to happen after retrieval, then the general clause on research would normally suffice.

- Investigate use of the Organ Donor Register to capture more detailed information about a person's wishes during life. A required response to a yes/no type question would be preferable.
- Investigate current practice and follow-up options for follow-up information to be offered to families.

## **8. Recipient consent**

### 8.1. Technical points

- Once the organ has been transplanted into the recipient, it becomes part of their body and all consent requirements from the donor cease.
- After retrieval but before transplantation, consent to research on the organ is required from the donor.

Comment

8.2. The consent process for recipients needs to start at the time they go onto the waiting list, and time should be taken over the process. Information overload is a significant risk, especially for heart, lung and liver patients. If patients refuse initially, they should be followed up as they may change their minds over time. [Post-meeting note: This implies that the opposite should also be true – patients who have given consent for research should be followed up from time to time in case they have also changed their minds].

8.3. From the recipient perspective, recipients need to be aware of the medical and emotional risks of participating in research. Patient interest groups are a useful source of advice but are not necessarily representative of individual patients on a transplant list. Participating in research can also lead to closer monitoring or seeing more senior members of the team than might otherwise be the case, which some find beneficial.

8.4. It was recognised that this is a very difficult area, and recipients may well feel pressurised to agree, but research is vital if transplantation is to improve. It is important to put the risks of research into context with other equally relevant issues. These include being offered organs from donors who do not meet the ideal criteria. Currently recipients are not always given a right to choose whether or not to accept an 'extended criteria' organ, although new guidelines are being produced to address this.

### 8.5. Recommendations for action

Proposals for best practice –

- If the organ is modified before allocation, then it should be offered using standard allocation schemes on a 'take it or leave it' basis.
- If the organ will be modified after allocation, then it should be offered to the individual identified as the recipient using standard allocation schemes, with the research intervention not taking place if that recipient does not consent.

- If an organ which would otherwise be unsuitable for transplantation is suitable following the research intervention, then the potential recipient identified using standard allocation schemes should be consulted. If that recipient does not consent, it should be offered to successive individuals identified on by the standard allocation schemes.

## **9. Multiple research trials and prioritising research**

### 9.1. Technical points

- Recipients may be asked to participate in a number of trials  
Comment

9.2. Recipients may be asked to participate in more than one trial. The usual advice from an ethical perspective is to leave it to the patient to decide whether or not they wish to participate in more than one trial, providing there is no threat to their health or to the science as a result. This relies on the patient having a full understanding of the consequences of any decision they make. Researchers and recipient clinical teams need to be aware of all the trials or studies a particular patient is involved in. This has to be the case for scientific reasons as well.

9.3. If studies are in conflict then the study which has most potential benefit to the patient should have priority, with the study carrying the greatest risk to the patient being dropped. Some form of governance structure to advise on relative risks and benefits might be useful, and the British Transplantation Society should be asked to advise on how best to set this up.

### 9.4. Recommendations for action

- [Are current systems for flagging who is on which trial adequate? Presumably everything should be captured in the patient's records?]
- Consider a governance structure for advice on relative risks/benefits.

## **10. Research on associated tissues**

### 10.1. Technical points

- Stored tissue samples from donors, removed originally for tissue typing purposes, provide a potentially valuable resource for research.
- Using this tissue requires consent under the Human Tissue Act.
- The Human Tissue Authority is currently considering whether a generic consent to research would be adequate to cover the use of such material.

Comment

10.2. The legal requirement is that consent for research should come from the donor. There was consensus that going back to a donor family, possibly some years after the original donation, would be both intrusive and impractical. There are exemptions to the consent requirements if the material is anonymised, but the nature of record keeping in transplantation services means this would not be the case.



- 10.3. The National Information Governance Board for Health and Social Care (NIGB) has a role in approving use of material where consent cannot be obtained. This should be explored further.
- 10.4. This was a further area where expansion of the ODR to include additional information about the views of the donor would be helpful. UKDEC might also consider this in more detail, particularly whether tissues could be used without explicit consent from either donor or recipient.
- 10.5. Once organs have been transplanted, recipient consent is required. So the use of samples removed after transplantation require recipient consent for research, and the donor has no further role. It was unclear what the consent requirements would be if the recipient had died.
- 10.6. Recommendations for action
  - The general consent to research on the donor consent form should encompass research on associated tissue.
  - Work by the HTA in this area is welcomed, and the possible role for the NIGB should be explored.
  - Any expansion of the data held on the ODR relating to wishes for research should include associated tissues.

## **11. Cardiac donation from a non-heartbeating (DCD) donor.**

### Comment

- 11.1. There was no specific ethical concerns were raised regarding the use of a heart from a DCD donor. It was recognised that some donor families might have a stronger emotional response to cardiac donation which could risk damaging the reputation of the organ donation programme. It was unclear whether consenting to transplantation would incorporate consent to cardiac donation.
- 11.2. There was a strong view that clinical outcomes for recipients were improved if the donor was given systemic heparin at the point of treatment withdrawal. Current legal guidance from the Department of Health (with equivalent guidance in Scotland) advises that systemic heparinisation is not appropriate due to the risk of harm to the potential donor. The evidence needs to be reviewed. If there is no evidence of harm, and evidence that outcomes for recipients are improved, then it could be argued that systemic heparinisation is in the donor's best interests as it will enable them to fulfil their wish to become a donor more effectively. Consideration should be given to incorporating information about additional treatments such as heparinisation into the ODR.
- 11.3. Recommendations for action
  - Review the evidence relating to heparinisation (see practice in N America and Australia). Consider evidence of risk of harm, and evidence for improving outcomes in recipients.

- Consider inclusion of information relating to wishes about additional treatments into the ODR.

## **12. Legal and procedural issues**

### 12.1. Technical points

- The allocation process for Research Ethics Committees does not have provision for transplantation proposals involving donors.
- Under the Human Tissue Act, samples (such as blood samples) can only be taken for research if the premises are licensed by the Human Tissue Authority for research. Organs or associated tissues (including blood) taken for the purposes of transplantation are exempt from the licensing requirement.
- The Human Tissue Authority is currently looking to extend the licences for post-mortem rooms to include operating theatres, which would allow additional samples to be taken.

Comment

- 12.2. The process of allocating any research proposal to a Research Ethics Committee (REC) involves working through a tick-box menu. There is no tick box for research on deceased organ donors, or their organs. The nearest category is research on patients without capacity, and this diverts these proposals to a REC with specialist knowledge, including having regard to the Mental Capacity Act which governs research on patients without capacity. This is inappropriate – donors are dead, and Human Tissue Act is the legal framework that applies. It is also arguable that the consent issues as they relate to recipients, who are patients with capacity, are more challenging. There was a strong view that this allocation process needed to be improved. There was some discussion of having a specific REC identified which would receive transplantation proposals, but clarifying the allocation process was the first priority.
- 12.3. There was a strong feeling that the Human Tissue Act and its associated licensing requirements were not working as originally intended. The current requirements appear perverse – if it is appropriate to take blood for the transplantation, surely it is appropriate for the same team to take blood for an associated research programme, which will have had REC approval and take place on premises licensed for research.
- 12.4. Participants heard how one researcher had explored whether her work could be described as ‘service development’. This would mean the project would be treated as a routine part of transplantation for licensing purposes. The research collaborators had felt uncomfortable with this reclassification, and ultimately the UK team had to withdraw. In this international study researchers in the US and New Zealand were able to proceed without any licensing problems. A similar study has been carried out on renal transplant recipients from living donors. The donors gave informed consent, [and the licensing issues do not apply].

- 12.5. The legal framework as currently interpreted is creating a perverse incentive to reclassify what most would define as research as service development. While this might be a pragmatic work-around, it also has the effect of removing proper safeguards such as oversight by a Research Ethics Committee.
- 12.6. Current work by the Human Tissue Authority to find ways of conducting transplantation research within the current legislative framework were welcomed. In particular the group heard how the HTA is working with a number of trusts to extend post-mortem licenses to cover operating theatres. This would have the effect of enabling those trusts to remove samples for research purposes where the sample is sent on to a licensed research establishment
- 12.7. Longer term a change in the law is needed to facilitate legitimate transplantation research. The likely changes forthcoming to the status of the Human Tissue Authority and research governance more generally may provide an opportunity and UKDEC and the wider transplantation community should press for change.
- 12.8. More generally there was a consensus that the legal requirements relating to transplantation research were not well understood and these should be disseminated more widely.
- 12.9. Recommendations for action
  - Amendments to the REC allocation process to ensure transplantation proposals are not inappropriately assigned to specialist RECs for patients without capacity.
  - Current action by the Human Tissue Authority to enable transplantation research within the current legal framework is welcomed and should continue
  - Options for legislative change should be explored, in particular to remove the requirement that premises where tissue is removed for transplantation research should be licensed for research.
  - The various legal and procedural requirements relating to transplantation research are not well understood and should be disseminated more widely.

### **13. Feedback from workshop participants**

- 13.1. 40 of the 65 participants completed a feedback form at the end of the day. All 40 respondents indicated they had found the workshop useful, with 37 out of 40 strongly agreeing it was useful. A similar strongly positive response was given in response to more detailed questions about format of the day. General comments further reinforced it had been a useful and informative day for many participants, and gave some ideas for topics that could be the focus of similar workshop style meetings in the future. Collated feedback is attached at Annex 5.

### **14. Conclusion**

- 14.1. The workshop provided a forum for dynamic and wide-ranging discussion, with clear priorities for action emerging. This report is

presented to UKDEC as a rich source of information and focus for action to tackle the many difficulties that researchers in transplantation face.

**Annex 1**

**Membership of the UKDEC Research sub-group**

|                          |   |
|--------------------------|---|
| Anthony Warrens (Chair)  | Honorary Consultant Physician and Dean for Education, Barts and The London School of Medicine & Dentistry   |
| Paula Aubrey             | Regional Manager, NHS Blood and Transplant  |
| Graham Brushett          | Lay member, heart and kidney transplant recipient   |
| Heather Draper           | Professor of Biomedical Ethics and Director of the Centre for Biomedical Ethics, Department of Primary Care Clinical Sciences, University of Birmingham |
| Hugh Davies              | Research Ethics Advisor, National Research Ethics Service   |
| Peter Friend             | Director, Oxford Transplant Centre and Professor of Transplantation, University of Oxford   |
| James Neuberger          | Associate Medical Director, NHS Blood and Transplant  |
| Chris Watson             | Transplant Surgeon, Cambridge Transplant Unit, Addenbrooke's Hospital and Department of Surgery, University of Cambridge                                |
| Pauline Weaver           | Donor Family Network  |
| Helen Lovell (Secretary) | Secretary, UKDEC  |

**Annex 2:**

**10 November UKDEC/NRES Workshop Delegate List (65 Attendees)**

|                           |   |
|---------------------------|---|
| Kosh Agarwal              | Institute of Liver Studies, Kings College Hospital  |
| Paula Aubrey              | (UKDEC) London OD Services Team Manager NHSBT   |
| Natalie Akenzua           | Specialist Nurse-Organ Donation NHSBT   |
| Leslie Brent              | Emeritus Professor  |
| Joe Brierley              | (UKDEC) – Paediatric & Neonatal Intensive Care GOSH   |
| Graham Brushett           | (UKDEC) – Transplant Recipient  |
| Michael B Buck            | Lay Member Herts REC  |
| Rachel Burman             | Institute of Liver Studies, Kings College Hospital  |
| Barbara Canning           | Coventry & Warwickshire REC   |
| Martina Conlon            | Specialist Nurse Organ Donation - NHSBT – Northern Ireland Team                                 |
| Nicky Connor              | Consultant Epidemiologists HPA  |
| Antonia Cronin            | Clinical Research Consultant Nephrologist, MRC Centre for Transplantation, Kings College London |
| John Dark                 | Lung & Heart Transplant Surgeon, Newcastle upon Tyne  |
| Hugh Davies               | (UKDEC – Research Subgroup) NRES  |
| James Douglas             | Clinical Pharmacology & Medical Ethics Queen’s University Belfast                               |
| Heather Draper            | (UKDEC) Professor of Biomedical Ethics & Director of the Centre for Biomedical Ethics           |
| Phil Dyer                 | Consultant Clinical Scientist, Director of SNBTS Histocompatibility & Immunogenetics Services   |
| Peter Friend              | (UKDEC – Research Subgroup) Professor of Transplantation Honary Consultant, Oxford              |
| Susan Fuggle              | Oxford Transplant Centre  |
| Barry Fuller              | University Dept of Surgery, Royal Free & UCL Medical School                                     |
| Alison Galloway<br>Turner | Specialist Nurse-Organ Donation NHSBT   |
| Kate Haire                | National Commissioning Group  |
| Rachel Hilton             | Consultant Nephrologist, Renal, Urology & Transplantation Directorate, Guys                     |
| Catherine Hutchinson      | Specialist Nurse-Organ Donation<br>South East Donation Service                                  |
| Hamid Jalal               | Consultant Medical Virologist, Addenbrookes Hospital, Cambridge                                 |
| Penney Lewis              | (UKDEC) Professor of Law, School of Law & Centre of Medical Law & Ethics, Kings College, London |
| Helen Lovell              | (UKDEC Secretary)   |
| Helen Lucas               | GP & Member of South West London REC  |

|                     |   |
|---------------------|---|
| Liz McAnulty        | HTA   |
| Mignon McCulloch    | Paediatric Nephrologist for Renal Transplant Patients, Guys & St Thomas                             |
| Maryon McDonald     | Robinson College, Cambridge   |
| Helen Mc Manus      | Specialist Nurse-Organ Donation South Central Team NHSBT  |
| Nandor Marczin      | Consultant Anaesthetist, Harefield Hospital   |
| Victoria Marshment  | HTA   |
| Jorge Mascaro       | Heart and lung Cardiac Surgeon, Queen Elizabeth Hospital, Birmingham                                |
| Emiliano Mazzaretto | Specialist Nurse-Organ Donation NHSBT   |
| Alison Mitchell     | Specialist Nurse Organ Donation NHSBT   |
| Myfanwy Morgan      | Kings College Dept of Primary Care & Public Health Sciences   |
| Paolo Muiesan       | Liver Surgery Consultant, United Hospitals Birmingham   |
| Fidelma Murphy      | HTA   |
| Suku Nair           | Consultant Cardiothoracic Surgeon, Papworth Hospital  |
| James Neuberger     | (UKDEC) NHSBT   |
| Jane Nuttall        | CTAG Recipient Transplant Co-ordinator Representative   |
| Sara Owen           | Vice Chair Oxfordshire Research Ethics Committee A  |
| David Parkes        | Cambridgeshire REC  |
| Thamara Perera      | Liver Surgery Consultant, United Hospitals Birmingham   |
| Gurch Randhawa      | (UKDEC) Professor of Diversity in Public Health   |
| Karen Redmond       | Surgeon, Harefield Hospital   |
| John Richardson     | Chair REC Cambridgeshire 3  |
| Marlene Rose        | Professor of Transplant Immunology Harefield  |
| Sally Ruse          | Transplant Research Nurse   |
| Michael Simmonds    | Cambridgeshire 1 REC  |
| Peter Simpson       | (UKDEC Chair)   |
| Becky Smith         | NHSBT Yorkshire Organ Donation Services Team  |
| Magi Sque           | Chair in Clinical Practice & Innovation University of Wolverhampton & Royal Wolverhampton Hospitals |
| Susan Tonks         | Research Support Associate, Clinical Trials & Research Governance                                   |
| Eleanor Updale      | (UKDEC) Author  |
| Anthony Warrens     | (UKDEC) Dean for Education Barts, LSMD, Prof of Renal & Transplantation Medicine                    |
| Chris Watson        | (UKDEC Research Subgroup) Transplant Surgeon, Cambridge   |
| Pauline Weaver      | (UKDEC Research Subgroup) Donor Family Network  |
| Doreen B West       | Vice Chair Outer West London REC  |
| Lorna Williamson    | Medical & Research Director of NHSBT  |
| Alison Wooster      | Cambridgeshire 1 REC  |
| Katharine Wright    | Nuffield Council on Bioethics   |
| Nizar Yonan         | Director of Cardiothoracic Transplantation Wythenshawe Hospital                                     |

## Annex 3: Presentations

(attached separately)



## **Annex 4**

### **JOINT UKDEC/NRES WORKSHOP 10 NOVEMBER: ETHICS OF TRANSPLANTATION RESEARCH**

This paper sets out a number of scenarios we will be using during the course of the workshop. They are intended to illustrate the most common and most difficult issues that arise in developing protocols for transplantation research. Some of the issues may be unlikely, but considering how to deal with the extremes may help us in clarifying the principles that should apply across all cases. Please take a few minutes to read these before the workshop and consider what your responses might be. Please also consider if any issues are missing, as there will be an opportunity on the day to consider additional scenarios.

At the workshop you will be asked to discuss these and to put forward:

- Principles that might be used by researchers and RECs to develop answers to ethical issues of the type described;
- Other problems encountered in each scenario (legal requirements or practical difficulties), and possible solutions

#### Scenario 1: The context of research and deceased donor consent

Recent work has demonstrated that cellular mitochondrial morphology correlates with post-transplant function. The Cambridge renal transplant team therefore propose to biopsy all kidneys prior to transplant to assess this. All recruited recipients will be followed up and renal function parameters collected (blood samples).

Standard practice for donor consent will be followed. The Specialist Nurse for Organ Donation (SNOD) (formerly known as the Donor Transplant Co-ordinator) is responsible for gaining consent from the donor (usually their families) to participation in research. The SNOD first takes the family through the consent process for organ donation. This is a lengthy process, with detailed questions about the potential donor's medical history, as well as considering each organ in turn. If the family consent to donation, then the SNOD will present the study. Researchers are concerned that giving relatives full information, with a further consent form running to several pages may be too burdensome.

There is concern that this can be a protracted and involved process at what is a very difficult time for relatives, coming to terms with the unexpected death of a family member. At the same time the need to remove the organs in a timely manner means that the time available for discussion and consideration is limited.

Issues:

- In this context, what is appropriate for consent for research?

## Scenario 2: Recipient consent, what is best practice?

Transplant units build relationships with patients over a period of time while they are on the transplant waiting list, and staff can discuss the option of being involved in research studies during this time. The fundamental question is how can the recipient give informed consent without this seeming to be the application of undue influence, given the long waiting times for organs.

Scenario: A renal physician contacts the REC for advice on his arrangements for informing and seeking consent for research from his patients on the transplant waiting list. Current arrangements:

1. General flyer to his renal transplant patient interest group explaining that the unit takes part in research to improve transplantation.
2. When a patient is put on the list, they receive a letter reiterating this and offering an opportunity to discuss this with the transplant co-ordinator. It is also explained that they will not necessarily be advised to take a researched organ even though they have agreed to participate in research.
3. The unit only joins a particular study if the patient interest group agrees. All patients then receive information about the study and are given an opportunity to discuss any concerns with their clinical team, and wishes not to participate are recorded.
4. If an organ suitable for research is found and is matched to a patient on the waiting list, the patient is consented if time allows.

Issues:

- How can recipients be given the opportunity to make an informed decision without undue influence being applied?
- What else should the researcher consider? Should potential recipients who do not wish to participate be followed up?
- What if the organ is an excellent match for a patient who has not consented to research?

## Scenario 3: Whose consent takes priority?

Transplantation involves a donor and potentially several recipients. If the donor family consent but the recipient does not, does the recipient's clinical need take priority so the transplant goes ahead without the intervention, or does the need to continue to improve transplantation and go ahead with the research study taking priority, so the organ is offered to the next recipient who has consented?

This is further complicated when there are several recipients. If the intervention is on the donor before the organs are retrieved, so all the organs are affected, then what happens if one of the recipients does not want to participate?

One study of this type is being planned at the moment. The intention is to put a non-heart beating donor on extra-corporeal membrane oxygenation (ECMO) after death to perfuse the abdominal organs (circulation to the brain will be prevented). The donor family will be consented. All the organs will be affected.

Consent can be done beforehand so the views of potential recipients are known.

Issues:

1. If the allocation procedure matches the liver to a recipient who does not want to participate, but the kidney and pancreas recipients are happy, whose views take precedence?
2. What happens if there has not been time to identify recipients before the research intervention takes place?

#### Scenario 4: Research, equipoise and consent.

The UK consortium of liver transplantation units proposes to randomly allocate livers for transplant to Ringer solution infusion or cold storage. The consortium conducted an independent systematic review of these alternatives which came to the conclusion that there was no evidence favouring either method. They concluded that there was equipoise and an RCT comparing these methods should be ethically acceptable. Ongoing transplant function will be collected through the UK transplant national audit.

Issues:

1. Should donor consent be sought?
2. Should recipient consent be sought?
3. At the REC review the researchers indicate they will not be seeking donor or recipient consent. Is this acceptable?

#### Scenario 5: Restoration of cardiac function in a DCD donor.

Hearts are not yet retrieved for transplantation from donors who are certified dead by cardio-respiratory criteria in the UK (DCD donor). The concept of restoring cardiac function in a donor who has been certified dead because of irreversible cessation of cardio-respiratory function is challenging. It is of interest as pressure on transplant waiting lists means it is desirable to make use of as many organs from donors as possible.

A protocol is put forward to demonstrate resuscitation of the DCD heart and evaluate its function, with a view to establishing viability for transplant.

DCDs deemed suitable for liver and kidney donation will be given full systemic heparin and placed on normo-thermic cardio-pulmonary bypass via a median sternotomy 5 minutes after cardiac arrest. Cerebral circulation will be prevented by cross-clamping the aorta. Liver and kidney donation will

proceed as normal. Meanwhile the right and left ventricles will be vented to prevent distention. Cardiac function is expected to be restored (after DC defibrillation with 10 to 20 joules and atrial pacing at 100 beats per minute) following the establishment of cardio-pulmonary bypass. Once cardiac activity is restored the ventricular vents will be removed and oversewn. Pressure-volume data from the right and left ventricles of the reanimated heart will be used to quantify cardiac function and reserve, with a view to establishing whether transplantation is viable.

Issues:

1. What issues arise? How could they be dealt with?
2. Would the issues be different if the heart was removed from the donor and resuscitated ex-vivo?

#### Scenario 6: Which research takes priority?

Donors are a scarce resource. As noted above there is always pressure to make more effective use of donated organs, and to push the boundaries of what organs can be transplanted effectively. This may mean that there are a number of research projects going on at the same time, which may (or may not) conflict.

Issues:

1. Is it ethical to consent donors or recipients for more than one research study?
2. If studies conflict, how should work be prioritised?

#### Scenario 7: Research on associated tissue.

Lymph nodes and spleens of donors are removed and sent with the organs to the tissue typing labs of the recipients. After tissue typing is complete these will be stored. This creates an archive of potentially very useful material. Any study involving this material could have implications for all the recipients.

Going back to the source tissue in this way constitutes research, which requires consent under the terms of the Human Tissue Act. This is donor tissue, and the donor family will not have consented to a research project which was not conceived at the time of the donation. Going back to the family, often after a number of years, is impractical and likely to be intrusive.

Issues

1. Is it ethical for donor families to be asked for a general consent to future research on stored tissue? Is this consistent with legal requirements?
2. Do recipients need to consent? (There may be several of them).
3. What other issues arise?

## Scenario 8: Licensing for research, and research vs service development

A researcher was asked to take part in an International Trial to evaluate the efficacy of the 'Endothelial Cross- Match Kit' in Heart and Lung transplant recipients. Only cadaver donors could be used. This means instead of testing patients' sera against donor leukocytes (from the blood or lymph nodes) one tests them against donor endothelial cells. To obtain donor endothelial cells requires taking 80 mls of donor (peripheral) blood, the blood is taken back to the Tissue Typing Lab of the recipient hospital and lab workers use magnetic beads coated with antibody to positively select the 'endothelial precursors'. Hence, we had to ask the coordinators to ask the surgeon take 80 mls of peripheral blood in addition to the usual 50 mls.

The first application to a REC indicated donor relatives would be asked for informed consent. The REC recommended that consent should not be sought, so as not to unduly upset them. A favourable opinion was given to a revised protocol.

HTA advised that:

- If blood is taken for research, the site must be licensed with the HTA for research
- If blood is taken for transplantation, the site is exempt from licensing
- If ethical permission has been given, the project is research and a licence is required.

At that time (2009) very few hospitals were licensed for research which made the research project impractical, given that donors may be in any hospital. Currently, only about 20% of hospitals (from where deceased donor organs originate) are licensed. After considerable further discussions permission was granted by the local Clinical Practice Committee to reclassify the work as 'service development'. This would enable the blood sampling to be regarded as necessary for transplantation and hence exempt from licensing. However other collaborators felt there was a conflict between need to give results of the new test in real time to comply with it as a 'service development' and requirements for a research project that results are not given to the clinicians, but held back for retrospective analysis to determine if they affect/predict patient outcome. This conflict could not be resolved. There were also ongoing concerns about the lack of consent from relatives.

The team had to withdraw from the international study.

A similar study has been conducted involving living donors. Blood samples were taken with informed consent of the donors.

Issues to consider:

- a) Should relatives be asked for consent? What are your reasons?
- b) What exactly did the HTA mean when they said the blood has to be 'for the primary purpose of transplantation'?
- c) Why does having ethical permission mean it is research and not service development?

- d) What distinguishes research from service development?
- e) Unless one accepts the licensing limitation, the licensing law means that one cannot obtain 'extra' samples for research in the UK from deceased donors, even for ethically approved projects. Is this acceptable? If not, what is to be done?

**Annex 5**

**UK Donation Ethics Committee/ NRES Workshop Evaluation  
Ethics of Transplantation Research**

**SECTION 1: FEEDBACK**

| <b>Overall comments</b>  | <b>Strongly disagree</b> | <b>Somewhat disagree</b> | <b>Somewhat agree</b> | <b>Strongly agree</b> |
|--|--------------------------|--------------------------|-----------------------|-----------------------|
| 1. Overall, I found the workshop useful  | 0                        | 0                        | 3                     | 37                    |
| 2. The style of the workshop suited the topic                                  | 0                        | 0                        | 2                     | 38                    |
| 3. The opening presentations were pitched about right<br>1 NO COMMENT RECEIVED | 0                        | 0                        | 7                     | 32                    |
| 4. The pace of the workshop was about right                                    | 1                        | 3                        | 13                    | 23                    |
| 5. I would recommend the workshop to colleagues                                | 0                        | 0                        | 5                     | 35                    |

| <b>Group work</b>  | <b>Strongly disagree</b> | <b>Somewhat disagree</b> | <b>Somewhat agree</b> | <b>Strongly agree</b> |
|--|--------------------------|--------------------------|-----------------------|-----------------------|
| 6. The scenarios covered the right range of topics                   | 0                        | 0                        | 21                    | 19                    |
| 7. The group size was about right                                    | 0                        | 0                        | 15                    | 25                    |
| 8. The balance of expertise was about right<br>1 NO COMMENT RECEIVED | 0                        | 1                        | 14                    | 24                    |
| 9. The time for discussion was about right                           | 0                        | 5                        | 19                    | 16                    |
| 10. The facilitator was helpful<br>3 NO COMMENTS RECEIVED            | 0                        | 0                        | 7                     | 30                    |

| Plenary sessions  | Strongly disagree | Somewhat disagree | Somewhat agree | Strongly agree |
|---|-------------------|-------------------|----------------|----------------|
| 11. Feedback was captured effectively                               | 0                 | 2                 | 8              | 30             |
| 12. The time for discussion was about right                         | 0                 | 3                 | 13             | 24             |
| 13. The conclusions were clearly presented<br>1 NO COMMENT RECEIVED | 0                 | 3                 | 13             | 23             |
| 14. The next steps were clearly presented                           | 0                 | 2                 | 12             | 26             |

## SECTION 2: Feedback

Provide a better venue - 2

Cover topics in greater detail - 7

Provide more information in the opening session - 2

Reduce the size of the groups - 1

Allow more time for discussion in groups - 7

Allow more time during the breaks - 2

## SECTION 3: further comments

Comment 1. It was very good to keep going with the general discussion throughout the morning. It was much more productive than the group sessions. Afternoon very laborious. Don't bother with the groups.

Comment 2. I found the workshop extremely useful and the discussions that arose as a result very interesting – highlighting topics that require further discussion/investigation.

Comment 3. Very wide range of topics. Could be more focussed in future. Initial overview would be useful. All 7 people – no Intensivist. Basement room induces afternoon stupor.

Comment 4 – Less topics should be covered

Comment 5 – Very useful meeting to be followed with more of the same

Comment 6 – I think the workshop needed more time – there was so much to discuss and more time for detail would have been great.

Comment 7 – Generally interesting. Good presentations.

Comment 8 – Clarity of scenarios v important.

Comment 9 – More specifics from HTA. Coffee break between scenarios to maintain attention.

Comment 10 – Very stimulating discussions that have exposed a number of paradoxes and failures in the law and practicalities of organ transplantation. Definitely need more days like this.

Comment 11 – A most productive, enjoyable, well structured and important meeting! Lunch was probably too generous; you could have saved money. Thank you.

Comment 12 – I thought it was advantageous for members of the group to know which scenarios they are involved in as they will do more preparation and then quality will be higher.

Comment 13 – Information in opening session was very good and helpful background to the group discussions.

Comment 14 – Some of the discussions were a bit unfocussed.

Comment 15 – Excellent workshop – allowed time for pursuit of topics/themes – good legal input.



Comment 16 – It was fine to extend the plenary sessions under the circumstances. Might be good idea to change the composition of groups if you have 2 x discussion sessions (ie mix us up again)

Comment 17 – Excellent day & discussions

Comment 18 – Very informative and useful workshop

Comment 19 – A very interesting and worthwhile day. Ability to feedback on summary details excellent, thank you. Would like to help further in future.

Comment 20 – Perhaps fewer scenarios to discuss. Afternoon session interesting but felt a bit long. The summary & feedback via email is an excellent idea. I look forward to reading this.

Comment 21 – Going around each individual table took too long and was quite repetitive. Morning was very good.

Comment 22 – Perhaps more involvement of donor transplant recipient participants could be useful.

Comment 23 – Very useful, well organised. I learned a great deal.

#### **SECTION 4: FEEDBACK**

Please provide details:

Comment 1. A more practical examination of problems practioners and patients experience on the ground.

Comment 2. All of the topics of today would benefit from future discussion, perhaps in 1 year.

Comment 3. Donor management –

Place/ Manner - of withdrawal of treatment in DCD Donor treatment

Comment 4. Would suggest a workshop meeting dedicated to heart lung transplantation with the Heart/Lung, Transplant teams, lawyers and ethicists Recipients consent; When/how much to say? Smoking & other vices need disclosing.

Comment 5. Possibly looking at case scenarios that have been presented to UKDEC, by Donation committees, CLOD's and SNOD's. Real life/everyday issues that come up frequently.

Comment 6 – Electronic format Y/N to questions useful when consensus not reached.

Comment 7 –Could be useful to involve members of EU Countries e.g. Spain, Netherlands, Germany in discussions to bounce ethical issues off. They seem to have some things right, we seem to have some things right – maybe we could outline the “all right” ethical stance on transplantation issues. Could use SKYPE to involve EU colleagues if necessary.

Comment 8 – How allocation processes are established.

How cost effective transplantation can be increased in times of restricted finances maintained.

Comment 9 – Blanket consent for organs to be donated as well as research. Some families would like to consent for all organs & issues to be donated

for transplantation without having to go through each organ & tissue that may be donated.

Comment 10 – Post transplant ethics ie. Relation between recipient interests against donor confidentiality; more insight into our legal system.

Comment 11 – Scenarios – Patient who is brain stem dead where family want to see the heart stopping. Patient is legally dead. Is it ethically acceptable to give a high dose of potassium to stop the heart and reduce warm Ischaemic time?

Comment 12 – Marginal organs – Childrens organs and brain death requirement in under 2 years.

Comment 13 – I am a paediatrician – possibly 1 or 2 topics/scenarios or case studies looking at issues in children. Enjoyed it!

Comment 14 – More detail on use of surplus tissue research. NHS pathology labs constitute an enormous resource for research and many researchers unsure about can/cannot be done with these samples. Update course following new EU Guidelines/Regulations in 12 -24 Months. Regs change and are difficult to keep up with refresher workshop.

Comment 15 – Consent for marginal, heart beating donor (DBD) organs.

Comment 16 - Live Donor Transplantation not covered. The “Secretarial” Service (Summaries) outstanding.

Comment 17 – So many issues revolve around the quality & detail of consent. Perhaps a workshop just on the consent related issues would be useful. Eg How to overhaul the ODR?