National Research Ethics Advisors' Panel (NREAP)

1. Nature of human bodily material and first-in-human trials

Human bodily material

The use of human tissue in research has great potential to produce benefit but the circumstances under which the tissue is obtained together with the kinds of tissue required (from blood cells to whole organs) needs careful consideration. The meaning and value of human tissues, emotional impact, and symbolic significance to the donor or person giving consent is very context specific and should be given careful consideration by the researcher.

The NREAP are concerned that appropriate attention ought to be given to the terminology used when referring to human tissues in the context of research. The NREAP advise researchers to use neutral terms and accurate descriptions. For example, the use of terms such as “residual biological samples” is to be preferred to terms such as “waste” “spare” “surplus” tissues. The latter ought to be avoided as they may be inconsistent with the emotional meaning the tissue may have for the donor or imply a lack of value which is inconsistent with the level of ethical prudence that should be shown in the research context. Researchers should be specific when providing information to donors about the type, and volume of tissue. For example tissue donated to a Brain Tissue Bank may include whole brains and spinal cord as well as peripheral nerves and blood vessels whereas another kind of Tissue Bank may simply require a blood and urine sample; all could be described as “human tissue”.

Questions

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

No

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

All human tissue should be regarded with an appropriate level of ethical diligence mindful of the circumstances in which they are obtained and the purposes to which they will be put. We are perhaps just beginning to realise the potential social and ethical impact of research using human tissues and the NREAP would endorse the need for more research to be conducted into these aspects of bio-science research.

Tissue with the potential to create new life and immortalised cell lines are just two areas of research which may engage with complex ethical issues, although all uses of human tissue have this potential.

Some very promising areas of research are also highly sensitive, for example, the use of human foetal and embryonic tissue donated following a termination of pregnancy can raise complex social and ethical issues if that tissue is used to create stem cell lines. There is a growing body of empirical evidence that donors may regard this as a continuation of the “life” of the foetus, particularly controversial if such stem cells are later used to produce “artificial” gametes. Immortalising other forms of cells can also

prove to be controversial as has been the case with the HeLa cell line. Although immortalisation may not be *per se* wrong it has the potential to compound other wrongs. Human egg and embryo donation for research is another growing area of research interest that also engages with similar issues. Particular regard ought to be given to informing donors of the actual and potential uses of their tissue when researchers seek consent. The key in any context of tissue donation is adequately informed consent for a process that allows the donor to reflect upon the information they have been given. Special consideration should be given to these issues when an REC is asked to approve a RTB that is either requesting "open consent" or requesting power to approve other studies without returning to the REC for approval.

3. Are there significant differences between providing human bodily material during life and after death?
Yes, as there is the potential for the living to change their mind and therefore to withdraw from a study or research tissue bank. Living donors may of course benefit directly but there is also the potential for direct harm t through their involvement in research All of these issues should be recognised by the researcher and given careful consideration by the REC.
The dead have no contemporaneous control over their tissues but may have stipulated conditions for the use of their tissues via an advanced directive. We would advise RECs to explore with researchers the extent to which they have made themselves aware of any advance directives regarding the use of tissues after death. In addition, researchers should, as far as is practicable, ensure that the use of tissue is compatible with the wishes of the donor. It is possible that the use of tissue from the dead may raise issues which could be regarded as a form of harm to the deceased (for example, issues related to privacy, confidentiality and reputation.) whilst it is impossible to legislate for such harms we would encourage researchers to reflect upon this potential when weighing the ethical aspects of their research.

The use of tissues in research sourced from both the living and the dead may have implications for their relatives and this should be taken into account by researchers when seeking permission to use tissue in research.

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.

This is too general a question since much hinges on the particular circumstances of human tissues in research. Respecting the rights, interests, dignity and safety of research participants is the priority of NREAP (supporting NRES and the ethical principles informing the Governance Arrangements for Research Ethics Committees (GAfREC)) – but RECs ought also to take into account, and weigh ethically, the wider implications of donating tissue to research including the impact on the family and wider society.

Participation in first-in-human trials
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? Please feel free to respond with your own personal opinions, with comment on a range of possible positions, or with your organisation's policy, as appropriate.

The NREAP is not convinced that it is necessary to single out first-in-human studies for special consideration. The issue of "whole body" donation is at stake in many other instances of research and there are often equally serious risks in early-phase clinical trials though we acknowledge that first in man studies are likely to carry a higher risk since less is known about the investigational medicinal product at that stage. The NREAP takes seriously its role to support the NRES core ethical principles, which states a clear responsibility to respect the rights, interests, dignity and safety of research participants and to facilitate ethical research as its priority. The NREAP seeks to support RECs in providing the highest possible ethical scrutiny of scientifically robust research proposals, prioritise the interests and safety of the participant with specific regard to the particular vulnerabilities of different participants – in general this responsibility may be expressed in differences of degree rather than kind when considering healthy volunteers and patient volunteers

- Ensuring researchers minimise the possibility of therapeutic misconception for patient participants;
- Ensuring researchers have set out the alternatives for patient participants (e.g. palliative care);
- Ensuring measures are taken to minimise the possibility of undue influence of volunteers through disproportionate remuneration;
- Protecting the interests of potentially over-used or vulnerable volunteers.

2. Purposes of providing bodily material/volunteering in a trial

The NREAP recognises that donation of tissues for research can be ethical when:

- **Directed in some way –** for example, when it is donated to a particular research project, or to a particular biobank with some restrictions on the use of the tissue;

- **Non-directed**, where the person providing the material has no control over who will benefit from the donation.

Both contexts raise particular ethical concerns.

NREAP seeks to offer guidance to RECs to enable them to adequately explore with research applicants the potential ethical implications of limited, conditional and unconditional donations. In the case of unconditional (or open) consent researchers should clarify for potential participants the range of possible uses of their tissue. This is because a significant number of participants may object to, or wish to know about such uses. However we accept that it is impossible to predict the development of new technologies and therefore to anticipate all future uses. In some instances it will be impracticable or impossible to gain consent for a new application and therefore there should be some discretion for the REC to determine whether a new application is ethical based upon a range of considerations.

Questions

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

Researchers should alert potential donors to the likelihood that their tissue may be used in (non-human) animal experiments, for commercial purposes in which there is the potential to develop lucrative bio-technology, and to the potential for the non-medical uses of their tissue, for example in the development of cosmetics thus providing an opportunity for donors to consent to the conditional use of their tissue.

3. Ethical values at stake

Questions

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

The NREAP will always emphasise the duty of care that a REC and the researcher has towards the research participant. Although this duty of care can be understood in terms of key values such as respect for autonomy and non-maleficence there is a justification for RECs to act in a protective way which prioritises the welfare and safety of the research participant over other values. (A form of justified paternalism or “parentalism” does seem legitimate with respect to the role of the REC.)

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

NREAP will always support RECs in their task of balancing the interests of the research participant within the context of the necessity to conduct ethical research using human subjects.

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?

Remuneration / expenses/ in-kind benefits must not be disproportionate so as to unduly influence the research participant. Volunteering is socially desirable and seems consistent with the principles of a publicly funded health care system such as the NHS. The NREAP, however, holds the view that although participation in research should remain broadly voluntary it is likely that there is more than one ethically justified approach including, in some instances, paying volunteers. NREAP does not endorse one approach over another but would advise RECs to consider the particular issues associated with the application before them.

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?

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?
Please feel free to respond with your own personal opinions, with comment on a range of possible positions, or with your organisation’s policy, as appropriate.

NREAP does not adopt a position as to whether there is or is not a moral duty to participate in research of any kind. It is reasonable to ask patients and healthy volunteers to participate in research even with identifiable risk, burden and inconvenience to themselves. The decision to do so, however, must be based upon a valid consent from the individual, their legal representative or based upon the advice of an appropriate consultee (in keeping with the legal frameworks for such decisions).

4. Responding to demand

Supply and demand

Question

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

NREAP recognises that there are perceived research priorities but it is for the REC to evaluate ethically the proposed application and ensure that any major ethical issues are addressed and to balance any likely harm versus any likely benefits. The NREAP supports NRES’s recent pilot of proportionate review which will allow research with no material ethical issues to be approved promptly. In addition, there is already a facility for the expedited review of urgent research as in the recent case of research related to the potential flu pandemic.

Current regulatory framework

Questions

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?

The NREAP recognises that different forms of incentive may be compatible with ethical research but emphasises that the decision to participate in research should be based upon a valid, free and informed consent in circumstances in which the possibility of undue influence is minimised.

Questions

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

Some forms of incentive are of course unethical; these may also be illegal as well being perceived as no more than outright bribery. It is likely that instances of research where participants are explicitly rewarded with priority access to health care and treatment will be unethical either because of the potential for the undue influence of patients or because of the injustice to patients not participating in the research.

Family and friends may well offer incentives and RECs should explore with researchers the extent to which they can prevent this from occurring through the recruitment methods used.

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

Although there may well be a difference between these forms of compensation in terms of their likely influence on participants, any form of compensation has the potential to be unethical and should therefore be carefully weighed by the REC.

5. The role of consent

Consent for future unknown ('secondary') uses of bodily material

Question

23. Are there circumstances in which it is ethically acceptable to use human bodily material for additional purposes for which explicit consent was not given?
Please feel free to respond with your own personal opinions, with comment on a range of possible positions, or with your organisation's policy, as appropriate.

NREAP supports the position that there are certainly ethically acceptable circumstances in which tissue can be used in research without consent. RECs will have a role in determining those circumstances but in all cases will be guided by the Human Tissue Act and guidance provided within the Human Tissue Authority's Code of Practice. The NREAP would always encourage RECs to consider the particular case being made to justify non-consensual use of human tissue bearing in mind any likely harm versus the benefits.

Role of families: living donation
Question

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

There is a clear difference both in terms of legislation (for example the Mental Capacity Act 2005), and ethical issues. If one is making a decision for someone else then it is necessary to consider what they are likely to have wanted, and also what is in their best

interests. The decision that you make for someone else may therefore be different than the decision that one would have made for oneself.

Role of families: donation after death
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?
Please feel free to respond with your own personal opinions, with comment on a range of possible positions, or with your organisation's policy, as appropriate.

The NREAP recognises that this is a very sensitive issue. In principle we would support the position that the valid consent, or clearly expressed wishes, of a person prior to their death (or incapacity), should determine what happens to their tissues after their death (or incapacity). We would encourage RECs to explore thoroughly such matters with researchers seeking to utilise tissues obtained in these circumstances. Researchers should make very clear to the REC their experience in this field, and the resources they have available to inform, support and counsel relatives who are approached following the death of a family member. However it may still be unwise for a researcher to override a family member's opposition even where the deceased has given their consent.

6. Ownership and control
Property rights
No NREAP position

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 or purpose of the bodily material, please say so and explain why.
Please feel free to respond with your own personal opinions, with comment on a range of possible positions, or with your organisation's policy, as appropriate.

In principle the person should have the degree of control consistent with the terms of consent put to them at the time. In reality this may mean very little control if tissue is donated to a research tissue bank with "open" consent. As we have indicated, tissue donated post mortem can raise complex social and ethical issues where relatives object. As we have also indicated above, participants should be as well informed, as far as this is possible, about the range of likely, and possible, uses of their tissue. Researchers should provide the widest possible opportunity for participants to withdraw from a study whilst emphasising the practical limitations on such withdrawals. It is also

reasonable to explain to the participant the potential impact that withdrawal may have on the success of a particular study or programme of research.