MRC interim guidance on ethics of research involving human material derived from the nervous system

Contents

Foreword

This interim guidance is primarily for MRC-funded scientists, but we hope that other researchers, and those involved in reviewing or supervising research, will also find it helpful. It updates the ethical section of *The MRC's role and guidelines for MRC-funded brain banks* (1995), in line with *Human Tissue and Biological Samples for use in Research* (MRC Ethics Series 2001), and takes account of current government guidelines (see References). The guidance will be modified as necessary to reflect expected changes in legislation and any updates will be highlighted on the MRC website (www.mrc.ac.uk).

Introduction

This updated guidance provides an ethical framework for ongoing research into the human nervous system, particularly the brain. This research is vital to improve our understanding of neurological disease. Research on brain and spinal cord tissue, obtained both from living patients and post mortem, has already driven major advances in patient management, the development of new treatments, and the discovery of previously unknown disorders.

Examples of the value of such research, which usually involves the use and comparison of tissues from more than one person, include the development of the first effective drugs for Alzheimer's disease, Parkinson's disease, and motor neuron disease. Post mortem studies have revealed new diseases, such as dementia with Lewy bodies and variant Creutzfeldt-Jakob disease. And careful correlation of clinical features, pathological findings and appearances on brain imaging have immeasurably improved the understanding of other dementing illnesses. Human post mortem studies have also clarified how infection, inflammation, and injury cause brain disorders. Much of the work on the genetics of brain disease requires well validated collections of human post mortem tissues and monitoring the effects of new treatments also requires post mortem examination of material from treated patients. Maintaining and adding to suitable collections, subject to any necessary safeguards and consideration about their origin, is essential to enable future research in emerging areas.

Research on human post mortem material has been and will continue to be essential for progress towards treatment. The defining ethical principles in using such material are:

- that the expected benefits of research must outweigh any risks to the associated individuals,
- that the research is based on explicit and valid consent,
- and that respect for the human body, and peoples' confidentiality, is maintained at all times.

This guidance covers research on human material derived from any part of the nervous system from people either living or dead, but excludes tissue used for clinical practice, including transplantation, and the use of embryos and stem cells for research, which is covered by other guidance. While the custodian of the collection is the day-to-day manager, most collections should be overseen by a **management committee** which would normally have an independent Chair and include independent and lay members, as well as representatives of the funding organisation and the custodian.

1. Consent for removal, retention and use of human material (new collections)

1.1 Consent and information

Consent should be specifically obtained for all new collections of human material used for research and education, whether from living or deceased patients. This applies equally to material taken originally for diagnosis (and only later put to other uses) and to material retained for research from the outset.

Sufficient information should always be made available to the person(s) asked to provide consent. Materials, whether from a living donor or post mortem, should be viewed as donations or gifts, highlighting the altruism of the donor and the fact that there is unlikely to be immediate benefit to the particular individual or family. Information should be as comprehensive as possible while, for post mortems, remaining sensitive to the needs and preferences of the family at a time of distress[1]. Information should be provided about the purpose(s) of the research and about what will be kept and for how long, as well as the disposal options (See section 4). The likelihood of future research, the specific details of which may be unforeseen at present, should be emphasised (See sections 2 and 6). Reassurances about confidentiality and continued ethical scrutiny should also be provided (See section 5).

Consent for hospital post mortem examination (which will be deemed to have continuing validity) should be comprehensive and therefore include the following components, which also apply to surgical biopsies.

a. Consent for the basic diagnostic procedure; this includes sampling and retention of small parts[2] taken from the major organs, blood or fluid samples as well as likely whole organ (brain and spinal cord) retention in patients with neurological disease.

b. Consent for use in education and for training purposes[3].

c. Consent for research. This includes consent for research on material taken originally for diagnosis, and consent for removal and retention of material specifically for current research purposes[4]. Consent for research will be a specific component of the forthcoming nationally agreed *post mortem* consent forms (subject to any locally agreed wording to equivalent effect). Researchers should ensure that this section of the form is discussed in detail with relatives and that their consent is duly obtained

1. *Families and Post Mortems: A code of Practice, forms and information leaflets*, Department of Health website **www.doh.gov.uk/tissue**.

2. Retained pieces from solid organs and tissues generally measure about 2 x 2 x 0.5 cm but would be smaller in babies where occasionally the organ may be so small that all of it has to be kept.

3. The use of human material for education and training is addressed in the Department of Health's consultation document - *Human bodies, human choices* (chapter 10) and will be covered by ensuing DH guidance and legislation.

4. Specific consent is required for research on retained tissue left over from making blocks and slides for diagnosis. While it is likely that blocks and slides will become part of the medical record, the overall views of the donor (in the case of biopsies) or of the relatives (for post mortem material) about research should be taken into account when deciding to use blocks and slides as well as residual tissue or organ samples which have not previously been turned into blocks.

As well as consent for current and immediate research, specific consent should be considered for:

- future research (see section 2)
- genetic research (see sections 3 and 6)
- dispersal of material to other research groups for research that has ethical approval (see section 9)
- review of associated medical records (see section 5)[5]

The family should also have the opportunity to express views on any other individual matters, in the form of limitations or specific permissions. Researchers may decide that if a family imposes too many constraints it would be unwise to include that material in a research project. If relatives or those closest to the person disagree on consent issues, research should not normally go ahead. To prevent ongoing use of the resulting samples beyond the consent provided, the agreements and any limitations resulting from these discussions should be stored in a way that makes them readily accessible to the research group at all times.

While the relatives and the custodian of the collection do not have rights of ownership over the human material, it is recognised that they have a legitimate interest in what happens to it.

1.2 Consent for research in the medicolegal setting

The great majority of post mortem examinations are undertaken on people whose deaths have been referred to the Coroner or the Procurator Fiscal. Consent for the basic procedures defined at (a) in Section 1.1 is not required for medicolegal procedures and the responsibility for this rests with the Coroner or the Procurator Fiscal. However rights of consent for use of medicolegal post mortem material for education, training and research (as at b and c in Section 1.1.) revert to the family and cannot be subsumed by the Coroner or Procurator Fiscal. Research groups must respect this right of the family to give or withhold consent. Coroners and Procurators Fiscal cannot generally authorise retention of human material beyond the provision of a diagnostic report, unless the death may be subject to further enquiry (but see also sections 3.1 and 4.1). However small tissue samples will be retained from the major organs in the form of blocks and slides and may in future be formally regarded as part of the medical record. Families need to be aware of this.

1.3 Who seeks consent for research and from whom?

Consent for research should be sought by an appropriately trained practitioner who is knowledgeable about the surgical processes or the post mortem examination, who is sensitive to the needs of the individual family and who understands the purpose of the research. Consent may be sought by a member of the research group. Particular attention should be given to transparency of the procedure in these circumstances and it is advisable that an independent witness is present. The DH publication, *Families and post mortems: A code of practice*, addresses the question of who can give consent in detail.

1.4 Pre-consented research studies

People may have expressed a strong commitment while they were alive to the use of their tissues for research after death. Evidence for this should be documented and witnessed and is valid only if the person was fully competent to give consent at the time. Such people should be urged to make their wishes known to their family doctor and to their relatives, since it is inadvisable to use the tissue of the deceased for research in the event of strong objections from the family after death.

5. Medical records, including photography, are the subject of General Medical Council Guidance, which should be consulted with respect to publication.

2 Use and re-use of established collections

Although in future valid consent procedures should provide a clear framework for legitimate research, there may be ethical issues concerning research use of human material collected in the past when the original consent for research was -

a. not obtained (as applies to virtually all previous Coroner and Procurator Fiscal post mortem examinations), or not recorded (some older and historic material).

b. inadequate (this includes material not recently collected that may well have been retained with a standard of consent that would now be regarded as insufficient).

c. obtained for a specific purpose, but the material is now clearly useful for a study which was not envisaged, or not possible, at the time of consent.

The Retained Organs Commission (ROC) has advised that:

> "access to identifiable human organs and tissue following a post mortem examination prior to March 2000, where the position in relation to consent is unclear or uncertain, will for the immediate future be restricted to minimally invasive use for research and teaching only, and only for research which is deemed to be important".

Advice on whether use in a particular case could be deemed to be 'minimally invasive' and the research 'important' should be sought from an appropriate NHS Research Ethics Committee (REC). As a broad guideline, however, the ROC has defined 'minimally invasive' as involving less than 5% of the total organ, piece of tissue or block involved. Further details are set out in the recently issued *Interim Statement on the Use of Human Organs and Tissue*[6].

The scope for seeking renewed consent from families for further research should be considered and weighed against other factors. In many cases this is recognised as being impractical and would run the risk of causing great distress when a long time has elapsed since the death. Seeking renewed consent where there is no evidence that the family is aware that material has been retained, should be seen as a last resort. However, there is also a risk of causing distress if material from a long-dead relative were found to have been kept and used for research. In some situations like this it may be advisable not to go ahead with the research. In any case, research should proceed only after the defining principles listed in the introduction have been carefully applied and the relevant REC has been consulted. Replacement of archived collections of uncertain consent status with new collections of properly consented material will address this problem in future, but it is recognised that some archived collections are unique and irreplaceable.

6. *The use of Human Organs and Tissue: An Interim Statement*, Department of Health, (April 2003)

3 Particular categories of research activity

3.1 Medicolegal cases

While many medicolegal post mortem examinations are not linked to criminal charges, there are some categories of unexplained or sudden death where members of the family may be suspected of being the perpetrator. This may lead to problems in seeking consent in such cases. However there may be an urgent need for further research in likely criminal cases (eg, non-accidental head injury in children). Research in such circumstances should proceed only after consultation with the Coroner or Procurator Fiscal, and with the REC. The majority of medicolegal post mortem examinations do not result in legal proceedings. In these circumstances, consent should be sought prospectively for planned research and teaching activity. Any regulatory arrangements introduced by new legislation may have to be taken into account in due course.

3.2 Genetic research

Genetic analysis of post mortem material may reveal that the person it came from carried genetic changes predictive of disease, or merely of susceptibility to disease. While the former may have implications for other members of the family, it is clear that not all genetic research falls into this category. These issues should be considered when seeking consent from the family and agreement from the REC. Predictive genetic research should be undertaken in a planned context with prior informed consent when it is known whether or not relatives wish to be told of the results, and where counselling can be provided to discuss the implications.

3.3 Research by commercial enterprises

Commercial enterprises may be able to expedite some kinds of research and should not be denied access to the necessary material. However, custodians of collections should not enter into an exclusive relationship with any one commercial enterprise and should take care to avoid conflicts of interest. While the material has no commercial value in its own right, data from its use in research may become valuable intellectual property, conferring rights to patent on those undertaking the original research. It should be made clear to relatives (or to living patients) that they can have no monetary interest if something like this happens - as would also be the case if the research were carried out by academic researchers.

3.4 Human material from fetuses, children, and adults unable to give consent

Material obtained from fetuses is currently covered by the Polkinghorne guidance. Following consultation on *Human Bodies, Human Choices*, the Department of Health intends to revise this as a prelude to new legislation. Obtaining parental consent for the use of post mortem material from children requires particular sensitivity. For mentally incapacitated adults, research in life and research associated with post mortem examination is discussed in the DH consultation report, *Human Bodies, Human Choices* (7.4 -7.5), the MRC guidelines, *Human Tissue and Biological Samples for Use in Research* (12.4), and DH Interim Guidance, which should be consulted. Research involving people unable to give consent requires consultation with the family and with RECs.

3.5 Human material obtained from other countries

Human material obtained from other countries should be used for research only if the source country and hospital has a similar ethical and legal framework to the UK. Research proposals for use of such material should also be referred to a REC in the UK. The DH has published a non-statutory *Code of Practice on the Import and Export of Human Body Parts*. The UK Health Departments (this will apply throughout Great Britain and Northern Ireland) recommend that anyone seeking to import or export body parts takes account of the principles set out in the code and (in Great Britain) seeks advice from HM Inspector of Anatomy. New legislation is expected to cover this area.

4 Disposal of retained human material

4.1 Blocks and slides

These chemically treated biopsy or post mortem tissues are likely to have been used for diagnosis in the first place and retained long-term for hospital or medicolegal examination according to the Royal College of Pathologists' Guidelines. With valid consent, blocks and slides may be used for research and education at any time and retained indefinitely.

4.2 Formalin fixed tissue and organs

Human material preserved in this way is still useful for some research, which can go ahead if valid consent is given. The material may be retained indefinitely for further research if the family has donated it to a collection. If consent has been given, this material can be used for research before eventual disposal, or return to the family. Families should be asked about their views on disposal when consent is sought. If they want the sample returned, the material may be cremated or buried and should be collected by a funeral director on the family's behalf. If the family ask the custodian to dispose of material when it is no longer needed for research, they should be told that this entails separate incineration in a sealed opaque container.

5 Confidentiality

For collections of diagnostic material, access to patient records is implicit for the diagnostic process, but further access to these records in research studies requires specific consent. Patient information should only be released to authorised personnel and in a form that prevents individual patients from being identified. The degree of anonymity of human material and of associated records will depend on how close the researcher is to the central collection and database. The custodian should issue samples in a linked anonymised way so that the end user does not know the identity of the person the material was taken from. The use of coding will make it possible for the custodian to incorporate the research results in a central database. Recognition of these complexities should foster the development of strategies for operating a collection of material to the highest standard of confidentiality appropriate to the aims of the study. Laboratory records, human material and databases should all be secure and accessible only to authorised staff. The operating procedures should reassure any legitimate enquirer as to the confidentiality of data. Researchers should be particularly careful in situations where on one hand it is usual practice for a patient's full clinical and diagnostic information to be made available to their clinician, family doctor and family, while on the other, the research requires a high standard of non-disclosure. In very rare disorders, for example, variant Creutzfeldt-Jakob disease, even minimal details can lead to identification. The deceased may have expressed views about this in life. Researchers should consult the Management Committee/REC on difficult issues.

6 Imparting research results

Donors including relatives and family groups may want to know the results of research. The responsibility for seeking this information should rest with them and not with the custodian. Families should be told as part of the initial procedure how they can seek such information in the future. Research groups should develop policies to deal with research findings that have implications for the present or future health of family members. Decisions to disclose that information should be taken in consultation with Management Committees, clinicians, family doctors, and RECs as appropriate. Arrangements for counselling should be in place if this is likely to be needed. The consent procedures should have disclosed the likelihood of genetic testing and discovered whether relatives wish to be informed of the results.

It should be made clear to relatives that findings from individual research studies are often not definitive and are likely to require validation by further investigation.

7 Research Ethics Committee submissions

All activities which use human material for research should be subject to REC scrutiny. It may be appropriate to seek MREC approval rather than LREC approval for brain banks if multiple users are likely, or if human material is obtained from multiple sources. REC approval is needed to establish, maintain and add to collections of human material intended for research use, including brain banks. It is also needed for research use of material retained originally for diagnosis.

Proposals to RECs should be transparent about the procedures to be used and should make explicit the likely difficulties. They should specifically mention all the categories of material to be used, including archival and medicolegal cases. Care should be taken to highlight issues about which there could be debate, for example research which might be redefined as development of the diagnosis, and therefore exempt. If it is unclear whether or not work should be classified as research (eg, audit), it should be submitted to a REC. Regular progress reports on research activity levels should be submitted to RECs as required. Any change of activity or of personnel involved in the research should be notified to the REC in writing.

8 Ownership or custodianship?

While the status of human material is not clearly established under existing law, it is becoming clear that neither relatives nor the person removing the tissue from an individual becomes the owner. The transfer of such material may be viewed as a gift held in trust by the recipient. Custodianship has been advocated as a useful description of the role of the day-to-day manager of a collection of human material. The custodian has responsibility for ethical maintenance and use of both the material and the data, as well as responsibility for dispersal and ultimate disposal, but without rights of property. The day-to-day custodian should be a recognised named individual who holds a contract, but the institution where the custodian works should take a long-term view of over-arching custodianship to ensure the continued maintenance of a valuable collection. This will allow for a planned hand-over to the next named custodian. Both the custodian and the caretaker institution will find it useful to appoint a Management Committee responsible for advising on issues to do with high standards of management of a collection. Collections of material which is diagnostically validated and accompanied by detailed clinical data are now too precious to be disposed of at times of management hiatus or if research funding comes to an end. If no local solution appears obvious, arrangements should where possible be made to transfer a collection to another custodial bank elsewhere in UK, with the approval of all concerned.

9 Releasing human material and accompanying data to users

The value of a good collection of human material is greatly enhanced by making it available to other users provided valid consent is in place for this purpose. The custodian should release material only to *bona fide* researchers who must accept the same requirements for confidentiality and provide evidence of ethical approval. The material should be made anonymous as far as possible. In turn, the users should be assured that material passed to them has been obtained ethically and released to them legitimately. Users should undertake not to pass the material to another group and should be required to return data to the central source once the rights of research publication have been satisfied. The custodian, in consultation with a Management Committee, is responsible for prioritising requests or refusing them if not satisfied of their ethical status, or if users have flouted the conditions of use. If resources are scarce, the custodian and Management Committee may reserve the right to place the needs of internal researchers above those of external users.

10 Funding for research using human material

Researchers have responsibilities to their funders as well as to the donor patients or families. If funding is obtained from a private source, the financial arrangements and independence of research will be examined as part of the normal REC process. No exclusive arrangement should be entered into with a commercial enterprise. Human material may not be exchanged for money, but it is legitimate to charge users for any reasonable costs associated with supplying and transporting material.

11 Research governance and integrity

The custodian of a tissue collection is responsible for ensuring the integrity of research undertaken locally and for emphasising the importance of training to achieve this. The custodian should ensure that:

- Project and experimental records are maintained regularly and are retained within the group in the long-term, even when staff leave.
- Confidentiality is preserved in all procedures and by all staff.
- Investigations are blinded and anonymised as far as is possible.
- Work is recorded in a reproducible way.
- Analysis of data does not ignore unexpected or inconvenient results.
- Allegations of scientific misdemeanours are followed up and acted upon.

The Management Committee can help the custodian to do this. The custodian should ensure fair and proportionate representation on publications emerging from the research group and is responsible for declaring conflicts of interest.

Glossary

Human material
All biological material of human origin, including organs, tissues, bodily fluids, teeth, hair and nails, and substances extracted from such material as DNA or RNA.

Human tissue or sample collection
Any samples of human biological material to be kept for reference, teaching or future research use.

Human organs
Any part of the human body consisting of structured arrangements of tissues which, if wholly removed, cannot be replicated by the body.

Tissue blocks
A small piece of tissue is placed in a small (usually plastic) box. The tissue is chemically treated to remove water which is replaced with wax. The result is a hard block of wax in which tissue is embedded.

Tissue slides
Tissue blocks (see above) are cut into very thin sections. These are placed on glass slides and stained with special dyes to enable cells to be examined under the microscope.

Genetic research (predictive and susceptibility)
Investigation of variation in the nuclear or mitochondrial DNA that forms the genome of an individual and may be inherited from parent to child. This may involve direct analysis of DNA or analysis of gene products.

REC
Research Ethics Committee

MREC
Multi-Centre Research Ethics Committee

LREC
Local Research Ethics Committee

References

Families and Post Mortems: A code of Practice, forms and information leaflet, Department of Health (April 2003)

Draft Code of Practice on the Import And Export of Human Body Parts, Draft for Consultation, Department of Health (July 2002)

Guidelines for the retention of tissues and organs at post-mortem examination, The Royal College of Pathologists (March 2000)

Human Bodies, Human Choices: The Law on Human Organs and Tissue in England and Wales, A Consultation Report, Department of Health (July 2002)

Independent Review Group on Retention of Organs at Post-Mortem: Final Report, Scottish Executive (November 2001)

Human tissue and biological samples for use in research - operational and ethical guidelines, MRC (April 2001)

NI Human Organs Inquiry - summary and recommendations (June 2002)

A Consultation Document on unclaimed and unidentifiable organs and tissue; A possible regulatory framework, Retained Organs Commission (February 2002)

Review of the Guidance on the Research Use of Fetuses and Fetal Material (Chairman: Rev John Polkinghorne) (1989). The Polkinghorne guidelines are to be revised: see *Human Bodies, Human Choices*, section 15.

The MRC's role and guidance for MRC-funded brain banks (December 1995)

The use of human organs and tissue: An interim statement, Department of Health (April 2003).

Tissue Blocks and Slides: an information note, Retained Organs Commission (April 2001)

List of organisations

- General Medical Council
- Department of Health
- Scottish Home and Health Department
- Crown Office (England and Wales as well as Scotland)
- Retained Organs Commission
- Royal College of Pathologists
- Medical Research Council
- Polkinghorne Committee
- Higher Education Funding Council

Appendix 1

Advisory group to review MRC interim guidance on ethics of research involving human material derived from the nervous system

Terms of reference

To review MRC current guidance, as contained in

- *The MRC's role and guidelines for MRC-funded brain banks* (December 1995)
- *Human tissue and biological samples for use in research: operational and ethical guidelines* (April 2001)

And to issue new MRC guidelines when appropriate, taking account of other relevant documents and developments.

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