

Access to samples and tissues for research and clinical practice

A Workshop Report

18th January 2006

Notes from Tissue Samples/Secondary Uses meeting (18.01.06)

On the 18th January 2006, the Oxford Genetics Knowledge Park and the Genetic Interest Group ran a workshop on *Access to Samples and Tissues for Research and Clinical Practice in Genetics*. The aim of the workshop was to provide an opportunity for those involved in research and clinical practice, whether as clinicians, researchers, patient groups, research funders or regulators, to identify and consider the practical ethical and legal issues arising in the secondary uses of data and samples.

In recent years, following the Alder Hey and Bristol reports, the work of the Retained Organs Commission, and increasing awareness of the existence or proposed existence, of large-scale genetic databases such as Biobank, the storage and use of samples, including genetic samples, has received a great deal of legal, ethical and political attention, leading ultimately to the Human Tissue Act and the creation of the Human Tissue Authority. As the HTA begins its work, the Genetic Interest Group and the Oxford Genetics Knowledge Park considered it timely for those involved in the day-to-day work of clinical genetics and associated research, whether as clinicians, researcher or patients to discuss how the new regulations may or may not work in practice and how best to ensure both that important research and treatment are not hampered by inappropriate restrictions or regulation and also that appropriate protections are in place for individuals and their families, whether as research participants or as patients. The focus of the meeting was particularly but not exclusively concentrated on genetic issues arising from the regulations concerning the taking, storage and use of tissue samples for research and treatment.

The workshop was attended by a number of clinicians, genetics researchers, lawyers, social scientists, ethicists and patient groups,

What follows are draft notes on the discussion which took place at the workshop.

Tissue and Samples in Clinical Practice

1. Some key features of the NHS clinical genetics service relevant to the discussion of the use of samples and tissue are:

- The focus in clinical genetics is often on the care of families as well as individuals. This leads clinical geneticists to feel a duty of care to family members as well as the patient in front of them.
- A key part of the service is the assessment of risk for patients and to do this accurately often requires information about other family members, whether living or deceased.
- A similar set of issues apply in relation to diagnosis
- Access to tissue, information and samples of third parties form therefore a key part of care planning and decision-making in clinical practice.

- Improved opportunities for developing novel diagnostics and therapeutics often depends on research using identifiable samples and information from family members other than the proband.
- Advances in research are not yet fully incorporated into clinical service delivery in the NHS. This leads to ethical and legal issues around the relationship between clinical practice and research and its implications for the use of tissue and other samples.

2. In the making an accurate risk estimation, detailed information, which can only be obtained through the analysis of tissue derived from other family members, can make a huge difference. Estimating genetic cancer risk for example, is sometimes only possible where there is knowledge of the mutation in an affected family relative. This raises issues about access to their tissue.

Where a relative is alive it is possible to seek consent to analyse/re-analyse their tissue. Tissue samples from the deceased however, are rather more complicated. Until recently such tissue was generally accessible unless there was a specific refusal. However recent events such as Alder Hey and the impending legal changes have introduced anxiety among clinicians, researchers and laboratory staff as new regulation regarding this area has been interpreted in numerous ways by NHS trusts, research institutes etc. A demand for the obtaining of (signed) consent from next of kin, nominated representative etc plus sometimes checks to see that relatives are not unhappy have now become more of the norm. This is not straightforward however for a number of reasons:

- 'Next of kin' is not a legal term although often thought to be one, and it is difficult to know who ought to play this role.
- It may be felt that in some cases the person to get consent from may be the spouse/partner but it is the biological relatives who stand to benefit or to lose out from this decision. This can sometimes lead to tensions and problems in practice.
- Finally, there are a number of practical and ethical difficulties associated with contacting third parties, particularly when this comes out of the blue e.g this may cause anxiety to family members.

3. One of the biggest problems facing clinical geneticists is the fact that there is a great deal of uncertainty and this has led to inconsistency between the policy and practice of different pathology Labs and between Molecular Genetic Labs and Cancer Registries.

4. Current practice is regulated by a combination of the law (e.g. Access to Health records Act 1990, common law on negligence etc.) and professional guidance from the GMC etc, all of which generally consider it acceptable to breach confidence after death in order to prevent serious harm.

5. The Human Tissue Act introduces criminal sanctions. This is likely to generate defensive behaviours on the part of scientists and clinicians. The codes of practice, regulations and Acts differ in certain areas and clarification is needed. BUT: Non-cellular DNA apparently falls outside the scope of the Act..

Developments in law and regulation

6. Access to tissue is regulated by the 1961 Human Tissue Act until September 2006. Tissues can be removed from the deceased without consent unless there is a pre-existing objection or a spouse/relative objects. Common law and case law apply in the case of tissues from people who are still alive.

However, the possibility of objecting is dependent on having the knowledge that an action is intended and the removal is happening. This raises the issue of what is to count as having made a 'reasonable effort' to contact relatives?

7. The HGC raised concerns about the deceitful analysis of DNA for purposes such as un-consented paternity testing, and the Human Tissue Act has created a criminal offence of non-consensual analysis (with certain expectations).

8. The provisions of the new Human Tissue Act come into force in September 2006. Amongst other requirements the act will make it unlawful to hold bodily material for purpose of DNA analysis without consent. Exemptions include clinical treatment and diagnosis, but not research or for the benefit of other people.

The Act also distinguishes the living and the dead (there are more exceptions with tissue from living people). There also needs to be further discussion and clarification regarding what happens to a sample taken from a living person, when this becomes a deceased patient.

9. There is a grey area regarding the boundary between clinical practice / service review, audit and research.

10. There are a number of areas where confusion about what the law actually says and what people may think it says. This may result in variations in practice and/or defensive behaviour by institutions or individuals fearful of the possibility of criminal sanctions where explicit guidance in lay language would be very beneficial. (For example use for 'the benefit of others', and what is to constitute reasonable efforts to trace etc.)

11. With regard to consent, the Act gives guidance on who needs to be asked but not what would demonstrate that the consent is valid. In the case of DNA analysis, one 'OK' suffices, but the adamant objections of others with a legitimate interest (if known) might be taken account of.

12. Rules differ regarding tissues from the dead and tissues obtained from patients who were living at the time but have subsequently died.

Confidentiality and anonymisation

13. Whilst it may be theoretically possible for a person with access to de-identified DNA samples and other databases to work out the identity of an individual, it is important to set regulations that are proportionate both to the likelihood of this happening and of the potential harm to those identified (and in the context of other sanctions that may be applied should this happens). There appears to be two distinctions in the implications of identifying a patient. One is simply to identify that person or their name. This may be a consequence of the information, coding process or indeed that the condition is so rare that one knows from who it came but the second and more concerning distinction would be if this information was actively used or if it were attempted to contact that patient. Draconian measures against unlikely events are likely to prevent more good than harm emerging. Given the possibility of criminal sanctions it is also vital that the rules are clear. Examples of issues where clear guidance would be beneficial are: What is to count as de-identification? What are the roles of key holders and the Caldicott Guardians in relation to this data and these samples?

14. People affected by serious and or rare genetic conditions are in practice often well-known to clinicians and other health care professionals, as well as to family members and their immediate community so the question of their confidentiality may be a somewhat academic one in practice.

Relationship between clinical practice and research

15. Where research which uses DNA derived information from patients is approaching or crossing over into clinical utility it is unclear at what point clinical responsibilities, such as a duty of care or the right of access to records do (or ought to) come into operation. When has research, particularly translational research, become clinical practice? How is 'clinical applicability' assessed? When does the boundary get crossed? At what point has 'translation' happened? When does the clinical duty of care exist? And when does the new guidance from the Human Tissue Authority protect researchers?

16. Some researchers suggest that research lab results ought to be confirmed by clinical labs before being communicated to patients but this may not always be straightforward. Not all tests are available through clinical NHS laboratories, particularly for very rare conditions. For studies on rare (single gene) disorders re-confirming a diagnosis in a clinical lab may be a practical step to take at some point. With large scale data/sample banks however there may be considerable cost-implications both for the research budget and for the NHS.

17. There may be a conflict of interest in securing consent when the clinician is also the researcher.

Feedback

18.Communication of progress and or results varies between sample collections/databases. A code of good practice defining the triggers for feedback and the ways in which this should be done ought to be developed in order to clarify to donors of samples what they can and cannot expect, and how communication will occur. This will prevent confusion and secure consistency between sample banks/databases – especially with regard to crossing the line between research and clinical practice.

19.What should happen if a high risk change is identified with an available intervention in a volunteer donating tissue sample to a large scale biobank or database? Is the ‘non-feedback’ position really sustainable? Or as part of the consent process one of the questions could ask, “would you want to hear anything back?, or is it just to donate?” Or other questions, obtaining a sequential consent. Would this be feasible?

Secondary Uses

20. Is open-ended/broad consent acceptable? What is ‘adequate consent’ in this context? There is a need to see the requirements for consent spelled out.

21. There is a need to consider seriously the ethical implications of destroying samples at the end of a study when they could potentially be used for further research. Patients generally want to see the maximum value possible obtained from samples provided for research or clinical purposes rather than seeing them destroyed. This raises the issue of securing consent that is broad enough to allow this to happen without being so non-specific as to invalidate the notion that the donor is actually consenting to future use.

22. The future uses of samples may not be foreseeable even at the conclusion of the use for which the sample was originally obtained (e.g. a research project or a clinical investigation). This does not necessarily mean that they should be destroyed. There needs to be a framework (properly resourced) for maintaining sample collections so that knowledge of their existence constraints on their use and issues of ownership/custodianship are clear, and the tendency to dispose of samples because the costs/implications of keeping them are thought to be too great is minimised.

23. What would constitute appropriate audit and governance of these processes and collections? Would looking at other bodies such as the HFEA help to understand these processes?

24.Although it was the Government’s wish (stated in Parliament during the debates on the Human Tissue Bill) that broad/generic consent was acceptable and desirable, a significant proportion of applications to RECs have been rejected because consent is insufficiently specific.

25. What is the role of consent? Is it to protect those who consent from harms or is it to obtain their permission, or both? The answer to this question has important

implications for research e.g. If the aim of consent is about seeking the permission of those who gave samples for uses other than those for which the sample was provided anonymity and low risk of harm will not obviate the requirement for consent to be sought.

Commercial uses

26. Whilst patients/sample donors are generally keen to support research many have reservations about commercial gain arising from the use of their samples.

The changing nature of genetics research

27. Implications for research in genetics in a changing research environment e.g. the move from genetic sample collections towards genotype/phenotype collections e.g. Wellcome Trust Case Control Consortium. Potential for identification through the bringing of collections together needs to be recognised and guarded against.

Regulation of research

28. RECs and Trust R & D Governance offices hold disproportionate power over what research is/is not permissible. This can lead to an apparent belief that researchers are “not to be trusted”, making researchers dance to the REC/R & D offices tune – and those who create the regulations will do so in ways which protect their own position. Whilst those attending the meeting were not demanding complete de-regulation, it was felt by many that the development of regulation in response to extreme situations and events was not a good basis for the construction of an appropriate research framework as it will tend to produce disproportionately draconian requirements and inhibit ethical research. It was also felt that once regulation was in place it was important that REC committees and R&D Boards were aware of the regulation and how to implement it as well as having more understanding and awareness of the issues surrounding such regulation.

29. There is a discontinuity in the relationships around the regulation of research. Researchers feel they are in fire fighting mode, with a sense of loss of control and a lack of shared understanding as to the practice of biomedical research. While the aims of the HT Act may be laudable, there is a danger of regulatory drift in the interpretation/misinterpretation of the Act’s requirements given that the law will be effective at a number of levels – HT Authority, Universities, NHS Trusts, Funders, Heads of Departments etc. Without clear guidance a defensive culture in the research community may arise, inhibiting collaboration and threatening patients hopes for benefits.

30. The HT Act does not operate in isolation. Other legislation (e.g. the Clinical Trials Directive and the Data Protection Act) also impact on research and clinical services. Guidance needs to take account of this complex and potentially contradicting legislative framework. The deployment of criminal sanctions and

career ending consequences in the event of a mistake being made will generate pressure for more caution than is necessary/desirable, and to opportunities being foregone at worst, or at least to inconsistent behaviour between individuals, labs, institutions etc.

31. In the light of the above concerns it was felt that there is a need for patients (who the legislation is designed to protect) to address this issue in Partnership with other stakeholders but leading from the front and also for good quality empirical work on the attitudes and beliefs of patients with regard to research.

32. Whilst patients are supportive of research in general, they (and the groups they belong to) are sometimes unable to be sufficiently critical of the quality and goals of the research proposed, or even of the researcher proposing it because of lack of expertise, training and support. There should be a development programme for patient groups to enable them to evaluate research proposals using appropriate critical standards. This is particularly important in respect of some rare diseases where the number of researchers may be very small, and resources extremely limited – imposing an even greater imperative to spend money wisely.

33. What protections do patients and participants actually want? What is the empirical evidence? Input from patient groups at the meeting suggested that: participants are likely to want

(i)protections in place from familial coercion and pressures;

(ii)skills for patient groups to assess good quality research and researchers;

(iii) that practice should be in accordance with patient and participant expectations (this implies information and consent)

(iv) controls on the commercial use of samples and data.

34.The regulation and governance of genetic databases and sample collections need to be sensitive to the varieties of types of research. For example, it needs to be capable of dealing appropriately with the distinction between research on common conditions and that on very rare conditions e.g. the costs associated with the regulation of research on very rare conditions may mean that the research doesn't happen.

Actions

A number of suggestions were made for actions that would help to bring clarity to the regulatory framework. For ease of reference, these have been grouped under 'general actions/recommendations', 'actions for researchers and clinicians', 'actions for patients', 'actions for regulators'. Where actions relate to more than

one group (but not all) appropriate pointers are included at the end of each action point.

General Actions/recommendations

35. Taken together, the comments above suggested the need for a significant amount of work to be done on the clarification, analysis and resolution of ethical and legal issues around consent.

36. A flow chart of the stages of research from the original idea to the use of the results, with issues and pitfalls at each stage clearly laid out for each step of the journey would help patients, researchers and regulators focus on the key issues at each step.

37. The COREC information sheets seem to focus in what patients/donors “ought” to ask, not necessarily what they want to know. For genetic testing studies there may be a different set of issues arising (and different issues and priorities may be important for different types of genetic study). A publication with Q&A’s lead by patient organisations would help researchers, clinicians and patients.

38. Whilst guidance must be consistent with the advice of the HT Authority, the familial nature of much of the genetic research needs to be taken into account. The HGC’s concept of “genetic altruism” is an important guiding principle. Advice should also seek to clarify “boundary issues” with research arising from clinical practice (and research crossing back into clinical practice), and look at indirect studies as well as direct ones.

39. As well as biomedical research there is a need for research into ethical questions too – especially with regard to issues and processes rated as important by patients and consumers at all levels from fundamental biology to Health Services Research. This could usefully (and straightforwardly) be done through or in collaboration with GIG and its member groups.

40. Ethical and funding structures create a complex moral landscape. It is important that this is not disabling, but for this to be the case sophisticated judgements have to be made. Research leading to guidance as to what the issues are, how to balance them and so lead to endorseable conclusions as to what is ethical will help to support a climate of trust within which research and clinical practice can flourish (rather than a climate of managerialisation where trust is lost and health gain for patients potentially suffers). N.B. Trust must be rational, not blind.

41. There is a need for leadership on a policy level from patients (i.e. GIG) as disinterested voices of the ultimate end users/beneficiaries of research and clinical care. Whilst GIG can play a role in this, it must be in partnership with others able to address the broader context beyond genetics.

Amongst the topics for where clarity would be appreciated by all stakeholders are:

- What are the “property” issues?
- Definition over who has legitimate interest in the sample and in the information that arises from it?
- How can we achieve proportionality?
- Can we deliver appropriate parameters for consent?
- Where is the boundary between audit and research?
- What are the differences between rare and common disorders?
- How to secure clarity/realism of expectations for research outcomes/clinical benefits?

In addition there is an urgent need for guidance as to where there is actually clarity and as to how the requirements of the legislation will be interpreted in regulation – i.e. those issues where we can be confident that the regulations are clear. Tensions between issues relating to the individual and the family need to be explored.

42. It is vital that the views of patients and the public on issues around medical research are taken seriously. There is a need for more high quality empirical research in this area. If the views of the patients and patient groups at this meeting are anything to go by, some of the key concerns of patients will be:

- The facilitation of high quality research
- Good quality regulation of the commercial uses of samples and data
- Protections in place from coercion especially from family members
- Further access to training and support to help patient groups assess the quality of the research they are considering funding.
- Research practice to be in accordance with the expectations of those who sign up to participate

43. Whilst those attending the meeting were not seeking complete de-regulation of research or clinical practice and a free for all, there was a lot of uncertainty from the different stakeholder groups at present, and there is an urgent need for clarity – both about what is known/declined, and what is not yet clear/decided so that legitimate research and clinical medicine (and hence patient benefits) can flourish to the fullest extent possible.

Actions for researchers and clinicians

1. Variations currently appear in the manner in which researchers and clinicians interpret the regulations. There is a need to map what is **actually** required and a common code of practice developed. This guidance should be in lay terminology and piloted. This process needs to involve the beneficiaries of such research – the patients.
(included in patient actions too)

2. Clarification is needed in regards to what researchers and clinicians legally can and cannot do when obtaining tissue samples from a deceased person as compared to those from a living person who has since died.
(included in patient actions too)
3. A flow chart of the stages of research from the original idea to the use of results, with issues and pitfalls at each stage clearly laid out for each step of the journey would help patients, researchers and regulators focus on the key issues and develop appropriate guidance as to good practice.
This could be complementary to point 1
(Patients and Regulators as well)
4. Production of information sheets for patients answering questions they want to know the answers to. These would be produced by GIG, following qualitative research. This would also help researchers and clinicians in their understanding of patients needs and expectations when getting involved in research. There is a sense that current information sheets focus too much on what patients ought to ask not on what they want to ask or feel they need to know.
(patients and regulators as well)
5. As well as biomedical research there is a need for research into ethical questions too – especially with regard to issues and processes rated as important by patients and consumers at all levels from fundamental biology to Health Services Research. This could usefully (and straightforwardly) be done through GIG and its member groups.
(patients as well)
6. A flow chart of the stages of research from the original idea to the use of results, with issues and pitfalls at each stage clearly laid out for each step of the journey would help patients, researchers and regulators focus on the key issues and develop appropriate guidance as to good practice.
This could be complementary to point 1
(patients and regulators too)
7. A code of conduct to establish best practice where information and /or tissue samples move from the clinic to the research setting and back to the clinic is needed to clarify where clinical responsibility is in operation with regard to patients providing samples and data
(researchers and clinicians too)
8. See point 9 in patient section
9. See point 10 in patient section

Actions for Patients

1. Information to spouses and relatives of the possible taking of a sample should be provided in a way that makes them aware of the opportunity to provide (or withhold) consent for possible future uses.
(patients too)
- 2 See point two in Researchers and clinicians
- 3 See point three in Researchers and clinicians
- 4 See point four in Researchers and clinicians
- 5 See point five in Researchers and clinicians
- 6 See point six in Researchers and clinicians
- 7 Many patient organisations are not well equipped to determine whether the standard of research into their condition that they are funding (and in which the organisation and members are involved in) is being carried out to “best practice” standards. There is a need for a development programme for patient groups to enable them to evaluate the research proposals they review, fund and are asked to take part in. This is especially important when looking at rare diseases where the number of people interested in carrying out research is likely to be limited.
8. A flow chart of the stages of research from the original idea to the use of results, with issues and pitfalls at each stage clearly laid out for each step of the journey would help patients, researchers and regulators focus on the key issues and develop appropriate guidance as to good practice. This could be complementary to point 1
(Researchers and clinicians and regulators too)
- 9 Production of information sheets for patients answering questions they want to know the answers to. These would be produced by GIG, following qualitative research. This would also help researchers and clinicians in their understanding of patients needs and expectations when getting involved in research. There is a sense that current information sheets focus too much on what patients ought to ask not on what they want to ask or feel they need to know.
(researchers and clinicians, regulators and patients too)
- 10 .As well as biomedical research there is a need for research into ethical questions too – especially with regard to issues and processes rated as important by patients and consumers at all levels from fundamental biology to Health Services Research. This could usefully (and straightforwardly) be done through GIG and its member groups.
(researchers and clinicians too)
- 11 See point six in Regulators

Actions for Regulators

1. There is a grey area regarding the boundary, in between clinical audit and research. The boundary needs to be defined and guidance produced which is endorsed by the professional bodies as well as regulators in order to avoid misinterpretation and time being wasted. Clarification around boundary issues that arise from clinical practice and research that crosses back into clinical practice need also to be identified,
2. Proportionality. The issues surrounding anonymised or pseudo-anonymised data within databases and the potential for the data to be traced back to the donor generate anxiety for regulators and RECs. However patient and family concerns about this may be very different and some feel that the measures in place currently are too draconian, preventing research from taking place. Evidence from GIG states that in many cases for small research studies the patients and clinicians are known to each other so an undue emphasis on patient confidentiality creates artificial hindrances that patients feel to be unnecessary.
(regulators)
3. See point six in Researchers and Clinicians
4. See point eight in patient section
5. Ethical and funding structures create a complex moral landscape. It is important that this does not hinder good research, but for this to be the case clarification and judgements need to take place, on issues which can, in some cases, be sensitive.
Research into these issues such as, how we balance the concept of “genetic altruisms” against individual’s priorities. The findings need to lead to endorseable conclusions as to what is ethical. This will help to support a climate of trust within which research and clinical practice can flourish.
(NB Trust must be rational, not blind).
(regulators)
6. There is a need for leadership on a policy level from patients, as the key beneficiaries and end users of research. This leadership must be in partnership with other stakeholders in order to address the broader issues and make an impact on the current situation. A number of areas of interest have arisen in discussions with GIG and key stakeholders
 - What are the “property” issues?
 - How can we achieve proportionality?
 - Can we deliver appropriate parameters for consent?
 - What are the differences between rare and common disorders, when looking at research and how regulations are applied?

- How to secure clarity/realism of expectations for research outcomes/ clinical benefits?
(patients and regulators)
7. The respective responsibilities of RECs and PCT research governance offices and R & D committees need to be defined clearly, and procedures harmonised so that unnecessary duplication of information provision is avoided and each body focuses on issues within its sphere of competence.
This will promote effective decision making, and avoid the waste for time, energy and resources. Guidance for researchers and regulators relevant to the role of each should be developed. (regulators)