



**Research and Rare Genetic Disorders
Report of a workshop
19th April 2002**

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This workshop was convened by the Genetic Interest Group under the Chatham House Rule. Invited participants come from patient groups which support research, the clinical and academic community, ethicists and regulators, industry, research funding bodies and government.

Setting the Scene

Individuals and families affected by rare genetic disorders are at the heart of any research programme designed to throw light on their condition. Such research is often complex and can involve many different people in collaborations. The rarity of such conditions, along with the collaborative and clinically-based nature of the research raises a number of ethical, legal and practical issues unique in their combination. Some of these issues are integral to the rare condition. Others arise from the nature of the current legal and regulatory framework, which is designed to consider projects where the condition under investigation is much less rare and the distinction between clinical practice and research is easier to draw.

Two typical scenarios facing the researcher into rare conditions and the affected families are highlighted in the following case studies:

Case 1. A medically qualified researcher was telephoned by a clinical geneticist to discuss a patient with an unusual combination of clinical features, presenting a dilemma for diagnosis and therefore for counselling of the correct genetic risk. Two months later, the clinician sent the researcher DNA from the patient, together with clinical photographs and copies of clinic letters. Investigation of mutation hotspots in relevant genes was negative and the sample was added to a "research panel". Further contact was made by the clinician two years later, enquiring whether there were any positive results (the reply was negative) and providing some further clinical information. Eventually, a further year and a half later and after tests of 13 genes had proved negative, the researcher contacted the clinician to say that a potentially pathogenic change in the DNA had been identified. A request was made for the clinician to obtain samples from the unaffected parents. The mutation was shown not to be present in either parent, establishing that the change had arisen *de novo* in the patient and was therefore the cause of their clinical problem. Hence, three and a half years after the initial contact, the researcher had established unequivocally the correct diagnosis, mechanism of inheritance, and appropriate molecular test for the patient's condition.

Case 2. A researcher received an unsolicited letter from a clinical geneticist from another country. This contained a three-generation pedigree showing the segregation of a rare clinical disorder that the researcher was working on and stating "If you accept, I can send their peripheral blood specimens to you". The clinician subsequently sent blood on several members of the family. The accompanying annotated pedigree indicated that two individuals "refuse the giving of blood", implying to the researcher that a process of informed consent had taken place. Subsequently the grant sponsor requested that written consent be obtained from the individuals sampled. The information sheets, letters of invitation and consent forms, in English, were relayed by the researcher to the clinical geneticist. Copies of the original forms (in English) were later returned, one duly signed by each individual sampled, indicating that they had discussed the study with the referring clinician.

Because the first family was in the UK and under one legal and regulatory "umbrella", a number of issues and questions can be identified. These are listed below. In the case of the second, overseas family, a number of additional questions are raised. These are separately identified in the following section.

Key Issues (UK families)

1 There is a lack of clarity as to the boundary between clinical practice and research. Good clinical practice in

rare conditions will involve an amount of "detective work" but precisely where this shades over into research is unclear. Whilst there is a danger that any firming up of boundaries will cause new problems if the line is wrongly or arbitrarily drawn, the current lack of clarity may leave researchers and clinicians exposed.

- 2 Whilst consent for research is absolutely necessary, the extent and specificity of the consent (and the associated paperwork that accompanies it) required to ensure that research subjects feel they have been adequately informed and protected is unclear. There is a lack of consistency between projects and between ethics committees.
- 3 The cost, time and complexity of obtaining research ethics approval is similar for a large project investigating a common disorder and a small project involving a handful of subjects dispersed across the UK. Hence, regulatory frameworks designed for large-scale research projects bear down disproportionately on those investigating rare disorders. This is an added discouragement to research into rare disorders, which has difficulty in attracting researchers and funding in the first place.
- 4 The current regulatory framework seems to place much emphasis on protecting the research subjects from possible exploitation but rather less on encouraging research (which affected families are often very keen to support). If the regulatory framework is in itself a significant obstacle, this constitutes a form of discrimination that makes it less likely that potentially valuable research projects will be initiated and carried through. This highlights a potential conflict between legal constraints imposed to protect research subjects and the ethical imperative to seek solutions to severe, intractable and often fatal health problems.
- 5 Insistence on sample anonymity may not be desirable or feasible in relation to rare conditions. Progress may require clinical linking to be maintained, with access by the researcher to detailed information on both the family history and the phenotype.
- 6 Case finding in rare disorders is a major challenge and in many cases will evolve from the identification of a single family to a search for additional affected individuals nationally or even internationally. This creates a chicken-and-egg situation. The research (and associated ethical review) cannot proceed until a critical mass of cases is located, but the corollary is that the initial process of locating the cases may occur without any clear ethical framework in place.
- 7 The small size of families available for research in rare disorders demands a different scientific approach. This may require a fair amount of guesswork, involving the testing of multiple candidate genes. This raises issues about the extent of testing that may be undertaken under any given consent; additionally, the logic behind the research procedure may not be apparent either to ethics committees or to grant-funding bodies. Yet this approach may be the only way forward and sometimes yields rich rewards.
- 8 The use of samples from healthy individuals in research into rare disorders is often misunderstood. If the condition is fully penetrant the subject will know if he/she is affected. There is no issue about future health prediction.

- 9 An important problem not raised by the case study concerns the use of samples from people who have died. In the case of rare conditions that are lethal in early childhood, post mortem samples may be the only way to undertake the research. Confusion over issues of consent presents significant obstacles to research into this category of disorders. What is the status, for example, of (1) the post mortem use, for research, of samples originally taken for diagnostic purposes or (2) the change in status of samples taken ante mortem for research (such as cell lines) once the individual has died? Clearly the use of post mortem samples poses both regulatory and practical issues which would need to be addressed and resolved before the law were amended in ways that work to the benefit of patients with rare disorders.

Key Issues (Overseas Families)

Whilst the globalisation of research has brought many benefits, systems designed to work in one legal and cultural context may be difficult to mesh with those in another context. Inflexibility can act as a substantial deterrent to progress. Clearly some issues are "non negotiable" – especially where consent is concerned – but attention must be given to the steps necessary to demonstrate that valid consent has in fact been obtained and that disproportionate costs are not imposed in obtaining it.

- 1 It is not clear whether all paperwork required by MRECs in the UK needs to be translated and made available to patients overseas, or whether locally developed forms and practices can be taken as evidence of consent.
- 2 Cultural factors – deference to authority, hostility to perceived "bio-piracy" etc – may all play a part in the giving or withholding of consent by individuals.
- 3 Weighing the evidence – how much credence should be given to a standard (English) form signed by a sample donor whose first language is not English and who is located in a hospital in another country?
- 4 Gaining access to research and clinical practice. The types of relationship described in the case above may be the only realistic way in which people with rare conditions in many countries will be able to gain access to diagnosis.

These problems will need to be addressed if good quality, ethical research into rare genetic disorders is to be promoted and not impeded. Clearly these issues are complex and many may not be resolved completely. Further research and consultation is necessary and should be put in place. Uncertainty, inappropriate regulation and a disproportionate drain on scarce resources will otherwise become a real deterrent to progress, leading to the continuing vulnerability of an already vulnerable group of patients and families. In the rest of this paper we discuss these issues in more detail and make some tentative recommendations.

Introduction

Individuals and families affected by rare disorders have the same hopes and expectations as those with common conditions. For many in this position, one of the most important "hopes" is that effective treatments and possibly even cures will be developed or that new knowledge will enable these disorders to be prevented from occurring in the first place. For this to happen there must be a sustained commitment to research and development. Notwithstanding the wish of many of those affected to see this happen, the rarity of these conditions militates against doing

research. The regulatory framework set up to ensure that research is ethical and protects the interests of potentially vulnerable patients can sometimes appear to act as an obstacle course rather than as a facilitator to getting the work done.

Clearly there needs to be regulation. A proper regulatory framework gives confidence to the researcher and provides protection for the patient. But the regulatory framework needs to be appropriate and to reflect the reality of the situation if it is to fulfil its obligation to all stakeholders appropriately.

Questions raised by any proposed research that involves human subjects centre on issues of consent, the protection of confidentiality and privacy and respect for the rights of patients not to be exploited or treated in ways that are detrimental to their well-being. For researchers, regulators and volunteer participants the key questions about rare disorders relate to whether or not the rarity of conditions per se creates special difficulties or responsibilities for the researcher, or whether the issues are common across biomedical research whatever the prevalence of the condition being investigated, with the difference residing in the measures needed to resolve them?

A clinical and scientific perspective

Doing research on rare genetic disorders has been likened to competing in the "legal and regulatory framework steeplechase" both in respect of the hurdles that have to be cleared before the research gets under way and those which seem to have been placed between the researcher and the attainment of a successful outcome to the project.

In order to set the current situation in its proper context it is necessary to go back more than 20 years. In the early 1980's genetic research was focused on the common Mendelian disorders, in a relatively unconstrained legal and regulatory context. Towards the end of the 80s and in the early 90's the research emphasis shifted somewhat and the importance of addressing ethical questions prior to doing the research moved more to the forefront. Issues such as testing of children or the healthy carriers of adult onset conditions were discussed and debated by academics and in patient groups. At the same time, as the genetics of the common Mendelian conditions became clearer, the research emphasis shifted to include the rarer Mendelian disorders and the common complex ones. This had several consequences: -

- The ethical framework for clinically based research became more complicated.
- As technology developed there was a transfer of methodology from the investigation of more common Mendelian disorders into the study of rare conditions.

Much of the discussion and many of the subsequent procedures for obtaining ethical and regulatory approval focussed on the situation and experiences of those investigating common complex disorders. This led to the development of a regulatory system rather less suited to the review of projects investigating rare conditions. To address the issues for rare disorders, those affected by them and those wishing to research them it is necessary to understand the process of gene discovery in such diseases and why the framework inhibits rather than helps ethical research in this area.

Research or clinical practice?

The clinical genetics researcher with a known interest will often receive a clinical referral "out of the blue". This will include information about the patient: where the phenotype includes

unusual physical features, it may include a photograph together with a request for genetic analysis. In order to establish the most productive approach to the subsequent clinical investigation there has to be an on-going dialogue between the researcher and the clinician (and often the patient too) which can extend for several years and which will involve checking of clinical signs and gathering more information over time.

In parallel with this clinical dialogue, 'candidate' genes will be screened on the basis of the individual clinical phenotype. Devising a protocol for obtaining ethical approval for screening of such candidate genes against specific phenotype(s) is difficult, as this process is essentially a "fishing trip" approach to gene discovery. There is also at this stage genuine uncertainty about whether this is really research or an extension of clinical management.

Eventually a causative genetic change may be discovered. At this point samples will be needed from other family members to see if this is inherited or a new mutation – this is essential if correct advice is to be given to other family members and also for the benefit of others in the programme whose situation may be enhanced by this knowledge. Thus there are clear clinical benefits for those affected, but these can only be realised because it is possible to do the work in a research setting – but again, is this research or is it clinical management?

Arguments that would swing the balance towards this activity being considered as research, are that a diagnosis may take years to arrive at; it is made as a result of the discovery of a previously unknown mutation; and it often results in the publication of a scientific paper discussing the findings. Arguments pulling in the other direction are that this activity is part of a clinical consultation and is a central feature of clinical practice in this area. This consequence of this process of clinical evolution is however that in practice, the subject's/patient's explicit consent to participate in 'research' may not be obtained and this sits uneasily with the current legal and regulatory framework.

The Advisory Committee on Genetic Testing (ACGT) published guidelines in 1998, which suggest: -

- a) **Anonymity for those participating.** Yet in many cases it is only possible to obtain the answer that the patient and referring clinician seek if the patient is known to the researcher, so that evolving hypotheses can be checked out against the individual in question.
- b) **A clear separation between research and service delivery.** Again this is not feasible in the context of very rare genetic disorders whose basic biology is not yet understood and where the elucidation of the research question depends on being able to access clinical information and where the delivery of a good clinical service requires the answer to the research questions.
- c) **Explicit consent for further genetic testing is obtained.** A "candidate gene" approach may involve testing a large number of genes before the correct one is identified. Going back to the patient each time would be expensive and impractical. It could also be seen as unnecessarily intrusive, particularly as research progress may only be made over an extended period dependent on new knowledge arising from elsewhere. There is also the suggestion that new ethical approval should be sought before further genes are tested. To follow these guidelines would paralyse research, clog up the research ethics committees with trivial questions and leave the patient, who has a vested interest in knowing the answer, in a position of ignorance when they

might otherwise have had access to the information that they need.

- d) **Samples taken from healthy individuals run the risk of "medicalizing" them.** Yet in the case of rare genetic disorders, where the penetrance of the gene is often close to 100%, it is essential for the clinical advice that can be given to other family members for the clinician to know if the index case arises from an inherited or a new mutation.

Whilst the ACGT guidelines lay down a framework that works for much genetic research and which provides a basis against which many proposals can be properly evaluated, they do not meet the needs of families with very rare conditions and if used rigidly they could stop progress being made for those affected.

Clearly in addition to the practical/clinical problems described above there are many ethical issues raised by clinical genetics research. Some of these are generic such as: -

- The legacy of historical eugenic abuses
- Communication with participants about the nature and scope of the project
- Obtaining samples from children or those incapable of giving informed consent
- Storage and future use of DNA and cell lines
- Uncertainty about interpretation of results (especially when these are used in a clinical context)
- Inadvertent discovery of non-paternity
- Disclosure of carrier status
- Implications for other family members
- Disclosure and confidentiality of the outcomes

These have been widely discussed and there is widespread consensus (at least within the UK) as to how these issues should be addressed.

Research involving very rare congenital disorders raises in addition two specific issues, which are not found with complex disorders or the more common Mendelian ones. These relate to sample anonymity and the testing of candidate genes. Both of these features **need to be recognised**.

The present regulatory framework has a number of other potential inconsistencies, which also need to be addressed in the interests of the research and also more particularly of the patients. These include:

- a) The provision of signed consent by the patient: what does this mean in practice? Samples are often provided by clinicians from many countries, operating under different ethical and cultural imperatives. Are consent forms designed for the UK and written in English to be supplied (and do they have to be translated)? Or is it more valid to request that local collaborators in the referring institution obtain appropriate local consent? Are funders willing (able?) to bear the additional costs of securing the consent deemed to be necessary?
- b) Samples from more than one centre require approval from MREC. This can generate a paper mountain that takes months to climb, significantly reducing the time available to a researcher on a time limited contract actually to do the work which he or she was recruited. The paperwork is the same whether the study involves 1 or 1000 patients from a given centre. In the case where the genetic analysis takes place in the UK, but samples are from abroad, is MREC approval the appropriate vehicle to ensure protection for research subjects?
- c) There is often an inconsistent interpretation of the risks by



Local Research Ethics Committees. Different studies in the same centre will be treated differently and different centres will reach different conclusions about the same study.

There are a number of other, practical difficulties that need to be resolved if research in rare diseases is to be eased, notably: -

- The volume of paperwork relative to the number of subjects
- Establishing the right "legal and regulatory jurisdiction" where families are dispersed across the UK or come from abroad.
- Anonymity is not possible if the study is to take place.
- Standardisation of approach is not possible because each case is unique.
- The boundary between clinical practice and research is not clear.
- There is clinical and research benefit to be gained by taking samples from healthy individuals.
- Diagnostic hypotheses may be speculative, but they occasionally provide a rich harvest.

In conclusion there is no question that a regulatory framework is necessary and beneficial. Intrusive and unregulated genetic research is unethical. In the long term it would also result in a withdrawal of the mandate given by the public for this type of work to proceed. But: -

- Cumbersome frameworks discourage research into rare disease and discriminate against those affected by these conditions. This too is unethical.
- Different types of study pose different problems. Guidelines need to be sufficiently flexible to take this into account.

In seeking to create the right framework the balance must be struck between too draconian an approach, which will result in the stifling of research that is supported and endorsed by patients as legitimate, necessary and desirable, and too loose an approach permitting undue intrusion and possible harm to those at risk. Research funders, ethics communities, scientists, clinicians, families and patients all have a part to play in developing a constructive understanding of the complexity of researching rare genetic diseases, particularly when these can often be seen to straddle the clinical/research interface and there are no alternative sources of information and support for those directly affected.

An Ethicist's Perspective

Many of the difficulties experienced by those wishing to undertake research in the field of rare genetic disorders are an artefact created by the coming together of two different systems – the NHS and the research funders.

In many ways this area of activity has more in common with traditional investigative medicine than with much of the activity that others would recognise either as basic research or as clinical care. Defining this work as "research" is an artefact. However, once this has been done it is brought within the scope of the Research Ethics Committee approval system and the REC's have to try and deal with the situation in ways permissible under their terms of reference. These have been drawn up with more "typical" large-scale studies in mind.

Given that we cannot start from a clean slate, creativity will be necessary if a satisfactory outcome is to be obtained within existing constraints.

The first problem in reworking the regulation of research into genetic diseases is the definition of 'rare'. Rarity has to do with prevalence in a population and is a relative concept. Some conditions are rare in the UK population but common elsewhere (for example, TB or malaria). But Mendelian genetic disorders are numerically rare everywhere, save in some small isolated populations. So in order to create a regulatory framework for rare conditions we need to say what prevalence in the UK or world population will count as making a condition 'rare'. One clue is from the US federal Orphan Drugs Act, which defines an orphan condition as one which has a prevalence of less than 200,000 head of US population. This is a cut off of about 0.1% prevalence. We could define a condition as rare if it has this order of prevalence.

Another problem arises because of the dispersed nature of the subject population. Small numbers scattered across many countries make the identification of "cases" difficult in the first instance. Finding a researcher interested in the issues can of itself be a problem. Even if someone is prepared to take the question up, then defining which REC's could or should have any jurisdiction can then be an issue, which, in turn is often exacerbated by the case finding approach that is an essential feature of this type of research.

If we move from considering the isolated incident of a clinician referring a single case to an interested researcher/clinician, to the systematic collection of such cases in order to establish the underlying genetics, then further ethical problems can arise. This is especially the case where those with the condition may be invisible to the system due to the absence of a specific diagnosis (which it is the purpose of the research to establish). So how does the researcher advertise his/her interest and how can they link up with patients, their samples and their records when the purpose is not of immediate clinical benefit for those identified and, in effect, consent may only be obtainable after a potentially suitable subject has been identified?

A central question here is the consideration of any possible risks to the subject of these investigations, and whether these are any greater as a result of being included in a research study – or is the existing exposure that arises from being affected by a rare disease such that the additional risk from the research element is to all intents and purposes negligible? – remembering that this research will normally be conducted in an environment where the normal constraints imposed by the disciplines of medical confidentiality apply in any case.

Moving from the individual to the group suggests the desirability of creating registers of those affected and the question arises whether these should be complete or only contain details of those who volunteer. Clearly there is a public interest in ensuring completeness and there is also an individual interest in respecting privacy. It is not clear where the balance between the two should be struck – or whether there are any additional costs from being on a register above those which come by virtue of the rarity of the condition giving those affected a greater prominence or visibility.

Although many individuals with rare disorders display eagerness to be included on a register one cannot presume that all members of a family will share the same view or that the public interest will over-ride the private. Unaffected family members in particular may feel less inclined to participate; although the familial nature of genetic information may seem to impose a biological imperative on all members who are related, the family social map may in practice be very different from the biological one. Not all members of a family will be altruistic and willing to help. Other factors – anger, bad relationships etc can play a stronger role.

Doukas and Berg in "The Family Covenant" suggest that the geneticist or the family doctor takes on the role of "honest broker", helping families draw up a contract over what they will do in a range of possible outcomes – putting the framework in place before the stem breaks, so to speak. However, this assumes that such a contract can be made and kept. This is often not how families work and there may be a range of influencing factors, which determine their engagement with the research programme. These may include: -

- The urge to "do something" to feel that you are taking control, not being pushed along by your condition.
- The urge to help others in the same position
- The obligation felt to "repay" the support that you have received yourself.
- The hope that being part of the research process will give early access to treatment if and when it is developed.

Families affected by very rare conditions often seek to overcome the sense of isolation that they experience as a result of the widespread ignorance of their situation by coming together to form a patient support group. They do this to construct a common cause and to help to make sense of the problem, which affects them. Such a coming together helps to build a body of shared values based on trust and mutual understanding that can be stronger and more powerful than a formalistic "contract". Coming together in a group can also help to define goals for research by codifying the problem – turning it into a piece of "interesting biology" that will attract researchers and setting goals such as the development of a diagnostic test or even, eventually, some form of therapy. Of course, having transformed the perception of the problem into a scientific or industrial one of "interesting biology" or "marketable product", there is a risk that the original clinical problem and patient perspective will be lost: this is why it is very important to keep patients and clinicians involved throughout the research process.

Working as part of a group can also contribute to the management of expectation on the part of those affected – seeing the compromises that might have to be made between the interest of an individual and that of the group, dealing with the failure of research to deliver, or the delays that occur between the bright idea and its fulfilment.

Being part of a group can make the attainment of the "critical mass" necessary to interest sponsors and researchers in a particular disorder that much easier. A partnership between researchers, sponsors and patients can also help to address some of the difficult issues that may arise once the research is underway. Questions of strategy and approach – when and how to commercialise and how to resolve conflicts of interest – tend to work out better when all stakeholders are in a relatively equal relationship. (For a discussion of one of the issues see "The Ethics of Patenting DNA" Nuffield Council on Bioethics 2002.)

For RECs a partnership model can have significant attractions. REC's have an important role in protecting vulnerable subjects and will take steps to do this almost as a default position unless there are good reasons to convince them that another way of working is better. For rare conditions, networking, with a linked community of members who know one another is often a central feature of the research effort. The members will be interested professionals and also affected individuals and families who know and trust each other. The credibility of the researcher rests upon his or her relationship with the family, for if they do not trust him/her, then they will withhold their co-operation, effectively denying access to the network beyond the initial reference case. The Alzheimer's Society has been very

successful in bringing families and researchers together in making research decisions, whilst the Juvenile Batten's Disease Society (and many other groups for very rare genetic disorders) form a very close knit community which may provide a model that can be developed for broader consideration.

REC's have a legal responsibility to protect vulnerable subjects and the regulatory and governance framework for research reflects this. For those with rare disorders, the question of consent and especially the scope of that consent, is an issue that has to be addressed to secure their endorsement. Any guidelines that might be drawn up ought to enable answers to be made to a number of key questions to give authority to the researcher to proceed.

Such issues include: -

- a) What do we mean by a rare disease? Is it something, which is absolutely rare or just rare in the UK? (The EU defines a rare disease as being one with a prevalence of less than 5 in 10,000 EU citizens). This is probably too common to warrant special arrangements being made. Any dividing line is going to be drawn at an arbitrary point, but the issues really begin to bite in cases where fewer than say 250-500 people are affected throughout the UK (equivalent to a prevalence of 1 in about 100,000).
- b) How are issues relating to the interest of young children, babies and the unborn to be resolved?
- c) Are genetic diseases a sub-category of all orphan diseases, or does their specifically familial nature create special issues that do not apply elsewhere?
- d) Do rare genetic diseases fit within current regulatory arrangements (suitably modified) or are they a special case requiring different treatment? If the latter is the case, does this resolve the difficulties or create more problems by shifting these to another part of the research spectrum?
- e) How are dissenters to be accommodated?

It is necessary to try and develop ways of working that are inclusive and which encourage participation, especially in genetics where family participation is often integral to the resolution of the research question.

Discussion

The preceding sections have emphasised the nature of the regulations set in place to protect patients from the risk of exploitation or undue pressure to participate in research, against their better judgement or their interest. This draws its legitimacy from a concern to base research on a sound ethical foundation. However, in striving to act ethically in the prevention of abuse, the issue of the ethical consequences of not doing a particular research project is often overlooked. In this respect the system of research regulation can be seen as paternalistic and patronising to families with rare genetic disorders. It has the effect of preventing research, which they feel to be necessary and desirable, from proceeding.

Given that much of the research into rare genetic disorders is funded, at least in the initial stages of characterising the condition and its underlying biology, by monies raised from the public by patient groups, the time taken to get approval from ethics committees for a project to proceed can often consume a disproportionate amount of the total resources available. Examples of 10-12 months of a 3-year project being taken up with this were quoted. This makes rare disease research disproportionately expensive when compared with that into more common conditions, where ethics committees are familiar with the issues and can act more swiftly. Patient groups wish to see research under way. Those with rare



disorders often have problems attracting the interest of able scientists who may be unwilling to commit their career to a possibly obscure field of interest where there is a reduced opportunity for progression, even without the regulatory system putting additional barriers in their way. In addition to providing funding, patient groups provide access to their members – a valuable "pool" of participants that could not easily be recruited by other methods. However, this lays a duty of confidentiality on patient organisations. They cannot let (potential) researchers just travel through their records in a speculative "fishing trip". Some organisations (e.g. the Tuberous Sclerosis Association) ask researchers for their Patient Information Sheet, which they then circulate to relevant individuals or families with the suggestion that they contact the researcher directly. Once the contact has been made any further involvement comes under the scrutiny of the Research Ethics Committee. If the individual/family does not wish to be involved they do nothing, they are not approached again about the particular project and their confidentiality remains intact.

It is accepted without question that patients have an absolute right to refuse to participate in research if that is their wish. Post Alder Hey, the issues raised by limited consent are much more complicated. It is not clear, for example, what is the position of historical samples and the uses to which they may be put without a renewed consent being obtained from the next of kin. In this context, it is relevant to consider what might constitute a "sample". Is there a line to be drawn between histological slides and the retention of whole organs? If, so where?

The US Bioethics Association holds the view that it is unethical not to use samples for the purpose for which they were originally obtained when given for research. The legal position, however, is unclear. It would seem that the samples become the property of the persons doing the work (the researcher) if they were obtained in good faith, but the Human Tissue Act of 1961 gives the surviving spouse rights of veto over the use of post mortem samples, that over-ride those of close relatives. Thus a husband can prevent testing for breast cancer genes in his deceased wife's tissues even if his daughters want (and need) the information in order to make significant health decisions. The converse could also apply and the daughters could veto, even if the sponsor wishes to agree to testing.

With ante-mortem samples the position is different, and the views of the donor have to be respected. However, the current consultation by the Retained Organs Commission envisages a single regulator having the final say over the regulation of uses to which post and ante-mortem samples can be put.

In stigmatised conditions (e.g. mental health problems) family consent for research is sometimes an issue that generates considerable sensitivities.

When considering samples from overseas there needs to be consideration given to whether or not the absolute rarity of the condition in question gives rise to a "special case" situation. The Human Genome Diversity Project ran into difficulties because of a lack of consideration about the sensitivities of those being sampled, which resulted in the project being delayed for several years. But the issues involved in normal population sampling of different ethnic groups (which centre around racial sensitivities and ethnic differences in disease susceptibility) should not be confused with those for people suffering from rare disorders. A system of informed consent is essential, but separate ethics committee permission for single samples from multiple international sources is unworkable.

Even when research is confined to the UK, securing ethical approval is a complex process. Local research ethics committees have a responsibility for patients in their area. They want to have a say over research issues and to ensure that the individuals investigating the patients are responsible, bona fide researchers. As has been indicated above, research into rare genetic disorders often happens in a context where the clinical/research interface is blurred. Whilst it is clear that the provision of a blood sample by a clinician does not in itself require LREC approval, current practice would indicate that any further involvement – such as the provision of clinical information of the type essential for the successful undertaking of the research and without which the sample is of little value – does require LREC approval. Yet is simply sending a sample for the purpose of diagnostics really research as far as the sending clinician or patient is concerned? Or is it rather part of best practice in the clinical management of that doctor's patient?

Clearly the LREC system is not set up to deal effectively with rare disease research that falls in the area of "extended clinical investigation" where research techniques are essential in addressing individual patient's needs as well as contributing to the resolution of broader questions of fundamental scientific understanding. However it is not clear if and when consent given by a patient for a clinical investigation of a presenting problem ceases to be adequate to cover research, or when the emphasis of the ongoing investigation shifts from a primary focus on clinical care into one of basic research. A case can be made for an "evolution of consent" which covers a range of possible outcomes (including the retention of samples for future re-use that links with the original purpose for which they were taken). Care must be taken in securing this evolutionary consent that it is genuine and that the paper work needed to secure the audit trail does not get in the way of genuine understanding on the part of the patient as to what is being proposed.

If we accept that the boundary between clinical care and research in the case of rare genetic disease is blurred, then it may be helpful to consider the analogy of detective work as compared with basic research. For the referring clinicians and the patient the need is for an answer. That answer may be known somewhere already or it may still await discovery. Clearly there is no point in undertaking research if the answer is already known and this is where the detective work comes in. In order to find that which is unknown, it is first necessary to eliminate the known but the patient does not care if the answer comes from the pages of a journal or the printout of a gene sequencing machine. The two are interlinked, but one does not need ethical approval, whilst the other does. Nor is the process a linear one. Detective work and research often overlap and leap frog one another in the search for a result. It is bureaucracy that draws the distinction.

Research laboratories operate in a different context from clinical service laboratories in the NHS. Rightly the NHS does not fund non-approved testing, so for research labs the obligation is to get REC approval prior to embarking on investigations. But the distinction, as we have seen is blurred, so the question becomes one of establishing the appropriate level of scrutiny that will legitimise and protect without stifling the emergence of new knowledge.

There would appear to be a number of key elements to any scrutiny procedure: -

- Firstly, the person setting up the research should be responsible for securing any necessary approval.
- A degree of trust in the local "sender" of the samples (especially when they are from overseas) is necessary over matters of individual consent.

- The research "hub" needs to have sound clinical links with the referring physicians.
- Bureaucratic issues arising simply as result of geographical separation between researcher and referring clinician should not themselves create artificial barriers.
- The outcome should be an important factor in the decision as well as the process by which it is reached.
- Any adequate scrutiny procedure will have to be sensitive to the necessity of the close relationship between clinical practice and research. There may in some cases be very little difference between the two and in these situations to regulate research is also at the same time to regulate clinical practice and accessibility to diagnosis.

Genetic diagnoses of rare disorders often take a long time. This is a reflection of the absolute rarity of the conditions and the difficulty in generating a sufficient critical mass of samples to allow samples to be tested against hypotheses. To reflect this, care should be taken to ensure that consent remains valid if new investigations are within the original scope of the inquiry. New consent should not be needed for each new test of a candidate gene for example. Provided it was clear in the initial consent that the research would be testing for a (unspecified) number of candidate genes the original consent will suffice. The individual must know what is to happen to the sample, but this does not necessarily extend to receiving a list of the genes being tested. Unless new actions (for example undertaking an investigation into a different condition) have new implications for the subject or the family that they are unaware of then the initial consent is not undermined and no new consent needs to be sought. This is an issue for the REC insofar as it needs to agree the information given to patients and determine whether broad consent is valid. Explaining to patients about the nature of the research process is a communication issue, not a matter for RECs per se. Whilst a "blind eye" may be turned to the issue of re-consenting for each subsequent DNA analysis this inconsistency creates tension for researchers and renders them potentially vulnerable.

LRECs have a "duty of care" to patients, but this duty should not be exercised in a stereotypical manner. There is a case in studies involving patients with rare disorders for the LREC in which the researcher(s) is based to take lead responsibility, with others delegating their responsibility to this lead agency. The use of electronic communication for (e.g.) consent forms, information about the project etc makes this entirely feasible and should help to ensure consistency as a given LREC would generate a body of specialist expertise relevant to the research interests of clinicians interested in rare genetic disorders in their area.

The brief of LRECs might also be broadened to include the establishment of broad principles of good practice in this field, as many research projects in this field raise very similar issues. The challenge for LREC members (or for MREC perhaps?) would be to develop principles that were not so general as to be bland or so draconian as to be unworkable. A tiered structure of approvals might emerge as a result with, for example, the simple sending of a blood sample needing no consent other than that normal in clinical investigations, whilst a clinical trial, with the higher level of risk that would necessarily be incurred, needing something akin to the present structure.

No "one size fits all" model is likely to be sophisticated enough to cover the range of eventualities that will be encountered. For example, the willingness of apparently unaffected relatives to be tested is likely to be influenced by a number of factors, including their closeness (both biological and emotional) to the index case, as well as the nature of the disease being tested for and its implications for the sample donor. This is an everyday issue in clinical genetics where there is no research element to the

obtaining of samples for analysis and well worked out protocols are available to guide the profession addressing these issues. LREC's do not need to re-invent the wheel, but should be content to ensure that existing good practice is applied where relevant, especially where the researcher is also a clinician and so is bound by the relevant codes of professional conduct. His or her duty of care to the patient is to ensure that the appropriate range of tests is undertaken to facilitate diagnosis and/or treatment – in other words to act as a competent professional within the scope of his or her responsibilities and competence. Once a duty of care has been established between the researcher and the patient, whether or not this involves an intermediary clinician then the obligation is upon the researcher to discharge this duty. Where the researcher is not a clinician (e.g. a scientist) a similar professional responsibility ought to be seen to exist although this should also involve an intermediary clinician. The responsible professional also has a duty to refuse unreasonable requests, so the balance of responsibilities ought to be a manageable one.

Whilst similar lack of clarity about the boundary between research and clinical care may exist in other medical specialties (e.g. innovative surgery) there is one valuable safeguard that will act as a brake on the enthusiasm of researchers in the field of rare genetic disorders. This is the fact that, ultimately, for the research to proceed the families of those at risk must see it as valuable and necessary. Carrying out linkage studies requires access to family members other than the index case. If they choose not to participate for any reason the clinician has no means to coerce them. They simply do not attend for the provision of the necessary samples. The index case is the channel for the recruitment of his or her relatives and the clinician is entirely dependent not only on securing his or her consent to the research in the first place but also on his or her ability to recruit family members. This is the fundamental underpinning for the research. Without it progress is not possible. This needs to be reflected in the regulatory framework. If it is, then progress can be made; if it is not then there is a very real risk that the framework will stifle, not succour research that families want to see happening. This may leave them in ignorance when new knowledge might have furthered their understanding of the situation in which they find themselves, and about which they might have been in a position to make decisions and take more control of their lives.

Disclaimer

This is a subjective report of a workshop. Inevitably it is partial in that it is not a verbatim account and also with respect to the points identified and the weight placed upon them. Whilst every effort has been made to reflect the content and the tone of the discussion any errors of fact or interpretation are the author's responsibility alone.

All participants at the workshop were there in a personal capacity and were not speaking on behalf of any institution or organisation with which they might be associated. The workshop was conducted under the terms of the Chatham House Rule.

**Genetic Interest Group
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