



Research and Rare Genetic Differences:

Frequently Asked Questions

An information leaflet for members of Research Ethics Committees

Produced by The Genetic Interest Group, The Oxford Genetics Knowledge Park and The Ethox Centre

Summary of key points arising from this leaflet

- Appropriate ethical governance provides valuable protection for researchers and patients/participants, and underpins the integrity of the outputs of legitimate, high quality biomedical research.
- It is in no-one's interest to try and create a "one size fits all" model of governance, where this would be inappropriate.
- The views of patients and families regarding the desirability of undertaking any proposed research and the acceptability of any risks associated with it should be taken into consideration when making the decision to approve or reject any proposed project.
- The regulatory regime should be as light as possible concomitant with the requirement to ensure quality, appropriate methodology and the protection of vulnerable subjects.
- Preventing or delaying research is not necessarily the best / or most ethically positive outcome. The costs / benefits of a REC decision to reject must be weighed alongside the costs / benefits of an REC decision to proceed, in the best interest of those with most to gain / lose namely the patients and families with the conditions under investigation.

Research Ethics Committee (REC) approval is a valuable safeguard for researchers and patients alike. Satisfying a research ethics committee helps to ensure that researchers have thought about the implications and the impact of what they are proposing to do, and so reduces the risk that potentially vulnerable patients will be disadvantaged by their participation in a research study. REC approval provides reassurance to patients and other volunteer participants that the proposed study is ethically sound, thereby maintaining confidence in the integrity of the researcher, and of the study, but also in the process of research itself. In addition to, and as part of, protecting patients, research ethics review facilitates good quality research.

In research into rare inherited disorders, the process of securing ethics committee approval for a proposed study can however sometimes prove disproportionately burdensome and this can, in some cases, undermine the viability of good-quality research.

This is particularly the case where such research is funded by patient groups. In the eyes of many such patient groups, who have had to work hard to raise funds to support research into “their” disorder, the bureaucracy of the REC process and, the questions asked by some RECs, can seem inappropriate, appearing to demonstrate either misperception by the REC about why what is proposed is proposed, or the application of an ethics framework more appropriate to a very different kind of research e.g. a large clinical trial, but inappropriate to smaller studies.

To help clarify this situation the Oxford Genetics Knowledge Park and the Genetic Interest Group (GIG), the UK alliance of charities and support groups for all those with genetic disorders, convened a number of workshops to explore this issue, the first of which was funded by a symposium grant from the Wellcome Trust. These workshops, which included patients, researchers, research funders, members of research ethics committees, ethicists, social scientists and medical lawyers, generated a list of “frequently asked questions – FAQ’s” that were indicative of the issues which RECs have seemed to find challenging when evaluating proposals.

This booklet has been written to help highlight some of the common questions and concerns that RECs raise when looking at research proposals relating to genetic disorders. We hope that this document will help RECs to answer some of these questions.

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Frequently asked questions

1. Is genetic research into rare disorders different?

The major difference between genetic research and other types of biomedical research, involving patients with rare diseases, is that it may have implications for close blood relatives. It is important to remember, however, that it is not the case that DNA analysis is the only route to information with these implications (a genetic diagnosis can be reached in many cases by other routes e.g. clinical or other investigations such as electrocardiograms, biochemistry, dysmorphology etc.). Whatever its origin, it remains the case that knowledge of an inherited condition present in one family member can have an impact on their relatives, a risk that is not normally susceptible to reduction or elimination through the actions of the person initially diagnosed (unlike infectious diseases, for example).

In addition to the differences between genetic research and other non-genetic types of research, there are also important differences between genetic research in general and research into very rare genetic disorders. These differences tend to emerge in three main areas: the close relationship between clinical practice and research, the difficulty of anonymisation due to the small number of people with the condition and, the methodological requirements of working with very small sample sizes. Paragraphs 2, 3 and 4 below address these issues directly.

Apart from this however, most research into rare genetic disorders is not fundamentally different from other types of biomedical research, and it should be judged to the same standards – although not necessarily by the same processes.

2. When does clinical practice become research?

Good clinical practice in the case of families with rare genetic diseases inevitably involves detective work. A tentative diagnosis may be made, and then a range of investigations commissioned in order to confirm or refute this. If the condition remains undiagnosed, then the question is, “If it’s not a, b, c etc, then what is it?” and a sample can become a subject for hypothesis testing. Whilst this may seem like a “fishing trip”, pulling out genes apparently at random to see if they are the one sought, this is not the case.

For example, a mouse model of the disease may have indicated promising areas to search and test, or an emerging pattern amongst samples collected over time may provide pointers to the right part of the genome to analyse. The only way in which candidate genes can be evaluated is by examining them individually for causal links or associations with the condition in question. Such investigations are a necessary route to answering the clinical question that was originally posed,

and one that is quite frequently successful although the process can take months or years.

It is often felt by families, and individual family members, that it is in their interest that such “detective work” is done. They are eager to move to a situation where a definite diagnosis can be made in order to allow them to understand what has happened to them and take actions wherever possible. That is, to secure a greater degree of control over their own lives and those of their children.

3. What about consent?

Because of the blurred boundaries between clinical investigations and research, consent can appear to be a difficult issue for some RECs. When establishing consent requirements, the following should be borne in mind:-

- 3.1 Generating sufficient samples for a study can take a considerable time. People with a rare disorder do not live within one small geographical area, nor are they all born within a narrow time frame. Yet all share a common desire to secure a diagnosis for the condition affecting their family. For this reason consent has to be open ended with regard to the genes to be analyzed. Few, if any, families want to be re-contacted time and again to be asked if they consent to another candidate gene being examined. Indeed, to require this can place an unacceptable burden on them and also consume a disproportionate quantity of scarce funding (It is important to stress that this does not mean that any research at all on their sample is acceptable, i.e. that not compatible with the initial consent).
- 3.2 Families with rare disorders have first-hand experience of the impact of their condition. They are often highly motivated to participate in research, seeing it as a way of taking control of their disease rather than being controlled by it. As a consequence, not all of them want or need to be told in detail what is proposed by a researcher. It is perfectly possible in some cases, for them to be informed enough to give valid consent without an in-depth explanation, should they not wish it. This does not of course mean that it is acceptable to deny research participants access to important information about their participation in the study but it does mean that the purpose of providing information (i.e. to enable the participant to make an informed assessment of whether or not to participate), should be kept in mind.
- 3.3 An important part, perhaps the most important part, of the consent process is that patients and family members should be completely free to refuse to

be involved in a study. Researchers need to be aware that family pressure – either to opt in or to opt out of a study can be considerable, and efforts should be made to reduce any possibility of the coercion of unwilling subjects and check with physicians providing samples (if this is not the researcher him/herself) that participation in the study is truly voluntary.

4. How can anonymity be guaranteed?

In many studies the small number of families affected and the fact that very few clinicians or scientists are interested in the particular disorder means that most affected families are well known to the academic and clinical community. Indeed many researchers have long-standing links with families either directly or through the relevant patient support group. In such a situation, anonymity within the circle is impossible to guarantee. Indeed it may be undesirable in many cases as it is necessary to track back to the families providing the original samples in order to test out candidate genes etc. This may also involve other family members – for example when checking if a mutation is a novel one or if there are others potentially at risk. This can be important clinically, and those at risk ought to be given the opportunity to know if they wish. RECs should not require anonymity to be preserved if this is unrealistic, undesirable or contrary to the research subject's expressed wishes.

Whilst it should be recognised that anonymity isn't always possible, researchers should take care when writing up their studies to effectively anonymise their findings.

5. What sort of genetic research is proposed?

Not all genetic research is the same. Large-scale population studies such as the UK Biobank look for statistical correlations between observed genotypic patterns and common complex disorders. Epidemiological studies are seeking population variations. An example of this is the International Haplotype Mapping project, which is seeking to identify genetic variations between populations across the world. Pharmacogenetic studies are looking for evidence to indicate susceptibility to disease or for the better targeting of pharmaceuticals. In all these the normal standards of consent and confidentiality that are applied to any large-scale study are relevant and appropriate.

However, small-scale studies, seeking the gene “for” a given rare disorder, are different as indicated above (see 2 above), and it would be inappropriate to apply the same requirements to them. Some would say it would be unethical to do so because of the likelihood of impeding progress were this to be required.

6. What do we mean by “genetic” information?

Whilst the most obvious source of genetic information is the direct analysis of DNA, it is not the only route by which it can be deduced. RNA analysis also reveals information about heritable risks, as does the study of family history and clinical investigation. Biochemical tests (for example for the detection of PKU (phenylketonuria)) and dysmorphology also provide routes to a diagnosis of genetic disease. The key issue is the nature of the information revealed, not the route by which it is arrived at. DNA should not be artificially separated from other types of biomedical information unless compelling reasons can be given for treating it differently.

7. Are there any follow-on consequences?

As has been indicated earlier, information about highly penetrant single gene disorders can have consequences for other family members – including the revealing of a hitherto unsuspected genetic risk (or unsuspected absence of risk). In considering proposals RECs should satisfy themselves that the researcher and the referring clinician (where these are different) have given consideration to their duty of care to individuals who might find themselves in this situation, and that arrangements are in place to provide appropriate clinical support to individuals who may discover themselves to be at risk or affected – i.e. if they move from being a “research subject” to being a patient through the acquisition of unlooked for knowledge. This situation arises frequently in the course of normal service delivery and where this happens in the research context, best clinical practice guidelines should be applied.

8. Are people expecting too much from research?

Families in which a rare genetic disorder is present can sometimes invest too much in the outcome of a given research project. Whilst hope of a cure is central to the ability of some families to keep going, care must be taken to avoid raising unwarranted expectations from any single project. This is not specific to genetics, but the public view of genetics research can afford disproportionate power to the gene. While the identification of the “gene for” is an important milestone it should not be construed as being tantamount to a cure.

9. Whose DNA is it?

For the patient the benefits to be derived from the research are in terms of improved clinical care and greater understanding following the feedback of results. The normal “gift” relationship applies to samples used in researching rare

genetic disorders as in other types of research. Should the question of patenting and intellectual property rights arise, the apportionment of these should be clear beforehand and appropriate consent secured for whatever is proposed. In this respect a partnership approach to the design of research can be particularly useful i.e. the involvement of patients or patient groups at an early stage. This is no different from other types of medical research.

10. How do we strike the right balance between protection and inhibition?

This is an issue where a sense of proportionality is essential. Families with rare genetic diseases usually want and need research to proceed as quickly as possible. They are often part of a small community of families known to each other and who share a common purpose. If their collective view is that a line of enquiry proposed is reasonable and worth doing then this should be given due weight – particularly as the funding for the research has often been raised through the efforts of these families and they have approved the grant that makes it possible. To make the research more difficult than it needs to be can exert a disproportionately large negative impact on the morale and motivation of families and researchers alike. In granting approval to projects, RECs should take account of the possibilities that may arise in future. For example, new technology may permit the reanalysis of old samples and the yielding of new, clinically significant information that would be of immense benefit to the families concerned. To be able to benefit, samples must retain a link to an identifiable donor. This approach differs from an epidemiological one where the re-visiting of old samples is for population benefit only – something very different.

On the other hand, researchers and RECs do need to be aware of the need to protect vulnerable family members and other vulnerable research participants e.g. from family pressure to participate. The key aim here should be for RECs to aim to both protect vulnerable family members and at the same time to facilitate ethical research.

RECs should also be aware of the requirements created by the physician's duty of care to his/ her patients and consider whether conflicting pressures are created by the research protocol and the demands of good professional practice as stipulated by legislation, the GMC etc. In such research, professional guidelines and the law will always be paramount because ultimately, it is in the context of the doctor (or nurse)/patient relationship that consent is either properly obtained or not.

11. Can we rely on research findings?

By their very nature research findings are more tentative than those derived from genetic testing carried out in NHS molecular genetics service laboratories. They are for example, not subject to the same quality-control mechanisms. Nevertheless, the information revealed can still be helpful to families, and RECs should make sure that sufficient attention has been given by the researcher/referring clinician as to how the tentative nature of the information revealed can be disclosed to the family so that they can make an informed judgement about its utility, and not simply take it on trust as either complete or totally accurate and reliable. Once the research has been completed the RECs should look for an intention, if appropriate, to submit the test to the UK Genetic Testing Steering Committee for approval for clinical service use so clinicians can use it with confidence.

12. How long should we allow consent to continue?

With very rare genetic diseases there may only be a handful of cases in the country, and not many more identifiable from further afield. The consequence of this is that it may take some years before sufficient samples are collected to permit the emergence of clinically relevant information. During this period children who have provided samples with the consent of parents may have become "Gillick competent" or even become adults. Where contact with the family is still possible it may be appropriate in some circumstances to secure consent from the individual if he/she is able to provide it. Where this is impossible, it may be appropriate in some circumstances for the proxy consent from the parent to be presumed to be still valid in order to avoid undermining or rendering the project non-viable or disproportionately bureaucratic and cumbersome, thereby hindering progress towards a greater understanding of these rare genetic diseases. RECs and researchers need to think carefully about this possibility when initiating a project and develop an appropriate policy. This will especially be the case where the findings of the research are to be fed back to the families at some point in the future.

Conclusion

Families affected by rare genetic disorders are not there by choice. An event over which they have no control has made them members of a club that they didn't want to join, and which they would wish to leave. Few, if any, people choose to join a support group for those with a given rare genetic condition out of curiosity or because they are looking for something to do. Membership arises as a result of the condition being in the family.

For most families the way out is through the development of an effective therapy – preferably one that prevents the disease or cures it before it does too much damage. The way this will be brought about is through the pursuit of high quality targeted research. The role of the REC, to both patients and researchers is to set standards and regulate practice – but these must be appropriate, proportionate and in line with take into account the wishes of those who have most to gain from the successful pursuit of research and its outcomes, and most to lose if this is thwarted: naturally, the patients and families themselves.

Many of the difficulties arising in research ethics review might be ameliorated if researchers, funders and patient groups were, wherever possible, to work towards a partnership model in which patient groups, funders, researchers (perhaps in liaison with RECs) were to explicitly work together in the design of research projects.

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