



Minutes from Research Approval and Rare Genetic Disorders

Workshop held 30th April 2003, Oxford.

Genetic Interest Group (GIG)

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GIG is a registered charity (Number 803424)

Introduction

This meeting was a follow-up to an event held in London in April 2002, at which researchers, clinicians, ethicists and patient group representatives discussed some of the difficulties posed by the existing regulatory frameworks for research into rare genetic disorders. At this meeting a second group of participants, with a greater bias towards patient-group funders and directors of research, sought to take the discussion forward by amplifying, modifying and critically examining the findings of the first meeting and making suggestions for a framework that would work for rare genetic disorders.

1. Summary of Previous Workshop Introduction

Two main themes of the previous workshop were isolated:

- 1) For the rare and especially very rare genetic disorders it is often difficult and sometimes impossible to distinguish between clinical and research investigations. However, if the work is categorised as research, a new set of regulations have to be met.
- 2) Many of the regulatory frameworks for research were designed with large-scale studies in mind. Some of provisions, e.g. those covering confidentiality, do not make sense for studies of rare genetic disorders where the individuals are known and may also need to be known to the researcher. In some instances the researcher is the clinician looking after the patient. Other provisions, when applied in a uniform way, can be disproportionately burdensome for investigations into rare disorders, which, while small in scale, may involve patients and families scattered across the country.

At the previous meeting, these two points were expanded upon through discussion of the 1998 Advisory Committee on Genetic Testing (ACGT) guidelines.

“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 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 question.

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 patients 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 “medicalising” 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.”

Additionally, for many of the patients and the groups that represent them, the issue is not simply a question of the scale of the research projects: the emphasis in guidelines is on protecting patients / research subjects, and less on encouraging research, which is the main priority of many of the groups. Similarly, while ‘detective work’ or ‘fishing expeditions’ for candidate genes might require very careful handling from the point of view of satisfying regulations, for the patients involved this is often an unproblematic research activity.

Discussion

A participant noted that in the case of her group, many people had in fact been diagnosed because another family member had died of the condition. It was often very high profile, so keeping anonymity would be impossible.

“Getting a diagnosis or understanding of the condition is what the patients want”

Some of the other points raised with regards to the obstacles involved with Ethics approval and research were: -

- When dealing with rare genetic disorders what may start out as a clinical study becomes research as well. The nature of the regulations can make this transition very difficult.
- Projects are being moved between MREC’s as some are busier than others. This adds further time to the approval process.
- It can be crucial for charities to receive ethical approval as grant giving bodies often require this approval in order to confirm their funding.
- As the forms are geared to larger programmes they can therefore be difficult to fill in for the rare disorders.
- Participants felt that there is a need to have people on the ethics committees that have a degree of understanding about genetic conditions.

One participant noted that it had taken nearly a year to receive ethical approval for a research project, which leaves only a few months for the research. This process eats up the money raised by charities for the research. *“We are not fulfilling the wishes of the public who have raised the money for the research”* LREC’s sometimes exceed their powers and demand changes that MREC’s should cover or take different stances in different places. On applying for approval to 18 LRECS, 13 approved the research

and 5 were very difficult, for examples they asked the charity in question to amend wording on a national leaflet.

Clinical Vs Research

One context in which it is possible to isolate the point at which the transition from clinical investigation to research takes place was suggested: if the wider family were not involved initially, and it became necessary to request say blood samples from them to test for the frequency of candidate genes, then that would indicate that a line had been crossed from one to the other.

It is extremely easy to go from clinical to research when working on such rare conditions as mentioned previously. For example if you are looking at a new mutation in a patient a medical professional may want to contact family members to see if they carry this same mutation, and may also be at risk. Although research may not necessarily be delayed, as the work was service provision to start with, it can hold up the potential benefits to families, who in most cases have no problem with participation in the search for candidate genes

Some Research Ethics Committees dictate that the number of projects a young person participates in is limited. This risks limiting research without offering protection against an obvious harm in many cases.

Photos

This can be a delicate area, as photos can be used for many years and can also be used in the public domain. Some people felt that this was inappropriate and that photos should only be used in the context for which they were taken, eg for research. It was also felt that there should be some time limit on the use of photos, as parents may find it distressing to see pictures of a deceased child being used. However, it was also pointed out that many people are very happy to have their picture used in research and publications; indeed, that they positively wished to see their picture widely in print.

2. What Would a Framework That Worked For Rare Genetic Disorders Look Like?

It is unlikely that major changes will be made to the structure of the current system of ethics review in the short term. The second part of the discussion therefore focused on improving the system that is currently in place for ethical approval.

Teaching and Education.

It was felt that the best way to improve the conditions for research into rare conditions was to put effort into educating and training the members of the research ethics committees about the problems raised by research into rare disorders, and into discussions with scientists about how best to navigate the system. Several methods were proposed

- Training for ethics committee members about genetic conditions.
- Contact the centres that organise the training that committee members receive now (eg Kings College, AREC, Keele).
- Training for the groups applying for research approval, in order to help them minimise the time spent.
- Encouraging the Ethics committees to see the special issues arising in such research concerning the close relationship between clinical practice and research.
- A need for more specialist knowledge to get projects through the regulatory process
- Having someone familiar with genetic issues on Ethics Committees makes a difference to the committees ability efficiency in dealing with genetic applications
- Opportunities for feedback to Ethics Committees. Perhaps an event to air the difficulties those conducting clinical / research investigations into rare genetic disorders experience.
- More flexibility in the guidelines. Could they incorporate “guidance” to organisations?
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Empirical Research

There is a need for research to ascertain the size of the problem and its nature. This could be research carried out by academic researchers e.g. in the knowledge park environment. Or it could take the form of a survey sent out to the membership of GIG. In either case it would be important to ensure that the methodological aspects of the research were sound. Members of the Oxford Genetic Knowledge Park would be willing to help with this. GIG would be willing to coordinate the research itself. Some of the research questions discussed included:

- How many projects are failing or not getting started?
- What specific experiences and issues have arisen?

- Is there a distinction between the problems caused by ethics review per se and the issues specifically caused by rare conditions?
- What are the attitudes of patients to more open forms of consent, allowing further testing and research?
- Should there be a limit on the number of projects any individual can be involved in?
- How should we balance the desire for good research to happen against the desire to ensure research is adequately regulated?

Next Steps

Further research and writing should be done on the clinical-research interface in genetics and its implications for rare research. Mike Parker said he would be interested in doing some of this, perhaps as part of his work for the Oxford GKP in collaboration with GIG and Ed Blair.

Generally, Mike Parker, Alastair Kent, John Gillott and Melissa Winter will meet to formulate some concrete proposals to take the work forward. These will be circulated for discussion and approval to the attendees of the two workshops held so far.