

Chapter 7

Genetic research on mental disorders: ethical and legal issues

Introduction

7.1 So strong is the opposition of some people to genetic research into mental disorders that they regard it as ethically inappropriate. This viewpoint appears to be based on a reductionist interpretation of such research (paragraphs 1.4–1.7). If this was indeed the rationale for undertaking genetic research, it would be of considerable concern to the Working Party. In practice, however, this does not seem to be the case. On the contrary, we would construe it as unethical to exclude people with a mental disorder from the possibility of benefit arising from an improved understanding of mental disorders. There is, nevertheless, a need to consider in detail how best to safeguard individuals who may participate in such research.

Consent to involvement in research

7.2 A request for consent to participation in research is an expression of respect for persons and for human dignity; as with any procedure this extends to a legal requirement when body contact is involved. If harm were to follow from research not involving contact, in the absence of the participant's valid consent, this too could be an invasion of legal rights. In this chapter the aim has been to draw out the specific issues relating to research into the genetics of mental disorder.

7.3 Most people with mental disorders will be competent to consent on their own behalf to participation in research. There is, in law, a presumption that an adult has the capacity to make decisions unless there is evidence to the contrary.¹ In relation to research into the genetics of mental disorder, the competence of most other participants to consent is even less likely to be in doubt. Most relatives, for example, will not themselves have a mental disorder nor be likely to develop one and many volunteers are unlikely to be patients in any sense other than that they are registered with the National Health Service.

7.4 As noted in Chapter 5 (paragraphs 5.22–5.27), an individual's capacity to make a particular decision will depend partly on the complexity of the issues and partly on its risks and benefits. In considering the risks and benefits of participating in genetic research, a person with a mental disorder will face similar issues to those with any other kind of disorder. In most cases the personal benefits are likely to be small, at least in the short term, and advantage is most likely to be conferred on sufferers as a group. Physical procedures involved in genetics research are generally not hazardous, involving perhaps the withdrawal of a small sample of blood from a vein. It is now feasible, although less common, to take a sample from the lining of the mouth (a sample of so-called buccal mucosa), which may be obtained with a mouthwash or a gentle scrape of the inside of the cheek. For those with a mental disorder, and indeed for some with a physical disorder, the attendant structured interview and family study may, however, be psychosocially intrusive and even hold the potential for creating difficulties and tensions within the family.

7.5 Consent to participation in research as opposed to treatment may raise special difficulties because, by definition, the risks and benefits of any given procedure are unlikely to be fully known. In some therapeutic research, the likelihood of immediate benefit is at its highest. For the rest, although the research may be likely ultimately to bring benefits for the class of people to which the putative participant belongs, it is unlikely to carry any direct specific benefits for individual participants. Benefits such as a sense of contributing and increased attention should not be underestimated, but these, like placebo effects, are non-specific. Such non-therapeutic

¹ For England and Wales, see the Law Commission (1995) **Mental Incapacity**, No 231, HMSO, London.

research may be most likely to attract legal problems (paragraphs 7.11–7.18). Some have argued that the capacity for consent to research in this field should be of sounder quality than the capacity to make other health care decisions. Others argue that the approaches to clinical research and clinical practice should be similar and should not be needlessly burdensome for patient or participant.²

- 7.6 Either way, the capacity of patients is usually a matter of subjective judgement on the part of, at best, someone who is primarily working in the interests of the individual. In the case of someone with a mental disorder, this is usually the consultant psychiatrist but, if the consultant is also the researcher, then capacity should be judged by someone independent of the research team. There are now tested methods of assessing such consent more objectively,³ but they are time-consuming, and therefore also costly, and raise further questions about when and if they should be applied to research. It is more than likely that their widespread use would inhibit research by proving too costly for researchers and too burdensome for potential participants who might decline to continue. This might indirectly damage the prospects of the group of people with the disorder under study. It may be, however, that specific tests of competence could be of value in very difficult or contentious circumstances.
- 7.7 For many individuals with mental disorders, mental capacity varies and it is desirable, and almost always possible, to involve them in relevant genetic research at a time when they are competent to consent on their own behalf. **The Working Party recommends that individuals who are intermittently competent should only be approached about participation in research when competent.** In these circumstances, the problems in obtaining informed consent from individuals suffering from psychiatric disorders are not qualitatively different from those encountered in research on other medical disorders. Unaffected relatives or unrelated participants included as control groups also need to give informed consent to participation in research.
- 7.8 Informed consent may be given verbally or in writing. Commonly, ethics committee requirements in this regard depend on the nature of the research. Invasive research invariably requires written consent, while for non-invasive research, such as interview-based studies, verbal consent alone has sometimes sufficed given the consent implied if the subject continues with the interview. Although genetic research tends now to be minimally physically invasive, **the Working Party recommends that written consent for participation should be the general rule.** Some professional and scientific journals now require written confirmation of the nature of the consent to participation in the research.
- 7.9 The need to obtain genuine consent was discussed in Chapter 5 (paragraph 5.25). Particular circumstances may impede the process of obtaining genuine consent. There may be some grounds, for example, for believing that in the past, prisoners have been overtly or covertly coerced into taking part in research. It is particularly important in circumstances where potential participants in research may be confined in an institution, or may be detained patients, to be clear that participation cannot and will not be used for bargaining. Another concern in relation to freely given consent is the issue of personal reward. Small fixed, or individually calculated, sums of money for time spent are sometimes offered to individuals participating in projects. With respect to each funded project, it must be a matter for careful ethical consideration.

² Tobias J and Souhami R (1993) Fully informed consent can be needlessly cruel, *British Medical Journal* 307:1199–201.

³ Appelbaum P and Grisso T (1995) The MacArthur Treatment Competence Study: I Mental illness and competence to consent to treatment; Grisso T, Appelbaum P, Mulvey E and Fletcher K (1995) The MacArthur Treatment Competence Study: II Measures of abilities related to competence to consent to treatment; Grisso T and Appelbaum P (1995) The MacArthur Treatment Competence Study: III Abilities of patients to consent to psychiatric and medical treatment, all in *Law and Human Behaviour* 19: 105–26, 127–48 and 149–74.

The assumption, for which there is no evidence, is that people with a mental disorder may be indirectly coerced into participation by the offer of payment. (It is arguable that a more pernicious practice was their attempted recruitment or retention by supplying cigarettes.) **The Working Party recommends that any proposed payment for participation in research should always be carefully considered by research ethics committees and by grant-giving bodies.** Researchers who make no explicit comment on this point should be asked to do so.

- 7.10 An important issue is that consent may not be for all time. Those deciding to withdraw from a research project should be able to do so without any sense of failure or disadvantage. Nevertheless, it is important that an indication of intent to withdraw is met with attention similar to that given when consent was originally sought. The researcher must fully understand the problems that have led the participant to ask to withdraw; for example, any unforeseen problems in the research design or presentation. The participant should also understand the implications of his or her withdrawal including a possible contribution to misleading research findings.⁴ Although this may risk the appearance of coercion, withdrawal is a serious problem and a competent participant is unlikely to be harmed or unduly pressurised by a properly given explanation of the situation. There have been suggestions that the nature of some mental disorders makes withdrawal particularly likely as ambivalence or fluctuating commitment may be intrinsic to the disorder. It may be that if these cases exist, the contingencies should place greatest weight on safeguarding as far as possible data already gathered, since the greatest risk lies in distortion of the data collection and therefore misleading findings in relation to the condition. Another, more real, concern is that the capacity of the person to consent, and therefore the validity of that consent, may fluctuate with the course of the disorder, for example in dementia. The possibility that the potential participant's capacity to consent to the research might change during the course of that research, with proposed contingencies for dealing with that, should be presented to a research ethics committee at the outset and appropriate procedures agreed with participants.

Safeguards for individuals considered to be incompetent

- 7.11 Some people may, by reason of their disorder, have a profound and continuing lack of understanding. Most commonly these are people with severe mental retardation or advanced dementia. Some will be both young and of impaired mental capacity. Problems like this are particularly likely to arise for some with a rare, single gene disorder. This leads into discussion of the ethics and law relating to those unable to consent on their own behalf to involvement in research.
- 7.12 Provided that the research is therapeutic, that is, aimed at least in part at benefiting the individual patient, it is likely to be lawful. It is not always easy, however, to determine whether research is indeed therapeutic.⁵ If the research is non-therapeutic, in other words is not of any *immediate* benefit to the individual patient, then in the current state of the law it is of doubtful legality. In relation to children, the rigour of this position may be mitigated by permitting the parent to consent on behalf of the child relying, not on the usual test of whether an intervention is in a child's best interests, but on the test of whether it is 'not against the child's best interests'.⁶ This

4 Edlund M, Craig T and Richardson M (1985) Informed consent as a form of volunteer bias, *American Journal of Psychiatry* 142:624-7.

5 A similar problem has arisen in the context of HIV testing of children. See *Re HIV Tests* [1994] 2 FLR 116, in which the courts recognised that the question raised "considerations ... both of law and of social policy". There is no authority on whether such testing will be in the child's best interests and the High Court has directed that applications under the Children Act 1989 directed at the HIV testing of a child should always be heard by a High Court judge.

6 See the discussion in Dworkin G (1987) Law and Medical Experimentation *Monash University Law Review* 13:189.

test has been applied where there is an important interest served by the intervention but it is not strictly speaking in that specific child's best interests.⁷ In the case of mentally incompetent adults, however, since no one may consent on behalf of another adult, it would appear that, in the current state of English law, non-therapeutic research is unlawful.⁸

7.13 This is also the case for a patient detained under the Mental Health Act 1983 who is specifically mentally incompetent to consent to treatment for his mental disorder. Such treatment is only lawful if it falls within the terms of Part IV of the Mental Health Act 1983.⁹ Whereas therapeutic research and genetic treatment could be described both as treatment for a mental disorder and in the patient's best interests, non-therapeutic research and genetic testing might not be properly so described.

7.14 Several responses to the Working Party's consultation argued that research on mentally incapacitated patients should be "*explicitly restricted to therapeutic research, that is, research which is potentially beneficial for the individual research subject.*"¹⁰ The Working Party does not consider that such a stance is tenable when individuals are suffering from a condition, or particular presentation of a condition, which would render all such people incapable of complex decisions; we would regard an automatic bar on non-therapeutic research in such circumstances as an unacceptable disadvantage to people with that condition, necessarily limiting progress into the understanding and, indeed, treatment of their disease. We think that the more restrictive view is likely to reflect a need for wider and more considered education beyond the immediate disciplines concerned. There is also a need for further inquiry, research and debate on best practice in this particularly difficult area. In the meantime, we endorse the views summarised below.

7.15 A number of bodies have concluded that non-therapeutic research involving adults unable to consent to participation on their own behalf may, in certain circumstances, be ethical, and some of the principles regarding ethical research with children may help here.¹¹ In particular, even though the process may not constitute legal consent, involvement of the patient's next of kin or nearest relative and, where relevant, the patient's legal adviser would be good practice. MRC guidance states that an individual unable to consent should be included in non-therapeutic research only if:

- it relates to the individual's condition and the relevant knowledge could not be gained by research involving those able to consent;
- it is approved by the appropriate Local Research Ethics Committee (LREC);

7 See, for example, *S v. S, W v. Official Solicitor* [1972] AC 24, [1970] 3 All ER (HL). These two appeals, heard together, concerned the permissibility of having a child's blood tested in order to establish paternity. The case is the English authority on the legality of medical interventions which are not, on the face of it, intended to be therapeutic. The House of Lords found that the child's interests were best served by the truth being made known.

8 See the Law Commission (1995) **Mental Incapacity**, No 231, HMSO, London, paragraph 6.29: "If, however, the participant lacks capacity to consent to his or her participation, and the procedure cannot be justified under the doctrine of necessity, then any person who touches or restrains that participant is committing an unlawful battery. The simple fact is that the researcher is making no claim to be acting in the best interests of that individual person and does not therefore come within the rules of law set out in *Re F*" (*Mental patient: Sterilisation*) [1990] 2 AC 1]. "In some cases relatives are asked to 'consent' to what is proposed, and do so. It appears that some funding bodies and Ethics Committees stipulate for consent by a relative where the research participant cannot consent. As a matter of law, such 'consent' is meaningless. It appears that the question of the legality of non-therapeutic research procedures is regularly misunderstood or ignored by those who design, fund and approve the projects." In paragraph 6.25, the Law Commission suggests that the genetic testing of a person without capacity to consent would be unlawful, unless connected to a specific treatment for that person.

9 See, in particular, section 63 which provides that the consent of the patient shall not be required for any medical treatment given to him or her for the mental disorder from which he or she is suffering (save for certain treatments described in sections 57 and 58) if the treatment is given by, or under the direction of, the responsible medical officer. There is some suggestion in the reported cases that such treatment must also be in the patient's best interests (see, for example, *B. v. Croydon District Health Authority* [1995] 1 All ER 683).

10 Response from the Centre for Bioethics and Public Policy to the Working Party's consultation and others.

11 Nicholson R (ed) (1986) **Medical Research With Children: Ethics, Law and Practice**, Oxford University Press, Oxford.

- the individual does not object or appear to object in either words or action;
- an informed, independent person acceptable to the LREC agrees that the individual's welfare and interests have been properly safeguarded; and
- participation would place the individual at no more than negligible risk of harm and is not against that individual's interests.¹²

7.16 A similar approach has also been recommended by the Law Commission for England and Wales¹³ and the Council of Europe.¹⁴ The options are summarised in a Consultation Paper issued by the Lord Chancellor's Department.¹⁵ It has been suggested that the options differ somewhat in the degree of risk or harm to the research participant considered ethically acceptable. The language differs, but in the absence of legally tested definitions of terms we remain convinced by the principle rather than by any particular variant of its expression. Thus, the Council of Europe refers to "*risks ... not disproportionate to the potential benefits of that research*", and entailing "*only minimal risk and minimal burden for the individual concerned*" (Articles 16 and 17). The Law Commission refers to "*minimal risk and minimal invasiveness*"; and, in its Draft Mental Incapacity Bill "*that the research will not expose a participant to more than negligible risk, will not be unduly invasive or restrictive ... and will not unduly interfere with a participant's freedom of action or privacy*". The MRC guidance (quoted in paragraph 7.15) seems to differ only in terms of adopting the general concept of 'interests' rather than in the detail. A medical position on degrees of risk in this context is that 'negligible' is 'risk less than that run in everyday life'; 'minimal' is 'risk questionably greater than negligible'; any greater risk is referred to as 'more than minimal'.¹⁶

7.17 **The Working Party recommends, therefore, that non-therapeutic research involving people lacking the capacity to consent to participation on their own behalf should be considered ethically acceptable, subject to strict safeguards.** Whether or not some additional, statutory body is created (paragraph 7.18), the expertise of existing Research Ethics Committees (RECs) to consider such research may need to be broadened, and a mechanism established by the Department of Health, which provides guidance in such matters, by which consistency can be ensured. The Working Party welcomes the first annual report of the Advisory Committee on Genetic Testing¹⁷ which notes that RECs have been raising questions about genetic testing and that it proposes to produce information for RECs setting out 'points to consider' and 'questions to ask' when presented with research proposals which involve genetic testing. **The Working Party recommends that every research ethics committee should include at least one member who has experience in the area of competence in decision making about research participation.** Where necessary, committees should seek to co-opt such a person on occasions when such research is to be considered.

7.18 The question of legislation exercised the Working Party considerably. It would appear to be an important protection for the interests of such people as a group, for researchers in this field, and, especially, for individual participants, that there should be legislative backing for, and controls

12 MRC Ethics Series (1991) **The Ethical Conduct of Research on the Mentally Incapacitated**, London, Medical Research Council. Presumably, the same guidance would now be expected to apply to the recently established Multicentre Research Ethics Committees.

13 The Law Commission (1995) **Mental Incapacity**, No 231, HMSO, London.

14 Council of Europe (1996) **Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine**, Council of Europe, Strasbourg, Articles 16 and 17.

15 Lord Chancellor's Department (1997) **Who Decides? Making Decisions on Behalf of Mentally Incapacitated Adults**, Cm 3803, Lord Chancellor's Department, London.

16 British Paediatric Association (1980) Guideline to aid Ethical Committees considering research involving children. **Archives of Diseases of Childhood** 55:75-7.

17 Advisory Committee on Genetic Testing (1998) **First Annual Report July 1996-December 1997**, Health Departments of the United Kingdom, London.

over, non-therapeutic research, as outlined above (paragraphs 7.15–7.17). The Law Commission has called for a new statutory ‘Mental Incapacity Research Committee’ on the grounds that RECs (and multi-centre RECs) have no statutory power to make a researcher’s actions lawful. While recognising the need both for new legislation on non-therapeutic research, and for regulation of all research on people with mental incapacity, we are not persuaded that an additional Ethics Committee would be appropriate. An alternative might take the form of review of the work of LRECs and MRECs in these matters. **The Working Party recommends that further consideration be given to the details of legislation and regulation to safeguard the interests of people with mental incapacity with respect to participation in research.** The necessary legislative framework could be found in the present review of mental capacity under the auspices of the Lord Chancellor, or form a part of the promised wider review of mental health legislation. Alternatively, it could be free-standing.

Boundaries between research and clinical work

- 7.19 In a rapidly evolving field such as human genetics, it is probably inevitable that research and clinical work will be closely entwined. Research aimed at identifying genes related to particular disorders may depend on assembling the largest possible collection of families with the disorder. Contact with family members develops as they may be asked to contribute DNA samples and information about themselves and other family members. Many will have questions about the disorder which runs in their family and researchers at the forefront of their field may be better placed than other clinicians to answer these (but see paragraph 7.24 below). In some areas of genetics (for example, cancer genetics) researchers have set up special clinics to which family members at risk may be referred for genetic counselling.
- 7.20 Provided that appropriate guidelines are followed and patients are not pressurised to be involved in research, such arrangements should not raise any particular ethical problems. Indeed, such clinics may be a very effective way of providing well-informed genetic counselling and other clinical support to members of families that carry some of the rarer genetic disorders. Difficulties over financing may arise, however, as such clinics are often initially financed by research funding but research bodies may be reluctant to continue to support clinics that provide a routine clinical service. As the discovery rate of rare disease genes is accelerating rapidly, this difficulty is likely to increase.
- 7.21 More complicated ethically are situations where DNA samples have been collected for research purposes and researchers later discover information which is of clinical significance to the donor of the sample. This is quite a common situation in research aimed at identifying disease-related genes. When such a gene is identified and its location and sequence published, most research groups working in the area will screen DNA samples in their possession for relevant mutations. Correlating the presence or absence of particular mutations with information about the development of the disease in individuals can provide important insights into the disease process. Such research should be covered by the general consent that individuals will have given when they provided DNA samples and information about themselves and other family members.
- 7.22 When such a disease-linked gene has been identified and significant mutations found, the question arises as to how to deal with any clinical implications for individuals who have contributed DNA and information to a research project. For those who have been found to have the condition and a relevant mutation, there could be implications for relatives (who may or may

not have consented to take part in the research), in terms of their risk and also possibilities of direct testing. For those in the research sample who do not have the condition, the presence of a mutation may indicate a risk of developing it in the future while its absence may suggest that the individual will be free of the condition that runs in their family.

- 7.23 The ethical difficulty arises because the process of obtaining the informed consent required for research does not usually include consent for disclosure of identifiable data to clinics outside the strict environs of the research. Nor is the kind of genetic counselling included that would be required for an individual seeking a genetic test for clinical purposes. To provide an individual with information from a research study about gene mutations which they might or might not carry and which, at the time samples and information were collected, could not have been foreseen, could be to give them information they would choose not to have, and/or information for which they or other members of the family are not prepared or cannot understand in terms of its implications.
- 7.24 A further difficulty is that quality controls and procedures used for clinical testing may be different and sometimes more rigorous than those used in research studies. For example, in some protocols for direct predictive testing in Huntington's disease, DNA samples are collected on two separate occasions from an individual who chooses to undergo testing. These are tested independently and only if these yield identical results is the result regarded as valid. Such checking procedures are unlikely to be used in a research study. **For these reasons the Working Party recommends that, as a general rule, those who consent to take part in research should be told that individual information derived from analysis of their DNA will not be given to them.** This principle should certainly apply in all situations where the genetic loci under study would, at best, identify only weak susceptibility to a disorder. A summary of the overall findings of the research can be provided if the participant wishes.
- 7.25 **The Working Party further recommends that, in any research study that could yield genetic information which is clinically relevant to a research participant and/or their relatives, consent to that research should make it clear whether or not such information will be made available.** If it is to be made available then, before consenting to the research an individual should receive genetic counselling, and give written consent to make it clear whether or not they wish their designated medical adviser to receive information of clinical relevance derived from analysis of his or her own DNA, and/or to receive such information personally. Where information is to be given to research participants (or, with their consent, to their medical adviser), the procedures used for collecting and processing samples should be of the same standard as those used in clinical services, and accompanied by further appropriate advice.

Consent for further research use of samples and data

- 7.26 Many, if not most, studies into the genetics of mental disorder are likely to depend on longitudinal accumulation of data for their maximum value. This may be so for at least two reasons: first, the outcome depends on being able to follow the individual and any changes in their state, during a lifetime; and, second, over the years, more sophisticated possibilities in testing may arise. Another issue that may arise in relation to research where there is a large, established and reliable data bank is that, for reasons of efficiency, other researchers may seek to have access to some of the material. They may, however, only require aggregate data which will be anonymised, which raise few problems and are often obtainable in published tables.

7.27 Researchers may also seek named data or seek to use registers or cohorts as a source for identifying groups of individuals with rare conditions. Once again, there is a need to consider the special needs of those who are not competent to make their own decisions. **The Working Party recommends that, when a person is considered to be incompetent to make his or her own decision about participation in research, data collected for non-therapeutic research purposes should not be used for any other purpose.** For individuals deemed competent, discussion about the possibility of further research should be included in the original process of seeking consent. In some cases, much of the additional data may be collected without further reference to the person. In this case it would be expected that the initial consent process would take account of how further research might be conducted. For some further research it will be necessary to meet the individual again to collect additional information or to take further samples, so that consent for data sharing can be sought in the usual way. At the very least, either approach must include the principle that any new research requires referral to a research ethics committee, together with an indication of what constitutes new research: for example, to include new data collection, the application of previously unavailable tests to material already collected, and the supplying of any part of the data to others, explicitly for research. Research ethics committees have a responsibility to check the progress of any research and to ask what the data has been used for. **When an individual participant is regarded as competent, the Working Party recommends that any possible further use of data in the longer term should be discussed with him or her as part of the consent procedure; new research should, as a minimum, be submitted for approval to a research ethics committee before proceeding.**

Use of research data by outside agencies

7.28 An often cited concern is whether agencies for which data were never intended may be able to get access to research information. These agencies may include health or social services (the latter may still have an open records policy which can extend to other local authority departments), but also to the police or sectors of the criminal justice system, and, sometimes of most concern, insurance and other finance agencies. As with clinical information (Chapter 5), access to research data, without permission, needs strong justification. The European Human Rights Convention and recent EU initiatives on data protection address the protection of privacy. If anything, research data are likely to be safer because they are kept under entirely separate records systems and because, by their nature as research databases, they tend to be seen as likely to be less meaningful than routinely collected clinical data. Potential problems around confidentiality should not be exaggerated. We know of no instance in which raw research data have been used for non-research purposes without the knowledge or consent of the researchers, nor of any where the latter may have been forthcoming inappropriately. Researchers do have a responsibility to take all reasonable steps to ensure that their raw, individualised data will not be used for any other purpose. In one case where this seemed more possible because research was with pre-trial prisoners, express guidance was sought from the Director of Public Prosecutions (DPP) before proceeding with the research. While, in line with the law, the DPP was not able to offer guarantees nor rule out the possibility of subpoena, the advice was that withholding of research data was likely to prove defensible in all but the cases of greatest public interest and that perhaps these alone should be avoided. In practice, this proved to be good advice and, even in these circumstances, notwithstanding a few inquiries about the data, none was demanded or given for non-research purposes.

7.29 Participation in research also raises a question about how a participant should respond if they were ever to have to complete an insurance or mortgage questionnaire which requires them to state if they have ever been tested for a genetically transmitted condition. The process of giving consent for the research should include this as part of the counselling. As discussed, the results would not, in any event, be available for the company, and probably not to the individual completing the questionnaire. Further, with respect to mental disorder, in almost all cases genetic information would in reality add nothing to a clinical risk assessment (paragraphs 4.18–4.20). In the very few cases where it may, for example Huntington's disease, then the issue would emerge anyway in a good clinical history. **The Working Party recommends that genetic information obtained during participation in research should not be made available to organisations such as insurers or employers.**