

BRAIN UK

UK Brain Archive Information Network

Existing Holdings

**POLICY FOR THE DISCLOSURE OF CLINICALLY SIGNIFICANT
INFORMATION**

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1. Introduction

1.1 The Nuremburg Code and the Declaration of Helsinki

The modern legal and ethical concerns governing the research upon human subjects and their tissues was a direct result of the Nuremburg war crimes trials. The Nuremburg Code of 1947 was drawn up as a response to this and set out a number of principles to be satisfied for human participation in medical research or clinical trials including the need for consent, the right of withdrawal, that human experimentation should only be considered when other approaches had been exhausted (e.g. the use of animal models) and that there should be consideration given to the balance between the expected benefits of any research and the risks run by research subjects^[1, 2].

The principals of The Nuremburg Code were adopted and developed subsequently by the World Medical Association in the Declaration of Helsinki. This fundamentally recognised the principal that research utilising human participants should not take precedence over the interests of science and society in general. The Declaration also emphasised that all research carries inherent risks and that this should be assessed and managed and that any risk is outweighed by the importance of the research question. As part of this appraisal process there should be evidence of scientific rigour and independent ethical and peer review processes and that informed consent from participants or their legal representatives should ideally be sought^[1, 2].

1.2 Benefits of Research

Medical and biomedical research is of great importance to human health and society in general. Through high quality research factors influencing or causing human diseases or disorders can be identified which, ultimately, may lead to reliable and efficacious therapies being developed through the use of animal and *in vivo* models and refined through clinical trial protocols. This will ultimately, through an altruistic interpretation, benefit both individuals and society at large by reducing the social and economic burden of morbidity and mortality by improving an individual's health and quality of life. However, central to the use of humans in medical research and clinical trials is the principle that participants should be fully informed of any inherent risks and that, with an appreciation and understanding of this knowledge, their informed consent should be forthcoming.

All types of medical and biomedical research have the inherent capacity to reveal biological data and information that may have clinical or psychosocial implications for participants and their relatives. This is especially true for research investigating the genetic and heritable basis of human disease which could reveal data relating to paternity issues or indicate if an individual is predisposed to a particular condition (in the case of monogenic disorders) or at an elevated risk of developing diseases such as cancer or neurodegenerative conditions later in life (in the case of multifactorial diseases). Data accrued from genetic research also has implications for those who share a common ancestry with the participant and those who are yet to be born. In addition to the medical implications of such knowledge, there are also other, perhaps less obvious, social, legal and financial implications for example, stigma, exclusion, anxiety, stress to family relationships and the ability to obtain health, life, disability or any other kind of insurance and may have a bearing upon an individual's prospects of employment.

The offer and receipt of research results to participants and their relatives has a number of potential benefits and may have direct implications for their quality of life. Beyond a purely scientific basis, the disclosure of data generated as part of biomedical research may aid in demonstrating at a societal level the benefits of research by engaging the general public in terms of its enthusiasm and support for the principal of medical research. However, although there is an ethical onus to disclose findings of clinical relevance to the families of participants where appropriate, there will be situations when an individual does not wish to receive such information or where disclosure may be of more harm than benefit to an individual.

2. Disclosure of Clinically Relevant Data

There currently exists no encompassing consensus concerning the responsibility of researchers to disclose individual results to participants in human research and information and guidance that is available demonstrates that this is a complex, potentially contentious and highly variable issue. Research may be undertaken with the full knowledge and anticipation that any data generated may have clinical significance for the participant and their relatives. In this case, the mechanisms and protocols for disclosure should be established at the protocol planning stage. However, it is accepted that clinically meaningful results may not be anticipated although this scenario but they should be considered during the planning of any research as it constitutes best practice.

2.1 Cost of Disclosure^[3]

Although largely arbitrary, the cost of disclosing data must be weighed against the risk (be that physical, emotional or societal) to the individual or their relatives. The cost of disclosure may be measured in the following ways:

1. Each study will present a variable risk to those individuals participating dependent upon the study question being addressed. As risk increases, disclosure is more likely to happen and be expected and at greater cost, in terms of time and finance, to the study group. This type of risk should be factored into the funding structure of a particular piece of research with high risk research requiring greater funds to disseminate data appropriately and to validate results independently.
2. The size and structure of a study will present logistical difficulties. For instance a large multicentre study with disparate geographical scatter would increase the costs associated with disclosure. Again, the contribution of logistical factors should be incorporated into the funding process for each particular study.

2.2 Requirements for Disclosure^[4, 5]

The disclosure of clinically important information to the relatives of donors should only occur if the following can be reasonably satisfied:

1. All findings are scientifically valid and confirmed through repeat and accredited experimentation. The analytic and clinical validity should be assessed and the predictive value of the results determined.
2. Findings have significant implications for the subject's health concerns and for the health concerns of future individuals *e.g.* the discovery of a genetic predisposition in tissue previously believed to be normal.
3. A course of action to ameliorate or treat these concerns is readily available.
4. Results indicate an enhanced susceptibility to environmental factors *e.g.* increased susceptibility to adverse drug reactions.

Investigators should formulate and integrate plans about appropriate disclosure of individual genetic results when designing their research studies.

2.3 Means of Disclosure

All clinically significant data should be delivered by Healthcare Professionals that form part of an individual's medical care team (*e.g.* General Practitioners) but it is important that protocols are in place to enable researchers to communicate effectively with the relevant bodies (such as General Practitioners, NHS Trusts and Primary Care Trusts) and such measures should be ideally factored into the funding structure of each research study for contingency purposes.

All disclosure methods should receive the approval of a UK Research Ethics Committee and it is the sole responsibility of each researcher to ensure that such approvals are in place prior to undertaking any research.

3. Determination of Disclosure Threshold

The decision to offer to disclose data or not will be made on a case-by-case basis and will utilise a result-evaluation approach based upon an ethical framework^[5] which incorporates the principals of:

- *Beneficence*: Are results clinically useful or likely to contribute towards a participant's physical and emotional well-being?
- *Reciprocity*: Consideration of the nature, depth and duration of the relationship between participant and researcher.
- *Justice*: Consideration of the balance between a participant's preferences and resource allocation to maximise the benefits of the research to society as a whole.

The result-evaluation approach should consider the following facets in determining whether a minimum threshold has been achieved in permitting clinically significant results to be offered to participants and their relatives:

3.1 Analytic Validity

Results of a clinically significant nature should be of the highest quality and should be validated by additional testing. This is best achieved using the facilities of a laboratory accredited to undertake such testing and relevant samples should be made readily available to ensure that this can proceed efficiently.

3.2 Clinical Utility

Clinical utility is an empirical measure of whether a result can be used to improve a participant's well-being. It is based upon three assessments: clinical validity, the likelihood of a clinically effective outcome and the value of that outcome.

Clinical validity is a measure of the strength of association between a result and a particular clinical outcome. Some results will be more strongly associated with a particular clinical scenario and this will, in turn, be based upon the body of reliable scientific evidence. Where a strong association can be demonstrated this is supportive of an offer to disclose such information to the participant or their relatives.

The likelihood of a clinically effective outcome should determine whether intervention is safe and that such intervention will offer palpable benefits when compared to no intervention at all.

The value of outcome determines whether any intervention or disclosure will be of clinical, emotional or other benefit to the participant or their relatives or enables them to make better informed life choices (*e.g.* reproductive decisions). It is also important to consider the personal meaning of any disclosure to individuals and whether such information would have any effect upon relationships and personal identity.

3.3 Study Context

The context of a study is also important in being able to rationally determine whether a disclosure threshold is reached. In reaching a decision, it is prudent to consider the following: the capabilities of an investigator and the relationship between a participant and an investigator.

The capability of an investigator to undertake the appropriate communication of results to individuals or their representatives and whether they have the capacity to validate any

clinically significant results independently or to be able to offer advice and support where required.

The nature, depth and duration of a relationship between a participant and an investigator is extremely important in determining whether information should be disclosed. For studies which extend for many years and involve regular meetings there may be a rapport and level of trust may develop which puts greater emphasis upon disclosure than a single meeting or complete isolation.

3.4 Decision Making

The ultimate decision as to whether a particular study should offer to disclose clinically important data will be ultimately made by the relevant NHS Trust after being informed of a clinically significant result by either the *BRAIN UK* Committee or the Chief Investigator of the research study in question. *BRAIN UK* is not in a position to determine alone whether disclosure should occur but can, at the application stage, make an informed decision concerning the risk that a particular research study presents in terms of generating clinically significant results. If a particular study does present an above 'minimal' risk then it may be required for a particular study to obtain approval from a UK Research Ethics Committee for that work.

The decision-making process will be augmented by the feedback of results from researchers in the form of papers and abstract presentations. *BRAIN UK* would expect all researchers to contact the Committee and/or the relevant NHS Trust if they were in the possession of novel data of a clinically significant nature.

4. Consent

Consent, as previously discussed, forms the basis of any relationship between a participant and a researcher in medical and biomedical research. However, the *BRAIN UK* 'virtual' brain bank does not rely upon a traditional model for a tissue banking facility. By definition, all participants in those studies supported by the *BRAIN UK* network of tissue archival centres are deceased and the obtaining of consent is therefore complex if not unachievable. *BRAIN UK* will not be attempting to obtain consent for access to and disclosure from patient records or to the use of archived tissues for research purposes for the following reasons:

1. Our pilot study indicated that there are approximately 150,000 potential cases throughout the UK that could be included as part of this initiative. To attempt to obtain consent from this cohort would be insupportable in terms of both time and expense.
2. Approaching relatives at times of bereavement could cause distress and harm especially if the nature of the bereavement related to a distressing condition or incident.
3. As many of the cases date from many years or decades ago it would be inappropriate to return to bereaved relatives so long after death.
4. There may be difficulty in tracing relatives or in contacting them many years after death due to factors such as migration and death.
5. The absolute requirement for consent would limit the size and scope of the *BRAIN UK* database with available resources and diminish its potential benefits to the research community and the UK as a whole.
6. The use of linked anonymised data renders the probability that any individual could be identified by the recipient of such data to be extremely small. For practical purposes, this data may be considered as anonymous thus there is no concomitant requirement for consent.

In addition, *BRAIN UK* will be utilising tissues archived prior to 1st September 2006 which are classified as 'Existing Holdings' by the Human Tissue Act 2005 and the Human Tissue

(Scotland) Act 2006. This legal definition allows the use of such tissues for research purposes without consent so long as such research is approved by a UK Research Ethics Committee and that tissues are supplied in an anonymised form.

5. Anonymisation

All data and tissue specimens provided by participating centres will be in a linked anonymised format *i.e.* they will have a site-specific laboratory number or equivalent attached. As the key relating to this data will be maintained by the participating centre providing that tissue it will be extremely difficult to obtain any patient identifying data (*e.g.* name, date of birth, address) from this information alone.

However, in cases where there is considered to be an above 'minimal' risk for the need to offer the disclosure of clinically significant data to the relatives of participants, tissue and attendant clinical data will only be offered in fully anonymised form. This will be achieved by reblocking paraffin embedded material or supplying unstained sections for such research.

6. Policy Declaration

Based upon the criteria discussed above, the majority of research studies that would potentially utilise the archival tissue holdings of participating centres in the BRAIN UK network would not, by default, be in a position to offer the disclosure of clinically significant information for the following reasons:

1. The tissue held is diagnostically verified therefore, for diseased tissues, there would be reduced scope to discover additional information of clinical pertinence. For instance, if an individual had been diagnosed with Huntingdon's disease, it is probable that family members at risk would already have been identified and would have received appropriate counselling and testing. It is therefore assumed that the value of outcome has been determined and that subsequent life choices (*e.g.* reproductive decisions) would have been addressed.
2. The tissue archive collections are retrospective and, in some instances, extend back a number of decades. It would be inappropriate to return to individuals if many years had elapsed since the death of their relative; to do so may cause harm especially if the events surrounding such a death were traumatic.
3. The majority of neurological and psychiatric diseases and disorders remain incurable and there is limited scope in terms of effective curative therapy. Therefore the likelihood of an effective clinical outcome would remain low for most research particularly that relating to neurodegenerative disorders and dementias.
4. In terms of study context, there would be no existing relationship between the relatives of donors nor would it be likely that one would exist in the future. This would indicate, as a consequence, that to approach relatives would be inappropriate. However, if researchers were to pursue living relatives in terms of gaining additional clinical information as part of their study, this would require the approval of a UK Research Ethics Committee and this undertaking would be the sole responsibility of that researcher.

In essence, it will be the policy of BRAIN UK not to offer to disclose clinically significant information to the relatives of donors. All tissue and clinical data supplied to researchers will be in a linked anonymised format which, for practical purposes, may be considered as fully anonymised, a requirement of the Human Tissue Act 2005. In the case where the extraction and subsequent analysis of DNA or RNA is intended and that there is an above 'minimal' risk that any data obtained is likely to have clinical significance, then all tissue and data will be supplied in a fully anonymised format. In addition, for such scenarios BRAIN UK will require evidence that the ethical questions surrounding the disclosure of clinically significant

information have been addressed by the researcher and that the study proposal has the approval of a UK Research Ethics Committee.

However, it is recognised that there may be very rare occasions when the question arises that it may be appropriate to offer to disclose clinically significant data. If so, the question will be considered by the *BRAIN UK* Committee which will seek appropriate advice and discuss the possibility of disclosure with the relevant NHS Trust.

A particular example would be when tissue has been supplied as being pathologically normal but, in its use as reference material, it becomes apparent that this is not the case *e.g.* the identification of a gene associated with an increased risk of developing a particular heritable disease or disorder. In such cases, which will be analysed using the results-evaluation model, a minimum threshold in terms of analytic validity, clinical utility and study context would need to be attained before the offer of such data to living relatives of donors. Although *BRAIN UK* and the relevant research group may offer advice and guidance on such matters, the decision to offer to disclose clinically significant data will be ultimately made by the relevant NHS Trust.

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