



European Network of Research Ethics Committees

Informed Consent and Data Protection in Multicenter Genetic-Neuroimaging Studies

Informed consent is a major prerequisite for research. However, obtaining adequate informed consent can be a challenging task, particularly within the context of multicenter studies involving countries with differing laws and customs. The process can be especially challenging when biomaterials and phenotype data are collected for future as well as for immediate use, since the techniques that will be available to exploit the data at future time-points cannot be foreseen.

In the following, these difficulties will be illustrated using the practical example of the informed consent procedure for IMA-GEMEND (www.imagemend.eu). The aim of this large multinational study is to identify the neurobiological causes of mental illness, and the research focuses on the development of effective imaging tools for the diagnosis, monitoring, and management of mental disorders. Genetic and neurobiological data (as collected from imaging, neuropsychology assessments, interviews etc) which have, and will be, obtained at the various study centers will be combined for meta-analytical analyses.

Before discussing issues surrounding informed consent, the following text outlines the current status of research into the etiology of psychiatric disorders.

Mental illness is the major contributor to the global burden of disease.

However, despite decades of research, little is known about the underlying pathophysiology of psychiatric disorders, and no biological markers are available to guide diagnosis or predict response to medication or outcome. Formal genetic studies have shown that both genetic and environmental factors are involved in the etiology of psychiatric disease, with heritability estimates ranging from 50% (e.g. for alcohol dependence and depression) to 80% (e.g. for schizophrenia and autism). Over the past decade, the advent of new technology has rendered feasible a systematic search for these genetic risk factors on a molecular level. In this approach, genetic variants

are compared between thousands of patients and controls. The approach is not limited to psychiatric disorders; it has also led to the detection of risk genes for other common diseases such as cancer, diabetes, and hypertension. Experience to date has shown that: i.) the success of such studies depends on the size of the samples, and requires the investigation of many ten to hundreds of thousands of individuals; ii.) many frequent low-risk variants which act in combination, and many very rare variants with larger risk effects, exist; iii.) only a very small fraction of the contributing variants have yet been identified, and although these have provided insights into disease etiology, they are insufficient in terms of the prediction of disease development and outcome; and iv.) classical diagnostic categories, such as schizophrenia and bipolar disorder, are too broad, too heterogeneous, and overlapping. This indicates that larger datasets, obtained using more refined phenotypic characterization which takes into account findings from neuroimaging and neuropsychological assessments, are necessary. The recruitment of such large and extensively characterized samples can only be achieved through large multicenter studies.

The establishment of the corresponding biobanks and datasets, and the analyses performed with these data, touch upon diverse ethical issues. As outlined above, communicating research aims and inherent ethical issues to potential participants is a challenging task, given the long-term nature of these research efforts and the ever expanding possibilities for the analysis of the resultant data. A further problem - a detailed discussion of which is beyond the scope of the present article - is that informing patients with psychiatric problems about the aims and risks of research requires consideration of a number of specific issues. Depending on their mental state at the time of interview, such individuals may be particularly vulnerable and/or prone to misunderstanding information.

An important pillar of IMAGEMEND is the establishment of Europe's largest integrative database for imaging-, genetic-, environmental risk- and clinical data. The value of both the data and the biomaterials is dependent upon how broadly they can be used both at the time of collection and in the future. This raises an important question, i.e. how should potential research participants be informed of as-yet-unforeseen data exploitation techniques?

The task of the IMAGEMEND workpackage (WP) "Ethics" is to address ethical concerns associated with the development and application of novel predictive biomarkers for mental illness,

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and WP members were given the opportunity to present and discuss these topics at the 2014 Ordinary General Meeting of the European Network of Research Ethics Committees - EUREC (August 12, Berlin – Brandenburg Academy of Science and Humanities, Jägerstraße 22/23, 10117 Berlin).

The discussion with EUREC members addressed the following points:

- Open versus narrow informed consent (transfer of rights, duration of use, topics of research, benefits to participants)
- Data protection (data exchange, publication)
- Withdrawal from research participation
- Result-based re-contact
- Incidental Findings

All participating IMAGEMEND members have, of course, obtained the approval of their local ethics committees for their existing informed consent procedures. To be eligible for use within IMAGEMEND, this informed consent must address the following points:

- Protection, confidentiality, and privacy of data
- Voluntary participation and the ability to withdraw at any time from the research without explanation or adverse consequences
- Point of contact for questions concerning the research and the rights of participants
- Re-contacting patients (e.g. for clinical follow-up, acquisition of environmental risk data)

IMAGEMEND members asked the „Ethics“ WP to formulate an informed consent document which could be used as the basis for future informed consent procedures within the consortium. The informed consent procedure outlined by the „Ethics“ WP is based on the informed consent procedure currently in use at the Central Institute of Mental Health, and which has already been approved by the local (Heidelberg) ethics committee. This informed consent is based in turn on the following two documents: *“Template for the donation, storage and use of biomaterials as well as the collection, processing and use of data in biobanks”* (9 November 2013); and the *“Template for the patient information and informed consent for genetic analysis of samples of adult persons who are capable to consent”* (27 November 2010). Both documents were formulated by the Working Party of Research Ethics Committee in Germany.

During the discussion with EUREC members, Jorg Hasford, who is the President of this Working Party, explained that these templates have not yet been translated into English, despite numerous requests from other countries. The reason for this is that the authors do not consider them a suitable 1:1 blueprint for all EU countries, as they are based on German law and were written from a German ethics perspective. However, the Working Party is of the opinion that they may be used by other EU researchers as a basis for formulating informed consent procedures, taking into account national law and customs. Their templates must then, of course, be presented to their respective ethics commissions for approval.

Open versus narrow informed consent

The text of the recommended informed consent reads:

...., at the present time we are unable to state the exact research objectives. Your samples and data will also be used for medical

research objectives which we cannot foresee today. You should be aware that in consenting to participate in this study, you are granting us very wide-ranging authorization. Therefore, we request you to express your consent to this wide-ranging authorization explicitly by ticking the respective boxes on the informed consent sheet”.....

EUREC members expressed differing opinions as to whether such broad consent is feasible. Some members queried whether consent can be termed “informed” when not even the researcher (at the time s/he informs the participant about the research) is aware of how exactly the biomaterials and the data will be used and what the results may be. Others considered these arguments circular, since the results of research are always open, and thus researchers are never able to foresee exactly what the results and consequences of their research will be. Another question under discussion at the meeting was whether it is ethically acceptable for individuals to transfer the right to their genetic data to researchers, as a substantial proportion of these data are shared with family members and thus do not belong to the participant alone.

This consent allows researchers to use the data in a manner they consider reasonable. This includes the ability to transfer all rights, an open time-frame for use of the data, and no limitation of data use to any specific research question. Some EUREC members stressed that a free citizen must have the right to provide such consent, and that open consent of this nature is not the same as blank consent, since the participant is informed that researchers plan to use his/her data for research purposes, as well as about potential problems concerning issues such as data protection and incidental findings. EUREC members stressed that opinions – even if they have only minority support- which caution against open consent and its inherent problems (such as the protection of data) must not be neglected, but respected and discussed.

Even those EUREC members who were in favor of open consent were more cautious, or argued against, open consent in children and/or in patients. In the case of patients, the reason for this was that patients may not feel entirely free to decline the request/offer to participate in a study.

Most EUREC members agreed that in studies involving open consent, the respective ethics committees should be re-contacted and informed as and when new research questions or possibilities to analyze the data become available. Some EUREC members argued that this should be obligatory, as researchers are not objective enough to decide whether or not their research is ethical. Other members expressed the opinion that it is the responsibility of the researcher to seek advice from ethics committees, and that these ethics committees should not place researchers under permanent suspicion or actively control them. However, there was an overall consensus that it may be favorable to involve ethics committees, as they may base their decision on more general considerations. This may include weighing benefits and risks, while taking into account the pervading view at that time and not simply the literal wording of the informed consent document.

Data protection

Data protection is an important aspect of research, and its importance is likely to increase in parallel with future advances in data analysis and growing sensitivities in society concerning data privacy. Rules on data protection must be in place in medical research in order to ensure transparency, guide researchers, and to identify any researcher who fails to adhere to good practice. EUREC members pointed out that in the (very near) future, European Law on data protection may be applied to biobanking. The application of these very strict data protection laws would render broad consent obsolete.

EUREC members expressed general agreement that potential participants should be aware that no 100% assurance of correct data handling can be provided, in particular when genome-wide data are transferred to countries with less strict data protection rules, or when these data are published or placed in public databases. This issue is addressed in the IMAGEMEND informed consent documentation:

"...Each collection, storage and transmission of data from your biomaterials for research projects bears confidentiality risks (i.e. the possibility of you being identified), in particular with regard to the information on your genetic material. These risks cannot be completely ruled out and increase the more data can be linked together, in particular if you yourself publish genetic data on the Internet (i.e. for genealogical research)Upon request, the double encrypted biomaterials and medical data can be passed on to other universities, research institutes and research companies, if necessary abroad, under pre-established criteria for medical research.... Under certain circumstances, this also applies to the transfer for the purpose of research projects abroad with potentially lower levels of data protection...."

Withdrawal

"You may withdraw your consent to the use of your biomaterials and data at any time without any reason and without adverse consequences for you. If you revoke your consent, you may decide whether your biomaterials shall be destroyed and the associated data deleted, or whether they may be used in an anonymous form for further research projects. However, once the reference of the biomaterials and the remaining data to you personally has been deleted, the destruction is no longer possible. In addition, data from previously performed analyses can no longer be removed. Despite revocation, a later attribution of the genetic material to you personally via other sources can never be excluded."

EUREC members acknowledged that it may be misleading to state that a study participant always has the possibility of withdrawing from the study, especially when data are rapidly transferred to other partners or published.

Result based re-contact

"It may be useful to contact you again.... due to results relevant for the study."

If researchers intend to re-contact participants in order to inform them of specific clinical or genetic results, this should be stated in the informed consent documentation. In some coun-

tries, the re-contacting of participants on the basis of genetic findings may be illegal.

Incidental findings

Numerous reports have discussed the issue of incidental findings, and a degree of consensus has been reached with respect to how the possibility of incidental findings in brain imaging and the assessment of psychopathology should be addressed within the informed consent documentation. Debate is still ongoing with respect to genetic studies, e.g. the issue of whether researchers should actively seek for pathogenic variants when conducting genome-wide sequencing.

Several EUREC members raised the point that in studies such as IMAGEMEND, incidental findings cannot arise if the analysis of pathogenic variants is omitted. However, researchers cannot totally exclude the possibility that a mutation which has hitherto been considered non-pathogenic will ultimately prove to be disease-relevant.

EUREC members welcomed the view that research subjects should have the right to be informed of incidental findings, and emphasized that they already have the legal right to be informed about any stored information (e.g. genetic data) that relates to them. However, discussion is ongoing in the field concerning the circumstances under which this information should be revealed, (e.g. should genetic counseling be involved? If so, who should pay for this?). The right to not to know was also emphasized.

For studies such as IMAGEMEND, EUREC members pointed out that it can be helpful to indicate the frequencies and the consequences of incidental findings (if known) in the informed consent documentation. They also suggested that study participants should have the option of choosing which type of incidental findings s/he wishes to be informed about:

*„1) I agree that I will be informed about medically-significant findings not related to the aim of the current study for which a targeted therapy or preventive strategy is currently available.
2) I agree that I will be informed about medically-significant findings not related to the aim of the current study for which there is no treatment or preventive strategy currently available, but they may be important for my life planning.“*

To summarize:

Although harmonization of informed consent documentation across different European countries is warranted, the legal conditions and customs of each particular country must be respected. Due to changing European laws and the rapid pace of technological advance, which will allow as-yet-unforeseen exploitation of the data and the biomaterials, ethics committees should be included in the decision as to whether the obtained informed consent is valid in terms of these new approaches. It is likely that informed consent documentation will require adaptation in order to match new requirements.

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Biobanks – A Challenge for Research Ethics Committees

Today, biobanks are a well-established and widely used tool for biomedical research. At the same time there is an ongoing controversy about ethical and legal issues in connection with biobanks. Among other things questions regarding data protection and benefit sharing are at stake. However, problems with informed consent are in the centre of the debate. Many people favour the concept of a 'broad consent' which is not related to a specific research protocol, but rather allows to use stored biological material and data for various research purposes. Arguably, such a solution poses a new challenge for research ethics committees.

By now, there is no agreed upon understanding of what a biobank exactly is. Candidates for inclusion range from large-scale infrastructures both for research or commercial purposes to small collections gathered in the context of Ph.D. projects or the like. Even in ethical and legal documents different concepts are being used, as Mariaelena Salvaterra has shown in a recent review. She comes to the following conclusion: "Current concepts comprise the following pairs of biobank definitions: a) individual and population biobanks, b) biobanks of data and biobanks of samples and data associated with them, c) biobanks of samples permanently preserved and biobanks of samples temporarily or permanently preserved, d) DNA biobanks and tissue biobanks." [1, p. 129] This situation seems unfortunate since an exchange about appropriate ethical and legal regulations presupposes a common understanding about the object of regulation. In an Opinion on "Human Biobanks for Research" the German Ethics Council has argued in favour of a broad definition. The advantage of such an approach is, according to the Council, that "[t]he question as to whether a collection is or is not a biobank within the meaning of the statutory provision does not then determine whether particular biobanks remain completely unregulated." [2, p. 23] A common regulation for all kinds of biobanks leaves, of course, room for specific requirements for different types of biobanks. The German Ethics Council has suggested the following three criteria as defining elements of a biobank: "a) It contains genetic material originating from humans with related data. b) Its samples are electronically linked to personal information (possibly pseudonymized) and further information, in particular relating to health. c) Its samples and data are collected, preserved or used for purposes of scientific research." It remains to be seen whether such an inclusive approach will win recognition on the EU level and internationally or whether a more limited understanding of biobanks is considered more appropriate.

Independent of the exact understanding of the notion of biobank it is widely acknowledged that such research infrastructures raise serious issues with regard to the classical concept of informed consent. Traditionally, in the context of research ethics informed consent has been conceived of in a strict and narrow sense. John Kleinig has provided an examination of the 'grammar of consent' according to which consent is a three-placed transaction, namely "A consented (to B) to ϕ ." [3, p. 5] In his insightful analysis Kleinig investigates "[w]hat needs to be true of A, B, and ϕ , if it is to be justifiably said 'A consented (to B) to ϕ '?" [3, p.5] In the present context, the important point is that, according to Kleinig's analysis, consent is necessarily given to a "person, a group of persons, or a quasi-person" [3, p. 6] and in view of a specific "course of action" [3, p. 7] Both conditions

can be problematic in the context of biobanks. As mentioned before, many favour a model 'broad consent' to the effect that donors give a more or less general authorization to use their material and data for any kind of research purpose. From a pragmatic point of view, such an approach is obviously appealing. Questions whether a certain sample or data set may be used for a particular research project do not come up and there is no requirement to re-contact donors. Many national and supra-national regulations for biobanks do in fact already include broad consent (see the overview in [1, pp136-137]). However, such a general authorization may fall short of Kleinig's conditions for a valid consent since it neither addresses a person, group of persons or quasi-person nor is it related to a specific course of action. The core question is then whether broad consent in the sense of a general authorization can still count as a form of (informed) consent.

Advocates of a 'broad consent'-approach are not limited to pragmatic arguments. They can raise the question why it should be prohibited for donors to give their tissue and data without limitations. It seems hardly sufficient to point to 'the grammar of consent' in order to impose strong restrictions on free and responsible donors. Even if one would agree that the traditional concept of consent included the idea of a particular addressee as well as a specific course of actions, it seems unclear why it should not be possible to modify the concept.

However, critics of the concept of 'broad consent' can easily refer to problems that arise already in view of the traditional concept of consent and which might become more serious if the concept is modified. It is well-known that research participants are often unable to grasp the full meaning of research protocols and the role they are asked to play within them. Empirical data has shown that the so called 'therapeutic misconception' is wide spread among research participants. A modification to the effect that consent is no longer linked to a particular research protocol, i.e. to a specific course of action, but rather a commitment to research in general likely aggravates the problem.

This is not necessarily a striking argument against the concept of broad consent. It does, at least, show the challenges connected to this approach. The demand to fully inform donors becomes more complex. It is clearly mandatory that they really understand what they agree to, in particular if they are asked to agree to an almost unlimited use of their samples and data. Therefore 'broad consent' is also a challenge for research ethics committees. Since it is their role to ensure that the demands of research ethics are fulfilled. They must make an effort that donors actually understand what they agree to. Special scrutiny is therefore essential in the review of informed consent materials. Whether this is sufficient or whether the objections against broad consent remain valid is open for further discussion.

Bert Heinrichs

[1] Mariaelena Salvaterra: Informed Consent to Collect, Store, and Use Human Biological Materials for Research Purposes. An International Framework. In: Peter Dabrock, Jochen Taupitz, Jens Reid (eds.): Trust in Biobanking. Dealing with Ethical, Legal and Social Issues in an Emerging Field of Biotechnology. Berlin: Springer, 2102, pp. 127-137.

[2] Deutscher Ethikrat: Human biobanks for research. Opinion. Berlin, 2010.

[3] John Kleinig: The nature of consent. In: Franklin G. Miller, Allan Wertheimer (eds): The Ethics of Consent. Theory and Practice. Oxford: Oxford University Press 2010, pp. 3-24.

General Information on EURECNET

Today, the ethical review of research projects which involve human participants has become a mandatory standard that is reflected in national laws as well as in supranational and international documents. Not only those people who are willing to participate as subjects in research projects, but also both, researchers undertaking projects and the general public, have come to expect that an independent review process is in place which ensures the highest degree of protection possible and, more generally, that research is carried out in an ethically acceptable manner. In the early second half of the 20th century review bodies started to emerge, mainly as a form of self-regulation of the medical profession and often in an ad-hoc form responding to concrete problems. However, in the past decades Research Ethics Committees (RECs) have, in most European countries and worldwide, been established as permanent and independent bodies. As such they build, at least in Europe and other western countries, the core of a robust infrastructure which monitors and reviews research projects.

EURECNET is a network that brings together national Research Ethics Committees (REC) associations, networks or comparable initiatives on the European level. The network interlinks European RECs with other bodies relevant in the field of research involving human participants like National Ethics Councils and the European Commission's ethical review system. Such a network forms the infrastructural basis to promote awareness of specific working practices of RECs across Europe, to enhance the shared knowledge base of European RECs, to support coherent reviews and opinions and to meet new challenges and emerging ethical issues. The central objective of EUREC as a Coordinating Action is to foster the already existing network of European REC networks.

In particular, the contribution of EURECNET aims at five different levels:

- fostering a sustainable infrastructure for European RECs to promote exchange and cooperation and to allow for international cooperation
- gathering information on RECs in Europe to build a basis for mutual exchange
- collecting and evaluating training materials for REC members to enhance the quality of review
- conducting capacity building to facilitate the development of national REC networks
- identifying emerging ethical issues to develop common solutions for challenges posed by new technologies and scientific methodologies.

Since September 2012 EUREC is listed as association in the register of associations. The EUREC Secretariat is located in Bonn. Full Membership is open to one national network per member country or the national research ethics committee where only one exists. Nominated networks must be independent having no commercial or other conflicts of interest. The Board of EUREC is responsible for the daily work of the Association, prepares and

chairs the General Assemblies, takes care of the information, and informs the Members about its work.

EUREC is connected with the EURECNET Project. The project is a consortium of twenty European research facilities, which has been established in March 2011 and is being funded by the European Commission under Framework Program 7 (FP7). It is coordinated by the German Reference Centre for Ethics in the Life Sciences (DRZE). Following already existing efforts, especially efforts within a previous project, one of its primary objectives is to foster a sustainable infrastructure for European RECs. In order to achieve this aim in 2011 a EURECNET secretariat has been set up which, aside from managing and coordinating the project as a whole, is responsible for managing the communication of the project partners with the European Commission and for making available the project's interim and final results to the public.

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