

GENOMEUTWIN

Ethics Manual

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**Compiled and written by
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(Ethics Core)**

Ethical and Legal Guidelines for Produced Data

Deliverable (D9)

QUALITY OF LIFE AND MANAGEMENT OF THE LIVING PROGRAMME (1998-2002)

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Project acronym: GENOMEUTWIN

QoL action line: Generic Activities Area 8.5

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World-wide web address: <http://www.genomeutwin.org/>

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HH

JH

Oslo, March 2007

1 Introduction

1.1 Description and purpose of the GenomEUtwin Ethics Core

This manual is developed by the Ethics Core of GenomEUtwin for the purpose of explaining the role of the Ethics Core within the GenomEUtwin project, to describe the main ethics-related issues identified during the course of the study and the methods employed to address and resolve those issues, and outline the activities undertaken by the Ethics Core during the tenure of the project.

The Ethics Core operates in conjunction with the other intellectual cores of GenomEUtwin (Epidemiology, Database, Genotyping and Statistics) to address and implement the ethical issues and procedures raised in this project. It is active in all three components of the integrated project; research, training and mobility of researchers and networking and has developed collaborations in several international networking and research projects.

The core is housed in Oslo at the Norwegian Institute of Public Health. Dr Jennifer Harris is the Leader (Chair) and Homa Hasan is the Bioethicist. It is composed of representatives from each of the participating centres (see Table 1.2) who are knowledgeable about the ethics codes in their respective country.

The three main ethics-related issues identified at the project start were:

- Informed consent
- Data security and confidentiality
- Return of results and information obtained from the study to participants

During the course of the study these points have been refined and examined in greater detail and procedures and regulations have been put in place as detailed later in this manual. These regulations are formalised and summarised in four main documents, as summarised in Table 1.1, that were developed during the project.

Table 1-1 Overview of GenomEUtwin Policy Documents

Policy Document	Issues Addressed
<i>The Data Access and Security Policy</i> – DASP (signed by all partners)	Conditions and restrictions related to data access and use, data security, data sharing, results generated from the project security auditing and security implementation of TwinNET
<i>The Security Policies for TwinNET</i>	(developed by the Database Core in conjunction with input from the Ethics Core) provides technical solutions for the DASP
<i>Biological Sample Transfer Agreement</i> – STA (signed by all partners)	Pertains to the use, ownership, confidentiality and return of biological samples used in the project.
<i>The Publication Policy</i>	(developed by the Publications Committee in conjunction with the Steering Group) describes the formal procedures for obtaining access rights to GenomEUtwin data for analysis and publication purposes.

The regulations covered in these documents are described in detail in later chapters. Briefly, the *DASP* outlines the conditions under which data can be accessed and shared within the federated database (TwinNET). *The Security Policies for TwinNET* provides the technical solutions and policy governing secure access of the TwinNET data. The *STA* explains the terms and conditions under which biological samples and data are transferred and confidentiality is protected. *The Publication Policy* describes the application procedures for using shared data for the purpose of scientific publications and also outlines the approval process for granting access to these data.

Several policy documents (*DASP*, *STA*, and *Publication Policy*) have currently been selected to be translated into the main European languages. Furthermore, the Scientific Advisory Board for GenomEUtwin has recommended these translated documents should be circulated to national governments and other institutions.

In order to address the needs of the project, The Ethics Core, or special working sub-groups of the core, has met on an ‘as needed’ basis or through telephone conferencing for follow-up work.

1.2 The Ethics Core - members

The ethics core is made up of one or more representatives of each partner country within the collaboration. In addition, there is an external expert consultant (representing the field of law and bioethics).

Table 1-2 Members of Ethics Core

Name	Institute	Country
Currently: Susan Treloar Formerly: Dixie Statham	Queensland Institute of Medical research	Australia
Kirsten Kyvik	University of Southern Denmark	Denmark
Kaisa Silander	National Public Health Institute	Finland
Jaakko Kaprio	University of Helsinki	Finland
Currently: Sirpa Soini Formerly: Tina Aitlahti	University of Helsinki	Finland
Carlo Petrini	National Centre for Epidemiology	Italy
Currently: Virgilia Toccaceli Formerly: Lia Cirrincione	National Centre for Epidemiology	Italy
Jennifer Harris (Leader)	Norwegian Institute of Public Health	Norway
Homa Hasan	Norwegian Institute of Public Health	Norway
Nancy Pedersen	Karolinska Institute	Sweden
Helena Andersson	Karolinska Institute	Sweden
Gonneke Willemsen	Vrije University	The Netherlands
Alun Evans	Queen's University, Belfast	United Kingdom
Currently: Ursula Perks Formerly: Lynne Molloy	St. Thomas' Hospital and UK twins	United Kingdom
External Expert		
Bartha Maria Knoppers	University of Montreal	Canada

2 Ethical Issues Associated With The Collaborative Project

At the time of application for GenomEUtwin (2001) the following issues were identified as the main ethics-related areas to be addressed in the project:

- Informed consent
- Data security and confidentiality
- Questions related to the return of results and information obtained from the study

It was anticipated at the study onset that the Ethics Core would be active in helping GenomEUtwin partners in preparing materials, namely participant consent forms, and applications to regulatory bodies. In actuality, most of the data to be used by GenomEUtwin had already been collected as part of the research programmes at the individual centres. In addition there was great variety in the status and nature of permissions and consents needed by each centre in order for them to participate with their data (these are summarised in Chapter 4, Table 4-2). These ranged from not needing any additional permission, to needing permissions from several regulatory bodies and also consent from participants and scientists associated with other research projects under which data had been collected. In addition, the criteria for participant consent varied for those relevant partners. Thus, it was more realistic for each participating centre to address the particular processes on a national (local) level than for the Ethics Core to create a universal ‘one size fits all’ document.

In the duration of the project the original broad ethical and legal challenges to be undertaken in the project have been broken down into more specific and detailed categories:

- Keeping informed, on a regular basis, of changes in legislation in participating centre countries. The changing landscape of legislation in the duration of the study has been far-reaching and unanticipated at the start of the study (see Chapter 4)
- Implementing a standard for sample transfer which defines the duties and obligations of participating centres and the collaborating laboratories (see Chapter 5)
- Protecting results and biological samples against unauthorised use or access (see Chapters 5)
- Implementing a policy to protect the rights (primarily of ownership and confidentiality) of data contributed by each participating centre (see Chapter 5)
- Implementing a policy to standardise data transfer and sharing so that the participating centres with the strictest legislative criteria are met (see Chapter 5)
- Identifying and describing potential issues surrounding Intellectual Property Rights protection for the Steering Board to consider (see Chapter 8)
- Evaluating the process of sharing results from the merged data at lay level, and consequently a public use of the GenomEUtwin website. This is primarily based on

the voluntary duty to provide information and feedback to participants but not on an individual level.

2.1 Feedback to participants

Participation in research that does not result in clinical benefit is often described as altruistic and, ideally, a research project would like to be able to provide individual results back to the participant in exchange for taking part in the research study. The proposal for the GenomEUtwin study clearly stated that results from the study **would not** be reported to research participants. This included results from genomic scanning, which was to be conducted at laboratories without clinical quality status. In addition the results from the genomic scans were impossible to interpret for any therapeutic use, nor were there staff routinely available or suitably trained, to report or explain results at lay level on a large scale (as needed by GenomEUtwin). However, it was been decided that requests for results by research participants would be decided on a case-by-case basis. Communication to the twins of the results from the project would go through the participating centre and not the labs analysing the DNA.

Participating centres are only obliged to give information as outlined by their national Data Protection Act, this encompasses information regarding study methodology, data handling and confidentiality. The practices of providing feedback vary from country to country and from research project to research project within any twin study centre. For example, all, but one, twin centre provides zygosity results to twin participants (who express an interest in receiving these results). Additionally, several participating centres provide feedback to the twins on clinical data collected in various studies (e.g. blood pressure, fasting blood glucose levels, blood lipid levels, etc).

As part of the recommendations of the GenomEUtwin study, three seminal papers from the study will be summarised and written in lay language to be hosted in the Public Area of the GenomEUtwin website so that research participants can get a flavour of results achieved by GenomEUtwin.

2.2 Issues and potential problems associated with providing feedback

It is important to recognize that identical twins can have different preferences regarding participation in research and receiving feedback. For instance, an identical twin participating in a study could receive high-risk test results but their co-twin may not want to be informed of such results or may not be a study participant. Although most twin pairs are eager to receive confirmed results indicating whether they are identical (MZ) or fraternal (DZ) twins, ethical issues can arise in relation to providing such results. Anecdotal reports describe difficulties experienced by twins who believed that they were dizygotic, but DNA analyses revealed that they were monozygotic. In such cases the twins had a co-twin who suffered from an illness and the unaffected twin was better able to cope with their own health expectations because they believed that they were genetically different from their co-twin. Another difficult instance is illustrated by a twin who had serious mental health effects after finding out that they were not monozygotic (identity issues).

Participating centres have reported that twins ask for further information, including queries regarding biological relationships in family studies or more specific questions related to the study they were participating in. Some want to know if their 'DNA profile' can be read and give them information on whether they will get certain disorders like depression. Some twins have requested if in the future they will be able to receive information regarding their genotypic data.

3 Specific Ethics Related Issues In Twin Studies

Many of the ethical issues of concern in GenomEUtwin are the same as those encountered in any human genetic research. However, twin and family projects also raise some unique ethical concerns. For example, being part of a monozygotic (MZ) twin pair can raise ethical issues regarding confidentiality and expression of free will. MZ twins have an identical DNA code, however, on a molecular level different genes may be expressed. If one of the twins in an MZ pair undergoes single gene testing (i.e. Huntington's Chorea), these results will apply to the second twin regardless of whether or not they wanted or were prepared for them. The same principle applies in research, including projects such as GenomEUtwin where health data and DNA are analysed. As described above, if one twin in an MZ pair does not want to take part in research, but the other twin does, and contributes data and a blood sample this impacts the autonomy of the reluctant twin.

Early on in the GenomEUtwin project the Ethics Core surveyed the participating twin registries regarding special ethics challenges they experienced in running the twin registry programs of research¹. The most sensitive issues arise due to the unique circumstances of twins. Examples include individuals not knowing that they are a twin due to adoption, and twins wanting to find their co-twin once they learn that they have one. Another issue arises if non-twins are mistakenly informed that they are twins and then develop false hopes of finding a lost sibling. When setting up research projects it is important to recognize each twin as an individual and not assume that co-twins automatically share all information. This is particularly relevant when designing recruitment protocols and composing letters of invitation. Such letters explain the rationale for the study, but this could inadvertently divulge confidential information about the co-twin and violate medical privacy. Most of the twin registries rely on address and vital status updates through national registries, however this process could be slow and a register can mistakenly contact twins in pair in which one of the twins has died. The nature of these special issues is extremely sensitive and should be handled by a senior person.

It is important to take time to talk with the twins or their families when these types of questions arise. Steps should be taken in all phases of the project design, planning and conduct to reduce the possibility that these types of problems occur. Although most twin research proceeds without problems the nature of the issues described herein highlight the need to think thoroughly through the ethics-related consequences of each particular study design.

¹ Harris, J. R., Willemsen, G., Kaprio, J., Kyvik, K. O., Pedersen, N. L., Petrini, C. & Cirrincione, L. (July 2004). Double troubles: Examples of special ethics issues in twin studies. Abstract from the 11th International Congress on Twin Studies. *Twin Research*, 7: 352

4 Coordination Challenges of Genomeutwin Across Eight Countries

The primary ethics-related challenges encountered in beginning a project of this nature were:

- Getting procedures in place for the participating centres to share and transfer collected samples and data
- Harmonising procedures for recipient laboratories for sample handling

It is critical in an international project of this type that every participating centre is able to contribute their data and/or samples. GenomEUtwin primarily utilises already collected longitudinal health data and samples. However, time was needed after the official project start date to make sure that all ethical requirements were in place such that these already collected materials could be used as part of this project.

This chapter addresses two key components of the ethical and legal requirements of participating centres taking part in the study: the national regulatory body requirements and the unforeseen legislative changes in the duration of the study to date (2002-2006).

Prior to the start of the project each country identified national legislation relevant to participating in GenomEUtwin and concerning the use of human biological material (biobank) and participant consent. Although some of this legislation is currently obsolete or changed, for historical and analytical purposes the original legislations in place at the time of application to the EU are described by country in the Annex section (11.1) at the end of this report. During the main implementation of the practical steps of GenomEUtwin a surprising amount of new legislation came into effect in the relatively short time since the start of this project – for example Norway and Sweden introduced Biobank legislation and the UK substantially revised its Human Tissue Act. The introduction of some of the new legislation necessitated time delays for one of the centres to contribute with already collected data to GenomEUtwin due to issues of re-consent. The effects of the new legislation is described in the latter half of this chapter (4.2)

A routine has been established to collate up-to-date applicable legislation. This collection is updated annually and a hyperlinked table of laws and regulations is hosted on the GenomEUtwin webpage². Table 4.1 (next page) provides an overview of the guidelines which are relevant for each partner country as of January 2007.

4.1 Permissions and consent regulations - National bodies

In order to participate in GenomEUtwin, participating centres have had to seek permissions from different bodies. These range from other researchers, national data surveillance agencies and ethics committees. A table of regulatory bodies and laws is given in Annex 11.2.

² http://www.genomeutwin.org/member/cores/ethics/docs/Table_of_laws%20GenomEUtwin_Jan_2007.pdf

Table 4-1 Legal documents and guidelines with weblinks of GenomEUtwin partner countries (Jan. 2007)

GenomEUtwin Partner	Acts + Regulations / Guidelines issued ³
Australia	<p>Privacy Act 1988 Act No. 119 of 1988 as amended ⁴ http://www.privacy.gov.au/publications/privacy88_030504.pdf</p> <p>Medical Research - Guidelines under section 95 of the Privacy Act 1988 http://www.privacy.gov.au/publications/e26.pdf</p> <p>Medical Research - Guidelines approved under section 95A of the Privacy Act 1988 http://www.nhmrc.gov.au/publications/_files/e43.pdf</p> <p>The Review of the Private Sector Provisions of the Privacy Act 1998 (2005) - see sections 7.3 and 7.4 http://www.privacy.gov.au/act/review/revreport.pdf</p> <p>Human Tissue Act (New South Wales) 1983 ⁵ http://www.austlii.edu.au/au/legis/nsw/consol_act/hta1983160/index.html</p> <p>Health Records Act (Victoria) 2001 http://www.dms.dpc.vic.gov.au/Domino/Web_Notes/LDMS/PubStatbook.nsf/edfb620cf7503d1aca256da4001b08af/e57a0a1ddcd389fbca256e5b00213f4d/\$FILE/01-002a.pdf</p> <p>Health Records Information Privacy Act (New South Wales) 2002 http://www.austlii.edu.au/au/legis/nsw/consol_act/hraipa2002370/</p> <p>National Statement on Ethical Conduct in Research Involving Humans (1999) http://www.nhmrc.gov.au/publications/_files/e35.pdf</p> <p>Human research ethics handbook –commentary on National statement (above) (2001) http://www.nhmrc.gov.au/publications/hrecbook/pdf/hrechand.pdf</p> <p>Inquiry on the protection of Human Genetic Information (March 2002) http://www.privacy.gov.au/publications/genesub.pdf</p>
Denmark	<p>Act on Processing Personal Data 2000 (amended April 2001) http://www.datatilsynet.dk/eng/index.html</p> <p>Amendment (Danish) http://www.retsinfo.dk/ LINK_0/0&ACCN/A20010028030</p> <p>Scientific-ethical committees and the treatment of biomedical research projects (2003) http://www.retsinfo.dk/ GETDOCI /ACCN/A20030040230-REGL</p>

³ All links last accessed in January 2007

⁴ The impact of Privacy Legislation on NHMRC stakeholders http://www.nhmrc.gov.au/publications/_files/st8.pdf

⁵ Under review. States and territories pass/ratify statutes individually.

	<p>Circular on the interpretation of Biobank research on Scientific ethical committee law (above) 2005 http://www.cvk.im.dk/cvkEverest/Publications/cvkvx2Eimx2Edk%20x2D%20doku%20menter/20061129100511/CurrentVersion/Brevfortolkning.pdf</p>
Finland	<p>Personal Data Act (523/1999) http://www.tietosuoja.fi/uploads/hopxtvf.HTM</p> <p>Act on Medical use of human organs and tissues (2001) http://www.finlex.fi/pdf/saadkaan/E0010101.PDF</p> <p>Medical Research Act (1999) http://www.finlex.fi/pdf/saadkaan/E9990488.PDF</p> <p>Medical Research Decree (1999) http://www.finlex.fi/pdf/saadkaan/E9990986.PDF</p> <p>Act on the National Public Health Institute (1981) (in Swedish) http://www.finlex.fi/sv/laki/alkup/1981/19810828</p> <p>Amendment to Act on the National Public Health Institute (2001) (in Swedish) http://www.finlex.fi/sv/laki/alkup/2001/20010327</p> <p>ETENE Working group on DNA and Epidemiology (2002) http://www.etene.org/dokumentit/GeenimuistioENfin.pdf</p>
Italy	<p>Personal Data Protection Code 2003 http://www.garanteprivacy.it/garante/doc.jsp?ID=1030925</p> <p>Guidelines for the activities in medical genetics (2004) http://www.governo.it/Conferenze/c_stato_regioni/Atti/dettaglio.asp?d=22925</p> <p>Guidelines for the institution and the certification of biobanks (National Committee for Biosafety and Biotechnologies 2006) www.governo.it/biotecnologie/documenti/8.allegatibiobanche.pdf</p> <p>From pharmacogenetics to pharmacogenomics (The National Bioethics Committee, 2006) www.governo.it/bioetica/testi/farmacogenetica.pdf</p> <p>Biobanks and research on human biological material. Opinion of the National Bioethics Committee on a recommendation of the Council of Europe and on a document of the National Committee for Biosafety and Biotechnologies (2006) www.governo.it/bioetica/testi/biobanche.pdf</p>
Norway	<p>Personal Health Data Filing Systems Act 2000 http://www.ub.uio.no/ujur/ulovdata/lov-20000414-031-eng.pdf</p> <p>Health Data Act 2001</p>

	<p>http://www.ub.uio.no/ujur/ulovdata/lov-20010518-024-eng.pdf</p> <p>Biobank Law (2002/3)</p> <p>http://www.lovddata.no/all/hl-20030221-012.html</p> <p>Regulations regarding the transfer of Biobank material outside of Norway (2004)</p> <p>http://www.lovddata.no/for/sf/ho/ho-20040226-0511.html</p>
Sweden	<p>Data Protection Act 1998</p> <p>http://www.sweden.gov.se/content/1/c6/01/55/42/b451922d.pdf</p> <p>Biobanks in Medical Care Act (2002:297)</p> <p>http://www.sweden.gov.se/content/1/c6/02/31/26/f69e36fd.pdf</p> <p>Law on ethical review of research involving humans (2003:460) in Swedish</p> <p>http://www.notisum.se/rnp/sls/lag/20030460.htm</p> <p>Sweden's National Board Of Health And Welfare Regulations (SOSFS 2002:11) Regulations and general advice regarding Biobanks</p> <p>http://www.sos.se/sosfs/2002_11/fs0211.pdf</p> <p>Amendment (2006:19)</p> <p>www.sos.se/sosfs/2006_19/2006_19.pdf</p> <p>Guidelines for Biobank research and regulatory framework (2004)</p> <p>http://www.datainspektionen.se/pdf/rapporter/biobanker.pdf</p>
The Netherlands	<p>Data Protection Act (1999)</p> <p>http://www.dutchdpa.nl/indexen/en_ind_wetten_wbp_wbp.shtml</p> <p>Medical Research Involving Human Subjects Act 1998 ⁶</p> <p>(page 16 onwards) http://www.healthlaw.nl/humsub.pdf</p> <p>Amended Version 2006 (in Dutch)</p> <p>http://www.ccmo-online.nl/hipe/uploads/downloads_catw/WMO%20per%201%20maart%202006.pdf</p> <p>Guide to Medical Research Involving Human Subjects</p> <p>http://www.healthlaw.nl/humsub.pdf</p> <p>The Multicentre Research Review Procedure Directive (revised 2004)</p> <p>http://www.ccmo-online.nl/hipe/uploads/downloads/RET-eng.pdf</p>
U.K. (Incl. N.I.)	<p>Data Protection Act 1998 ⁷</p> <p>http://www.hms.gov.uk/acts/acts1998/19980029.htm#aofs</p>

⁶ Guidelines regarding Clinical Trials revised –enforced March 1st 2006

⁷ Freedom of Information Act implemented 1.1.2005

	<p>Use and Disclosure of Health Data- Guidance on the application of the DPA 1998 http://ico-cms.amaze.co.uk/DocumentUploads/use%20and%20disclosure%20of%20health%20data.pdf</p> <p>Human Tissue Act 2004 http://www.legislation.hmso.gov.uk/acts/acts2004/20040030.htm</p> <p>Freedom of Information Act 2000 (implemented Jan 2005) www.hmso.gov.uk/acts/acts2000/20000036.htm</p> <p>The ethical approval regulations set out by COREC www.corec.org.uk</p> <p>4th report for House of Lords 2001 Human Genetic Databases http://www.publications.parliament.uk/pa/ld200001/ldselect/ldsctech/57/5702.htm</p> <p>MRC policy and guidelines on Human Tissue http://www.mrc.ac.uk/PolicyGuidance/EthicsAndGovernance/UseofHumanTissue/index.htm</p>
European Commission	<p>Data Protection (Directives 95/46/EC) http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31995L0046:EN:HTML</p>
Council of Europe	<p>Convention On Human Rights and Biomedicine (1997) http://conventions.coe.int/Treaty/EN/Treaties/Html/164.htm</p> <p>Recommendation Rec(2006)4 of the Committee of Ministers to member states on research on biological materials of human origin⁸ (See Chapters 4 and 5) https://wcd.coe.int/ViewDoc.jsp?id=977859&BackColorInternet=9999CC&BackColorIntranet=FFBB55&BackColorLogged=FFAC75</p>
UNESCO⁹	<p>International Declaration on Human Genetic Data (2003) http://portal.unesco.org/en/ev.php-URL_ID=17720&URL_DO=DO_TOPIC&URL_SECTION=201.html</p>
CIOMS¹⁰	<p>International Ethical Guidelines for Biomedical Research Involving Human Subjects http://www.cioms.ch/frame_guidelines_nov_2002.htm</p> <p>Draft – Special Ethical considerations for Epidemiological Research (2006) http://www.cioms.ch/special_ethical_consideration.pdf</p>

⁸ Anonymisation should be verified by an appropriate review procedure – this should be noted for GenomEUtwin purposes

⁹ No legal force, only moral

¹⁰ No legal Force, CIOMS is an NGO developed by WHO and UNESCO

4.1.1 Assessment of partner country regulatory requirements on the collected data

The following table illustrates the variety of regulatory requirements of the participating centres and the status of the centres in meeting those demands. Note that this information applies to the data collections that had already been completed or would be underway as part of GenomEUtwin as reported by the representatives of each participating centre. Countries, such as the UK, Netherlands and Australia have not needed to apply for permissions from regulatory bodies nor needed to seek additional consent from participants. This, in part, reflects differences between national regulatory requirements but may also reflect differences in the way in which the registries originally formulated protocols and consented research data collections and use. Finland has only had to seek permission of other research groups to use previously gathered data. Half the participating centres, namely Denmark, Sweden, Norway and Italy needed to apply to their Ethics Committee and Data Protection Agency for permissions to use their data in GenomEUtwin.

Table 4-2 Illustration of status of participating centres – consents, approvals and permissions (2005)

Country	Ethics Committee	Data Protection Agency/Datatilsynet	Others	Twins (samples)	
				Collected	New
Norway	✓	✓	Nn	Nn **	IP
Italy	✓	✓	Nn	✓	✓
Sweden	✓*	*	✓	Nn	
Denmark	✓	✓	✓	Nn	✓
The Finland.	Nn		✓	Nn	
Netherlands	Nn				
U.K.	Nn				
Australia	Nn				

Key :

- Nn - None needed
 ✓ - Process completed

Sweden * - For every analysis to search for specific genes, approval must be sought from the ethics committee (welfare and social affairs) and Datatilsynet

Norway ** - After a lengthy process involving the Regional Ethics Committee (REK) and the Social and Health Directorate (SHDir) an exemption has been granted for obtaining reconsent of collected (biobanked) samples to be sent overseas.

4.2 Changing legislation and its effects

The research undertaken in GenomEUtwin represents a rapidly changing and advancing field of science that relies on genetic tools and biobanking. The scientific and methodological advancements have developed at such a quick pace and many countries experience a lag in legislation to protect individual privacy rights and health data associated with genetic and genomic studies connected to research biobanks. This situation has led many countries to launch or revisit legislation governing the establishment and access of biobank samples and data. However, at the time of writing this manual the only EU/EFTA countries that have specific legislation regarding biobanks are Iceland, Sweden and Norway. Some countries have resorted to amending their Privacy or Data Protection Acts to encompass all kinds of data including biological samples as well as the transfer of health data and samples overseas and issues regarding genetic privacy.

Since GenomEUtwin began there have been several changes or amendments to legislation in several participating centres. As described below, some of these changes have had time implications for participating centre contributing samples.

4.2.1 Norway

The Norwegian GenomEUtwin partner's participation has been affected by the introduction and enforcement of two pieces of legislation¹¹; The Personal Health Data and Register Act (2000) and the Biobank Act (2003). The implications of these acts hindered sending biobanked samples to KTL for two reasons. The former Act invalidated the obtained consents as it required greater detail in withdrawal procedures and the precise nature of how the blood would be used in research. The latter act additionally demanded that participants should specifically consent to their blood (human biological material) being sent out of the country. Due to the large number of participants who would need to be recontacted for consent, coupled with time considerations for obtaining these consents, the Norwegian Institute of Public Health (NIPH) maintained that renewing consents would be an ineffective approach and would jeopardise the centre's participation in GenomEUtwin. In order for the renewed consent requirement to be waived the NIPH appealed to the Social and Health Directorate and Regional Ethics Committee (REK) to obtain an exemption from reconsenting the participants whose samples have been collected previously. In addition NIPH put forward a case to REK to implement a broad consent for new blood samples. These processes have been lengthy, as this case has set a precedent.

It is anticipated that new legislation will be introduced following a consultation report on Medical Health Research. This new legislation is designed to simplify bureaucracy involved in the research process and to make international collaboration easier.

¹¹ Full links to these laws are in table 4-1

4.2.2 UK

The Human Tissue Act (2004) has come into effect following a lengthy debate regarding use of human tissue for research purposes and consent issues. Consent is a fundamental principle to this act that set a framework for regulating storage and use of human tissues. Registration (licences) will need to be applied for in order to establish and operate a biobank for research purposes. The UK GenomEUtwin partner should not be affected though it is fair to note the application of the act is still in its infancy.

The potential effects of the new Freedom of Information Act UK (2005) have also yet to be determined because the Act was passed in 2000 but only came into effect in January 2005. This act gives people a general right of access to information held by or on behalf of public authorities and promotes a culture of openness and accountability of the public sector bodies. The UK GenomEUtwin partner has stated that the enforcement of this act brought about changes in the method by which data were stored, aside from that, there have been no other implications reported in relation to this act.

4.2.3 Italy

Italy has amended its data protection code in the last two years. At the moment there are no direct implications for the involvement in GenomEUtwin. However, the Italian Data Protection Authority will issue a new authorisation for the use of genetic samples and data. At the moment this authorisation is under advisement along with issues regarding establishing and licensing biobanks, activities in genetic research and limitations to patenting of human gene sequences.

4.2.4 Denmark

The Danish Act on Ethics Committees has been amended and updated in 2003. The changes have not adversely affected the participating centre. There amendments include: greater transparency regarding study sponsor (aimed at industry), deadlines for the ethics committees (previously applicant could wait for up to 3 months for a decision), and the most important amendment for the GenomEUtwin participating centre - interview and questionnaire studies are only to go through the committees if sampling of biological material is included in the project.

4.2.5 The Netherlands

The Netherlands has seen a recent amendment in its Medical Research involving Human Subjects Act. The changes will have no effect on GenomEUtwin as they are based on implementing clinical trial guidelines by the EU into the Dutch legislation, which have no relevance to the Dutch participating centre.

4.2.6 Australia

During the early stages of GenomEUtwin The Australian Law Reform Commission (ALRC) performed a joint enquiry with the Australian Health Ethics Committee (AHEC) to produce final report—Essentially Yours: The Protection of Human Genetic Information in Australia (ALRC 96)¹². This was tabled in federal Parliament in May 2003 and several of the recommendations have been implemented in the duration of GenomEUtwin. One of these was the creation of an independent expert advisory body - the Human Genetics Advisory Committee.

A summary of relevant recommendations from the report are described below:

- Criminal offence to send someone's sample for genetic testing without consent (special reference to paternity testing)
- National Health and Medical Research Council (NHMRC) should establish and administrate public registers of human genetic research data and develop conditions of registration. No genetic research can be conducted unless database is registered.
- National Statement amended to provide guidance on the use of a 'gene trustee' system as an additional protection of privacy
- Specified guidance on obtaining consent to **unspecified** future research
- The Australian Health Ministers' Advisory Council should develop nationally consistent rules governing disclosure for law enforcement purposes of genetic samples and information held in human genetic research databases
- Each Australian State and Territory has enacted legislation that regulates the donation of human tissue and organs for transplantation and research (Human Tissue Acts (HTA)). There should be an inquiry to review amending HTA to give effective means to protect privacy. Until then, regulations regulating the handling of genetic material should not rely primarily on amendments to the HTA.
- Legislation should not be enacted to confer full propriety rights in human genetic samples
- Privacy Act amendments in Human Generics Research. The NHMRC should develop advice for best practise regarding:
 - Mechanisms for coding/de-identifying genetic samples
 - Independent intermediaries to hold key codes
 - Legal/ethical obligation to inform donors of health implications of testing samples
 - Disclosure by researchers regarding commercial activities
 - Develop consent forms (include graduated consent options, ownership, commercial aspects, methods to protect privacy, withdrawal of consent).

¹² Accessed May 2004, <http://www.austlii.edu.au/au/other/alrc/publications/reports/96/>

4.3 Legislative issues for the future

For studies that follow GenomEUtwin, it would be useful to keep a close eye on the following countries (of the GenomEUtwin consortia) as changes or amendments affecting Biobank research are currently under advisement. These include Finland, Sweden, Norway, Denmark, Italy and Australia.

5 Data Access and Security

5.1 Introduction

The GenomEUtwin Ethics and Database cores have responsibility to establish secure routines surrounding data access and use in GenomEUtwin. To this end the Ethics Core has created two main policy documents. *The Biological Sample Transfer Agreement* (signed by all partners) covers transfer and protection of the biological samples. The details of the document are discussed at the end of this chapter.

The second document, *The Data Access and Security Policy (DASP)*, contains terms and conditions under which data are merged, accessed, loaned and shared. It also describes procedures for long-term data storage, storage of key codes for sample ID and confidentiality. The DASP is the precursor to *the Security Policies for TwinNET* created by the Database Core. It was developed through a working group composed of members (see below) from the Ethics Core, the Database Core plus outside experts. The policies generated by the working group were then discussed and modified through discussion with the GenomEUtwin Steering Group.

Working group members for the DASP:

<u>Norway:</u>	Jennifer Harris (chair, Ethics Core and DASP working group), Jon Roy Johansen, Homa Hasan, Ingunn Brandt
<u>Denmark:</u>	Kirsten Ohm Kyvik and Lars Hvidberg
<u>Finland :</u>	Kaisa Silander
<u>Sweden:</u>	Jan-Eric Litton (chair, Database Core)
<u>Canada:</u>	Cynthia Chassigneux & Bartha Maria Knoppers (consulting experts)

The *DASP* outlines the routines and policies put in place to ensure a high degree of protection for data contributed and shared by all the participating centres. It defines and sets out rules for sharing, access and security measures employed for all researchers and participating centres. The *DASP* identifies Cores and groups that are responsible for key tasks such as long term data storage and security measures. Many of the security measures outlined in the *DASP* have required technical solutions and routines which have been described and put into effect by the Database Core as detailed in document '*Security Policies for TwinNET*'.

5.2 GenomEUtwin Data Access and Security Policy

Below is a copy of the GenomEUtwin *Data Access and Security Policy*. The policies have been specified and ratified in a signed agreement between all sites. Original copies of the documents are filed at the National Public Health Institute in Finland.



Data Access and Security Policy

The GenomEUtwin Ethics and Database cores have responsibility to establish secure routines surrounding data access and use in GenomEUtwin¹³.

This is an agreement between the centres participating in GenomEUtwin

- Queensland Institute of Medical research Australia
- University of Southern Denmark Denmark
- National Public Health Institute Finland
- University of Helsinki Finland
- Finnish Genome Centre Finland
- National Centre for Epidemiology Italy
- Norwegian Institute of Public Health Norway
- Karolinska Institute Sweden
- Uppsala University Sweden
- Leiden University The Netherlands
- Vrije University The Netherlands
- Queen's University, Belfast U.K. (MORGAM)
- St. Thomas Hospital and UK twins United Kingdom

Key to terms of references –

TwinNET- GenomEUtwin collaboration network, secure communication through the Internet.

Publications Committee – This committee is appointed by the steering group of GenomEUtwin. It approves publication proposals, appoints leaders for approved publications, and keeps the list of all publications and presentations by the GenomEUtwin project. It furthermore is responsible for obtaining consent from the GenomEUtwin Steering Group for all publications.

Data – this term refers to research data utilised for the purpose of GenomEUtwin or generated by GenomEUtwin

¹³ DASP Working group members:

Norway Jennifer Harris (chair), Jon Roy Johansen, Homa Hasan, Ingunn Brandt

Denmark: Kirsten Ohm Kyvik, **Finland:** Kaisa Silander, **Sweden:** Jan-Eric Litton

Canada: Cynthia Chassigneux & Bartha Maria Knoppers (consulting experts)

Merging, Sharing and Loaning GenomEUtwin Data

- Each participating centre agrees to follow the principles of data merging and sharing and loaning as described in this document.
- Data from the participating centres (PCs) will be merged only for the purpose of scientific analyses conducted to fulfil the analytic work described in approved publication proposals.
- The principle of equal sharing of the data and scientific results between all contributing centres will apply.

Confidentiality

- Security measures are detailed later in this document; in addition participating centres and scientists have an obligation of confidentiality. No communication of any data to any unauthorised party or person (i.e. outside the GenomEUtwin consortia) is allowed
- Internal confidentiality agreements between institutes and personnel handling GenomEUtwin data are recommended.

Data Access

- Technical solutions for data access to the TwinNET are established by the Database Core and described in their manual on Standard Operating Procedures (SOP). All centres will work with the Database Core to ensure that their data access procedures adhere to these configurations and solutions.
- Local access refers to who may connect to TwinNET for the purpose of retrieving data from multiple centres. Each PC agrees to keep the number of individuals who have local access to TwinNET to a minimum (2-3 individuals).
- The designated lead scientist on the GenomEUtwin contract for each PC will provide names of the individuals who have local access to the genotyping hub (Juha Muiilu) and the phenotyping hub (Ann Björklund).

Data Use

- Prior to making data available each PC must ensure that their current permissions and approvals from ethics review boards and local data protection agencies allow that their data may be shared for research and scientific purposes within GenomEUtwin.
- The specific data that may be accessed will be described in a publication proposal that has been approved by the GenomEUtwin publications committee.
- Once the data have been accessed they may be made available to the researchers specified in the publication proposal who will be conducting the analyses. The 'working' data sets will be kept on a secure site during the analysis phase. The Database Core will advise on the feasibility and necessity of encrypting the working data sets. If encryption is decided upon then the encryption procedures will be provided by the Database Core.
- The data may only be used according to the intents and research goals outlined in the publication proposal for which the data were accessed.
- Exceptions can be made and the data may be used for new purposes upon receipt and approval of a new proposal through the normal publication procedures.

Long-term Data Storage

- The aggregated data upon which each published manuscript is based will be stored for a period of 15 years following publication.
- The Database Core will have responsibility to develop a centralized and secure procedure for cataloguing and storing each data set by the respective manuscript for which it was used.
- The Database Core will have responsibility for storing the manuscript data and associated documentation files.
- The Database Core will have responsibility for updating the storage format of these datasets so that they are maintained accessible as technology & software changes.
- Note that there has not been a procedure in place for tracking and storing the data in manuscripts already published in GenomEUtwin.

Procedures for handling data when a participant wants to withdraw

Each country has different procedures surrounding participant withdrawal from their respective sites and cases of participant withdrawal will be handled locally. It cannot be guaranteed to alter data or withdraw samples already undergoing analyses within GenomEUtwin due to data backup procedures and genotyping procedures.

Security procedures

- Technical (hardware and software) solutions for database security will be established by the Database Core and described in their operations manual.
- A security group will be established to help the PCs set up their data security procedures in accordance with the established requirements
- The security group will:
 - formulate rules for auditing the PCs to check that they are operating in accordance with the established requirements
 - have authority to request documentation of IT systems and run checks that security is not breached. The procedures for conducting such checks will be developed by the Database Core and approved by the Steering Group.
 - establish procedures for informing the Ethics Core and Steering Group when security is breached
 - work with participating centre where there has been a breach of security
 - in conjunction with the Steering Group, develop procedures for assigning authority to limit data access if procedures are not corrected within the agreed upon time frame
- The agreement to be signed between the PCs will indicate that failure to follow the data security procedures will result in denied access and disconnection from the TwinNET.

Procedures for storage of key or name lists

- Even though the routines for storage of key files and name lists satisfy national requirements within each country, a potential problem in one country could cause problems for the entire project. Therefore, each PC will follow a common procedure for the storage of key files and names lists. This procedure requires that key files with names or information that would allow linkage back to an individual:
 - are never made available via TwinNET or within GenomEUtwin
 - should be encrypted, password protected and kept under double lock. Encrypted and password protected key files may also be kept on limited access servers.

I have read the terms and conditions stated in this document and agree to abide by them.

Signed by:

_____ Signature of Legal representative

_____ Printed Name (of Legal representative)

_____ Date

_____ Signature of Scientific Person in Charge of Project

_____ Printed Name (of Scientific Person in Charge of Project)

_____ Date

5.3 Data security protocols and solutions

The Database Core, in conjunction with input from The Ethics Core, developed procedures and technical solutions to realize the terms and conditions set forth under the Data Access and Security Policy. The resulting solutions, policies and procedures are detailed in the document entitled '*Security Policies for TwinNET*' (available on GenomEUtwin website, members' area). It describes the configuration through which the GenomEUtwin partners can share and access data including the hardware requirements needed for achieving the security protocols surrounding data access and sharing.

The full scope of this document is not presented here, the content areas include a description of the strategies and procedures for data access and storage, secure communication through the internet, auditing, e-mail, security requirements for networks and equipment, policies pertaining to passwords, remote access, router and server security, virtual private networks, wireless communication and how breaches of security will be handled. The TwinNET Security Group is a working group under the database core and has responsibility to monitor proper usage of the TwinNET and to enforce the procedures as described in the Security Policies for TwinNET.

5.3.1 Biological samples

In dealing with samples arriving from international partners and the return of genetic analyses to the respective centres standardization procedures were established for the purposes of sample transfer and tracking. In addition, terms and agreements were put into place concerning the use of the samples and data derived from them. These procedures are described in the *Biological Sample Transfer Agreement*. This document describes the protocols for transfer of biological samples (as outlined by KTL), and the rights and obligations of the collaborating laboratories and participating centres for the duration of GenomEUtwin. It addresses issues of confidentiality, restriction of access to samples by 3rd parties, and protocols for sample return at project end.

The standardisation of mass volumes of samples arriving at KTL for DNA extraction, preparation and analysis requires careful data entry and minimisation of error. The first part of this chapter describes the laboratory procedures to achieve this, and the latter half describes the collaborative agreements that enforce the ethical and moral philosophy governing the transfer, access and sharing of biological samples.

The quality control of the genetic analyses procedures is described in the next chapter. During the tenure of the project, three collaborating laboratories have been involved in genotyping; these are the Finnish Genome Center, The Research Group of Molecular Medicine (Uppsala University) and Uppsala Rudbeck laboratory. KTL co-ordinates sample handling.

5.4 De-identification - coding samples

Procedures have been set up for coding of samples and data used in GenomEUtwin. These are described in detail in the special edition of Twin Research Journal¹⁴ -

The unique European twin identifier is referred to as the EUID number. It contains 12 digits. These 12-digits serve a further purpose of allowing KTL to run quality checks of the data entry by cross referencing, for example, each centre has a unique digit that identifies their country.

The EUID consists of four parts:

- Country code 3 digits – using ISO 3166 standard
- Randomized number 7 digits containing a random twin pair number
- Identification number 1 digit specifying a twin number within pairs
- Check sum 1 digit, a tool for aiding data security and accuracy which assures that assignment of identification numbers is correct.

De-identifying samples is a reversible process. Each participating centre retains the key linking personal identification to the EUID. These keys are stored under safety stipulations described in the DASP agreement and are never transferred to or made available within TwinNET. This ensures that data from individual participants remain functionally anonymous.

Anonymisation of samples is defined to be the irreversible act of destroying the key code linking identity. The purpose of using the term ‘functionally anonymous’ is to illustrate that, with the exception of the centre providing a sample, it is virtually impossible for collaborators within the GenomEUtwin to link a sample to the identity of any individual participant.

5.5 Transfer of information for processing samples

Instructions for sending samples and information required for genotyping have been assembled by the Genotyping Core and are available in a detailed document in the member web page (document titled ‘*Instructions to send samples and information for genotyping*’)¹⁵ .

This document describes the information needed for labelling and describing samples. This information is completed in Data Form 1 (see below) and transferred prior to sending samples. Every shipment contains one duplicate DNA sample for every 92 samples.

¹⁴ Litton J-E.; Muilu J.; Björklund A.; Leinonen A.; Pedersen N.L. Data Modeling and Data Communication in GenomEUtwin pp. 383-390(8) Twin Research Volume 6, Number 5, 1 October 2003, pp. 455-463(9)

¹⁵ http://www.GenomEUtwin.org/member/cores/gt/docs/Instructions_to_send_samples.pdf

An example of Data Form 1 is illustrated below.

Figure 5-1 DNA sample sheet

Number Information		Original sample information				
EUid number	CsampleID	Sample type before extraction	Anticoagulant (if whole blood)	Date of sample drawing	Date of freezing	Date of extraction
360026200113	1354	Whole blood	EDTA	01.12.2004	02.12.2004	6.1.2005
360026200225	5551	Whole blood	ACD	01.02.2005		1.2.2005
360026250091	2648	Buffy coat		03.11.2003	03.11.2003	5.6.2004

In addition, person information is needed in order to detect genotyping errors, including the ID number, sex, birthdate, family id numbers and zygosity. This information is completed in a separate form (Data Form 2) and is encrypted and then sent to the data managers of the genotyping centres.

5.6 Sample transfer

The procedures for sample transfer are such that neither Data Form 1 nor Data Form 2 accompanies the actual samples. All samples are sent via courier mail with return receipt. Detailed shipment instructions are provided for each type of sample (extracted DNA, blood samples) and are available online as are extensive contact details for questions and queries. The shipping documents include description of the goods, statement of the scientific value and country specific information.

5.6.1 Tracking samples

Prior to shipping the blood/DNA samples to KTL, the centres are asked to label all the samples with bar coded GenomEutwin IDs. On arrival to KTL, the blood/DNA tubes are labelled with KTL's internal numbers, unique to each GenomEutwin sample. Each sample is received in the database and checked against the sample lists provided by the participating centre. Sample storage locations, all the identification numbers, and other available sample information (concentration, volume, sample type etc.) are recorded in the database.

5.7 Biological sample transfer

During the Ethics Core meeting in Oslo¹⁶ (August, 2004) the need to develop an official transfer agreement between the participating centres was highlighted. After careful consideration and analysis the use of traditional Material Transfer Agreements (MTA) was rejected because MTAs are legal contracts used to describe the use and loan of rights of materials between research groups that have not engaged in a collaborative research project. Therefore, a custom-made policy document, the *Biological Sample Transfer Agreement (STA)*, was created for GenomEUtwin. This document describes the nature of transfer, sharing and use of biological samples within the collaboration. The EU IPR helpdesk¹⁷ was used as a resource for feedback to this document. An important feature of this document is that it has been styled and formatted to be understandable to staff with non-legal education.

A copy of the *Biological Sample Transfer Agreement (STA)* is inserted below. This document has been signed by all participating centres. It outlines the duties and obligations on the part of the participating centres that send the samples or completed genomic scans, and the laboratories that receive and analyse the samples.

It describes the nature of confidentiality, ownership of results and leftover DNA, use of samples and forbids further distribution of results or samples outside the GenomEUtwin consortia.

¹⁶ See minutes for meeting on http://www.genomeutwin.org/member/meetings/ET_MINUTES_19082004_OSL.htm

¹⁷ <http://www.ipr-helpdesk.org/controlador/principal?seccion=aboutus&len=en>

5.8 The Biological Sample Transfer Agreement



This is an agreement between the centres participating in GenomEUtwin

- Queensland Institute of Medical research Australia
- University of Southern Denmark Denmark
- National Public Health Institute Finland
- University of Helsinki Finland
- Finnish Genome Centre Finland
- National Centre for Epidemiology Italy
- Norwegian Institute of Public Health Norway
- Karolinska Institute Sweden
- Uppsala University Sweden
- Leiden University The Netherlands
- Vrije University The Netherlands
- Queen's University, Belfast U.K. (MORGAM)
- St. Thomas Hospital and UK twins United Kingdom

This document contains provisions to which centres participating in the GenomEUtwin project agree to abide to regarding sharing and access to biological samples and genetic data used in GenomEUtwin.

Key to terms of references –

TwinNET- GenomEUtwin collaboration network - secure communication through the Internet.

Publications Committee – This committee is appointed by the steering group of GenomEUtwin. It approves publication proposals, appoints leaders for approved publications, and keeps the list of all publications and presentations by the GenomEUtwin project. It furthermore is responsible for obtaining consent from the GenomEUtwin Steering Group for all publications.

Data Security and Access Policy – a separate GenomEUtwin document that describes the terms and conditions for data sharing and access.

Data – this term refers to research data utilised for the purpose of GenomEUtwin or generated by GenomEUtwin

Transfer of Samples

- For the duration of the GenomEUtwin project and if funding is available, participating centres (PCs) can either send blood or DNA samples to The National Public Health Institute of Finland (KTL) for processing. Alternatively, a PC can send, or make accessible, already completed genomic scans or genetic analyses to KTL,
- KTL will process blood samples sent by PCs by extracting DNA. DNA will be quality controlled and diluted for genotyping. Genotyping will utilise dried DNA plates. These plates will be sent to the genotyping laboratories at Helsinki University (Finnish Genome Centre), and Uppsala University,
- Remaining DNA will be stored (stock DNA) at KTL for the duration of the GenomEUtwin project or as long as agreed, and will be returned to PC upon completion of project or when requested (by PC),
- The genotyping laboratories will submit genotype information to TwinNET, which will then be available to the PCs, and to GenomEUtwin researchers for analysis purpose,
- Each PC must ensure they adhere to the procedures outlined in the 'Instructions to send samples' document and fill out Data forms 1 and 2.
([http://www.genomeutwin.org/member/cores/gt/docs/Instructions to send samples.pdf](http://www.genomeutwin.org/member/cores/gt/docs/Instructions%20to%20send%20samples.pdf))

Biological samples

- Each PC has a responsibility to make sure the terms and conditions stated in this agreement adhere to their own country's laws and regulations,
- The GenomEUtwin genotyping laboratories agree to handle the samples according to the terms and conditions of this document,
- Biological samples and resulting data will be labelled using the EUtwin ID number system. Participant identification data will be held by the originating PC only, thus all data is functionally anonymous to all other participating PCs (de-identified),
- The use of the samples is for research purposes only and not for commercial or 'for profit' use,
- The sample materials and data of GenomEUtwin participating centre's will not be distributed further to any individuals, labs or research institutions outside the GenomEUtwin consortia (3rd party) by KTL and collaborating laboratories for the duration of the project (this point will open for negotiation in the event of an extension),
- Upon completion of GenomEUtwin (Oct 2006) remaining DNA stocks will either be transferred back to the original participating Centre provider (PC) or destroyed, upon request of the PC, using standard laboratory protocols, except as described in the next point below

- In the case that GenomEUtwin collaborations are extended through a new research project the samples may be retained under new policies agreed upon by the PC as long as this is in compliance with existing IRB approvals (any extension of GenomEUtwin may require a new collaboration contract to fulfil existing Data Protection Agencies and Ethics committee permissions),
- Genotype results generated from GenomEUtwin laboratories returned to participating centres may be used for research purposes in future studies conducted by that PC.
- **Confidentiality**
No communication of any data to any unauthorised party or person (i.e. outside the GenomEUtwin consortia) is allowed, Participating centres and scientists have an obligation of confidentiality. Internal confidentiality agreements between institutes and personnel handling GenomEUtwin data are recommended.
- **Withdrawal of samples**
Additionally, each PC whose legislation requires action after participant request for withdrawal can:
 - anonymise data (within their own key code) submitted for analysis to GenomEUtwin
 - ask that biological samples stored at GenomEUtwin laboratories as DNA stock to be destroyed. Once a sample has been submitted for genetic analyses it cannot be removed from the dried DNA plates.

–NOTE: Publication datasets are not subject to withdrawal procedures

Status of original samples and data generated

- Original biological samples belong, at all times, to the PC providing the sample,
- Data generated from samples belong to the PC providing the sample, regardless of whether or not they were the contractor carrying out the analyses. This includes completed genome scans or other genetic analyses contributed by a PC. Each PC retains the right to decide which of the data (generated or otherwise) are shared in the TwinNET (see data security policy for further details),
- Collaborating laboratories in GenomEUtwin can access the data generated in GenomEUtwin following the guidelines of the Data Security Policy and in accordance with the goals described in the relevant manuscript proposal that has been approved by the GenomEUtwin Publications Committee. For details, go to <http://www.genomeutwin.org/member/ppolicies.htm>

I have read the terms and conditions stated in this document and agree to abide by them.

Signed by:

_____ Signature of Legal representative

_____ Printed Name (of Legal representative)

_____ Date

_____ Signature of Scientific Person in Charge of Project

_____ Printed Name (of Scientific Person in Charge of Project)

_____ Date

6 Genotyping Core : Quality Control Procedures

The Genotyping Core is operated at two geographical sites, one in Helsinki at the Biomedicum institute, and one at Uppsala University. The tasks of the genotyping core are to extract DNA from blood samples and to perform the genotyping work in the laboratory. Assigned genotypes are delivered from the Genotyping Core to a joint database for further statistical analysis. The Genotyping Core is responsible for establishing and implementing quality control (QC) procedures and routines. The project laboratories are not licensed to produce results of a clinical standard. This is one of the reasons why GenomEUtwin does not provide genotype results to participants. For clinical purposes, genotype results generated through research labs should be confirmed through re-analysis by an accredited lab using a fresh blood sample, before any reliable information can be given to an individual.

Procedures are required to ensure that data extracted from samples are of a high quality and free of errors to make it valuable to analyse and share with the consortia. There are several laboratories involved in genotyping analyses, their methods for quality control will be summarised in this chapter. Since the project start new systems have been put in place and the collaborating laboratory, at Uppsala University, headed by Professor Syvänen (participant 10 in consortia), has been one of the first laboratories in Europe to achieve ISO recognition.

6.1 Finnish Genome Center (KTL)

The Finnish Genome Center was founded to support genetic research on complex traits in Finland, and it provides genotyping services for both genome-wide scan and fine-mapping analyses. The Finnish Genome Center provides genome-wide scan genotypes using microsatellite markers for the GenomEUtwin project. The procedures described are those that were being used for the GenomEUtwin data from 2005¹⁸.

The genotyping process begins when samples are diluted and dispensed into microtiter plates. Thereafter all steps are carried out in this plate format. All individual samples belonging to the GenomEUtwin project are handled at the Public Health Institute in Helsinki, which provides the Finnish Genome Center with DNA-plates ready for genotyping.

Data collected during the genotyping process are stored in a relational data-base developed in house. The database serves as a basis for data management, quality control, and analysis operations. This database has a fire wall and password protection. The genotype and phenotype data are kept separately.

6.1.1 Overall QC strategies

Since thousands of genotyping reactions may be set up during a working day, specific check-points, to identify possible errors in the handling of samples and reagents are required. Errors

¹⁸ Source document by Elisabeth Widén, Finnish Genome Center

that may occur during the genotyping process are: sample and plate mix-ups, technical problems related to PCR and the visualization of alleles, errors in allele calling, and marker mutations (Table 6-1).

Table 6-1 Possible sources of errors in genotyping data-sets.

Source of error	Error detection method
Plate mix-ups	Negative plate control, reference samples
Electrophoresis problems	Manual electropherogram checks by two independent reviewers
Allele calling errors	Manual electropherogram checks by two independent reviewers Pedcheck (if pedigree structures are available)
Sample mix-ups	Test for deviation of expected allele sharing between siblings
Marker mutations, null alleles	Pedcheck (if pedigree structures are available)
Common null alleles (previously not tested fine-mapping markers)	Test for Hardy Weinberg equilibrium

6.1.2 Database quality checks

Reference sample genotypes are compared with the expected genotypes, a check for identical genotypes is performed (to identify MZ-twin pairs and duplicate samples), and genotyping success rates for samples and markers are calculated.

All completed GenomEUtwin genome-wide scan projects will be subjected to this deviation test using the software GRR (Graphical Representation of Relationships).

The X-chromosomal data are checked using both in-house scripts and Pedcheck software. Using in-house scripts, male individuals heterozygous for any X-linked locus and females homozygous for all genotyped X-chromosomal loci will be identified. Even though sibling-pairs without parents don't contain any information to detect non-mendelian inheritance for autosomal markers, non-inheritances can be detected for X-linked loci. Therefore the X-chromosomal data for sibling-pairs without parental genotypes will be subjected to a

segregation check using Pedcheck. All genotypes generating non-mendelian inheritances will be manually reviewed to resolve possible genotyping errors. If family structures are available all parental genotypes (including autosomal markers and X-chromosomal markers) will be subjected to a Pedcheck run prior to data release.

Cleaned genotyping data ready for analysis will be released to the GenomEUtwin genotype database (GtDB). Data for twin-pairs or pedigrees with unresolved errors in relationships or sex status will be retained. Twin-pairs who are classified to be monozygous according to the genotypes results are flagged.

6.1.3 Estimate of overall error rates

On each 96-well plate one blind duplicate sample is included. These duplicates are used to calculate the overall genotype discrepancy rate. The average overall discrepancy rate for genome-wide scan projects at the Finnish Genome Center is as low as 2-3 errors /1000 genotypes.

6.2 Uppsala

In the past 2 years Uppsala¹⁹ have implemented their own, new, IT system for genotype production called *Chiasma*. It is based on Microsoft's SQL Server database engine running on a dedicated database server machine.

6.2.1 Quality control

One of the advantages with *Chiasma* is the possibility to implement homogenous quality control procedures across all platforms. A dedicated client program which tests for duplicate errors, inheritance errors, and deviations from Hardy-Weinberg equilibrium carries out the quality control. Statistics such as allele frequencies, success rates and the number of failures in control samples are available. All of these figures are monitored as soon as new genotypes are added to the project and at the end of a project. Furthermore, the program can automatically produce a list of samples that must be genotyped again due to low success rate, duplicate errors or suspiciously low allele frequencies.

6.2.2 Quality Policy of the SNP technology platform in Uppsala

The SNP technology platform is accredited by SWEDAC according to the European quality standard ISO/IEC 17025. Flexible accreditation is granted for the complete genotyping process, including the selection of SNP markers and development of new SNP assays. The accreditation mark is a guarantee to other parties that the SNP genotyping is of high quality.

¹⁹ Source website <http://www.medsci.uu.se/molmed/snpgenotyping/quality.htm>

7 Publication Policy

All data sharing is granted based upon a manuscript proposal. This process is supervised by the Publications Committee.

7.1 Publications Committee

The Publication Policy was established by the Publication Committee and approved by the Steering Board. The members are Kirsten Ohm Kyvik, Ann-Christine Syvänen and Kari Kuulasmaa. The Publication Committee is responsible for monitoring the publication proposals and obtaining consent from the GenomEUtwin Steering Group for all publications.

7.2 Goals of the GenomEUtwin Publication Policy

The GenomEUtwin publication policy is designed to:

- encourage scientific publication of all types,
- maintain a high quality of publications,
- ensure the legitimate interests of all GenomEUtwin partners.

The GenomEUtwin Publication Policy is hosted on the GenomEUtwin website ²⁰.

7.3 Summary of Publication Policy

The policy refers to papers, abstracts and presentations of unpublished GenomEUtwin data. Rules are specified for three types of publications and presentations that may be generated through GenomEUtwin:

1. Publications and presentations from individual partners
2. Publications and presentations from collaboration between individual partners
3. Collaborative GenomEUtwin Publications

A Collaborative GenomEUtwin publication can be proposed by any partner. Data **cannot** be presented or published without the consent of the responsible person ²¹ of each GenomEUtwin partner. The publication policy describes the type of information to include in a manuscript proposal, the rules for authorship, information to include in the standard acknowledgement, rules for reviews and publication, and how disagreements are handled and rules for release of phenotypic and genetic data.

²⁰ <http://www.GenomEUtwin.org/member/ppolicies.htm>

²¹ This is a representative of a partner country who has a dual role of protecting the interests of their home institution whilst participating in GenomEUtwin.

The Publication Committee reviews the manuscript proposal to assess the appropriateness of the proposal, possibly with the help of the Steering Group, and decides whether the manuscript should be accepted as a GenomEUtwin collaborative 'Approved Publication', its priority, and who should be the manuscript leader. The GenomEUtwin Steering group monitors the progress of the publication. On completion, the manuscript is sent to all Partners for their approval. The Partners (responsible persons) approve the manuscript for publication and/or send their comments to the first author or the person(s) specified in the covering letter of the manuscript. This must be forthcoming within three weeks, and if no response is obtained the publication will proceed

A list of all publications will be maintained in the GenomEUtwin website.

7.4 Disagreement

If a disagreement arises regarding any GenomEUtwin Publication, and the Publication Committee is unable to solve it, the Steering Group can be asked to review the case. If this does not resolve the problem in a way which is satisfactory to all the parties in the conflict, the Scientific Advisory Committee can act as conciliator.

7.5 Rules for release of data

All GenomEUtwin partners have the responsibility of ensuring the security and confidentiality of the unpublished GenomEUtwin Data to which they are allowed access. As a general rule, no GenomEUtwin Data can be released to a third party without the consent of the responsible person of each relevant GenomEUtwin Partner.

7.5.1 Release of genetic data

The GenomEUtwin partners will receive the genetic data generated from their DNA. These data can be used by each Partner for analysis and publication of phenotypes not forming a part of the GenomEUtwin Project after proper agreement with the genetic laboratories who generated the data. These publication rules apply also to these manuscripts.

8 Intellectual Property Rights Issues

Glossary²²

Access rights

Licences and user rights to knowledge or pre-existing know-how owned by another person.

Knowledge

Term defined in the Model contract as "the results, including information, whether or not they can be protected, arising from the project governed by this contract, as well as copyrights or rights pertaining to such results following applications for, or the issue of patents, designs, plant varieties, supplementary protection certificates or similar forms of protection."

Infringement

Violation of an intellectual property right

Intellectual Property

Intellectual property covers two main areas: industrial property, covering inventions, trade marks, industrial designs, and protected designations of origin; copyright, represented by literary, musical, artistic, photographic, and audio-visual works.

Pre-existing know-how

Term defined in the Model contract as "the information which is held by contractors prior to the conclusion of the contract, or acquired in parallel with it, as well as copyrights or rights pertaining to such information following applications for, or the issue of, patents, designs, plant varieties, supplementary protection certificates or similar forms of protection."

Public Domain

- a) The legal situation of an invention, design, work, commercial symbol or any other creation that is not protected by an intellectual property right.
- b) In the law relating to confidentiality and trade secrets, that which is publicly known.

8.1 EU rules

The EU Commission seeks to make European research competitive with the rest of the world. It can deny access rights to 3rd parties outside of the EU. Where participants in certain countries do not protect their knowledge or waive these rights the EU commission will adopt protective measures and take on the obligations with the agreement of that participant, unless the participants can clearly demonstrate why protection would be detrimental for their legitimate interests. The following section²³ will illustrate the differences between the older

²² From the IPR Helpdesk glossary

<http://www.ipr-helpdesk.org/controlador/resources/glossary?seccion=glossary&cuero=glossary&letra=A&len=en>

²³ All the information in this chapter regarding FP5, FP6 and FP 7 has been accessed from documents created and hosted by the EU IPR helpdesk, www.ipr-helpdesk.org

fifth framework which governs GenomEUtwin and the newer sixth framework. These differences have had ramifications whereby project time has been dedicated to developing certain key procedures and policy documents which will be in place prior to project start dates under later frameworks.

8.1.1 Framework 5 and 6

The GenomEUtwin study is funded under the fifth framework programme (FP5). Presently, projects are underway in the sixth framework (FP6) and calls for proposals have been published for the seventh framework for projects to start in 2007.

The rules on IPR have evolved in the last six years since the call for proposals for FP5. The rules have become more comprehensive and management of IPR is expected to be part of the project. The IPR changes and requirements between FP5 and FP6 relevant for GenomEUtwin are as follows²⁴:

- A signed consortium agreement (including IPR issues) is mandatory for project start under FP6, whereas it was ‘strongly recommended’ for FP5. GenomEUtwin did not have a tailor made agreement at the start date.
- Under FP5 participants bring pre-existing know-how that is necessary to carry out the project. This is no longer the case for FP6, in that participants can explicitly exclude specific pre-existing know-how,
- Under FP6 the definition of ownership of results is broader and less restrictive. Furthermore, in FP6 the concept of joint ownership was introduced in collaborative research. In contrast under FP5 collaborators were left to agree among themselves regarding proportions of shares allocated for each participating centre,
- Under FP6 stricter rules for the transfer of knowledge have been set and a system for opposing a transfer of knowledge has been established,
- Under FP6 access rights are slightly different to FP5; request for access has to be in written format. There is equal access for all partners and limits are in place for the right of access for 3rd parties especially those outside of the EU,
- Under FP6 publications need to give a 30 day notice to The Commission. If the publication affects the protection of knowledge, then publication cannot proceed. This in contrast to FP5 where a 30 day notice is given to other parties in the consortia but not The Commission,
- Under FP6 access rights for use of research knowledge for exploitation purposes are far simpler. They are granted royalty free for partners, whereas pre-existing know-how can proceed under fair and reasonable conditions,
- Dissemination of project results is in the interests of the Community in FP5 but in FP6 the interests of the participants are given more importance. It is for this reason that the Technological Implementation Plan (TIP) is of importance in FP5. TIP is a final

²⁴ Taken from document ‘Intellectual Property Issues (IPR) :FP5 versus FP6
<http://www.ipr-helpdesk.org/guias/imprimible/cuerpo.jsp?guia=guia6&len=en&tipo=html>

report, under contractual obligation, which for some ensures adequate IPR management serves a monitoring purpose²⁵.

8.1.2 Framework 7

The Commission has a proposal for FP7. Responding to the proposal, EUCOMED (European Medical Technology Industry Association) published ten recommendations, the eighth of which could be of interest if GenomEUtwin is extended²⁶.

“ The eighth recommendation deals with improving intellectual property right (IPR) protection. For EUCOMED, IPR is an absolute prerequisite to technological progress, and it considers therefore that the Commission should pay particular attention to: reaching the objective of creating a community patent, possibly in addition to national patents; deepening contacts with the European Patent Office (EPO) and developing and implementing simplified procedures; establishing and maintaining contacts with OECD and other stakeholders. ”

8.2 IPR issues for GenomEUtwin

8.2.1 Ownership

In the process of preparing the policy documents for GenomEUtwin (such as the DASP and STA) the concept of joint ownership was discussed. This approach was rejected in favour of a concept of ‘loaning’ samples and data. This concept may need to be carefully examined to exclude any negative future implications. The concept of joint ownership was not in the FP5 framework but was introduced in FP6. It has certain benefits, especially if ownership is placed under one party. Only one set of rules and national regulation will apply as opposed to many different national legal rules if all parties were represented separately. A further step of establishing a single party to govern decisions will be required if financially viable interests are found during GenomEUtwin.

In the event of co-ownership several factors will need to be considered²⁷:

“

- Planning ahead for the assigning of share of the rights,
- Planning ahead for cost sharing,
- Deciding who will file for protection,
- Obtaining and maintaining patents and other intellectual property rights in effect,
- Payment of fees for registration and maintaining procedures - in which country and from whose account,

²⁵ <http://www.cordis.lu/fp5/tip.htm>

²⁶ Eucomed publishes ten recommendations on FP7 May 10, 2005

²⁷ Taken from document ‘Intellectual Property Issues (IPR) :FP5 versus FP6

<http://www.ipr-helpdesk.org/guias/imprimible/cuerpo.jsp?guia=guia6&len=en&tipo=html>

- Responsibility for detecting and taking civil or criminal action against third parties who in any way injure the rights conferred by the industrial property rights,
- Licensing to third parties to use the invention,
- Situations in which the consent of the co-owners is required, etc.”

8.2.2 Other IPR-related issues

Since GenomEUtwin was not required to have a consortium agreement at the time the project began, it is unclear which country's governing law will be used in the event of disputes. This should be a priority issue as years can be spent discussing this point before the dispute can be remedied. The Ethics Core investigated options with input from the EU- IPR helpdesk. They suggested that the governing law should reflect that of the country representing the greatest number of participating centres, the country of the Coordinator. Another option would be to have it mediated through Brussels. Optimally, GenomEUtwin would have put such procedures in place, however, the scientific partners did not pursue this further within the tenure of the project, partly because there was little concern that IP would become an issue during the phases of intense focus on harmonizing the research procedures. However, the Ethics Core, in concert with the EU, recognises the importance of resolving such questions for future projects prior to start dates.

As part of the procedure of coming to an end of a project it would be usual to ascertain if any material, database, knowledge, know-how or other intellectual property needs to be protected. An independent evaluation from an expert (in the field) patent lawyer would be useful. Another consideration that should be addressed is that dissemination of knowledge (for instance in seminars, conferences, workshops) requires special consideration with respect of protection of IPR

Participating centres are under increasing pressure to protect research and generate income for their universities or hospital trusts. In fact, it is increasingly common to have commercial departments in these institutions that are established to protect IPR and creating spin off companies.

9 Training, Networking and Research

9.1 Training and networking

The following meetings, seminars and training course were attended by the Bioethics Adviser, Homa Hasan or Jennifer Harris.

2003

- Biobanks for Health - Optimising the use of European biobanks and health registries for research relevant to public health and combating disease. Presentation 'Ethical issues in GenomEUtwin'.

2004

- AGNC Spring Meeting (Association of Genetic Nurses and Counsellors) May 6, 2004, London, UK
- The 11th International Congress On Twin Studies (symposia plus 2 presentations), July 1-4, 2004 Odense, Denmark
- **GenomEUtwin Ethics Core Meeting Aug 19, 2004 Oslo, Norway**
- **GenomEUtwin Ethics Course Aug 20-21, 2004 Oslo, Norway**
- Genetics and Healthcare: International Elsasgen Conference: Ethical, legal and social aspects of human genetic databases, Aug 25-28, 2004, Reykjavik, Iceland
- Ethics of Research on Humans (Introductory course) September 21-23, 2004, King's College, London UK
- GenomEUtwin - Young investigators' meeting (presentation), Dec 13-14, 2004, Rome

2005

- Open hearing regarding Cord Blood – status, future possibilities and private company storage services (organised by the Norwegian Biotechnology Advisory Board) March, Oslo, Norway
- IPR Seminar - Practical use of Intellectual Property Rights. April, Norwegian Research council, Norway
- Open hearing of DNA registers for the population (organised by the Norwegian Biotechnology Advisory Board) June 13, Oslo, Norway
- UK Twin Day, August, London.
- Population Genomics Conference : From Biobanks To Biomarkers: Translating The Potential Of Human Population Genetics Research To Improve The Quality Of Health of The EU Citizen, Wellcome Trust, September
- Invited Speaker – Value risks and genetic data collections – 'GenomEUtwin: Utilising genetic data collections across eight countries'. Nov 10-11th Geneva, Switzerland.
- Retention of Human Tissue (Human Tissue Act). King's College, University of London. Nov 18th 2005.

- Pre-implantation Diagnosis – open hearing, The Norwegian Biotechnology Advisory Board, Nov 28th 2005.
- Seminar – Religion and Bioethics. Section for Medical Ethics, University of Oslo, December 12-15 2005.

2006

- Genomics and Population Health. Royal College of Physicians, London, Jan 26th 2006.
- P3G International Working Group (Ethics) Meeting. Manchester 21st March 2006.
- Co-ordinated Action (PHOEBE), kick off meeting. Manchester 22nd March 2006.
- Poster presentation ‘Population research – Is it time to abandon the traditional idea of consent?’ -Genomics and Public Health, 4th International DNA Sampling Conference. Montreal, Canada, June 4-7th 2006.
- P3G working dinner, Ethics IWG, Montreal, Canada, June 5th 2006.
- Patenting of stem cells: Legal and ethical problems, University of Oslo. Prof. Dr. Sigrid Sterckx and Dr. Julian Cockbain, June 19th 2006.
- Who speaks for the children? – Open hearing, The Norwegian Biotechnology Advisory Board, Sept 6th 2006.
- Co-ordination (of regulatory permissions) in the management of medical research – utopia or feasible? Ullevål University Hospital, Oslo, Sept 20th 2006.
- ESF-EMRC Strategic Workshop for a Policy Briefing on Population Survey and Biobanking, December 6-8, 2006.
- GenomEUtwin young investigators’ meeting – presentation Rome, Dec 14-15 2006

9.1.1 Ethics Core training course

The Ethics Core in collaboration with the Section of Medical Ethics (SME), University of Oslo arranged an Ethics course in Oslo on Aug 20-21, 2004. The lecturers comprised of staff from the SME as well as International experts Bartha Maria Knoppers and Anne Cambon Thomsen. Many members of the ethics core, researchers at participating centres and Ph.D students from Norwegian universities took part in this two day ethics course. The agenda of this course is included at the end of this manual in the Annex 11.3. The PowerPoint presentations from this course have been hosted on the GenomEUtwin website (Members Area).

9.2 Ethics-related publications and presentations

9.2.1 Ethics Core

Harris J.R.; Willemsen G.; Aitlahti T.; Petrini C.; Evans A.; Silander K.; Cirrincione L.; Kyvik K.O. Ethical Issues and GenomEUtwin Twin Research, Volume 6 (5) October 2003, pp. 455-463.

Harris, J.R. Ethical Issues in GenomEUtwin. Presentation at EU workshop entitled "Biobanks for Health", Oslo, January, 2003.

Harris, J. R., Willemsen, G., Kaprio, J., Kyvik, K. O., Pedersen, N. L., Petrini, C. & Cirrincione, L. (July 2004). Double troubles: Examples of special ethics issues in twin studies. Abstract from the 11th international congress on twin studies. *Twin Research*, 7: 352

Hasan HS, Harris JR. Abstract of Spoken Presentation at 11th International Congress on twin Studies- Odense Denmark 'Crouching Target, Hidden Regulations'. *Twin Research*, Volume 7 (4) August, 2004.

Hasan HS, Harris JR. Abstract of Spoken Presentation at GenomEUtwin Meeting- Rome, Italy 'If participant consent is the answer – what was the question?'. *Twin Research*, Volume 7 (6) Dec 2004 Research Collaborations and Networks.

9.3 Collaborative research projects

The Ethics Core of GenomEUtwin is actively involved in other research projects and network collaborations

9.3.1 Mapping the Language of Biobanks

This is an interdisciplinary project funded through the Norwegian Research Council program in Ethics, Society and Biotechnology, in close collaboration with the Norwegian Functional Genomics Platform (FUGE). This research project²⁸, headed by Professor Jan Helge Solbakk at the University of Oslo, Norway, is a collaboration including experts in the fields of epidemiology and genetics with ethics, law and philosophy of science from seven different institutions in Norway, France, Portugal and the UK.

The aims of the project are to explore ethical, legal and social challenges that have emerged through research biobanking. Analyses investigate current legislation, other forms of regulation and public debates concerning biobanks in European. The project also includes an 'in-vivo' study of ethical, legal and social issues connected to two population biobanking projects, GenomEUtwin and Biohealth-Norway.

A list of publications and more details about the project can be found at the project website²⁹.

²⁸ Mapping the language of research-biobanks and health registries: Solbakk, J.H ; Holm, S.; De Faria, P.L; Harris, J; Cambon-Thomsen, A; Halvorsen, M.; Stoltenberg, C; Strand, R; Hofmann, B.; Skrikerud, A.M; Karlsen, J.R. Project Description - From traditional biobanking to research biobanking. Reykjavik: University of Iceland Press & Center for Ethics. Reykjavik: University of Iceland Press & Center for Ethics 2004. p.299-305.

²⁹ <http://www.bioethics.ntnu.no/biobanks/index.php?id=pres&loc=oslo>

9.3.2 The Public Population Project in Genomics (P3G)

P3G is an international consortium for the development and management of a multidisciplinary infrastructure for comparing and merging results from population genomic studies. P3G will enable the international research community to deliver more effective health care strategies aimed at disease prevention, and at tailoring medicines and other treatment regimens to individuals, families and communities.

GenomEUtwin is a founding of the P3G consortia. Members of the Ethics Core (Jennifer Harris and Homa Hasan) are also members of the P3G International working group 'Ethics, Governance and Public Participation' whose initial focus is on issues such as public engagement, governance, consent, ethics, biobank lexicon, public policy, public health (prevention/promotion) and commercialisation.

In addition, P3G has set up an observatory. The P3G Observatory is a central internet repository aimed at facilitating the development, realisation and harmonisation of population genomic research projects. Questionnaire responses have been collected from participating biobanks to help catalogue details of the biobank studies listed in the Observatory. Members of the GenomEUtwin Ethics Core have worked with the P3G Observatory staff in designing the questionnaire cataloguing information regarding Ethics and Governance. This feedback will be utilised in the roll out of phase two of the questionnaire.

9.3.3 Promoting the Harmonization of Epidemiological Biobanks in Europe (PHOEBE).

PHOEBE³⁰ is a coordination action under the EU FP6 programme involving 18 partners from 13 countries in Europe and Canada (project coordinator: Dr. Jennifer Harris at the Norwegian Institute of Public Health. This 3-year project began in March of 2006. It aims to create a harmonized network of population-based biobanks across Europe and in Canada and to identify and explore key issues to help Europe makes best use of its rich array of existing and new population-based biobanks and longitudinal cohort studies.

The work conducted under PHOEBE will contribute to the state-of-the art by helping to harmonise critical features by:

- (1) promoting communication between major biobanking initiatives,
- (2) enhancing the effective sharing and synthesis of information and data,
- (3) avoiding extra costs and inefficiencies due to duplicative efforts.

This harmonisation aims to optimise the ability of biobanks to: communicate with one another, share ideas, information and data, and collaborate effectively in a complex world where laws and ethical guidelines are necessarily rigorous, often differ between nations and

³⁰ www.populationbiobanks.org

alter with time as biomedical science advances and societal interests and concerns change and mature.

The PHOEBE workpackage (WP) structure was founded upon the core structure in GenomEUtwin and the PHOEBE WP entitled *Ethical and Societal Issues* (led by Anne Cambon-Thomsen, Bartha Maria Knoppers, and Jennifer R. Harris) collaborates closely with the GenomEUtwin ethics core. The aims of this WP are to increase the scientific value and the various usages of pre-existing and planned population-based genetic databases and biobanks through coordination and harmonization activities that will establish a basis for a platform of the ethical-legal and governance criteria. Key areas of focus will include ELSI issues related to children in long-term biobanking projects, special populations and promoting cross-talk regarding ELSI issues associated with biobank projects on clinical and disease specific outcomes versus population-based biobanking.

9.3.4 Public Health Genomics European Network (PHGEN)

PHGEN³¹ is an FP6 project that runs from January 2006 through December 2008. It is directed by the Federal Institute of Public Health of the State of Northrhine-Westfalia, Germany, with the University of Applied Sciences Bielefeld, Germany and the Public Health Genetics Unit Cambridge, UK as associated partners. This network in Public Health Genomics involves collaborating partners from the fields of public health and genomics plus representatives from relevant authorities from all EU Member States, applicant counties and EFTA-EEA countries. This entails identifying key experts, inventorying public health genomics issues and priorities in Europe, facilitating co-operation and exchange of information in order to enhance coherence and disseminate best practice, identification of legal differences and barriers in a cross-border market and promotion of countries' involvement and efforts in public health genomics.

PHGEN is networked with the Ethics Core of GenomEUtwin and PHOEBE, and Dr. Jennifer Harris is a member of the PHGEN steering group.

³¹ www.phgen.nrw.de

10 Recommendations

During the course of GenomEUtwin several issues should be taken in to consideration for further projects. These include:

- Commence Ethics/legal preparations well before other aspects of the project start:
 - Status of permissions – participating centres that required permission from their ethics committee and/or Data Surveillance Agency to take part in research using human biological samples. A project extension may require centres to resubmit applications or to simply send an amendment to their original applications detailing the change of circumstance,
 - A consortia agreement will be required to be signed at project start for FP7. This needs to include a strategy on IPR issues, data security transfer and storage.
- Raise the profile of ethics component by integrating as fully as possible across the other project components.
- Formalise ties (network) with ethics cores of other international projects involving population studies – there are many groups within Europe who are working on the legal and ethical framework of population studies. It would be useful to network and set up reciprocal visits so we don't duplicate issues and can exchange information and solutions.
- Expanding Law Expertise – the Ethics Core of GenomEUtwin would have benefited from having a formal tie with a law expert and additionally a PhD law student in the field from a participating centre. Although each representative has working knowledge of the laws governing their participation, it is unreasonable to expect they have the breadth of knowledge to interpret the application of legislation in different situations.
- Annual 'Ethics workshop', where practical research orientated ethics lectures can be given and workshops scheduled. Furthermore, the project website can be used as a greater resource to post relevant articles from ethics/bioethics journals, and to post summaries and key lectures of important Ethics conferences.
- Reporting of study results at lay-level. All projects should publish a lay level summary of their study results as a method of giving something back to their participants (reciprocal duty of researchers), especially if the participant are not going to receive individual results from the study. GenomEUtwin has chosen three seminal papers that will be hosted in the Public Area of its study website.

- Public Awareness – as population research utilising health data and DNA (population biobanks) gains momentum and greater awareness in the public forum, strategies for liaising with the public should be created. For example, lay level posters for public exhibition purposes could be produced for display at science fairs or exhibit at science and technology events. Many participating centres have reported the increased difficulty in recruiting research participants. Representation in local public events such as science fairs or science awareness events may prove to be a useful team in raising awareness in the public eye.

11 Annex

11.1 National legislations by country prior to the start of GenomEUtwin

In Denmark, data storage and handling is ruled by the Act on Processing of Personal Data, Act No 429 of 31st May 2000, which implements the Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data. (<http://www.datatilsynet.dk/attachments/20001061548/ENGELSK%20LOV.doc>)

Biomedical research is regulated by the Act on Scientific Ethical Committees. The Act on the Scientific-Ethical Committees system and the evaluation of biomedical research projects, Act No 69 of 08/01/1999; The Act on informed consent and use of human subjects in biomedical research, Act No 161 of 12/10/2000 With regards to biological banks these are to some degree regulated by the acts above and furthermore there is Evaluating report from the Danish Medical Research Council, The Danish Council on Ethics and the Central Scientific- Ethical Committee on Medical information - biological banks, SSVF/CVK 1996 It should be noted from the above regulations, that if any information is released to the participants, it is needed to have both the consent of the National Data Protection Agencies, and judicial counselling of the participant.

Relevant legislation in Finland includes the law on Patient's rights (1992:785 and 1998:333), which has mandated the creation of a National ethics board. The board supervises the activities of all local ethic boards that are based on hospital districts, but also issues guidelines regarding genetic research and consent, particularly for multinational projects. The Personal Data Act (1999:523, and addition regarding data transfer in the EU 2000:986) are based on the EU directive 95/46/EY. The Act on Medical Research (1999:488) legislates on all medical research, specifying procedures for informed consent, and ethical committees.

In Italy there is a law regulating the "Protection of individuals and other subjects with regard to the processing of personal data" (ACT no. 675 of 31.12.1996) that has been amended by various legislative decrees governing epidemiological and genetic data collection (<http://www.privacy.it>). The biological bank maintenance is not yet regulated by a law. A National Bioethics Committee, established by the President of the Council of Ministers (<http://www.governo.it/bioetica/>), expresses opinions and suggests solutions, also for the purpose of preparing legislative acts, to address the ethical and legal problems that may emerge as a result of the progress of biomedical research.

In the Netherlands, there is a law concerning regulations on medical research involving human subjects (Medical Research Involving Human Subjects Act, 26 February 1998) in Dutch:

http://www.ccmo.nl/item/pub/IPpub.cgi?ipP=default_eng
english (non-authorized translation):

http://www.ccmo.nl/item/pub/IPpub.cgi?ipP=frameset_eng&ipP2=ccmo_wett_eng

At the time of application Norway did not have national legislation regarding biobanks. The regulations are being developed, and are informed by similar work in Denmark and Sweden.

The biobank legislation is expected to be established in the spring of 2002. However, the extant comprehensive set of laws (listed below) directly or indirectly relate to various aspects of biobanking.

These include:

The Law of Health Personnel (LOV-1999-07-02-64)

<http://www.lovdatab.no/cgi-wift/wiftldles?doc=/usr/www/lovdatab/all/nl-19990702-064.html&button=s%d8k&dep=shd&>

This describes the requirements for the approval of health personnel, including those associated with biobanks. Issues of confidentiality and reporting of information are contained within this legislation.

The Law of Patients Rights: (LOV-1999-07-02-63)

<http://www.lovdatab.no/cgi-wift/wiftldles?doc=/usr/www/lovdatab/all/nl-19990702-063.html&button=s%d8k&dep=shd&>

Among other things this includes the rules and regulations for informed consent.

The Law Regarding Medical use of Biotechnology: (LOV-1994-08-05-56)

<http://www.lovdatab.no/cgi-wift/wiftldles?doc=/usr/www/lovdatab/all/nl-19940805-056.html&button=s%d8k&dep=shd&>

The Law on Personal Information from 1 January, 2002, which replaced the earlier legislation on personal register from 1998. Previous differences between European lands regarding this have now been harmonized in the EC areas according to EUs Directive 95/46/EF regarding the protection of individuals in connection with the use of personal information and data sharing.

Legislation regarding health registers is currently being developed and will be reviewed by Sosialkomitee (Social Committee) on March 27, 2002.

In Sweden, there are laws governing collection of biological and health related information (the Health and Medical Services Act (1982:763). Data collection and confidentiality are regulated by the Medical Records Act (1986:203), the Personal Data Act (1998:204), the Health Data Registers Act (1998:543) and the Medical Care Registers Act (1998:544). There is no law governing maintenance of biobanks, however, a proposal is currently under review.

The population-based cohort component of this study (MORGAM) includes in addition to above listed countries, participants from France, Ireland, Russia, Spain and United Kingdom. MORGAM samples differ from those of twin registers since all the samples represent archived samples. Importantly, a prerequisite for any centre to be a part of MORGAM is to have proper national ethical committees' acceptance as well as informed consent from the participants. MORGAM will follow the same guidelines as the twin registers, set by the Draft Additional Protocol to the Convention on Human Rights and Biomedicine, prepared by the Steering Committee on Bioethics (CDBI) of Council of Europe, or the national regulations when stricter.

11.2 Summary of Laws and Regulatory Bodies Governing GenomEUtwin

	DPA ³²	Biobank Law	Additional Acts	Regulatory Bodies
Australia	✓	None	Human Tissue Act (NSW) Health Records Act (Victoria) Health records Information Privacy Act (NSW)	Australian National Health and Medicine Council (AHEC), National Health and Medical Research Council (NHMRC), Human Genetics Advisory Committee ³³ (HGAC)
Denmark	✓	None	Scientific-ethical committees and the treatment of biomedical research projects	The Danish Regional Scientific-ethical Committees Central Scientific-ethical Committee
Finland	✓	None	Medical Use Of Human Organs and Tissues Medical Research Act and Decree Act on the National Public Health Institute	National Authority for Medico-legal Affairs (TEO) Ministry of Social and Health (STM) Regional Research Ethics Committees The National Advisory Board on Health Care Ethics (ETENE), subdivision of medical research (TUKIJA)
Italy	✓	None	* ³⁴	National Bioethics Committee
Norway	✓	✓ ³⁵	Personal Health Data Filing Systems Act	The National Committee for Medical Research Ethics (NEM) Regional Committee for Medical Research Ethics (REK) Ministry of Health and Social Affairs

³² Data Protection Act – Regulated by Data Protection / Surveillance Agency

³³ Independent expert advisory body - Ethical, Legal and Social Issues Working Group will look at a national DNA database as a future issue

³⁴ Law February 22nd, 2006, n. 78 (Implementation of the Directive 98/44/CE on the legal protection of biotechnological inventions). Official Journal n. 58, March 10th, 2006 – limits patenting of genetic research protocols and sequencing of genes. This may have an impact for benefit sharing of IPR of future collaborative projects.

³⁵ <http://www.regjeringen.no/nb/dep/hod/dok/NOUer/2005/NOU-2005-01.html?id=389605>, this consultation report on Medical and Health research will be made into law in the near future and will require amendments in the Biobank Law.

11.3 Ethics Course Programme 2004

Ethical Challenges in gene-epidemiological research and health registry research
Oslo, August 20 – 21, 2004
Program

August 20

- 08.30-09.15 The concept of goodness in health related research
Lecturer: Jan Helge Solbakk
- 09.15-09.30 Break
- 09.30-10.15 Prevalent misapprehensions in the debates on regulating genetic medicine
(*genetic exceptionalism, genetic determinism, genetic overgeneralization, the statistical overestimation of uncertainty, the obsession with drawing moral lines and boundaries*)
Lecturer: Jan Helge Solbakk
- 10.15-11.00 Discussion/Coffee
- 11.00-11.45 Autonomy: ethical guideline or rhetorical rubbish?
Lecturer: Bjørn Hofmann
- 11.45-12.00 Discussion
- 12.00-13.30 Lunch
- 13.30-14.15 The state of the art of international research ethics – part 1
Lecturers: Søren Holm and Jan Helge Solbakk
- 14.15-14.30 Break
- 14.30-15.15 The state of the art of international research ethics – part 2
Lecturers: Søren Holm and Jan Helge Solbakk
- 15.15-16.00 Discussion/Coffee

August 21

- 08.30-09.15 Informed consent: a practical procedure or misguided ideal in gene-epidemiological research and health registry research? – part 1
Lecturers: Anne Cambon-Thomsen and Bartha Maria Knoppers
- 09.15-09.30 Break
- 09.30-10.15 Informed consent: a practical procedure or misguided ideal in gene-epidemiological research and health registry research? – part 2
Lecturers: Anne Cambon-Thomsen and Bartha Maria Knoppers
- 10.15-11.00 Discussion/Coffee

11.00-11.45	Genetic information and genetic privacy (<i>autonomy and the duty to keep oneself genetically informed, autonomy and the right to genetic ignorance</i>) Lecturers: Jan Helge Solbakk
11.45-12.00	Discussion
12.00-13.30	Lunch
13.30-14.15	The institutional nature of research biobanks Lecturers: Søren Holm and Roger Strand
14.15-14.30	Break
14.30-15.15	Use of biobank materials – access-rights, data protection, confidentiality and regulation of research projects – part 1 Lecturers: Bartha Maria Knoppers and Anne Cambon-Thomsen
15.15-15.30	Break/Coffee
15.30-16.15	Use of biobank materials – access-rights, data protection, confidentiality and regulation of research projects – part 2 Lecturers: Bartha Maria Knoppers and Anne Cambon-Thomsen
16.15-17.00	Discussion

About the lecturers:

- 1) **Anne Cambon-Thomsen**, MD, Director of Research at Centre National de la Recherche Scientifique (CNRS) and Head of a research group in an Inserm Unit on “Epidemiology and analyses in public health” at the University of Toulouse III, Toulouse, France.
- 2) **Bartha Maria Knoppers**, B.A, M.A, LL.B., B.C.L., D.L.S, Canada Research Chair in Law and Medicine, Professor at the Faculté de droit, Université de Montréal and Senior Researcher at the Centre for Public Law (C.R.D.P.), Canada.
- 3) **Bjørn Hofmann**, M.Sc. (physics, electronics and biomedical engineering), Ph.D (medical ethics), Assistant Adjunct Professor and postdoctoral fellow, Center for Medical Ethics, Faculty of Medicine, University of Oslo, Norway.
- 4) **Søren Holm**, B.A., M.A., M.D., Ph.D., Dr.Med.Sci., Professorial Fellow in Bioethics Cardiff Law School, Cardiff University, Cardiff, Wales and Adjunct Professor of medical ethics, Center for Medical Ethics, Faculty of Medicine, University of Oslo, Norway.
- 5) **Jan Helge Solbakk**, MD, Th.M, Dr. philos, Professor and Director, Center for Medical Ethics, Faculty of Medicine, University of Oslo, Norway, and Adjunct Professor of medical ethics and philosophy of medicine, Center for International Health, Faculty of Medicine, University of Bergen, Norway.
- 6) **Roger Strand**, M. Sc. (biochemistry), dr.scient (philosophy of science), post-doctoral fellow, Centre of the Study of the Sciences and the Humanities, University of Bergen.