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Biobanks Information Paper  
2010

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| WORKING TO BUILD A HEALTHY AUSTRALIA |

## **Electronic document**

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### **Contact:**

National Health and Medical Research Council  
Level 1  
16 Marcus Clarke Street  
Canberra ACT 2601

GPO Box 1421  
Canberra ACT 2601

Ph: 61 2 6217 9000  
Fax: 61 2 6217 9100  
Email: [nhmrc@nhmrc.gov.au](mailto:nhmrc@nhmrc.gov.au)

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## Preamble

The National Health and Medical Research Council (NHMRC) has developed this *Biobanks Information Paper* to provide information relevant to the establishment, management and governance of biobanks in Australia. For the purposes of this Information Paper, a biobank is defined as a generally large collection of human biological materials (biospecimens) linked to relevant personal and health information and held specifically for use in health and medical research. The primary focus of this Information Paper is on biobanks falling within this definition, but the information provided is also relevant to other collections of biospecimens to the extent that they are used in health and medical research. The aim of biobanks is to facilitate health and medical research, particularly that which is multi-centre and multi-national, while appropriately protecting participants' interests and privacy.

This Information Paper was developed in response to recommendation 19-2 of the Australian Law Reform Commission / Australian Health Ethics Committee report titled *Essentially Yours: The Protection of Human Genetic Information in Australia* (2003). This recommendation required the NHMRC as well as the Australian Health Ministers' Advisory Council (AHMAC) to review the need for a nationally consistent approach in relation to the collection, storage, use, disclosure of and access to, human tissue collections including pathology samples and banked tissue.

The NHMRC has moved this recommendation forward in its revised *National Statement on Ethical Conduct in Human Research* (2007) (the *National Statement*), which is the core ethical guidance document for researchers and Human Research Ethics Committees (HRECs) in Australia. Chapters 3.2, 3.4 and 3.5 of the revised *National Statement* contain guidelines on databanks, human tissue samples and human genetics. However, these alone do not address all aspects of biobank activity and with that in mind, and in the light of the recommendations made in *Essentially Yours*, the NHMRC hosted a meeting of key stakeholders in Hobart in late 2007. The meeting strongly supported a document of this nature, separate from the *National Statement*, particularly given the proliferation of national and international information and guidelines and the complex definitional issues around biobanking in the Australian context.

Establishment of biobanks under various auspices or funding bodies including the NHMRC's Enabling Grant scheme further highlighted the need to support biobank operators in policy development including access and governance. It is anticipated that in future this Information Paper will inform the development of these policies by making information on best practice, both nationally and internationally, easily accessible to operators.

The Information Paper draws on a range of documents, from opinion papers to best practice statements and guidelines. The *Guidelines for Genetic Registers and Associated Genetic Material* (1999) was also considered as a component of the Information Paper but its scope is limited to registers for heritable disorders and it specifically excludes databases that are established purely for research purposes. The Guidelines document will be considered for revision in the 2010-2012 triennium. The Information Paper also draws on, supplements and expands on the *National Statement* in relation to issues specific to biobanks. It should be noted that Chapter 3.2 of the *National Statement* uses the term 'databanks', which encompasses a range of collections used in a variety of different types of research including epidemiology, pathology, genetics and social sciences. The *National Statement* chapters dealing with human tissue samples (Chapter 3.4) and human genetics (Chapter 3.5) do not directly refer to biobanks.

As the paper is **not** an NHMRC guideline, it does not prescribe a specific approach. It is prescriptive only where it quotes an existing Australian guideline. In the

absence of specific Australian Guidelines, the paper identifies best practice in regard to standardisation of biobank policies, practices and procedures based upon national and international literature. In some instances there is no consensus about best practice and in those instances this document discusses the issues that need to be considered by biobank operators as well as health professionals and researchers involved with biobanks. The aim of this document is to promote best practice in biobanks, and to stimulate thought and discussion about best practice, by identifying the issues to be considered. In this regard, good governance and best practice may extend beyond what the law requires, particularly in light of the limited scope of specific legal regulation in this area.

The Information Paper provides case studies to illustrate key points and concepts. Its proposed readership includes researchers intending to develop or work with biobanks, HRECs and individuals who are working in established biobanks. The paper may also be useful for research funding bodies and the public.

# Chapter 1: What is a Biobank?

## ***Introduction***

Biobanks are generally large collections of human biological materials (biospecimens) linked to relevant personal and health information (which may include health records, family history, lifestyle and genetic information) and held specifically for use in health and medical research. Their object is to provide a resource for researchers to use to advance our understanding of human health and disease. Biobanks are seen as increasingly important to research in two broad areas: understanding the risk factors that underlie complex diseases, and translating biomedical research into real improvements in health care, especially through advances in pharmacogenomics and personalised medicine, to minimise adverse drug reactions and match drugs more effectively to the patient.

Over the last decade, a number of such biobanks have been established in several countries (Hirtzlin et al 2003), including the Icelandic Health Sector Database, the Estonian Genome Project, UK Biobank, Generation Scotland, and the CARTaGENE project in Quebec; and others are planned, including the Joondalup Family Health Study in Western Australia. Advancements in bioinformatics and biotechnology have made it possible to store biospecimens and data on an unprecedented scale and, with globalisation and growing interest in trans-national sharing of biobank resources, there is an increasing push to harmonise biobank processes and regulation. This is an important consideration for those establishing or managing a biobank. The optimal value of a biobank is only likely to be realised in a climate of cooperation and sharing of resources and experience, domestically and internationally. The Public Population Project in Genomics (P<sup>3</sup>G) is an important resource in this regard. P<sup>3</sup>G is an international, not-for-profit consortium whose objective is to promote collaboration between researchers in the field of population genomics. It does this by providing resources, tools and know-how to manage data in ways that will support the transfer and sharing of knowledge.

The emerging trend towards the establishment of biobanks poses a number of legal, ethical and regulatory challenges. Regardless of size, biobanks inherently involve some risk due to the sensitive status of the data they contain. Their success also depends on community support and willingness to participate. For this reason it has become clear in every jurisdiction that seeks to establish or use biobanks that a mechanism for maximising public trust is critically important (Campbell 2007).

This Information Paper draws on the international and Australian literature to discuss best practice in biobanks across six broad areas: establishment (including discontinuation); consent; data management; governance; access; and commercialisation and benefit sharing.

## ***The National Statement: Databanks***

The revised NHMRC *National Statement on Ethical Conduct in Human Research* (2007) (hereafter the *National Statement*) includes, for the first time, a chapter on Databanks (Chapter 3.2). This Chapter establishes guidelines on research merit and integrity, data usage and consent to the use of the stored data for research. It covers 'a wide range of data types and methodologies' and common types of research using databanks, including 'epidemiology, pathology, genetics and social sciences'. In this sense, biobanks are a subset of the wider, more generic term 'databanks' as used in the *National Statement* but extended by the inclusion of biospecimens.

Chapter 3.2 of the *National Statement* distinguishes between tissue, data and banking. The Chapter recognises the defining characteristic of biobanks as the

increased ability to link data, particularly with 'advances in genetic knowledge and data linkage'.

Chapters 3.4 and 3.5 of the *National Statement* provide ethical guidelines on research involving human tissue samples and human genetics, which are also applicable to biobank research.

### ***Characteristics of a biobank***

Biobanks typically share a number of defining characteristics:

- They contain biospecimens that may be *linked* with phenotypic data (disease information, health linkages, health outcomes etc), genetic and genomic data and/or other non-health data (eg, genealogical records).
- They are ongoing in nature and typically will involve research projects in the future that may be unspecified at the time of establishment and data collection. This open-ended nature of biobanks has presented challenges for traditional understandings of consent (discussed in Chapter 3: Consent in the Context of Biobanking).
- They commonly provide access to researchers other than the custodians of the biobank for ethically approved research purposes (discussed in Chapter 6: Access to Biobanks for Research Purposes).
- While the banked information and biospecimens will not generally be identifiable to researchers, there is a requirement that they remain potentially re-identifiable by the custodians. This is for the two-fold purpose of fulfilling any ethical or legal obligations to act on new information that may have an impact on the health of participants (see, for example, paragraph 3.5.2 of the *National Statement*) and also for those limited circumstances where re-identification is necessary to achieve maximum research value.
- They have a public interest focus, being less concerned about individual benefit for participants themselves and more about public benefit for future generations.
- They tend to have established governance procedures that serve to protect participants' interests, including the requirement that all proposed research seeking access to biospecimens and relevant data be reviewed by a human research ethics committee.

Beyond these shared characteristics, there are a number of significant variables, such as:

- the size and scale of the biobank;
- the health status of participants – the biobank may target healthy people, those with a specific disease or condition, or a combination of both;
- the scope of potential research – for example, the biobank may be limited to a particular disease or field of research, or they may be intended for broad and unlimited research;
- the approach to coding and privacy and the extent to which data linkage is possible; and
- the nature of the collection: whether it is purely prospective, comprises pre-existing collections, or is a combination of both.

These variables will influence a range of biobank activities, including recruitment of participants; consent (and re-consent); data management, including issues with respect to privacy and recontact; governance arrangements; and access, commercialisation and benefit sharing.

Much of the international literature on biobanking focuses on issues raised by the large-scale, linked, multi-research, population biobanks. The Australian literature, however, tends to focus on smaller-scale multi-research or specific-research



collections and non-research collections, without drawing clear distinctions between collections where samples are linked to other personal and health information, and those without such linkages. For example, the ALRC/AHEC Report 96, *Essentially Yours, the Protection of Human Genetic Information in Australia* (2003) (hereafter ALRC/AHEC Report) uses the term 'human genetic research databases' rather than 'biobanks', and defines them as 'collections of genetic samples and genetic and other health information, in any combination, which have been established for the purpose of human research' (p. 471, paragraph 18.8). The Report notes that:

Different forms of genetic research can be conducted using human genetic databases. These include:

- linkage studies to identify the gene sequences associated with inherited diseases;
- association studies to find correlations between a disease and a genetic change where there is no obvious pattern of inheritance;
- genetic epidemiology studies of the interaction between genes and environment; and
- pharmacogenetic studies to determine if there is a genetic basis for certain adverse reactions to drugs.

Each of these studies requires access to a different type of human genetic database, or uses databases in a different way, and may raise different issues. (p. 472, paragraphs 18.12-18.13)

## ***Biobank definitions***

Whilst certain distinguishing characteristics of biobanks can be identified, the terminology used varies and there is no consensus on a definition. The term 'biobank' is increasingly being adopted as the umbrella to describe *any* collection of biospecimens or human genetic information that can be used for research purposes. Many organisations, however, use the definition of biobanks adopted in this Information Paper, that is, they limit the term to collections that link biospecimens with various forms of information. This would seem to exclude collections of genetic information and/or biospecimens that are *not* so linked. For example, in the US, the 2007 Report of the Secretary's Advisory Committee on Genetics, Health and Society entitled *Policy Issues Associated with Undertaking a New Large U.S. Population Cohort Study of Genes, Environment and Disease* (hereafter US Cohort Study Report) defines a biobank as:

a stored collection of genetic samples in the form of blood or tissue that can be linked with medical and genealogical or lifestyle information from a specific population, gathered using a process of generalized consent. (cited in Austin, Harding and McElroy 2003).

The OECD followed a similar line in its Guidelines for Human Biobanks and Genetic Research Databases (HBGRDs) (2009) (hereafter OECD Guidelines), describing biobanks as:

structured resources that can be used for the purpose of genetic research, which include: a) human biological materials and/or information generated from the analysis of the same, and b) extensive associated information.

The OECD's earlier report, *Creation and Governance of Human Genetic Research Databases* (2006) (hereafter OECD Report) largely avoids the term 'biobank'. It would seem, however, that the Report's term 'human genetic research databases' is intended to cover the same types of collections as those described as HBGRDs in the later OECD Guidelines. The OECD Report states that:

Genetic research involving the use of databases containing human genetic and genomic information, sometimes alone or in combination with other personal or medical information, has thus become increasingly important. More recently, the

databases contemplated and being developed for genetic research are quite different in nature and larger in magnitude. Many of these emerging databases focus on and include data, information and biological samples from populations. These population databases, also referred to as human genetic research databases (HGRDs), may contribute significantly to science's understanding of complex multi-factorial basis of diseases. (OECD 2006, p. 9)

The US National Cancer Institute *Best Practices for Biospecimen Resources* (2007) (hereafter NCI Best Practices) uses a similar definition, though it uses the term 'biospecimen resource' rather than 'biobank'. A biospecimen resource is defined as:

a collection of human specimens and associated data for research purposes, the physical structure where the collection is stored, and all relevant processes and policies. (National Cancer Institute 2007, p. 3)

The wide use of 'biobank' or similar terminology across all types of tissue and information collections creates difficulties, as the different types of collections and databases raise different scientific, technological, ethical, legal, and social considerations. Even when the limited definition adopted in this Information Paper is used, the nature and purposes of biobanks can vary widely. The US Cohort Study Report notes that:

In some cases, the biobank is directly linked to a study with a predetermined goal, such as identifying genes causing specific disease. In others, the biobank literally serves as a repository of genetic material, patient exposure data, and medical history information that is available as a resource to researchers who request samples for the study of a particular disease. The characteristics of biobanks, such as participant population, age, size, ethnicity, and environmental exposures, vary widely (p. 16).

Given these complexities, the OECD Guidelines allude to the difficulty of creating uniform guidelines:

It is intended that this Recommendation be applied as broadly as possible. It is recognized, however, that the Recommendation may not be fully relevant for all HBGRDs, given their diversity of structure, purpose and operation.

The Guidelines also note that it may not be feasible to apply these principles and best practices fully to some pre-existing HBGRDs. The Guidelines make clear that they are not intended to apply fully to HBGRDs established primarily for non-research purposes such as for diagnostic, therapeutic, treatment, forensic, transplantation, transfusion audit, public health surveillance purposes, for marketing authorization or quality assurance purposes or as teaching materials.

Although the OECD Guidelines do not make a clear distinction between biobanks and genetic databases, there are some significant differences, which will be highlighted in this document. Where relevant, distinctions will also be made between the large-scale, multi-research, linked population-based collections; smaller-scale, multi-research collections; collections for specific research; and other collections created originally for non-research purposes.

### ***Large and small biobanks***

While biobanks differ substantially in size, it is debatable whether it is appropriate to draw a clear distinction between large-scale and smaller-scale collections, given that risk rather than size is the key indicator for ethical consideration. The assessment of risk is a major aspect of ethical review under the *National Statement* (see Chapter 2.1: Risk and Benefit).

There are, nevertheless, some obvious differences between small-scale and large-scale biobanks. In particular, the smaller-scale collections may be restricted to particular population groups, or particular research programs, or particular research

groups. Often the operator of the facility also conducts the research using the materials stored in the facility.

The large-scale population biobanks are generally specifically created as resources for as yet unknown future research projects by future research teams who may or may not have a direct connection with the operator of the facility. Perhaps the best-known example is UK Biobank, but such large-scale population biobanks are being established at regional, national and international levels throughout the world to support large-scale longitudinal genetic research projects.

### ***Distinguishing biobanks from other collections***

A distinction has already been drawn above between biobanks and other more generic types of research databanks referred to in Chapter 3.2 of the *National Statement*. Biobanks that comprise biospecimens and linked information also need to be differentiated from:

- genetic research databases that store human genetic information but not human biospecimens. The genetic information stored will often be de-identified and compiled from multiple donors. It will often be made freely available online. There are a number of examples of large-scale genetic research databases. At the international level, for example, the successor to the Human Genome Project, the International Haplotype Mapping Project (the HapMap Project), is a collaboration between the United States, the United Kingdom, Japan, Nigeria, China and Canada. It aims to identify and compare genetic similarities and differences in collected human tissue samples in order to find genes that affect health, disease and medication responses. The 1000 Genomes Project is a follow-on from the HapMap Project. This project involves sequencing the genomes of approximately 1200 people from around the world to produce a high-resolution of biomedically relevant DNA variations. Further information on the 1000 Genomes Project is available at: <http://www.1000genomes.org/page.php?page=home>;
- collections of biospecimens and information made for the purpose of obtaining regulatory approval, for example, clinical trials for new pharmaceuticals; and
- other repositories of human tissue that are created for diagnostic or clinical purposes. The ALRC/AHEC Report makes a clear distinction between these collections (eg, Guthrie cards, pathology collections, etc – Chapter 19) and collections created for research purposes (Chapter 18). Whilst this distinction based on origins is clear, it can become more problematic in practice because collections made for diagnostic or clinical purposes may also be used for secondary research purposes.

Making these distinctions is necessary in clarifying the scope of this Information Paper, particularly in respect to how the key issues of access and consent apply to these different categories. In practice, however, the boundaries between biobanks and other research collections cannot always be easily or precisely drawn. Information provided in this Information Paper is thus relevant not only to biobanks but also to other collections of biospecimens, whether created specifically for health and medical research purposes, or created for other purposes but used also for research.

## Chapter 2: Establishment of a Biobank

Creation of a biobank *de novo* specifically for research purposes requires careful planning to ensure that the biobank follows best practice from the outset. The fundamental issues of consent (see *National Statement* Chapters 2.2 and 3.2), data management, biobank governance, access, and commercialisation and benefit-sharing, are discussed in later chapters.

This chapter focuses on basic policies, practices and procedures that might be considered at the time of establishment, as well as identifying those required by Australian guidelines and legislation. The chapter discusses the rationale for establishment; requirements for public consultation prior to establishment; recruitment; origin of samples and information; funding, resourcing and staffing; legal requirements; and procedures for dealing with discontinuation of the biobank.

### ***Biobanks created from existing resources***

The discussion presented in this chapter relates primarily to newly created biobanks. Often, however, biobanks will be created from resources that are already in existence, or will combine old and new resources. Whilst past practices may not be fully compliant with contemporary best practice, all the matters discussed in this chapter are as relevant to the future activities of biobanks created from existing resources as to those formed *de novo*.

#### **Case Study: The Australian Prostate Cancer BioResource**

The Australian Prostate Cancer BioResource has four patient accrual and tissue collection centres: at the Garvan Institute (Sydney), Hanson Institute (Adelaide), Monash Institute (Melbourne) and Queensland University of Technology (Brisbane). Each of these sites was home to one of Australia's leading prostate cancer research groups, and the motivation to form a national virtual tissue bank was that each of the groups needed access to tissue donated by men with early stage prostate cancer in larger numbers, sufficient for statistical power, and more than one site could provide. Although each group had ethical approval to collect and use human tissue in its research, only the group at Garvan Institute had a cryopreserved collection of sufficient size and structure to be called a tissue bank. Funds to underpin a national collection and to initiate a national retrospective tissue microarray program were obtained from philanthropic sources, and the groups subsequently united to apply for an NHMRC Enabling Grant to initiate prospective patient accrual and tissue collection at the hospitals associated with the four institutions.

With the formation of the national tissue bank, the custodian of the individual collection held at each node is the host institution. Because only the Garvan Institute had managed to build up an operating tissue bank for its own and collaborative research projects, and because its tissue resources could have been dissipated rapidly if distributed on a national basis, its pre-existing tissue bank was retained by the Garvan Institute and not incorporated into the Australian Prostate Cancer BioResource. Hence there was no need for any participant notification.

All participants provide a standard informed consent for future research in Australia or overseas. Consent rate is 99%. By agreement between the four institutions, a single Material Transfer Agreement (MTA) was developed to enable Queensland University of Technology (the Administering Institution for the NHMRC Enabling Grant) to release tissues for research on behalf of all four institutions. This obviated the need for four separate MTAs for any large cohort of tissues derived from all the nodes.

## **Best practice requirements**

The *National Statement* provides some guidance on best practice in biobank establishment, bearing in mind that the document uses the language of databanking rather than biobanking and that the context in which this term is used signifies that it is intended to embrace a wide range of collections of data. The *National Statement* provides that:

When planning a databank, researchers should clearly describe how their research data will be collected, stored, used and disclosed, and outline how that process conforms to this *National Statement*, particularly the requirements for consent set out in paragraphs 2.2.14 to 2.2.18. (paragraph 3.2.1)

The NHMRC *Guidelines for Genetic Registers and Associated Genetic Material* (2000) (hereafter the *Genetic Register Guidelines*) includes a chapter on Establishment of a Genetic Register. While these Guidelines do not cover databases and other collections created for research purposes (paragraph 1.2(c)), they do provide some useful guidance in regard to best practice in the establishment of biobanks. Requirements include:

- a rationale for establishment;
- approval by the host organisation and acceptance of responsibility;
- sufficient resources;
- secure space;
- a nominated keeper or custodian, with clear lines of accountability and assistance from an advisory committee that has expert knowledge, and with a replacement on hand;
- appropriately qualified, skilled and experienced staff;
- written ethical guidelines addressing privacy/confidentiality, cultural sensitivities and procedures;
- definition of the number and roles of staff;
- compliance with relevant legislative requirements;
- appropriate storage facilities (accredited if appropriate); and
- review of ethical guidelines and procedures by an ethics committee.

International groups engaged in this field have proposed that, wherever possible, biobank policies, practices and procedures should be standardised and harmonised, and that those wishing to establish new banks or improve their current activities pay heed to such an intent. For example, the OECD Guidelines have been developed to aid policy makers and practitioners who are establishing new HBGRDs and recognise the need for harmonisation to bring together the different strands of information, data and biological samples within these HBGRDs.

As previously noted, the P<sup>3</sup>G Consortium is an important resource in this regard. The P<sup>3</sup>G Observatory (<http://www.p3gobservatory.org/>) is an Internet repository of scientific information and tools to aid in developing, realising and harmonising research projects. It includes a series of catalogues documenting large population-based biobanks worldwide, and it allows a rapid overview of the similarities, differences and potential for harmonisation between participant biobanks. These harmonisation initiatives cover a broad spectrum, from highly-technical scientific matters, through to governance and access principles and procedures.

Various best practice guidelines provide further assistance in determining the parameters within which a biobank will operate.

Biobankers are also developing voluntary standards to address concerns about inconsistencies in the collection, storage and retrieval and distribution policies of biobanks. For example, in Australia and New Zealand, one of the activities of the Australasian Biospecimen Network (ABN) is the development of consensus

standards. The ABN is a non-profit scientific organisation with voluntary membership, which has been established to provide a forum to address technical, legal/ethical, and managerial issues relevant to human biospecimen repositories within Australia and New Zealand. Further information on ABN activities is available at <http://www.abrn.net/>.

Another example is the International Society for Biological and Environmental Repositories (ISBER), which released the second edition of its *Best Practices for Repositories: Collection, Storage, Retrieval and Distribution of Human Biological Materials for Research* in March 2008 (hereafter ISBER Best Practices). The ISBER's primary goal is to provide information and guidance on the safe and effective management of repositories of specimens.

In the US, the NCI Best Practices outline the operational, technical, ethical, legal, and policy best practices for biospecimen resources supported by the National Cancer Institute (NCI). OnCore UK has a similar role to NCI, with the remit of contributing expertise and advice on best practice to the biobanking and scientific communities. Information on its policies and procedures is available at [http://www.oncoreuk.org/pages/about\\_sops.html](http://www.oncoreuk.org/pages/about_sops.html).

### ***Public engagement prior to establishment***

Biobanks need public support, given that participation is voluntary (OECD Report, p. 68). The OECD Report emphasises the need to consider, from the outset, how the various publics will be engaged; and it points out the consequences of failure to do this.

The consequences of public disapproval are illustrated by the fate of the proposed Tongan biobank, which was to be developed by AutoGen Limited. It was abandoned in the face of strong opposition from church and human rights groups (OECD Report, p. 72).

It has become common practice for large-scale population biobanks to engage in public consultation prior to establishment. Methods include consultations with community representatives, focus group meetings, workshops, interviews, public meetings, deliberative democracy events, polls and surveys.

The OECD Guidelines emphasise the need to consult with members of the public and other stakeholders, (Principle 2.D) with the extent and type of consultations determined by the nature and design of the proposed biobank (Best Practice 2.5). Similarly, the US Cohort Study Report identifies the need for public engagement, stating that:

Public accountability is a hallmark of Federal stewardship of the biomedical, behavioral, and public health research enterprises. ... Given the many policy implications of an LPS [longitudinal population study], an extensive public engagement effort would be needed to gauge public opinion about the study and whether it should be undertaken. (p. 51)

Building public trust, according to the OECD Report (p. 72), requires transparent, clear and unambiguous language; a clearly thought-out scientific rationale; and a communication strategy tailored to the needs of the participants, the media, advocacy and community-based groups and publics.

Engaging the various publics and gaining trust is widely recognised as a necessary aspect of the establishment of a biobank, but it is also important to emphasise the need for ongoing engagement, given that the social environment of values and interests is fluid (Hunter and Laurie 2009).

Issues relating to transparency and public accountability in biobanking are discussed further in Chapter 5 of this Information Paper, which focuses on biobank governance.

## **Case Study: Community Attitudes to Biobanking in Tonga, Iceland and the UK**

The degree of public consultation undertaken can have a significant impact on the success of biobank projects. In particular, consultation is essential in relation to consent, as illustrated in the following examples.

### ***Tonga***

The Tongan Government granted exclusive rights to Autogen Ltd to research the genetic make-up of the country's 108,000 residents. Autogen proposed to take DNA and blood samples to trace gene-disease associations, with individual participants required to consent to either multiple projects or a defined few.

Negotiations between Autogen and the Tongan Ministry for Health were conducted in secret. The total lack of public consultation or discussion was interpreted as a lack of understanding of and respect for the local culture, particularly as the ethics policy was silent on the traditional role of the extended family in decision-making. In the face of widespread public opposition, the project was abandoned. (Barker 2003, Tansey and Burgess 2004, Duce 2000)

### ***Iceland***

deCODE Genetics was granted a 12-year exclusive licence to set up the Icelandic Healthcare Sector Database containing data from national patient health records and linked to a genealogical database and genetic information from the analysis of donated DNA samples. There was some public consultation in relation to the database, but not the biobank.

deCODE Genetics required informed consent for DNA sampling but used an opt-out system for access to health and genealogical records, with genealogical records to be publicly available. While the study has gone ahead, privacy concerns about the presumed consent and public access have led to 20,000 people withdrawing. (Barker 2003, Tansey and Burgess 2004)

### ***UK Biobank***

UK Biobank is linking health, medical and lifestyle information with urine and blood samples to form a picture of each participant and his or her environment. The biobank will follow 500,000 people aged 40-69 for 30 years to look at subsequent disease, cause of death and other factors.

There has been extensive public consultation throughout the design, planning and implementation of UK Biobank, including consultation on the Ethics and Governance Framework, participant information materials, and consultation on consent. Recently, UK Biobank commissioned a study on public attitudes towards balancing commercialisation and public good, which is being conducted independently by the University of York. With transparent design, planning and implementation, and opportunities for public consultation throughout, UK Biobank has recruited almost 300,000 participants. (UK Biobank Coordinating Centre 2007)

## ***Rationale for establishment: Intended nature and scope***

The nature and scope of the biobank, particularly in terms of the research that is intended using its samples and information, need to be determined or determinable when the biobank is established (OECD Report, p. 10, 58). The OECD regards this as crucial (OECD Report, p. 10) and its Draft Guidelines emphasise the need to formulate clearly the purpose(s) of the biobank, both present and future.

Large-scale population biobanks will often be established for broad-ranging research purposes and hence it may only be possible to describe their nature and scope in broad terms. The objectives of these initiatives vary widely. The US Cohort Study Report notes that:

In the case of UK Biobank, the goal is an epidemiological analysis of risk factors that contribute to disease, whereas the goal of the Estonian Genome Project is to maintain genetic information in a database as a resource for public health and biomedical research ... Biobank Japan aims to develop tools for personalized medicine, choosing medical procedures and drugs based on patients' genetic profiles. (p. 21)

The nature of the research to be undertaken will often determine the types of samples and information to be collected. The US Cohort Study Report (p. 16) notes that genotyping, transcript profiling, gene quantification and proteomic analysis all require different types of samples.

A further issue to be considered at this early stage is how the biospecimens and information will be stored and linked; in particular, whether information about the biospecimens will be held separately from personal identifying information, as well as from genealogical, genetic and health data.

Consideration might also be given from the start to whether the biospecimens in the biobank could be used for non-research purposes such as clinical genetic services, law enforcement, insurance, legal actions and identification (OECD Report, p. 58). The implications of access for such purposes are discussed in Chapter 6.

## **Recruitment**

The type of biobank defines the recruitment policy and plan. Relevant considerations include the population and the types of individuals to be asked to participate, as well as any cultural sensitivities that these decisions might raise. Consent requirements are always of paramount importance in the recruitment process, and are particularly challenging where children are to be recruited. Consent is discussed in detail in Chapter 3.

The population from which it is intended to collect samples and information needs to be determined before the biobank is established. For large-scale population biobanks, the OECD Report refers to the need for the collected resources to be representative both of the population under study and of the diversity of populations (p. 55). Whilst this may not be practicable from a research perspective, best practice still requires recruitment from as widely generalisable a population sample as possible (UK Biobank, Ethics and Governance Framework, p. 4 – hereafter UK Biobank Framework). Recruitment arrangements need to guard against research bias (*National Statement* Chapter 1.1-1.3, and 1.4)

The NCI Best Practices also emphasise the importance of collecting biospecimens from populations with demographic characteristics and diversity that are appropriate to the scientific goals of the research (p. 3, Best Practice B.1.1.2).

The nature of the population under study influences the types of research that can be undertaken. The US Cohort Study Report notes (p. 21) that population diversity has a major influence on biobank design. For example, in Iceland the population is homogeneous and extensive genealogical records support large-scale linkage analysis. Biobanks containing samples from more diverse populations (like UK Biobank) favour association studies to examine population distribution of genetic variants and their association with disease.

## **Individual participants**

Recruitment strategies will depend on the nature of the biobank; whether, for example, there is a particular disease focus, or if the biobank is intended as a more general resource for research. Relevant considerations include whether people who lack the capacity to consent, including children and 'protected adults', will be included and if they are, what special protections are to be in place (OECD Guidelines, Principle 4.C). For those biobanks with a particular disease focus, the



relevant population will be affected patients and family members, and recruitment may be through referral by health professionals, invitation by genetic registry staff, or self-referral. It may be desirable for biobanks to have Standard Operating Procedures to address these matters.

For biobanks with a more general research focus, recruitment will be more open. As the OECD Guidelines make clear (Principle 4.A), it needs to be non-coercive and equitable, and arrangements need to be in place to ensure this. To be 'non-coercive', recruitment needs to be carried out in a way that respects individual freedom of choice (OECD Guidelines, Principle 4.A). In ensuring equitable recruitment, the UK Biobank Framework (p. 4) points out the need to be aware of potential barriers to participation,

such as those relating to age, gender, ethnicity, social class, residence, employment and language, through location and opening times of recruitment centres and by translation of study materials.

### **Cultural sensitivity**

Cultural sensitivity is needed in all aspects of managing a biobank, including recruitment. The *National Statement* reflects this; for example, the provision on respect (paragraph 1.10) includes having due regard for the beliefs, perceptions, customs and cultural heritage, both individual and collective, of those involved in the research. Also relevant is paragraph 3.4.1(g), which requires institutional policies for collection, use, storage and disposal of human tissue in research to have regard to socio-cultural considerations; and chapters 4.7 and 4.8, on Aboriginal and Torres Strait Islander Peoples and People in other Countries, respectively.

The OECD Guidelines (Best Practice 5.3) also recognise the pervasive nature of cultural issues in the context of biobanking:

The HBGRD's policy on procurement, collection, labeling, registration, processing, storage, tracking, retrieval, dissemination, use and destruction of human biological material and data should take into consideration cultural heritage and/or religious beliefs known or disclosed by participants, and their representative groups.

The principle of non-discrimination is referred to in a number of international instruments (UNESCO *International Declaration on Human Genetic Data*, Article 7 (2003); Council of Europe, *Convention on Human Rights and Biomedicine* (1997) Article 11). To accord with this principle, the selection process needs to be broadly based, including coverage of minority groups and socially and culturally diverse groups. At the same time, particular care is needed to guard against potential harm to and exploitation of these groups. For example, the OECD Guidelines (Principle 4.C) states:

The operators of the HBGRDs should give careful consideration to any special issues related to the participation of vulnerable populations or groups, and their involvement should be subject to protective conditions in accordance with applicable law and ethical principles.

Special considerations also apply to indigenous populations, where there may be concerns about biopiracy (Canadian Institute of Health Research 2007; see also *National Statement*, chapter 4.7). Researchers need to work with community representatives to address these issues of potential exploitation and cultural harm and to ensure an appropriate process of consultation and consent with relevant communities.

### **Case Study: Respecting spiritual and religious beliefs of participants**

Prior to recruitment, biobanks are encouraged to consult participating communities to inform the development of policies for the collection, use and disposal of biological materials in line with the specific spiritual and religious beliefs of participants. A standard for collection, use and disposal of biological materials can not be assumed as issues may differ across and within spiritual and religious groups.

#### ***Christchurch Tissue Bank***

To encourage Maori participation the Christchurch Tissue Bank consulted the community through a Maori representative appointed to the Tissue Bank Board and close liaison with Maori advisors to both the Canterbury District Health Board (CDHB) and the University of Otago. These representatives, through consultation with relevant communities, have informed the development of culturally appropriate procedures at the Tissue Bank.

As a result of consultation with the Maori community the Tissue Bank offers to dispose of samples with a karakia ceremony. The karakia is an incantation, more specifically, the ancient rites proper to every important matter in the life of the Maori. It is essential in protecting and maintaining spiritual, mental, emotional and physical health, particularly in a health care setting. It typically precedes assessment or healing and is an integral part of the healing process.

To support the disposal of samples with karakia, the *Research Involving Maori- Guidelines for the Disposal or Retention of Samples and Specimens (2007)* (The guidelines) were developed by the Maori Research Development Komiti (MRDK) of the University of Otago. The purpose of The Guidelines is to ensure consistency with Maori practices and beliefs and to enhance the cultural safety of Maori participating in research. The development of the guidelines was guided by the consultation process committed to in the University of Otago *Research Consultation with Maori Policy*.

The Tissue Bank uses a distinctive label on samples to be disposed of with karakia which are stored until the next ceremony. Labelled samples disseminated to researchers must be returned to the tissue Bank, after a certain date or upon completion of testing, for disposal at the next ceremony. The karakia ceremony is performed by Maori chaplains in the Christchurch Hospital Chapel. Invitees include chaplains and general manager of the CDHB, members of the manawhenua ki waitaha, Maori members of the ethics committee, members of the Maori Indigenous Health Institute, members of the MRDK, Maori medical students and University of Otago staff.

Disposal with karakia ceremony has been requested by 96% of Maori participants and 35.6% of total participants. The Guidelines have been well received by researchers and participants and are now being used in other regions of New Zealand.

### ***Origin of biospecimens and information***

Biospecimens and related information may be obtained from a range of sources, including healthy individuals from the general population, a disease-specific cohort, deceased donors and biopsies or surgical procedures. Whenever biospecimens are to be procured, be the donor living or dead, respect for and integrity of the human body is fundamental (Opinion of the European Group on Ethics in Science and New Technologies to the European Commission, *Ethical Aspects of Human Tissue Banking* 1998, p. 7 – hereafter European Group Opinion, Tissue Banking). Consent issues are likely to be least problematic where the donors are healthy and competent adults. Particular consent considerations arise in relation to potential donors who are sick and/or vulnerable, and where biospecimens are to be obtained from deceased individuals or from biopsies or surgical procedures.

Each of the Australian state and territory Human Tissue Acts has extensive provisions relating to the removal of regenerative and non-regenerative tissue from living and deceased bodies. In respect of deceased donors, the *National Statement* specifies that any wish expressed by a person about the use of his or her post-

mortem tissue for research should be respected (paragraph 3.4.8). It goes on to say that, in the absence of such expressed wish, permission to take and use the samples should be obtained from the deceased person's next of kin. At the time of seeking consent, it should be agreed with the next of kin how the sample is to be disposed of when the research has been completed, and researchers should try to accommodate any reasonable wishes of the next of kin about this (paragraph 3.4.9).

As noted in the European Group on Ethics Opinion, Tissue Banking (p. 9), biospecimens from biopsies and surgical procedures may, with the consent of the patient, be procured for research. The sample may be from affected tissues, or surplus tissues from surgical residues.

## ***Funding, resourcing and staffing***

Addressing the practicalities of funding, resourcing and staffing is part of establishing a biobank.

### **Funding**

Funding is a crucial consideration in the establishment of any biobank. The funding agency and level of funding determine the conditions under which the biobank can operate and will continue to operate into the future. From the outset, biobank operators are likely to want some assurance that adequate funding will be available for the anticipated life span of the biobank. At the same time, the consequences of withdrawal of or shortfalls in funding need to be considered. Funding priorities and conditions are likely to change over time.

The OECD Guidelines state the need to plan from the start for the discontinuation of the biobank (Principles 10.A and 10.B). To prepare for these eventualities, the operators of the HBGRD should develop a strategy for ensuring its long term sustainability, which also addresses the event that funding is terminated or its nature changed (OECD Guidelines, Principle 2.C).

The OECD Guidelines emphasise the need to be explicit and transparent about funding sources (Best Practice 2.4). The OECD Report describes three types of funding structures: private, public-private and public (p. 59). There are examples of each of these categories from among the large population biobanks:

- In Iceland it was intended that the population database would be wholly privately funded. The company deCODE would hold an exclusive licence to create and operate the biobank in return for payment for matters such as establishment, operation and maintenance. The Icelandic database, however, has not yet been established (OECD Report, p. 59-60).
- The public-private partnership model was intended to be followed for the Estonian population database. When the database was created, a government foundation held the resource but a private company, EGeen had access rights. However, in 2004 the relationship with EGeen was terminated and the public funding model replaced the hybrid model (OECD Report, p. 59-60).
- UK Biobank is an example of the public funding model. It is a non-profit entity funded primarily by the Medical Research Council and a charity, the Wellcome Trust, with other input from the Northwest Regional Development Agency, the Department of Health, and the Scottish Government.

It is likely that many of the smaller, disease-specific biobanks will use the public funding model or be funded through charitable donations. The pharmaceutical biobanks, on the other hand, are generally privately funded. The hybrid model may prove successful in some circumstances, but issues of ownership and benefit sharing will need to be handled with some care (see Chapter 7).

## Resourcing

Proper resourcing is as important for biobanking as for all aspects of human research. Paragraph 1.1 of the *National Statement* is relevant here, particularly clause (b), which emphasises the need for research to be designed or developed using methods appropriate for achieving the aims of the proposal, and clause (f), specifying that research should be conducted using facilities and resources appropriate for the research.

The ISBER Best Practices provide guidance on resourcing requirements, including those for records management, facilities, storage equipment and environments, quality assurance and quality control. The NCI Best Practices also point to the need to record and track biospecimen resources effectively; to ensure that personnel are well qualified and trained to adhere to standard operating procedures; to ensure compliance with standardised protocols for preparation and storage; and to have proper shipping procedures to safeguard sample quality (Best Practice B.1).

The ISBER Best Practices on records management list the types of records systems that may need to be created. They include: training documents, protocols, standard operating procedures, informed consent documentation, procurement documentation, processing records, testing, equipment maintenance, audit and review documents, specimens storage location information, sample distribution, and quality control activities (ISBER Best Practices Section B: Records Management).

Biobank facilities need to ensure the safe-keeping of the sample stored, support for equipment, and a safe and effective working environment. Designing a biobank to achieve this requires knowledge of: the types of sample to be stored, the requirements of the storage and handling, the projected retention periods, projected growth, and projected use of samples (ISBER Best Practices Section C: Facilities). The storage equipment that is needed will also depend on the type of specimens to be stored, the duration of storage and the intended use. The size and physical design of the facility and the number of specimens to be stored are also relevant (ISBER Best Practices Section D: Storage Equipment and Environments).

A number of technical standards with regard to data collection and storage may be considered to ensure effective, secure and ethical biobanking. Current International Standards Organisation (ISO) standards are reflected in national laboratory standards, including:

- ISO 15189:2007 Medical laboratories - Particular requirements for quality and competence;
- ISO/TS 22367:2008 Medical laboratories - Reduction of error through risk management and continual improvement;
- ISO 15194:2009 In vitro diagnostic medical devices - Measurement of quantities in samples of biological origin - Requirements for certified reference materials and the content of supporting documentation.

Proposed international guidelines for biobanks suggest that at the time of establishment, procedures also need to be established to provide for quality assurance and quality control. Security is of primary concern because of the potential for misuse of data and samples (OECD Report, p. 111). Each of these issues is considered in Chapter 4.

## Staffing

As with resourcing, adequate staffing is as relevant to biobanking as to any other aspect of research involving humans. Clause (e) in Principle 1.1 of the *National Statement* is relevant here, stating that research should be conducted or supervised by persons or teams with experience, qualifications and competence that are appropriate for the research.

The ISBER also provides some specific guidance on best practices with regard to staffing matters. The director of the facility should be qualified by training and experience to fulfil the scope of activities conducted by the facility. Technical staff should also possess sufficient educational background, experience and training to ensure that assigned tasks are performed in accordance with established procedures (ISBER Best Practices Section A, Part 3: Staffing). All staff should be adequately trained to perform the tasks specified by their position description. Proper training is important to promote quality specimen handling, good ethical practices and compliance with appropriate policies and regulations (ISBER Best Practices, Section G: Training).

Some national and international instruments provide more general guidance as to the responsibilities of biobank staff. For example, the UNESCO *Declaration on Human Genetic Data* emphasises the obligation of responsible persons and entities to take necessary measures to ensure accuracy, reliability, quality and security of data and processing of samples. They should also exercise rigour, caution, honesty and integrity in the processing and interpreting of human genetic data, human proteomic data or biological samples, in view of their ethical, legal and social implications (Article 15 – Accuracy, reliability, quality and security).

The OECD Guidelines emphasise the importance of having suitable staff and resources to preserve records, data and human biological samples, and to handle requests for access to data and human biological samples (Best Practice 2.3).

## ***Legal and other obligations***

A large variety of laws, policies, guidelines and codes of practice have an impact on biobanks and need to be considered at the time of establishment. Because some Australian biobanks have established trans-border collaborations, international as well as national regulations apply.

### **General national legislation and other laws**

Human tissue legislation and general laws relating to contract, medical negligence, trespass to the body and breach of confidence are highly relevant. Anti-discrimination legislation and intellectual property legislation must also be considered.

The Commonwealth *Privacy Act 1988* and associated state and territory privacy legislation is of utmost importance with regard to biobanking. The applicability of this legislation is discussed in detail in Chapter 4. The National Privacy Principles and Information Privacy Principles prescribed in the *Privacy Act 1988* apply to the manner in which biobanks manage and disseminate health information. Where there is state privacy legislation, the State-based privacy principles have been developed to be interpreted, as far as possible, in a manner consistent with the National Privacy Principles and Information Privacy Principles. The Australian Law Reform Commission (ALRC) has recently recommended the introduction of Unified Privacy Principles, involving the consolidation of the current National Privacy Principles and Information Privacy Principles, which would apply to Commonwealth agencies and private sector organisations and would also form the basis of the proposed co-operative scheme involving the states (ALRC 2008). The 2008 ALRC report also recommends the introduction of specific health information regulations to apply in conjunction with the Unified Privacy Principles.

### **National policies and guidelines**

The *National Statement* is likely to have the most profound influence on biobanking in Australia. As previously noted, the *Genetic Register Guidelines* may also provide some useful guidance on some aspects of biobanking, as may other NHMRC documents.

## **International guidelines, instruments and policy statements**

The OECD Guidelines on biobanking and relevant ISO standards have already been mentioned above. The OECD *Guidelines on the Protection of Privacy and Transborder Flows of Personal Data* are also particularly relevant.

The UNESCO *Universal Declaration on Bioethics and Human Rights* provides broad guidance on consent, privacy and sharing of benefits, and a range of other relevant matters. The UNESCO *Universal Declaration on the Human Genome and Human Rights* has provisions relating to the status of the human genome as the common heritage of humanity. However, as noted in the OECD Report, the Declaration deals only with the human gene in its natural state and not with assemblages of data in biobanks (OECD Report, p. 61). While neither of these Declarations creates binding obligations on countries to enact legislation, they do provide important guidance as to international consensus on relevant matters. The *Convention on Biological Diversity*, signed by 150 government leaders at the Rio Earth Summit in 1992, has provisions relating to the exploitation of genetic resources, but these apply only to non-human resources (OECD Report, p. 61). On the strength of its analysis of these international instruments, the OECD has concluded that there is currently no comprehensive international framework setting out global consensus on the range of issues pertaining to biobanks, particularly with regard to matters of ownership, commercialisation, access and benefit sharing (OECD Report, p. 61).

It may also be useful to consult a raft of international and country-specific policy statements when establishing a biobank. The OECD Report notes that useful policy information is provided by the following organisations: European and American Society for Human Genetics; World Medical Association; Human Genome Organisation, particularly in its *Statement on Human Genomic Databases*; and the US National Centre for Human Genome Research (OECD Report, p. 61).

## **Country-specific biobank legislation**

While there is no specific biobank legislation in Australia, some countries have specific legislation relating to large-scale population biobanks. Examples include the *Act on the Health Sector Database 1998* (Iceland), and the *Human Genes Research Act 2000* (Estonia). It should be noted that the Icelandic legislation was declared unconstitutional in a decision of the Icelandic Supreme Court in 2003 (Gertz 2004a).

## **Biobank-specific principles and policies**

Although there are no Australian biobank-specific principles or policies, some guidance can be obtained from instruments from other countries. Examples include the RMGA Network for Applied Genetic Medicine Statement of Principles Human Genome Research (2000) and its Statement of Principles on the Ethical Conduct of Human Genetic Research Involving Populations, and the UK Biobank Ethics and Governance Framework. The UK Biobank Ethics and Governance Council is an independent committee, the purposes of which include acting as an independent guardian of the UK Biobank Ethics and Governance Framework and advising on its revision.

### **Case Study : Transferring material to researchers**

In 1998, the Peter MacCallum Cancer Centre (Peter Mac) established a Tissue Bank to facilitate cancer research programs at Peter Mac and at collaborating institutions. The Tissue Bank's activities are overseen by the Peter Mac Human Research Ethics Committee (HREC). Tissue in excess of that required for pathology assessment and diagnosis is collected from donors who give permission for their donated tissue to be used in future, unspecified research, to be controlled by the HREC. The Patient Information and Consent Document clearly describes the process, the manner in which tissue may be used and the oversight by the HREC. Central to the way in which this Tissue Bank, and many others, operates is the

're-identifiable' labelling of biospecimens and data. The Tissue Bank is, and has always been, an open resource, supplying biospecimens and data to researchers within Peter Mac and from external organisations. More recently, the Peter Mac Tissue Bank has joined with three other major banks in Victoria to form the Victorian Cancer Biobank. This process has expanded the number of biospecimens available to researchers and is open to applications from local, national and international research groups.

Donors are informed, through a clearly written information brochure, that the Tissue Bank acts as an 'independent intermediary', allowing clinical information to be gathered and supplied to researchers whilst protecting the privacy of the donors. Approval by a duly constituted HREC ensures that data and biospecimens will be subject to an acceptable level of oversight. In addition, requests for biospecimens are reviewed by the Tissue Research Management Committee, constituted as an arm of the HREC, to ensure they are scientifically sound and make efficient use of the resources available.

To ensure that the biospecimens donated to the Tissue Bank are used in research that complies with relevant legislation and protects the interests of participants, **all biospecimens and data are provided as 'coded' information. The key to the code remains with the Tissue Bank.** In addition, particular attention has been paid to putting in place mechanisms to ensure that material supplied to researchers is subject to an acceptable level of oversight. Before any biospecimens and/or data are provided to external researchers, a Material Transfer Agreement (MTA) must be signed by the recipient organisation. The MTA seeks to ensure that the following requirements are met:

- The institution and the researcher must comply with all conditions relating to the collection of the material and ensure that use of the Material will be controlled by the institution's HREC in accordance with the *National Statement*. Where material is requested by an international organisation, the Peter Mac HREC must be confident that a level of oversight similar to that required by current Australian legislation is in place.
- The institution and the researcher must comply with all relevant laws and standards in relation to the use of the material.
- If Peter Mac notifies the institution or the researcher (or both) that the donor or the donor's legal representative has revoked their consent to use the material, the institution must immediately destroy the material in the manner directed by Peter Mac, and must notify Peter Mac in writing when it has done so.
- The institution and researcher must not use the material for any purpose other than the specified research or other purposes expressly permitted under the terms of the Agreement.

## ***Discontinuation of the biobank***

According to the OECD Report, discontinuation of the biobank is a matter that should be considered at establishment (p. 117). Relevant considerations include whether all data and samples should be destroyed and if not what should happen to them, whether participants should be notified about the discontinuation and, if the biobank is operated by a private undertaking, whether the government should have the right to have it handed over to them, or the right of first refusal (OECD Report, p. 117). The importance of addressing this matter at the outset is also highlighted in other reports (for example, German Biobank Opinion, p. 55-56).

Reflecting the importance of this matter, the OECD Guidelines include a whole section on discontinuation and disposal of materials and data.

The three Principles are:

- 10.A The operators of the HBGRD should plan for its possible discontinuation and should have a suitably detailed policy setting out the manner in which the human biological materials and data that it holds will be dealt with in the event of its discontinuation.

10.B Where an HBGRD of scientific value can no longer be supported by its current operators, efforts should be made to transfer the human biological materials and data to another HBGRD or another entity.

10.C Once an HBGRD is no longer required or is no longer of scientific value and it has been determined that it will be discontinued, the human biological materials should be disposed of in an appropriate manner, consistent with the principles of consent, privacy and confidentiality.

Human tissue legislation in Australia and similar legislation in other countries prohibits trading in human tissue (see further Chapters 6 and 7). As noted by the OECD, 'the consequence of the application of such statutes would also need to be taken into account when developing such a policy [for demise]' (OECD Report, p. 117). There are relevant provisions relating to discontinuation for those large-scale biobanks created by legislation (OECD Report, p. 117). UK Biobank has indicated that it will develop a detailed strategy for handling contingencies in the event that UK Biobank Ltd has to close or make other substantial transitions in the holdings or control of the resource (UK Biobank Ethics and Governance Framework, p. 18).



## Chapter 3: Consent in the Context of Biobanking

Consent is a fundamental principle in modern medical ethics and biomedical research; this was explicitly established in the *Nuremberg Code* (1947) and *Declaration of Helsinki* (World Medical Association 1964). The principle of consent is closely related to the principle of autonomy and the affirmation of human rights and respect for human dignity (UNESCO 2008).

In Australia and other western societies, consent is a very individualistic notion yet in genetic research there is potential for a participant's family and other genetic communities to be impacted by an individual's participation. The familial nature of genetic information that can be obtained from biospecimens must therefore be borne in mind in providing information to individuals. Further, as discussed below (p.34-35) in some circumstances, sensitivity to cultural considerations may require consent to also be sought from a wider group.

In the context of biobanking, the issue of consent is central and maintaining a strong link between the donor's consent and the use of his or her data is a legal and ethical obligation in the collection, storage and use of biospecimens and data for research purposes (Porteri and Borry 2008). This chapter examines consent in some detail. To put the discussion in a broader context, there is strong community support for health research, including genetic research. People are generally comfortable with the concept of biobanking and, when surveyed, many indicate that they would be willing to participate.

### ***What is consent?***

Australia has well established principles in relation to consent, set out in the *National Statement*. The introduction to Chapter 2.2: General Requirements for Consent states that:

consent should be a voluntary choice, and should be based on sufficient information and adequate understanding of both the proposed research and the implications of participation in it.

The *National Statement* gives guidance on the information to be communicated to participants as part of the consent process (paragraph 2.2.6) and the form of consent (oral, written or other), as appropriate to the circumstances (paragraph 2.2.5).

In relation to biospecimens and information, participants need to have sufficient information, including information about anticipated procedures, risks and benefits, and options for withdrawal to enable them to make an informed choice about whether to provide biospecimens and data for future research (ISBER Best Practices, p. 47).

### ***Specific problems in relation to biobanks***

Consent, especially in the context of large-scale population biobanks, is recognised as one of the most complex issues for medical and scientific research (OECD Report, p. 89). As the NCI Best Practices (p. 16) acknowledges, the challenge in gaining consent to collect biospecimens and data for future research use, based on full information, is that the specifics of the future research are not known when the biospecimens are collected. Biobanks are typically set up as long-term resources, with biospecimen collection (and thus the consent process) separated from the actual research, which may possibly be years later and may involve research not contemplated when the biospecimens were collected (Rothstein 2005, p. 91). There has, therefore, been growing acceptance of the concept of 'broad' consent to future unspecified research use. Whilst this does encroach on the concept of

'informed' consent, in that participants can only be informed and consent to future research in broad terms rather than on the basis of full information (Caulfield, Brown and Meslin 2007, Caulfield 2007), there are sound arguments to support the concept, on grounds of principle as well as pragmatic considerations (Otlowski 2009).

### ***Broad and future consent***

The *National Statement* endorses the concept of 'broad' of consent, although using different terminology. In a section dealing with 'Consent to future use of data and tissue in research,' it provides that:

2.2.14 Consent may be:

- (a) 'specific': limited to the specific project under consideration;
- (b) 'extended': given for the use of data or tissue in future research projects that are:
  - (i) an extension of, or closely related to, the original project;
  - or
  - (ii) in the same general area of research (for example, genealogical, ethnographical, epidemiological, or chronic illness research);
- (c) 'unspecified': given for the use of data or tissue in any future research.

This section goes on to state:

The necessarily limited information and understanding about research for which extended or unspecified consent is given can still be sufficient and adequate for the purpose of consent.

The *National Statement* further provides that:

Extended or unspecified consent may sometimes need to include permission to enter the original data or tissue into a databank or tissuebank. (paragraph 2.2.15)

There is some support internationally for broad consent, for example, the *HUGO Ethics Committee Statement on Genomic Databases* (hereafter, *HUGO Statement on Human Genomic Databases*) and, more recently, the OECD Guidelines, which acknowledge the ethical permissibility of broad consent (Best Practice 4.6, Annotation 29). Some of the relevant statements, however, such as the *UNESCO International Declaration in Human Genetic Data* and the WHO statement on *Genetic Databases: Assessing the Benefits and the Impact on Human and Patient Rights*, make this support contingent on biospecimens being anonymised, which is often not practicable because of the need to maintain capacity to link data. Notably, the provisions in the revised *National Statement* are not so circumscribed.

The *National Statement* goes on to provide that:

when unspecified consent is sought, its terms and wide-ranging implications should be clearly explained to potential participants. Further, when such consent is given, its terms should be clearly recorded. (paragraph 2.2.16)

A helpful way to view consent in the context of long-term collections such as biobanks is to see it as having two components (using the terminology of the *National Statement*):

- *specific* consent to the taking of the biospecimen and related information and for storage, and
- *unspecified or broad* consent to the use of those data for future, as yet undetermined, research.

As the NCI Best Practices note (p. 16), whilst it may not be possible to know details of specific projects, efforts should be made to describe the nature and purpose of the research as specifically as possible. The amount of detailed information that can be provided to people when their consent is sought will vary depending on the nature of the collection: more specific information can be given in the case of a disease-based collection, where the research is disease-specific, compared with a biobank established as a more general resource to study gene-environment interactions and the impact of genes on disease. In the latter case, it will be important to provide clear information on the nature and purpose of the biobank. Further, as will be elaborated below, in view of the limited consent that can be obtained at the time that biospecimens and information are collected, biobanks have an ongoing obligation to provide more information once it becomes available, for example, about who is accessing the resource and for what purposes.

Given the complexity of consent in the context of biobanks, particularly in the case of large-scale population biobanks, the OECD Report (p. 91) states:

the guidance that is to be provided in the consent process should focus on how to provide appropriate information to prospective participants, [and] how to promote prospective participants' comprehension of such information...

In order to ensure that optimal arrangements are in place with regard to consent, governance and ethical arrangements need to be reviewed on a regular basis, always taking account of developments nationally as well as international best practice.

The following section deals with consent issues relating to human biospecimens and related information for prospective collections, from living donors who have decision-making capacity. Later sections deal with issues relating to substituted consent for people who lack decision-making capacity (p. 32) and the use of existing collections, established for other purposes, as a source of biospecimen and data (p. 37).

### ***Best practice for providing information to potential participants***

Biobanking is likely to involve minimal physical risk for participants (those risks being involved in the collection of biospecimens). The perceived risks and concerns that typically surface relate more to the personal nature of the biospecimens and information collected, its familial aspects, and the uses and potential misuse to which such data may be put. The information that needs to be communicated to potential participants will depend on the nature of the collection and will be different for a population biobank and biobanks set up for a specific research project. The requirements for consent for all human research, as set out in the *National Statement* (paragraph 2.2.6), include the nature, implications, and foreseeable risks and benefits of participation. When consent is sought for the collection and storage of biospecimens and related information and their subsequent use in research, the *National Statement* identifies additional items to be given careful attention. These are set out in Chapter 3.2, in the paragraphs on databanks (paragraphs 3.2.9-3.2.12), and Chapter 3.4, which deals with human tissue samples (paragraphs 3.4.5-3.4.7) and specific information to be given to people who are asked to consent to collection of their genetic material or information for research (paragraph 3.5.8).

The information to be provided to potential participants needs to be clear and explicit. The OECD Guidelines identify the need for such information to be written in clear, concise and simple language (Best Practice 4.3). The Guidelines state that communication strategies should take into consideration the different needs of the participants and that consideration should be given to employing different formats and modes for providing information to participants (Best Practice 4.11)

Protocols and processes need to be established. The OECD Guidelines state that:

During the informed consent process, the HBGRD should provide potential participants with sufficient information on the nature, implications, foreseeable risks and benefits of their participations, so that they can realistically assess the implications of their participation and can make an informed decision on whether to participate. (Best Practice 4.1)

Based on the *National Statement*, and drawing on other sources including the OECD Guidelines and NCI Best Practices, relevant information for potential biobank participants (or, where relevant, their decision-makers) includes the following (a number of these points are dealt with in more detail below):

- Intended purpose:
  - the purposes for which the data will be used and/or disclosed (*National Statement*, paragraph 3.2.9(a); OECD Guidelines, Best Practice 4.4);
  - clarification of ownership issues with respect to the biospecimens, information and the collection (OECD Guidelines, Annotation 35 ; UK Biobank Framework, p. 5);
- Nature of consent:
  - the nature of the consent that is being sought (whether it is specific, extended or unspecified) (*National Statement*, paragraph 2.2.14);
  - circumstances in which reconsent might need to be sought and/or in which a waiver of consent may be sought (OECD Guidelines, Best Practice 4.5);
  - whether child participants will be involved and whether, when and how a child's assent will be obtained (OECD Guidelines, Best Practice 4.7);
- Ethics and governance arrangements:
  - mechanisms in place for ethical oversight of the research, including, where relevant, details of the governance model of the biobank (see for example, UK Biobank Framework, p. 9, and the P<sup>3</sup>G generic information pamphlet, available at <http://www.p3gobservatory.org/>);
- Contact/recontact:
  - whether information from or about family members, in addition to that provided by participants, is required for the research (*National Statement*, paragraph 3.5.8(d));
  - whether participants will be re-contacted in the future, the circumstances in which re-contact will be permitted and the conditions that will govern re-contact (OECD Guidelines, Principle 4D; UK Biobank Framework, p. 5);
- Data storage, transfer and disposal:
  - the form in which the data will be stored (identifiable, re-identifiable, non-identifiable) (*National Statement*, paragraph 3.2.9(a); note also paragraph 3.4 with regard to human tissue samples), but noting that genetic material is in principle re-identifiable, even if identifiers are removed (*National Statement*, paragraph 3.5.8(a));
  - the duration of storage, transfer and disposal procedures, including, for international transfer of data where applicable (OECD Guidelines, Best Practice 4.4; note also *National Statement*, paragraphs 3.5.7 and 3.5.12(e));
- Confidentiality and privacy:

- procedures and safeguards used to protect confidentiality and privacy (*National Statement*, paragraph 3.5.8(c) and OECD Guidelines, Annotation 35);
- details of data linkage, including which health and other records are to be accessed (OECD Guidelines, Best Practice 5.1);
- the risk of psychosocial harms such as potential stigmatisation or intra-familial conflict, and the possibility that research may create or augment the risk of stigmatisation or discrimination of groups (OECD Report, p. 90);
- Release of information:
  - whether the research may reveal information of potential importance to the future health of participants or their blood relatives (*National Statement*, paragraph 3.5.8(e));
  - whether or not individual or aggregate research results will be released to the participant and/or his or her family or health care provider (OECD Guidelines, Principles 4H and 4I; NCI Best Practices, p. 18);
- Access:
  - whether biospecimens and genetic information will be made available for non-research purposes such as proficiency testing (OECD Guidelines, Annotation 34 );
  - the possibility of sharing biospecimens and data with commercial entities, including those from other countries, and the publication of data and its availability on the Web (*HUGO Statement on Human Genomic Databases*, Recommendation 4d; note also UK Biobank Framework, p. 5);
  - the policy with regard to access to biospecimens and data by third parties such as insurers, employers or law enforcement agencies (OECD Guidelines, Annotation 35);
- Communication strategy:
  - policy and procedures for ongoing communication with participants (OECD Guidelines, Annotation 35);
  - information for contacting the biobank (OECD Guidelines, Annotation 27);
- Commercialisation and benefit sharing:
  - potential commercialisation and whether participants will derive benefit from any such commercialisation (OECD Guidelines, Annotation 35);
  - the policy with respect to the sharing of benefits from the research (OECD Guidelines, 4H and Annotation 35)
- Right to withdraw:
  - the right to withdraw, the available types of withdrawal, the implications of such withdrawal, and whether it will be possible to withdraw biospecimens and data (*National Statement*, paragraph 2.2.1(g); OECD Guidelines, Principle 4G; OECD Report, p. 91);
- Death or incapacity of participant:
  - arrangements for the biospecimens and data in the event of incapacity or death of the participant (OECD Guidelines, Annotation 44; UK Biobank Framework, p. 5);
- Discontinuation of the biobank:
  - proposed arrangements in the event of the discontinuation of the biobank.

Given the planned long-term nature of biobanks as research platforms, there is growing support for viewing consent as an ongoing process between the participant and the biobank, rather than merely a once-and-for-all decision (Mascalzoni *et al* 2008). For this reason, UK Biobank has taken the approach that participants are consenting to 'participation in a biobank' (UK Biobank Framework, p. 5):

Because it will be impossible to anticipate all future research uses, consent will be sought for research in general that is consistent with UK Biobank's stated purpose (rather than for specific research).

Such an ongoing consent 'process' is limited only by the potential withdrawal of the participant from the biobank. It is therefore important to maintain good lines of communication through various modalities between the biobank and its participants, so that they can be kept informed of research directions.

### ***Recording consent and procedures once consent is obtained***

Whilst consent is generally obtained in writing, there may be circumstances where verbal consent would be acceptable; for example, if the person is illiterate or cannot write. In such circumstances, the process by which non-written consent is obtained needs to be recorded.

The *National Statement* specifies that once consent is obtained:

any restrictions on the use of participants' data should be recorded and the record kept with the collected data so that it is always accessible to researchers who want to access those data for research. (paragraph 3.2.11)

It further states that:

researchers and custodians of the databank should observe any confidentiality agreement about stored data with the participant, and custodians should take every precaution to prevent the data becoming available for uses to which participants did not consent. (paragraph 3.2.12)

### ***Withdrawal of consent***

Under national (*National Statement* paragraph 2.2.20) and international ethical guidelines, (UNESCO Declaration Article 9; OECD Guidelines, Principle 4G, Best Practice 4.13) all research participants, including those providing biospecimens and information for a biobank, have the right to withdraw their consent without penalty or explanation. This right of withdrawal is a fundamental principle enshrined in the Helsinki Declaration (1964). In practice, however, there are limitations to implementing that right of withdrawal in the context of biobanks, and potential participants need to be made aware of these. In particular, the possibility of withdrawing completely may depend on the timing of the request for withdrawal, whether the biospecimen has been distributed and used for research purposes, or if results are in the public domain or have been published (OECD Guidelines, Annotation 43). It may also depend on the nature of IT systems which might not allow complete deletion of personal data.

The consent documentation needs to make clear:

- the research participant's absolute right to withdraw consent;
- how this right is to be exercised (including relevant contact details);
- what will happen if this occurs (including what is to happen with any remaining biospecimens); and
- the *limitations* on withdrawal if the person's biospecimen and data have already been distributed.

Whilst unused biospecimens can be returned to the biobank and withdrawn from the resource, processed biospecimens and the research data generated from them

cannot be withdrawn. In these circumstances, individually identifiable information needs to be removed from the data (ISBER Best Practices, p. 48) and participants reassured that confidentiality and protection of their biospecimens and data will continue. The OECD Guidelines, Annotation 42 note that withdrawal of consent need not be an 'all or nothing' matter: as the UK Biobank model illustrates, there may be options for withdrawal, which can be outlined to the potential participant when seeking consent. The options it identifies are:

- 'No further contact' - no further contact with the participant, but permits the continued retention and use of the previously obtained samples and information, and to obtain further information from health relevant records.
- 'No further access' - no further contact with the participant or access to health records but permits continued retention and use of the previously obtained samples and information.
- 'No further use' - in addition to no longer contacting or obtaining further information about the participant, any information and samples collected previously would no longer be available to researchers. UK Biobank would destroy the person's samples (although it may not be possible to trace all distributed sample remnants) and would hold information relating to the person only for archival audit purposes. The signed consent and withdrawal would be kept as a record of the person's wishes. Such a withdrawal would prevent information about the person from contributing to further analyses, but it would not be possible to remove data from completed analyses. (UK Governance Framework, p. 9; note also OECD Guidelines, Annotation 42)

One mooted possibility is for participants to be given the option of withdrawing from a particular use or project. Such selective withdrawal was widely discussed by the UK Biobank Ethics Governance Council but was ultimately rejected as impractical, mainly because it is not possible to notify participants ahead of time of approved projects. Such notification would be clearly unworkable for large-scale biobanks, and even for small collections it would be very difficult to achieve.

The OECD Guidelines note that in circumstances where samples are anonymised, they will not be traceable back to the participants which has implications for withdrawal; accordingly, the Guidelines suggest that HBGRDs should consider the implications of anonymisation (Annotation 57).

## ***Recontact***

As noted above, the possibility of recontact needs to be addressed in the information provided to prospective participants in the course of obtaining consent. A biobank may wish to recontact participants for a number of reasons over the course of the biobank's operation. The approach of UK Biobank is illustrative, in its section on "Expectation of re-contact":

It will be explained to participants that they may be re-contacted by UK Biobank for various reasons, including:

- To collect new information (such as questionnaire data, measures of samples) for the resource
- To seek consent to proposed new uses that have passed scientific and ethics review but do not fall within the existing consent
- To ask participants whether they would be willing for researchers to contact them to discuss possible involvement in a study that requires new information or samples. (UK Biobank Framework, p. 8-9)

It will be emphasised that participation in all such assessments is entirely voluntary, and that any initial re-contact will be undertaken by UK Biobank.

Decisions on whether re-contact is appropriate for particular proposals will be made by UK Biobank with advice from the Ethics and Governance Council and will be subject to Research Ethics Committee approval...'

Contact for the purpose of providing results to participants is discussed in Chapter 4: Data Management, p. 43.

### ***Incapacity or death of donors***

The OECD Guidelines state that HBGRDs should have a clearly articulated policy about the effects, if any, of the participant's death or loss of legal capacity, and participants should be informed of this policy (Annotation 44). As noted previously, this is one of the matters that is best addressed before consent is obtained. As the examples in the OECD Guidelines (Annotation 44) make clear, there are a number of ways this situation might be approached.

Some biobanks make explicit to participants during the consent process that their biospecimens and data will continue to be included in the biobank after they lose capacity or die. For example, UK Biobank is clear that, whilst participants have the right to withdraw from the biobank at any time, a participant's legal incapacity or death does not give his or her relatives the right to withdraw on that person's behalf (UK Biobank Framework, p. 10). Furthermore, 'UK Biobank will not enrol potential participants who express the view that they would want to be withdrawn should they lose mental capacity or die because this would reduce the value of the resources for research' (UK Biobank Framework, p. 10). However, UK biobank will endeavour to honour the wishes of an enrolled participant who subsequently advises that he or she would want to withdraw in the event of mental incapacity or death (UK Biobank Framework, p. 10). However, as the Icelandic experience has illustrated, there may be potential legal problems with this approach, at least in Europe and relating to data protection and families (see Gertz 2004a and 2004b).

Other biobanks may wish to give the next of kin, or perhaps some other person nominated by the participant, the option of withdrawing that participant from the biobank after loss of capacity or death. Some biobanks may wish to specify that participants' biospecimens and information will be irreversibly anonymised when their death or incapacity becomes known to the biobank. To make an informed decision about participation, potential participants need to be clearly informed of the biobank's policy on this issue.

### ***Circumstances in which new consent will be needed***

There are situations where, although a participant's consent was given at the start of participation, new consent needs to be considered (there will also be circumstances where a biobank holds biospecimens obtained without specific donor consent; see the discussion on waiver of consent, p. 37).

Whether and to what extent participants' consent is valid for planned research uses is a matter to be kept under review (see above) and specifically considered by a human research ethics committee in relation to each proposal for research using the biobank resource. If the original consent does not cover the proposed uses, new consent would normally be required. This principle is encapsulated in the OECD Guidelines:

Throughout the lifespan of the HBGRD, the research use of human biological materials and data should be consistent with the original informed consent or new consent should be sought, except where otherwise provided by domestic law and consistent with international legal norms and ethical principles. (Best Practice 4.5)

It may also be necessary to obtain fresh consent from participants if there are major changes to the biobank, and in some limited circumstances it may be appropriate to seek waiver of consent (OECD Guidelines, Annotation 33).



As a logical corollary, there needs to be a process to identify when fresh consent is needed, and/or to initiate ethical review to determine whether the usual requirement for consent can be dispensed with. This is also provided for in the OECD Guidelines (Best Practice 3.1):

Review processes, in accordance with applicable law, including research ethics committees or comparable oversight mechanisms, should be in place for use in cases where human biological materials or data are to be used in a manner not anticipated in the original informed consent process including:

- for previously collected human biological materials or data where the use might deviate from the original consent;
- for cases where informed consent may not have been obtained at the time of collection;
- for determining when to seek re-consent; and
- for use of human biological materials or data where consent was obtained using a broader or layered format for uses unspecified at the time of collection, especially in the case of large-scale genetic epidemiology studies.

The issue of waiver of consent is discussed further below. The role of independent review bodies, operating in addition to human research ethics committees, is discussed in Chapter 5: Governance of Biobanks.

### ***Obtaining biospecimens and information from children and other vulnerable people or groups***

From a research perspective, it may be desirable to include as biobank participants children and other vulnerable groups, such as people who lack competence or 'protected adults', to support long-term research that aims to gain a better understanding of the issues affecting these groups, and of the development of genetic diseases. The vulnerable status of these groups and their lack of capacity to give effective consent, however, dictate a need for special care. As recognised in the OECD Report (p. 93), determining whether or not to allow children and/or protected adults to participate in genetic studies and contribute to biobanks is complex.

#### **Children**

Some biobanks have decided not to include children (for example, UK Biobank is recruiting only an adult cohort). Some biobanks may for practical reasons seek to recruit the children of parents who have been biobank participants, once those children reach adulthood. For biobanks that plan to include children whilst they are still minors, there are important issues in relation to consent to be addressed. In particular, involving children as biobank participants entails deciding what constitutes appropriate consent for their participation: whether it be consent from the parent, the child or a combination of both. The need for special care in involving children in research is widely recognised, in the *National Statement* and research codes in most countries, as well as international guidelines dealing with biobanks (OECD Guidelines, Principle 4.C).

The *National Statement* (see Chapter 4.2: Children and Young People) provides as follows:

Research involving children and young people raises particular ethical concerns about:

- their capacity to understand what the research entails, and therefore whether their consent to participate is sufficient for their participation;

- their possible coercion by parents, peers, researchers or others to participate in research; and
- conflicting values and interests of parents and children.

These considerations apply to all research involving children and young people. However, they assume special prominence in educational and health research, where there are particular tensions between not placing children at risk in studies of new interventions and the need for knowledge about how such interventions are best used for children.

Researchers must respect the developing capacity of children and young people to be involved in decisions about participation in research. The child or young person's particular level of maturity has implications for whether his or her consent is necessary and/or sufficient to authorise participation. Different levels of maturity and of the corresponding capacity to be involved in the decision include:

- A. infants, who are unable to take part in discussion about the research and its effects;
- B. young children, who are able to understand some relevant information and take part in limited discussion about the research, but whose consent is not required;
- C. young people of developing maturity, who are able to understand the relevant information but whose relative immaturity means that they remain vulnerable. The consent of these young people is required, but is not sufficient to authorise research; and
- D. young people who are mature enough to understand and consent, and are not vulnerable through immaturity in ways that warrant additional consent from a parent or guardian.

It is not possible to attach fixed ages to each level – they vary from child to child. Moreover, a child or young person may at the one time be at different levels for different research projects, depending on the kind and complexity of the research. Being responsive to developmental levels is important not only for judging when children or young people are able to give their consent for research: even young children with very limited cognitive capacity should be engaged at their level in discussion about the research and its likely outcomes.

The following points can be distilled from these various statements and guidelines as summarised by Chalmers (forthcoming):

- Child research entails special consideration and special responsibilities.
- Consent procedures and ethical review need to be developed for each research project involving children.
- Children have developing levels of maturity, from being unable to understand the research project, to understanding some relevant information, to understanding information but not being old enough to provide proper informed consent.
- The research project should not involve any more than low risk to the child (by and large, biobank inclusion would pose no more than low risk).
- There should be no harm to the child, and the child's safety and emotional psychological security and wellbeing should be specified in the signed consent and fundamental to the conduct of the research.
- Parental or guardian consent should be obtained.
- Overall, the project and ethical approval should pay due regard to the best interests of the child (even though there may be no direct benefit).

## Parental consent on behalf of children

Very young children, who would have no understanding of the process, not only lack legal capacity to consent, but are not in a position to participate in the consent process. With older children (eg, 8-10 years plus), who would be in a position to have an opinion on their participation but remain legally too young to give a valid consent, ethical guidelines indicate it is appropriate for the child's 'assent' to participation to be obtained, in addition to the consent of the parent(s). This is consistent with the *National Statement* on involvement of children in research generally – 4.2.7-4.2.9. Thus, the OECD Guidelines state that:

The operators of HBGRDs involving participants who are minors should have a clearly articulated policy on whether, when and how the minor's assent will be obtained, in accordance with applicable law and ethical principles. (Best Practice 4.7)

The OECD Guidelines Glossary defines 'assent' as follows:

This term is used in the context of a child participant in research. Even though a child may not be considered legally competent to consent to participate in research, the child may be considered competent to give his/her assent, that is – his/her opinion on whether he/she wishes to participate in the research.

The rationale for involving the older child and obtaining his or her assent is that it would be unethical to involve a child as a biobank participant if the child does not wish to be involved. Equally, if a child has begun to participate but later wishes to withdraw, regardless of the will of the parent, the child's decision is to be respected.

## Consent at maturity

Given the long-term nature of biobanks, questions arise about the ongoing validity of parental consent once the child matures and can form his or her own opinion on further research participation (even when this still falls short of legal capacity to consent). The OECD Report has suggested one approach, where the biobanks would:

... determine that below a certain age (eg, 10, 12, 14 years) the parents decide on the child's behalf. However, once that age is attained, it would be mandatory for the research team to actively seek the child's permission for further research, based on a number of elements. (p. 93)

In these circumstances, further research involving the child should not continue unless the child indicates his or her agreement. This is consistent with the UNESCO *International Declaration on Human Genetic Data*, Article 8c, which states: 'The opinion of a minor should be taken into consideration as an increasingly determining factor in proportion to age and degree of maturity.'

The OECD Guidelines (Best Practice 4.8) note the need to consider what happens once a child participant gains capacity to consent, either as an adult or a competent minor. It can be argued that that person's consent to continued participation ought to be obtained at that point, even where prior assent had been given in addition to parental consent. This is the view taken by the NCI Best Practices:

Studies that use identifiable biospecimens and/or data from children that are obtained with parental or guardian permission should consider the need for obtaining informed consent when a child reaches the legal age to consent for a research study. Such re-consent issues may best be addressed by IRBs at the time the board reviews the initial protocol. (p. 20, Best Practices C.2.2.11)

For children who are 'Gillick' competent (*Gillick v West Norfolk and Wisbech Area Health Authority* (1985) 3 All ER 402) (ie, are assessed to have sufficient maturity and understanding to make an informed decision) when ongoing participation in the biobank is being considered, their actual consent should be obtained and should be

a precondition to their participation. The UK Medical Research Council sees it as good practice to seek parental consent also (Medical Research Council\_2001, p. 26.)

If it is not feasible to seek assent and/or consent from minors (eg, because researchers do not maintain ongoing contact with participants), researchers need to seek ethics approval that authorises continued research based on the initial parental authorisation, but waives the need to seek the child's assent or consent. (Samuel et al 2008, p. 7).

Where children are to be involved in the decision-making, the documentation about the biobank needs to be presented in a form they will understand (OECD Report, p. 94).

In practice, some projects, such as UK Biobank, have chosen to focus exclusively on an adult cohort (500,000 people aged 40-69 at presentation), while others include children: for instance,

- the Avon Longitudinal Study of Parent and Children (<http://www.bristol.ac.uk/alspac>);
- the Canadian Healthy Infant Longitudinal Development (CHILD) Study (<http://www.canadianchildstudy.ca/ChildStudy/Guest/Home.aspx>);
- the US National Children Study (<http://www.nationalchildrensstudy.gov/pages/default.aspx>)
- the proposed Joondalup study: Western Australian Genome Health Project (<http://www.genepi.org.au/waghp>), which plans to recruit whole families.

### **Other vulnerable people and groups**

Other potentially vulnerable groups from whom biospecimens and information may be procured include people who are in dependent relationships, are dependent on medical care, or lack competence due to age or mental incapacity. Involvement of such people in research is governed by specific guidelines contained in the *National Statement* (see paragraphs 4.3-4.5) and equivalent statements from other countries. The intent is to safeguard the interests of a person who is incapable of making an informed decision, and the guidelines make clear that the vulnerabilities of these groups as research participants need to be taken into account.

Broadly, as summarised by Chalmers (forthcoming) ethical research guidelines establish that:

- Special considerations and responsibilities attach to research involving adults who are incapable of making an informed decision.
- The research project and ethical approval should pay due regard to the best interests of each such adult (even though there may be no direct benefit).
- Consent procedures and ethical review need to address these special considerations and responsibilities for each specific research project.
- Ethical review should recognise that some people may have some understanding of the research project, but not sufficient to provide informed consent.
- There should be no harm to the safety and emotional and psychological security of a person who is incapable of making an informed decision.
- The research project should not involve any more than low risk (which is usually the case with biobanks) to the person.
- The research question to be addressed should be one that cannot be addressed through research involving only competent research participants.
- The guardian or other required legal representative's consent must be obtained. (Chalmers, (forthcoming) p. 17)

Notably, there are quite a number of features in common between these guidelines and equivalent guidelines in respect of children, outlined above.

The *National Statement* and other guidelines identify that substitute decision-making can be carried out by a guardian or other person legally authorised to provide consent on behalf of an adult who is incapable of an informed decision. For example, the UNESCO Declaration on Human Genetic Data addresses substituted consent:

When, in accordance with domestic law, a person is incapable of giving informed consent, authorization should be obtained from the legal representative, in accordance with domestic law. The legal representative should have regard to the best interest of the person concerned. (UNESCO 2003, Article 8b)

Similarly, with specific reference to biobanking, the OECD Guidelines state that:

The operators of the HBGRD should give careful consideration to any special issues relating to the participation of vulnerable populations or groups, and their involvement should be subject to protective conditions in accordance with applicable law and ethical principles. (Principle 4.C)

Where people who are unable to give consent are to be involved in a biobank, efforts to involve them as far as possible in the decision-making (such as through the use of an assent process) are encouraged. For example, the UNESCO *Declaration on Human Genetic Data* Article 8c states that: 'An adult not able to consent should as far as possible take part in the authorisation procedure.'

Where a person who previously lacked capacity to consent gains or regains that capacity, the continued status of any earlier substituted consent needs to be reconsidered. If the person now has capacity to consent, his or her consent should be sought for continued research participation and would certainly be required for any further collection of biospecimens or data from the person.

As noted in Chapter 2, in some cases, biobanks may source biospecimens from deceased persons. They may also be sourced from aborted fetuses or placental/umbilical cord. This raises particular consent issues: in the case of deceased persons, involving next of kin, and in regard to aborted fetuses or placental/umbilical cord, the mother and, where appropriate, her partner.

## ***Cultural sensitivity***

As noted earlier, cultural sensitivity is a fundamental consideration in biobanking. In particular, genetic research, which is central to biobanking activities, is potentially an area of sensitivity for particular communities.

The OECD Guidelines advise that, among other things, the HBGRD's policy on procurement and collection of human biological material and data should take into consideration the known cultural heritage and/or religious beliefs of participants and their representative groups (Best Practice 5.3).

Similarly, the *National Statement* makes clear that due regard is required to the cultural heritage of all those involved in research (paragraphs 1.10 and 3.4.1(g), and chapters 4.7 and 4.8). In particular, the consent process should take into consideration the cultural sensitivities of the community in which the research is to be conducted (paragraph 3.5.11) as well as the participant's cultural and/or religious beliefs (see also OECD Guidelines, Annotation 29). The *National Statement* recognises that in some circumstances it is ethically appropriate for researchers to seek consent from appropriate community representatives as well as from the individuals concerned (see also European Society of Human Genetics Recommendations, European Society of Human Genetics 2003). The *National Statement* provides that this will be appropriate where:

- (a) researchers propose to collect genetic material and information from individuals who are chosen because of their membership of a particular community;
- (b) the research involves sensitivities for the community; and
- (c) there is known to be a culturally relevant community structure involved in such matters. (paragraph 3.5.11)

The means by which consent is recorded may also be influenced by the participant's cultural circumstances (*National Statement*, paragraph 2.2.5(b)).

### ***Using biospecimens and information from existing collections and waiver of consent***

In contrast to prospective biobank collections, a biobank may seek to draw on biospecimens and information in existing collections. As acknowledged in Chapter 1, there are, in practice, vast numbers of collections in existence, originally collected for clinical or diagnostic purposes, often with no consideration of consent for research purposes. There has been considerable debate in the context of biobanking about how existing collections may best be managed ethically, recognising that participant consent is likely to be problematic. The OECD Report (p. 94-95) recognises the value such collections can bring to research and their attractiveness to researchers, particularly if they are available for a period of ten or more years back and if there is potential for follow-up information.

#### **Case Study: Use of data without consent**

At the Menzies Research Institute, University of Tasmania, tissue has been obtained over many years with donor's consent to perform certain tests on it. This consent does not, however, cover participation in a broader investigational study. In the future, the Institute is looking to obtain a more generalised consent for use of tissue samples and data for future unspecified research.

Data that are currently used by the Institute without consent are those that are publicly available: data from the state Registry of Births, Deaths and Marriages, the Electoral Roll, and the Cancer Registry. The Institute can collate these data and identify individuals without their consent, but their consent is required to use the data for research.

Where the donor of tissue has died, privacy legislation now forbids the use of the person's tissue and related data without consent from the next of kin. This is not always available, particularly where the tissue was collected and the person died decades earlier. In such circumstances, the Institute has obtained HREC approval to use these tissues and data in research without consent. Waiver of consent by a HREC is discussed further below.

#### **Waiver of consent**

In the matter of waiver of consent, there appears to be a distinction between biobanks that are established prospectively and those that are based on or include existing collections. Most prospective biobanks are arranged in such a way that waiver is generally not applicable. However, even where broad consent is obtained for prospective biobanks, there may be circumstances in which there has been a major modification to the research direction for the biobank such that it is of a fundamentally different nature to that initially proposed. In these circumstances, it may be appropriate to seek re-consent from participants or, where that is not possible, to seek waiver of consent.

Waiver of consent is likely to be relevant to biobanks based on existing collections. Whilst consent is normally seen as a prerequisite for any research involving humans, to recontact all donors of existing collections to seek their consent for

research use of their biospecimens and information would be not only expensive, but impractical, especially with the passage of time, and the relocation and death of some participants. The guidelines of most countries, including Australia, provide for waiver of consent, allowing biospecimens from existing collection to be used in research provided that the project has scientific merit, is approved by a human research ethics committee, and the biospecimens are de-identified (Chalmers (forthcoming) p. 35). For example, the OECD Guidelines state:

In the situations of HBGRDs established from existing collections, the operators will need to consider whether the intended scope and purpose of the HBGRDs and intended research uses of the human biological materials and/or data are consistent with the original informed consent. Where the intended scope of the HBGRD or its intended uses are not within the ambit of the original informed consent or none was obtained, for example, the human biological materials and/or data may only be used if a new consent is obtained or if a waiver of consent is obtained from a research ethics committee or an appropriate authority, in accordance with applicable law and ethical principles (Annotation 33).

Drawing on the *National Statement's* general provisions in relation to waiver of consent (paragraphs 2.3.5-2.3.6), a human research ethics committee, before waiving the requirement for consent, must be satisfied that:

- (a) involvement in the research carries no more than low risk to participants;
- (b) the benefits from the research justify any risks of harm associated with not seeking consent;
- (c) it is impracticable to obtain consent (for example, due to the quantity, age or accessibility of records);
- (d) there is no known or likely reason for thinking that participants would not have consented if they had been asked;
- (e) there is sufficient protection of their privacy;
- (f) there is an adequate plan to protect the confidentiality of data;
- (g) in case the results have significance for the participants' welfare there is, where practicable, a plan for making information arising from the research available to them (for example, via a disease-specific website or regional news media);
- (h) the possibility of commercial exploitation of derivatives of the data or tissue will not deprive the participants of any financial benefits to which they would be entitled;
- (i) the waiver is not prohibited by state, federal, or international law. (paragraph 2.3.6)

It is clear from the above, paragraph (d) in particular, that consent should not be waived where that would be contrary to a participant's earlier expressed wish. A human research ethics committee may resolve to allow a project to proceed by waiving the need for individual consent, but imposing conditions such that the data may only be accessed in a de-identified form and access is restricted to specified researchers (Chalmers (forthcoming) p. 37).

Making data anonymous is sometimes raised as an option for accessing existing collections in the absence of specific consent; however, as recognised by the European Society of Human Genetics:

The decision to strip samples of identifiers irreversibly needs careful consideration. The benefits of having unlinked anonymised samples is to secure absolute confidentiality and thereby allows further use of the samples. However, retaining identifiers while requiring further consent from the subject will permit more effective biomedical research and the possibility of recontacting the subject when a therapeutic option becomes available. (European Society of Human Genetics 2003, p. S9)

The *National Statement* takes a similar position:

Identifiers of genetic material should not be removed without the consent of the participants, if removal would make it difficult to communicate personal results. (paragraph 3.5.5)

There has been much discussion also in the UK about problems related to the suggestion that the only approaches are 'consent or anonymise': see The Academy of Medical Sciences 2006.

### **Case study: Waiver of consent**

Hereditary non-polyposis colorectal cancer (HNPCC) is a preventable hereditary disease for which there is effective treatment. It was believed that the existing criteria for referral to Genetic Services based upon age and taking a family history was likely to miss many possible cases. With the advent of a simple immunohistochemical test for the proteins known to underpin this condition it was possible to perform cost effective screening of at risk cases. The test is a 'phenotypic' test in that it can only indicate people who may be at risk and does not define whether there is indeed a germ line genetic mutation which can only be done after consent has been given following counselling. A study was conducted to assess risk status for HNPCC in all persons treated for colorectal cancer in a large public hospital to determine whether cases had indeed been missed using the existing criteria and also to determine how many of those at high risk were known to Genetic Services of Western Australia (GSWA) (Zeps et al 2007).

The researchers believed that the individual and community benefits of the study outweighed the individual's right to autonomy; hence, they proposed to conduct it without patient consent. HREC approval was granted, based on the researchers' justification for waiver of consent and follow-up contact for those determined to be at high risk.

The justification for waiver of consent was that:

1. It was 'impossible or difficult or intrusive to obtain specific consent' (*National Statement*, paragraph 15.8):
  - a) Participants were unlikely to have the condition (0.3-3%).
  - b) Harm or invasion of privacy (public hospital confidentiality agreements) was outweighed by benefits.
  - c) A prospective study would be time-consuming and expensive.
  - d) Excluding deceased persons would create bias, but it would be a burden to contact next of kin.
  - e) Getting the consent of 1050 people and offering them counselling posed a substantial cost burden.
2. Obtaining consent may have been unethical and potentially harmful, and may have caused delay.

The justification for informing high-risk individuals was that:

1. Failure to inform can be seen as a failure of the basic duty of care.
2. There was no reason to give negative results.
3. Effective surveillance programs exist.
4. GSWA committed to managing individuals at risk.

Only one patient expressed negative sentiments regarding lack of consent. As a result of this study, the surveillance policy regarding age of diagnosis was changed from <45 to <60.



## Chapter 4: Data Management

This chapter focuses on data management at the ground level, after participants have been recruited and their consent obtained. It examines some important practical issues: data identifiability; data linkage; storage; privacy and confidentiality; formal material transfer agreements; quality assurance, security and technical standards; release of results to participants; and non-discrimination and non-stigmatisation. More general management issues for the biobank as a whole are dealt with in Chapter 5: Governance of Biobanks.

### ***Data identifiability***

Views differ on the identifiability of biospecimens and whether they can ever be fully de-identified. The *National Statement* urges a cautionary approach, as illustrated in the introductory section of Chapter 3.2, on Databanks:

With advances in genetic knowledge and data linkage, and the proliferation of tissue banks of identified material, human tissue samples should always be regarded as, in principle, re-identifiable.

This view is reflected in other parts of the *National Statement*, including provisions dealing with what people need to be told when seeking their consent to collect their genetic material (see paragraph 3.5.8(a)).

Clearly of utmost importance is whether biospecimens are *practically* identifiable. However, highlighting the potential identifiability of all biospecimens also highlights the need to ensure that the privacy and confidentiality of any stored biospecimens are protected. If it is assumed that it is *impossible* to make biospecimens completely anonymous, appropriate attention can be focused on data security and safeguards to minimise the risk of individuals being identified (see the section of this chapter on quality assurance, security and technical standards, p. 46).

As noted in the preceding chapter, as part of the consent process, potential participants should be provided with clear and comprehensive information about the form in which their data will be stored (whether identifiable, re-identifiable, or non-identifiable) (see *National Statement*, paragraph 3.2.9). Whilst participants can be advised that all reasonable steps will be taken to ensure protection of their privacy, it is important to be open and realistic. There can be no guarantee of absolute anonymity or a completely risk-free environment. Participants therefore need to understand that there are always some risks when data and or samples are shared but that the environment in which they will be participating is secure and managed by trusted parties. The *National Statement* makes clear that research involving data stored in an identifiable form (ie, 'individually identifiable data' or 're-identifiable data') cannot be used in research that is exempt from ethical review (*National Statement*, paragraph 3.2.10).

The potential for biospecimens to be identified has implications for biobank management and governance. This is acknowledged in the OECD Guidelines Principles:

6.A The HBGRD should be established, managed, governed, and operated in such a way as to prevent inappropriate or unauthorised access to or use of participants' human biological materials and personal data and/or information.

6.B The operators of the HBGRD should establish and implement specified policies and procedures for the protection of human biological materials and data, especially those permitting, whether directly or indirectly, the identification of the participant.

In contrast to the *National Statement*, some reports and opinions seek to distinguish between a theoretical possibility of re-identification and whether a biospecimen is in reality reasonably identifiable. For example, the ALRC/AHEC *Essentially Yours* Report (2003) states:

The Inquiry does not believe that genetic samples should be considered inherently identifiable for the purposes of the *Privacy Act*. Whether they are *reasonably* identifiable or not will depend on the surrounding context. In most circumstances, an unlabeled and uncoded sample may still be considered to be de-identified, despite a theoretical possibility of re-identification. (Paragraph 8.19)

A similar view has been adopted by the Data Protection Working Party of the European Commission (2007) in its Opinion on the Concept of Personal Data. This opinion states that 'a mere hypothetical possibility to single out the individual is not enough to consider the person as identifiable'; rather, the focus should be on 'all the means likely reasonably to be used' to identify the person, and if in light of such considerations, the possibility of identification is negligible or nonexistent, the person should not be considered as identifiable (p. 15). Notably, however, this statement is made in the context of personal data generally, rather than biospecimens and information specifically, for which, it could be argued, special considerations apply, given that genetic material is potentially re-identifiable if it can be linked to other relevant information relating to the person (see the paragraph quoted above from the introduction to Chapter 3.2 of the *National Statement*). Bearing in mind the approach of the *National Statement*, a workable solution is to recognise that biospecimens are theoretically or 'in principle' identifiable, and that therefore, a high level of care is required in the handling and management of such data; however, from a practical or functional point of view, what matters most is reasonable or practical identifiability.

### **Case Study: Potential for re-identification**

A biobank will by definition include some form of biological material from which DNA can be obtained. Most typically this will be a blood sample from which either DNA is extracted directly from white blood cells or in which the lymphocytes are transformed to create a cell line. In other cases it may be a saliva sample from which DNA is obtained, or the biological material may be a tissue sample such as a tumour.

All individuals can be uniquely identified from their DNA, a concept which is widely understood by the general public. Indeed, there is regular media commentary on such forensic identification of deceased individuals following war (eg, identification of individuals from mass graves) or disasters (tsunami, bushfires, explosions), with Australian forensic experts being highly accomplished in this area. What is not so well appreciated is that identification can only be made by comparison to a reference sample from the individual concerned or from close family members.

Several classes of biobank have been established with the express purpose of future re-identification. These include military and criminal biobanks.

#### ***Military Biobanks***

Since the early 1990s, all personnel serving in the United States Armed Forces have been required to submit tissue samples to allow later DNA identification. By 2003, the United States military's DNA depository contained 3.8 million samples, including samples from active duty and reserve personnel. Retrieval and analysis is performed only to identify human remains.

#### ***Criminal Biobanks***

The United Kingdom is reported to have the largest forensic DNA databank, which holds over 2.5 million samples of those who have been charged with one of a list of offences and, since 2004, those who have been arrested but not charged. A recent court decision ruled that

those who have not been convicted of a crime are presumed innocent and that retaining their genetic samples and DNA profiles indefinitely interferes with the right to respect for private life. Forensic DNA evidence has been used to determine the innocence of a number of convicted individuals; however, less than 0.5% of convictions are currently based, in whole or in part, on DNA evidence.

Biobanks established for research purposes are also able to allow future re-identification, whether planned or not. However, without identified DNA samples for comparison from relatives or potential biobank participants themselves, it is difficult to see how the biobanked samples could be re-identified.

There are, however, potential areas of legitimate concern; for example, if a research biobank were subject to a court order to provide DNA samples for potential criminal identification, or if DNA information were used in combination with phenotypic or demographic information to make positive or negative inferences on what is routinely considered personal information, such as health status or risk, or social or ethnic status.

## **Data linkage**

The ability to link data from different data sets is a feature of many biobank definitions (see discussion in Chapter 1). Whilst such linkage opens up significant research opportunities, it also creates potential for participants to be identified and their privacy breached. Special care is therefore needed in research involving data linkage, particularly where genetic data are involved, given the sensitivities associated with such data.

Chapter 3.2 of the *National Statement* provides guidance on research involving linkage of data sets, which has implications for identifiability of data. In particular:

3.2.3 Researchers' use of data from databanks must comply with conditions specified by the providers of the data; in particular, any conditions on the identifiability of the data... .

3.2.4 Where research involves linkage of data sets, approval may be given to the use of identifiable data to ensure that the linkage is accurate, even if consent has not been given for the use of identifiable data in research. Once linkage has been completed, identifiers should be removed from the data to be used in the research, unless consent has been given for its identifiable use.

3.2.5 It is the duty of the custodian to ensure that the data are used responsibly and respectfully, and that the privacy of participants is safeguarded.

Further, the *National Statement* (paragraph 3.2.7) notes the need, in some circumstances, for the data custodian to be independent. Chapter 5: Governance of Biobanks deals with this issue in more detail (see p. 59).

Sophisticated technology can be deployed to protect participants by ensuring that all data linkage is electronically recorded and can be subsequently traced and reviewed. This represents an important safeguard and promotes accountability on the part of biobanks and their users.

The ALRC/AHEC *Essentially Yours* Report, in examining best practice requirements for genetic research involving genetic databases, supported the use of an independent intermediary or 'gene trustee' between the researcher and the biospecimens and data (also sometimes referred to a 'trusted third party'), as a means of protecting the privacy of the biospecimens and data (recommendation 16-1). Again, this issue, which is an aspect of biobank governance, is discussed further in Chapter 5: Governance of Biobanks (see p. 59).

## Storage

This section addresses storage issues in the context of the collection and management of biospecimens and data. In particular, it discusses requirements in relation to duration of storage, related issues of data quality and viability, and implications for the consent process.

The *National Statement* addresses storage of data in general terms stating that data should be stored in such a way that they can be used for future research projects (paragraph 3.2.2), and identifying the need for institutional policies covering, amongst other things, storage of human tissue in research (paragraph 3.4.1). It is particularly important that electronic storage is organised in such a way that the data will remain readable well into the future, especially given the long-term nature of such biobank collections.

A distinction needs to be drawn between storage of biospecimens and data in clinical and in research contexts. In the clinical context, diagnostic laboratories in Australia are subject to national regulation that sets out detailed requirements in relation to biospecimen and record retention, including duration of storage (see the National Pathology Accreditation Advisory Council *Requirements for the Retention of Laboratory Records and Diagnostic Material*, 2007).

In the research setting, the focus of this paper, the relevant guidelines are contained in the *National Statement*. In addition to the general provisions noted above, the *National Statement* includes a number of more specific provisions relating to data storage, particularly in relation to consent for collection of identified or potentially identified genetic material. Paragraph 3.5.12(c) requires that potential participants be informed 'about any proposal, subject to participants' consent, to store their genetic material and data because it might be useful for as yet unspecified research.' Paragraph 3.5.12(d) provides that if such consent is not given, the participants should be informed that the genetic material and data will be disposed of at the end of the research for which consent has been given once the biospecimen storage and record keeping requirements of good research practice have been met (see NHMRC/ARC, *Australian Code for the Responsible Conduct of Research*, 2007).

In the case of biobanks, the issue of storage of biospecimens and information for future, as yet unspecified research is typically a central consideration rather than merely a possible by-product of research, and collection of biospecimens and information needs to be undertaken on this basis. Biobanks therefore need to establish and document a transparent and clearly defined policy on consent. This is well summarised in the OECD Guidelines (see also NCI Best Practices p. 2):

The operators of the HBGRD should have a clearly articulated policy on the duration of storage of human biological materials and data (OECD Guidelines, Principle 6.D)

The OECD Guidelines note the desirability of standardising procedures for storage (Best Practice 2.8):

In establishing new HBGRDs, consideration should be given to future collaboration and cooperation, especially as regards database compatibility and interfaces. Appropriate design elements providing for such compatibility and interfaces should be incorporated when creating the databases. The operators of the HBGRD should give consideration to using standardised approaches for the collection, storage and analysis of human biological materials and/or data so as to facilitate cross-HBGRD data exchange and sharing.

Where long-term storage is contemplated, quality control and assurance measures need to be in place to ensure ongoing research utility of the stored biospecimens and data. The NCI Best Practices document sets out detailed requirements for biospecimen storage (p. 4-5) and quality assurance/quality control mechanisms (p.

9-10), and recommends that biobanks should be reviewed periodically to determine the utility of existing specimens and the need for new specimens (p 16). The significance of appropriate storage of biospecimens extends beyond merely technical requirements. Back-up storage of biospecimens is also important ethically, given the biobank's role as custodian or steward of the biobank resource (discussed further in Chapter 5: Governance of Biobanks), as total loss of a collection defeats the altruistic intentions of donors.

The information provided to potential participants needs to include information about the proposed duration of storage of the participant's biospecimens and data and, where relevant, the likelihood of indefinite storage (subject to quality control and assurance issues); details regarding transfer, including whether this may entail international data transfers; and future disposal of the data (see Chapter 3: Consent in the Context of Biobanking, in particular the section on information to be provided as part of the consent process, p. 26).

### ***Privacy and confidentiality***

The concept of privacy is based on principles of human dignity and respect for individual freedom. Various international instruments recognise an individual's right privacy, which includes information privacy, as a fundamental human right, including United Nations', *International Covenant on Civil and Political Rights*; OECD *Guidelines on the Protection of Privacy and Transborder Flows of Personal Data* 1980. Privacy and confidentiality are two distinct concepts in the protection of personal health information from third parties. Privacy is principally concerned with the collection of information, whereas confidentiality focuses on the disclosure of personal information to third parties.

Genetic data have characteristics that heighten the need for special care in relation to privacy and confidentiality, including their predictive potential and relevance not only for the individual, but for his or her family and group or community. Unauthorised disclosure of personal information or access to data can place individuals at risk of discrimination, and related groups at risk of stigmatisation (these issues are dealt with in more detail at p. 51). Indeed, concerns about the privacy of genetic information and the potential for discrimination were the main impetus for the joint inquiry by the Australian Law Reform Commission and the Australian Health Ethics Committee into the protection of human genetic information, which was reported in *Essentially Yours* (2003). Implementation of the report's many recommendations for reform is underway; notably, the *National Statement* as revised in 2007, in Chapter 3.5 on Human Genetics, now expressly provides that:

Genetic information can sometimes be used to stigmatise people or discriminate against them unfairly. Researchers should therefore take special care to protect the privacy and confidentiality of this information. (Paragraph 3.5.6)

Research depends on safeguarding the privacy of individuals who contribute biospecimens and information to biobanks, and on maintaining the confidentiality of those data. Adherence to high ethical standards is necessary to ensure public trust in the biobank and the support and participation of research participants and researchers (NCI Best Practices, p. 20).

Biobanks have a legal and ethical duty to ensure the privacy of participants and maintain the confidentiality of their biospecimens and data. Privacy legislation in Australia (Commonwealth *Privacy Act 1988*) is consistent with the OECD privacy principles and covers the full life-cycle of information from collection through to storage, use and disposal of data. It applies, however, only to personal information, not to biospecimens *per se*. In *Essentially Yours*, the ALRC/AHEC recommended that privacy protection be extended to genetic samples, but this recommendation was not accepted by the Government, in its response (Australian Government

2005). Nevertheless, while samples do not fall within the scope of the national privacy regime, personal information extracted from those samples does. Further to the ALRC/AHEC recommendations, genetic information now specifically comes within the definition of health information (*Privacy Act 1988* s 6) and comprises 'sensitive information' under the legislation (*Privacy Act 1988* s 6), attracting a higher level of protection than other forms of personal information such that it cannot normally be collected or disclosed without the consent of the person to whom the information relates.

In a 2008 review of privacy, the Australian Law Reform Commission recommended major rationalisation of privacy coverage in Australia, including for the health sector (ALRC 2008). In particular, the ALRC report contains recommendations for harmonisation of Australian privacy law to a single set of uniform privacy principles (UPPs) and that the legislation should be amended to clearly state that the Privacy Act is intended to apply to the exclusion of state and territory laws dealing specifically with the handling of personal information by organisations. The Commonwealth Government has accepted these recommendations (Australian Government 2009).

The ethical requirements with regard to privacy and confidentiality are primarily contained in the *National Statement*. There are numerous provisions directed to researchers, custodians of databanks and institutions regarding protection of privacy and confidentiality, including information requirements when seeking participants' consent (paragraphs 2.2.6(f), 3.5.8), obligations with respect to data usage (paragraph 3.2.5), arrangements regarding transfer of genetic material or related samples (paragraph 3.5.7), and requirements in respect of storage of genetic data or research results relating to identifiable or re-identifiable participants (paragraph 3.5.13). Support for the protection of privacy of individuals and the confidentiality of their genetic data is also to be found in relevant international statements (UNESCO International Declaration on Human Genetic Data, Article 14; HUGO *Statement on Human Genomic Databases*, Recommendation 4c).

In order to comply with these legal and ethical obligations, biobanks should have clear and well documented policies and procedures for protecting the privacy and confidentiality of donors, and follow those policies and procedures transparently, particularly in regard to data that potentially permit the identification of participants. Indeed, biobanks will be generally required to demonstrate that these policies and procedures are followed (see OECD Guidelines, Principle 6.B).

In practice, privacy and confidentiality are best protected through a combination of mechanisms (OECD Guidelines, Best Practice 6.5). Possible measures include data encryption, coding, secure storage, establishing limited access or varying levels of access to the biobank, removing identifying information from biospecimens and data, implementation and maintenance of security measures to block unauthorised access, and use of a 'gene trustee' or honest broker system involving an independent third party who is responsible for ensuring that identifying information is separated from other data (see OECD Guidelines; UK Biobank Framework, p. 10-12; ISBER Best Practices, p. 48).

Confidentiality agreements need to form part of the employment contracts of all biobank staff. External researchers who are permitted access to the biobank resource can also be required to enter into material transfer agreements that deal specifically with the requirements for privacy and confidentiality (discussed further below and at Chapter 6: Access to Biobanks for Research Purposes, p. 66).

As noted previously, information needs to be communicated to prospective participants about the form in which their data will be held (identifiable, re-identifiable, non-identifiable), the level of protection provided, and the security measures in place to ensure privacy and confidentiality (see Chapter 3: Consent in the Context of Biobanking, particularly the section on information for participants,

p. 26). As noted, it is important that such information is provided to participants openly and realistically, to avoid creating unreasonable expectations of a risk-free environment. Participants need to understand that sharing of data and samples inevitably entails some risk, but that every reasonable effort will be made to minimise that risk.

### ***Formal material transfer agreements***

A material transfer agreement is a binding legal agreement between a biobank and the researcher(s) who is/are to receive the biospecimens and data, setting out the conditions of transfer and use. Material transfer agreements are an important mechanism for ensuring traceability of biospecimens and data, and transparency and accountability on the part of biobanks and their users. For example, they can stipulate requirements for the electronic recording of any data linkage and for recording any release of biospecimens and/or data. These agreements are discussed further in Chapter 5: Governance of Biobanks.

### ***Quality assurance, security and technical standards***

It is vital that biospecimen collection and storage processes are quality assured to ensure that the collection, handling, storage, processing, access and use of any biospecimens are not compromised by human or processing error. Formalised quality assurance and quality control procedures must be developed to minimise errors that could adversely affect scientific results (NCI Best Practice B3).

Security is also of primary concern because of the potential for misuse of data and biospecimens (OECD Report, p. 111). Decisions need to be made about the best methods for ensuring security, having regard to the objective of the biobank, and a balance needs to be struck between ensuring, on the one hand, that access to data and biospecimens occurs only in the permitted manner, and, on the other hand, that access is not unduly restricted. A combination of legislation and technical solutions is required.

Another approach to protecting privacy is to limit the amount or types of data released or accessible to researchers using the database (OECD Report, p. 111). For example, the National Institutes of Health *Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS)* (2008) (hereafter the NIH GWAS Policy) states that data held in its centralised repository of all genotype-phenotype datasets created through NIH-funding of GWAS projects will have multiple layers of security including sequential firewalls and independent networks (p. 9, Principle III).

A further possible mechanism for facilitating data security is to place limits on data access by, for example, use of approved passwords, and/or establishing access rules that are based on the roles of different users and may involve ongoing monitoring of use (OECD Report, p. 112). An alternative model that has been used by a number of biobank initiatives, including the Estonian CARTaGENE Project and the Icelandic HSD, is to allow only a very limited set of analysts to query the primary data directly, with external researchers allowed only indirect access, through these analysts (OECD Report, p. 113).

A number of technical requirements are important in ensuring effective, secure and ethical biobanking. Because health and genetic data are particularly sensitive personal information, they need to be appropriately protected. Data encryption is commonly used, typically in conjunction with other security measures (OECD Report, p. 113). Not only must computing systems be efficient and reliable, but they must also secure confidentiality and privacy of the information derived from the biospecimens. Specific privacy enhancement technologies are being developed to protect personal privacy, prevent unauthorised access to this information and,

most importantly, enable authorised access particularly for authenticating and checking information.

In addition, there are technical issues associated with the number of data points that must be collected in relation to each individual biospecimen and the actual coding of the collected sample. These technical decisions not only have an impact on the security of the collected sample, but also, equally importantly, determine the degree of interoperability for exchange of data between biobanks wishing to conduct international research projects. The NCI Best Practices emphasise the need for robust and reliable informatics systems and the key importance of functionality and interoperability (Best Practice B.5).

### ***General principles in relation to release of research results to research participants***

In research involving humans, it is normally expected that research participants will be provided with information in general terms about the research results (assuming that the participants are contactable), and that the results will be published in order to contribute to the advancement of public knowledge (Chalmers (forthcoming) p. 31).

Biobanks have the potential to reveal medically relevant information about the health or future health of participants and possibly their relatives and group or community; but the question of release of more specific research results back to biobank participants raises some difficult issues, including the management of participants' legitimate expectations. Such release has been the subject of debate, particularly about whether it is feasible or desirable to disclose individual research results (see also OECD Report, p. 96). This is particularly problematic for large-scale biobanks because of the scale of the research endeavour.

A recent study in the US explored public attitudes and concerns about a proposed national Biobank. The study used focus groups to look at the expectations for return of individual research results. The research participants voiced a strong desire to be able to access their individual research results and felt that biobank participants should be given ongoing choices as to which results they received (Murphy et al 2008). The range of potential issues involved in providing such feedback can be anticipated and addressed to some extent in the consent process; however, there are limits to the extent to which advance consent can address all the ethical and legal dilemmas that may arise in relation to disclosure of results.

From the outset, it is important to clarify the range of possible results or information that may be at issue, including results of individual participants or aggregated participants' results either from initial analyses or from the verified or otherwise tangible results of research using the biobank, as well as incidental findings.

Biobanks need to have a clearly articulated policy on the nature of the feedback to participants and, if feedback of either interim and/or final results is planned, whether it will be in the form of individual or aggregate results (see OECD Guidelines, Best Practice 4.9; note also the obligations on researchers identified in the *National Statement*, Chapter 3.5: Human Genetics, outlined in the next section). The policy should also address how incidental findings from the research are to be handled.

### **Feedback of individual results to participants**

Whilst the *National Statement* does not address the issue of feedback of individual results specifically within the context of biobanking, it does contain a number of relevant provisions. Chapter 3.2: Databanks provides:



Whenever research using re-identifiable data reveals information that bears on the wellbeing of participants, researchers have an obligation to consider how to make that information available to the participants. Where individual notification is warranted, the custodian of the data will need to take all reasonable steps to re-identify those data. (paragraph 3.2.6)

#### Chapter 4: Human Tissue Samples states that:

If the research is likely to produce information relevant to the health and wellbeing of the person from whom the tissue was derived, procedures to allow participants to be identified for appropriate follow-up should, wherever possible, be included in the research proposal. (paragraph 3.4.6)

The fullest coverage is in Chapter 3.5: Human Genetics, which sets out quite detailed guidance for researchers whose research may generate findings of relevance to the participants or their blood relatives:

- 3.5.1 Where research may discover or generate information of potential importance to the future health of participants, or their blood relatives, researchers must prepare and follow an ethically defensible plan to disclose or withhold that information.
- 3.5.2 This plan must take into account the clinical relevance of the research information, the types of genetic test used in the research, and the results of those tests. In addition:
  - (a) The plan should:
    - (i) enable participants to decide whether they wish to receive the information and who else may be given the information;
    - (ii) set out a process for finding out whether those other people want to receive information;
    - (iii) include procedures to inform participants that the information would remain potentially identifiable; and
    - (iv) include measures to protect the degree of confidentiality that participants wish to maintain.
  - (b) When participants or their relatives are to be given or notified of genetic information that may be important for their health, the plan should either provide access to genetic and clinical advice and counselling, or clearly recommend to participants that they seek these services. Such advice and counselling should be provided by professionals with appropriate training, qualifications and experience.
  - (c) Where participants or relatives prefer not to receive genetic information that is important for their health, they should be advised that they will be approached to confirm this decision when the results of the research are available.
  - (d) Where the potential relevance of genetic information to participants' health is not clear until after interim analysis of the research information, participants should again be given:
    - (i) the option of being notified of the existence of that information;
    - (ii) the option of receiving the information; and/or
    - (iii) access to, or a recommendation to seek, advice or counselling about the implications of these decisions.

- 3.5.3 Advice about the results of genetic research needs to include a clear explanation of the difference between research and clinical testing, and to clarify any need for clinical testing of research results.
- 3.5.5 Identifiers of genetic material or related information:
  - (a) should not be removed without the consent of participants, if removal would make it difficult to communicate personal results;
  - (b) should be removed if participants request it, provided they have been informed that the material or information would remain potentially identifiable.

Further, when people are asked to consent to the collection of their genetic material or information for research, the *National Statement* requires that they be advised that, if the research discloses that a family member may be at risk of a life-threatening or serious illness for which treatment is available or pending, this information may, with the approval of an HREC, be offered by a clinician to the family member, even if the research participant does not consent to this (paragraph 3.5.8(g)). The *National Statement* also addresses the issue of incidental research findings, stating that participants must be informed whether the research has the potential to detect previously unknown paternity or maternity or non-blood relationship to siblings, and whether, how and to whom this information will be disclosed, according to the approved research plan (paragraph 3.5.8(h)).

If individual results are to be released to participants, it is important to consider whether a genetic counsellor is required to assist with the disclosure or, at the very least, to be available to explain the significance of the results (see also OECD Guidelines, Annotation 46).

A recent amendment to the Commonwealth *Privacy Act 1988* permits the disclosure of genetic information to an at-risk relative by a medical practitioner when there is a serious (although not necessarily imminent) threat to that person's life, health, or safety, notwithstanding that the index patient has refused consent to such disclosure, provided that disclosure is necessary to prevent or lessen that threat. This legislation does not compel disclosure, but rather protects medical practitioners from liability for breach of confidentiality to their patient in the event that they do disclose such information. Guidelines are required to be approved by the Privacy Commissioner before the amendment can be used. Guidelines have been developed by the NHMRC and it is anticipated that these will be released in 2010.

A number of arguments have been put forward in support of offering individual results, including respect for persons, beneficence and reciprocity (see Haga and Beskow 2008, p. 528-529). On the strength of such arguments, some commentators have suggested that rather than making investigators the gatekeepers, participants should have the opportunity to determine what research information they wish to know about themselves (Shalowitz and Miller 2005, p. 737). Some support for placing individuals in control of access to their own genetic data can be found in the UNESCO *International Declaration on Human Genetic Data*:

No-one should be denied access to his or her own genetic data or proteomic data unless such data are irretrievably unlinked to that person as the identifiable source or unless domestic law limits such access in the interests of public health, public order or national security. (UNESCO 2003, Article 13)

There are, nevertheless, a number of reasons why release of individual results to participants may be problematic and the OECD Guidelines, Annotations state that operators of an HBGRD that envisages providing participants with individual-level results should give special consideration to the numerous complexities that doing so presents (Annotation 46). The results arising from biobank research are unlikely

to be scientifically validated, or meaningful to participants, and could potentially be harmful in the absence of informed interpretation, counselling and support. For this reason, it is generally assumed that release of individual results to biobank participants would not normally be appropriate, particularly in circumstances where there is no therapeutically useful course of action available. UK Biobank has been quite explicit in its policy:

UK Biobank will generally not provide health information to participants, and a clear explanation of this policy (and the few exceptions) will be provided on the participant information material. (UK Biobank Framework, p. 7)

One advantage of UK Biobank's approach of not disclosing results to individual participants is that it precludes some of the potential for discrimination (discussed below), and may, therefore, make it easier to promote the biobank to potential participants. This policy of not disclosing results has, however, come under criticism on the grounds that, in the UK and other European countries, there may be not only an ethical duty but also a legal duty to disclose, arising under Article 2 of the *European Convention on Human Rights* (Johnstone and Kaye 2004, p. 239). Whilst there is no equivalent human rights convention applying in Australia, it can be argued that there is an ethical obligation at least to offer disclosure if clinically relevant information comes to light that, if disclosed, could avoid serious harm to the participant. At the same time, as the *National Statement* recognises (paragraph 3.5.2(a)(i)), care must be taken to ensure respect for the participant's right not to know, as reflected in the *UNESCO Declaration on Human Genetic Data* Article 10. It is, therefore, important that this issue is clarified as part of the consent process. Notably, the *National Statement* states that even if participants or relatives indicate that they prefer not to receive genetic information that is important for their health, they should be advised that they will be approached to confirm this decision when the results of the research are available (see paragraph 3.5.2(c), set out above, p. 48).

### **Feedback of aggregate research results to participants**

As noted earlier, feedback of results can take a number of forms. One option is feedback of aggregate and more generalised research results to participants. This is the planned approach of UK Biobank, which, in its Framework, provides that 'the overall findings and implications of results that derive from UK Biobank will be made available to participants...' (UK Biobank Framework, p. 7). Feedback of results to participants in aggregate form avoids some of the difficulties associated with disclosure of individual research results. It could occur through publication of research results, and other formats such as newsletters and websites containing research summaries and lists of publications. It has been suggested that providing access to aggregate results helps to show respect for research participants; and in addition, by informing participants about the research to date, helps them to consider whether they wish to continue their involvement or withdraw their participation (Haga and Beskow 2008, p. 535).

As noted above, biobanks are well advised, as part of their consent process, to have a clearly articulated policy as to whether aggregate results are to be provided to participants.

### **Case Study: Availability of Research Results and Re-contacting Participants**

The Kathleen Cuninghame Foundation National Consortium for Research on Familial Breast Cancer (KConFaB) aims to provide a resource to develop appropriate strategies for breast cancer prevention, early detection, genetic counselling and medical management of those people who carry mutations in genes that predispose to cancer. KConFaB is looking to determine the:

- population rates of mutations in breast cancer genes;
- kinds of mutations that predispose to breast and ovarian cancer;
- risk of breast and other types of cancer;
- age at which cancers occur; and
- effect of lifestyle and environmental factors on risk of developing cancer and age of onset.

Participants are required to complete questionnaires in relation to health, diet and lifestyle, and consent to review of medical records, contacting family members, taking blood samples, and using tissue samples taken by pathologists. Participants can consent to all or part of the above.

#### **Research Results**

KConFaB provides aggregate research results to participants via newsletters published on their website, which contain information about the progress and outcomes of studies in a form that does not identify any individuals. See <http://www.kconfab.org/Index.shtml>.

#### **Re-contacting Participants**

In addition, participants can choose whether or not to be informed if an inherited mutation is found in their family. If a mutation is found in the family, letters are sent to blood-related participants who elected to be informed. The letter explains that a mutation has been found in the family and that the participant should contact a Family Cancer Clinic for genetic counselling and potentially testing for the inherited mutation. Participants can change their mind about notification at any time.

In the case that a mutation is found in the family, participants can consent to information being shared between KConFaB, the participant's general practitioner and the Family Cancer Clinic, to prevent duplication of testing.

### **Non-discrimination and non-stigmatisation**

Personal information relating to biospecimens stored by a biobank may form the basis of genetic discrimination (ie, discrimination against a person on the basis of their genetic status) if revealed to third parties such as insurers or employers. In Australia, the *National Statement* recognises the potential harms arising from the misuse of genetic information:

Genetic information can sometimes be misused to stigmatise people or to discriminate against them unfairly. Researchers should therefore take special care to protect the privacy and confidentiality of this information. Statutory or contractual duties may require participants to disclose the results of genetic tests or analysis to third parties (for example, insurance companies, employers, financial and educational institutions), particularly where results provide information about health prospects. Genetic research should be designed to minimise any resultant risk that participants will be deprived of benefits available to others in the community. Potential research participants should be advised of any such risks. (paragraph 3.5.6)

Internationally, there are numerous statements that warn of the risks of genetic discrimination and the need to protect against it. For example, the UNESCO *International Declaration on Human Genetic Data* provides:

a) Every effort should be made to ensure that human genetic data and human proteomic data are not used for purposes that discriminate in a way that is intended to infringe, or has the effect of infringing human rights, fundamental freedoms or human dignity of an individual or for purposes that lead to the stigmatization of an individual, a family, a group or communities. (UNESCO 2003, Article 7)

(b) In this regard, appropriate attention should be paid to the findings of population-based genetic studies and behavioural genetic studies and their interpretations.

There is growing recognition, as a consequence, of the responsibility incumbent on those engaged in research involving biospecimens and related information to guard against the risk of such discrimination. Clearly, this places obligations on biobanks that deal exclusively with such data, as acknowledged by the OECD Guidelines:

Appropriate measures should be taken to avoid discrimination against or stigmatisation of a person, family or group, whether or not they have contributed to the HBGRD. (Best Practice 1.4)

Further, it is recognised that 'in some cases, there may be risks to social groups or communities due to the release of aggregate research findings even when no individually identifiable information has been revealed' (ISBER Best Practices, p. 48). Thus, the risks involved relate not only to disclosure of an individual's information, but the potential for discrimination or stigmatisation resulting from research that may, for example, identify a correlation between a specific heritage and a particular disease (see OECD Guidelines, Annotation 10).

It is, therefore, advisable for biobanks to take all appropriate steps to safeguard biospecimens and related information, and protect against their unauthorised use and disclosure. Given the wide potential for discrimination and stigmatisation, there is a strong need for careful scrutiny of research that proposes to use the biobank's resources, to ensure that these risks are kept to a minimum. It is also advisable for biobanks to ensure that, as part of the consent process, participants are informed about the potential risks of such discrimination and stigmatisation (see further Chapter 3: Consent in the Context of Biobanking, in particular the section on Best practice for providing information to potential participants, p. 26).

### ***Cultural sensitivity in the use and disposal of biospecimens***

As noted earlier, cultural sensitivity is imperative in biobanking, including the collection, use and disposal of biospecimens. Some groups regard certain types of biological material as having a special status, particularly where it is removed post mortem, and as deserving of special treatment in its use and disposal (OECD Guidelines, Annotation 53). The *National Statement* provides that any wishes about the method of disposal will be recorded at the start of the research and taken into account at the time of disposal (paragraph 3.5.12(e)). This caters for the needs of diverse cultural groups that have specific beliefs about the use and disposal of their biospecimens (see also ISBER Best Practices, p. 48). Whilst such issues are most likely to be addressed during the consent process, this may not always happen; for example, where biobanks are formed using existing collections (OECD Guidelines, Annotation 53).

## Chapter 5: Governance of Biobanks

This chapter considers principles and mechanisms for governance of biobanks. The chapter first discusses the broad concept of governance, then turns to the potential role of federal or state and territory governments in overseeing biobank operations; it then discusses international best practice in governance and institutional governance arrangements. The chapter focuses on the regulatory and institutional arrangements needed for best practice in biobank operations. Specific aspects of biobank management are discussed in other chapters, notably recruitment, funding, resourcing and staffing in Chapter 2, and technical standards and security of data in Chapter 4.

Regardless of the scale of the biobank, the principles of best practice in governance apply. However, the practice of these principles may differ between large and smaller biobanks, and a distinction is drawn from time to time between them when considering the ways in which these best practice obligations might be met.

Some of the documentation referred to in the chapter relates to tissue collections more generally, rather than biobanks for research purposes, which are the specific focus of this Information Paper; however, this more general documentation provides some useful guidance.

### ***Governance principles***

The *National Statement* directs, in paragraph 3.4.1, that 'Institutions should develop a policy for the collection, storage, use and disposal of human tissue in research,' but it provides limited elaboration on what this might entail, aside from a list of relevant considerations, which include:

- (a) what information needs to be recorded about the source, nature and reason for collection of the tissue;
- (b) requirements about participant consent ... including circumstances where waiver of consent may be justified...;
- (c) confidentiality;
- (d) privacy of samples and information;
- (e) access to samples and information;
- (f) disposal of samples;
- (g) socio-cultural considerations bearing on these issues.

Most of the policy documentation on biobanking includes specific reference to governance arrangements, and the ALRC/AHEC Report specifically recommends that guidance should be provided on governance and operation of human genetic research databases (Recommendation 18-1).

Just what is meant by 'governance' in relation to biobanks varies, ranging from the narrow notion of institutional governance, relating to the biobank organisation's own structures and procedures, to a much broader concept which also encompasses both government and other forms of oversight, and public consultation. In essence, governance refers to the optimal operation of biobanks according to prescribed and published standards, including open review and recording to ensure best practice.

The OECD Report understands management as dealing with the day-to-day activities of the biobank, while governance involves oversight of operational matters, technical and legal issues, and biobank security, access and demise (OECD Report, p. 105). The OECD Guidelines consider the key governance principles to be

transparency and accountability (Principle 3.A). The Guidelines highlight the need for governance structures to ensure that:

- the rights and well-being of the participant prevail over research interests (Principle 3.C); and
- the operators of the HBGRD have in place oversight mechanisms to ensure that the governance, management, operation, access to, use of and discontinuation of the HBGRD comply with legal requirements and ethical principles (Principle 3.D).

Gottweis and Petersen (2008) point out that the term governance 'has multiple, contested meanings' and note that discussions and writings in the field tend to focus on ethics and regulation, 'mostly without reference to the socio-cultural, political and historical contexts that shape these developments' (p. 4). They go on to say that:

In the vast majority of the literature dealing with questions of biobanks the focus is on an interconnected set of issues around the questions of informed consent, personal integrity, self-determination, confidentiality and non-discrimination. In fact, it is no exaggeration to state that these key themes of ethics and bioethics have occupied the central place in the current public and political-regulatory debates on biobanks (Gottweis and Petersen 2008, p. 6).

They emphasise that these issues will vary between biobanks, regions and countries and that it is not simply a matter of adopting the 'right' ethical and legal techniques (Gottweis and Petersen 2008, p. 7). When considering these issues in relation to the governance of Australian biobanks it is wise to do so mindful of our unique socio-cultural, political and historical context (Gottweis and Petersen 2008, p. 12).

As noted in Chapter 4, biobank operators have a legal and ethical duty to ensure the privacy of participants and maintain the confidentiality of their samples and data. The governing body of the biobank is expected to assume responsibility for upholding these legal and ethical standards (Chalmers 2009).

## ***Government oversight***

Much of the modern policy literature in the life sciences recognises that government regulation and control is but one aspect of the broader concept of governance. Nevertheless, the need for some form of government-based regulation and control is acknowledged (Lyll, Papaioannou and Smith 2009). In the context of biobanking, there has been some discussion in the national and international literature on the need for a specific layer of oversight by government, in the form of biobank legislation or licensing or registration requirements.

## **Biobank legislation**

There is little support in Australia or internationally for generic biobank legislation or even generic genetic legislation. The Report by the Bioethics Advisory Committee of Singapore, *Human Tissue Research* (hereafter, Singapore Report), for example, states that:

... we do not think that it is appropriate to resort to hard-coding specific rules in legislative form for the regulation of research and commercial activity in the genetic and genomic sciences. Overly specific rules run the risk of rapid obsolescence, and of abuse by those minded to be seen to comply only with the letter but not the spirit of the law.

In general, we recommend legislative intervention only in situations where it is clear that effective professional self-regulation and a fair balance of rights and interests between individuals and the public in encouraging research cannot be achieved without legislative teeth (Singapore Report, p. 31-32).

The Singapore Report does, however, recognise the need for enabling legislation and empowerment of appropriate government agencies to exercise a supervisory jurisdiction as gatekeepers (p. 32). One suggestion (discussed further below) is for a statutory authority to supervise and licence biobanking (Singapore Report, p. 32).

The German Biobank Opinion also cautions against all-embracing controls on biobanks, over and above the requirements of general legislation. It states that the complex and expensive organisational requirements that might be appropriate for, say, national-scale biobanks must not be automatically applied to all biobanks. Account must be taken of the differing scales and structures of biobanks and the widely differing associated risks (German Biobank Opinion, p. 64).

With regard to the large-scale biobanks, while some were established by statute (see Chapter 2), others were established independent of specific legislation (OECD Report, p. 14). The OECD, which sees legislation as the codification of ethics and governance by the state (OECD Report, p. 105), recognises benefits in both approaches: 'While the creation of an HBGRD as a scientific endeavour may permit more flexibility, its establishment through legislation may facilitate the application of enforcement procedures and measures' (p. 105).

### **Licensing and/or registration**

To date in Australia there has been no call for a legislative model for regulating health and medical research through a licensing or registration system, aside from research using of human embryos, which is regulated by the Commonwealth *Research Involving Human Embryos Act 2002*. The preferred approach has been to utilise the *National Statement* and related ethical guidelines.

Generic Australian state and territory human tissue legislation deals principally with organ transplants and does not provide a regulatory regime for research using human tissue. By comparison, the UK *Human Tissue Act 2004* establishes a complex licensing scheme for use of human tissue. The Act requires that all establishments that have any dealings with human material must be licensed (section 16). The individual designated in the licence is required to supervise the licensed activity (section 17). The Act establishes the Human Tissue Authority as the regulatory body for all matters concerning the removal, storage, use and disposal of human tissue (excluding gametes and embryos) for Scheduled Purposes, which include research purposes (sections 13, 14; Schedule 1). Further guidance on the requirements for use of tissue for research purposes is found in paragraphs 114-115 of the Human Tissue Authority's *Code of Practice – Consent* (2006), authority for which is provided under section 26 of the Act.

In Australia, the ALRC/AHEC Report (p. 402) rejects the suggestion that human genetic research as such should be subject to any sort of mandatory licensing or registration obligations or that there should be legislation to enforce compliance with the *National Statement*. While the Report also rejects the introduction of new legislative constraints on the operation of human genetic research databases (p. 490), Recommendation 18-2 states that there should be a requirement in the *National Statement* for institutions to register their human genetic research databases with NHMRC.

The rationale for this recommendation is that NHMRC 'is capable of providing greater transparency and accountability in the operation and use of such databases, without subjecting institutions to onerous compliance costs' (ALRC/AHEC 2003, p. 491). In addition to the general registration requirement, the ALRC/AHEC Report states that there should be requirements to:

- nominate a gatekeeper or custodian who will have clear responsibility for the day-to-day operation of the database (custodianship is discussed below, in Chapter 7);
- comply with standards for collection, use, storage, disclosure and transfer;



- report annually to the institutional HREC and AHEC on database operations; and
- provide for audit of the database and its operations, on request by the HREC or AHEC (p. 491).

Paragraph 3.2.1 of the *National Statement* requires researchers to describe how their research data will be collected, used, stored and disclosed and Paragraphs 3.2.3–3.2.8 set out the obligations of researchers and custodians with regard to data usage (Chapter 4 explores the issues associated with collection, storage, use and dissemination of data more fully). However, there is no licensing requirement in the *National Statement* and there is no present indication from NHMRC that they intend to establish such a process.

Internationally, discussions on licensing requirements for biobanks are often framed around considerations relating to oversight of tissue banking more generally. For example, the Singapore Report recommends that all forms of tissue banking that permit research access should be statutorily supervised through licensing by a statutory authority (p. 17-18). The Report recommends a flexible and responsive legislative regime in which the statutory authority supervises and regulates through licensing of accredited institutions rather than through direct regulation of individual researchers and collections (p. 18). The emphasis should be 'on institutional responsibility and good internal self-governance, and on the promotion of adherence to the spirit rather than the letter of the law' (p. 18).

The German Biobank Opinion, discussing the desirability of licensing for tissue banking, draws a distinction between collections of tissue made for routine diagnostic purposes and those established explicitly for medical research (the latter being more relevant to the present discussion). It states that collections made for diagnostic purposes are, very often, formed with no intention of subsequent research use, and imposing a licensing requirement for the establishment of such collections would subject important areas of medical activity to specific individual control over and above the requirements of registration and approval. Thus:

the question arising is at most whether a licensing requirement should be imposed if these collections are to be used for research. This situation should be treated in the same way as that of biobanks to be established with the explicit intention of medical research (German Biobank Opinion, p. 62-63).

The German Biobank Opinion's over-riding concern is that medical research that depends on the collection and use of human bodily substances should not be subject to 'blanket prior control' (German Biobank Opinion p. 63). It does, however, accept that some form of 'compulsory licensing' may be appropriate for large-scale biobanks that are established as relatively permanent facilities combining major resources from different institutions. Nevertheless, the Opinion recognises that, while donor protection is essential, it is also crucial to safeguard appropriate access to such important research infrastructures (p. 63).

One issue raised in the international literature is how any licensing or registration requirements might be applied to private sector biobanks. There are some examples of for-profit entities managing large-scale population biobanks, for example in Iceland and Estonia, and there are likely to be many more private small-scale biobanks and other tissue banks.

The Singapore Report recommends that all research using banked tissue should be licensed by a statutory authority, and it discourages the creation of human tissue collections by private individuals. Rather, it recommends that such collections should be held by institutions, including hospitals, universities and research institutions (Singapore Report, p. 17). In exceptional cases, however, where private individuals who are not affiliated or directly accountable to any institution are involved in tissue collection, they should be required to apply to the statutory

authority for a restricted licence on such terms as the authority deems appropriate (Singapore Report, p. 18).

Similarly, Opinion No 11 of the European Commission's European Group on Ethics in Science and New Technologies, *Ethical Aspects of Human Tissue Banking* (1998), recommends that, in principle, tissue bank activities should be reserved to public health institutions or non-profit organisations. However, the Opinion does go on to recognise the difficulty in excluding commercial organisations, particularly large private laboratories (Recommendation 2.8).

Other policy documents do not draw such a clear distinction between public and private collections in terms of their desirability. Nevertheless, the need for different regulatory frameworks for biobanks with different legal forms and objectives is recognised more widely, for example, in the German Biobank Opinion (p. 26).

### ***Other sources of biobank oversight***

Small-scale disease-specific biobanks may be adequately and appropriately governed by those who establish them, and oversight of ethical considerations may be adequately dealt with by HRECs, guided by the *National Statement*. Other guidelines issued from time to time by the NHMRC will also guide small-scale biobanks with regard to governance and related matters.

Oversight of large-scale entities is likely to be somewhat more complex than for the smaller-scale biobanks for a number of reasons. Size of itself is not necessarily a factor. However, because the large-scale biobanks are generally established to provide access to a greater number of researchers than the smaller biobanks, ethical considerations are heightened, particularly with regard to consent and privacy. The large-scale biobanks also tend to be population-based and collect tissue and information from healthy participants, whereas many of the small-scale biobanks are disease-specific and source their collections from people whose disease status is already known. An important additional consideration with large-scale biobanks is that research may reveal the disease status of otherwise healthy individuals.

For those large-scale population biobanks established by legislation, provisions are generally included relating to governance structures, operation and regulation (OECD Report, p. 105). For example, the Icelandic and Estonian legislation includes: establishment and operation; collection, handling and access to biological samples; access to the database; monitoring and obligation to supply information; and penalties (OECD Report, p. 105).

Those large-scale population biobanks not created by statute tend to have governance frameworks or statements of principle that provide for similar matters, except that penalties are generally not dealt with (although these may be prescribed in general national or local legislation, particularly with regard to data protection) (OECD Report, p. 106). For example, UK Biobank has an Ethics and Governance Framework; and the RMGA Network for Applied Genetic Medicine has two statements of principles, the Statement of Principles on Human Genome Research (2000) and the Statement of Principles on the Ethical Conduct of Human Genetic Research Involving Populations, both of which provide guidance for the CARTaGENE project.

The OECD Report (p. 106) questions the legitimacy of self-regulation outside the legislative context, particularly with regard to powers of enforcement.

### ***Independent oversight for large-scale biobanks***

Oversight of biobanks by independent bodies may be required, given the particular ethical issues associated with large-scale banking of tissue, its linkage with genetic,

medical and genealogical information, and the associated layers of complexity. The German Biobank Opinion refers to the need for a consistent 'chain of responsibility' within the organisation (German Biobank Opinion, p. 26).

Some of the large-scale biobanks have established ethics bodies independent of management of the more general day-to-day biobank activities. These ethics bodies are charged with ethical oversight of the establishment, maintenance and use of the biobank. For example, the UK Biobank Ethics and Governance Council is independent of UK Biobank Ltd (UK Biobank Ethics and Governance Framework, p. 3). This has been referred to as an 'Ethics+' approach (Laurie, Bruce and Lyall 2009).

In addition to acting as an independent guardian of the Ethics and Governance Framework and advising the Biobank Board on revision of the Framework, the UK Biobank Ethics and Governance Council's remit includes: monitoring and reporting publicly on the conformity of the project with the Framework, and advising more generally on the interests of participants and the public. The Council discusses such matters as recruitment strategies, consent models, provision of health information to participants, recontact for future studies, barriers to participation by ethnic minorities, capacity to consent, confidentiality and access, and intellectual property. One example of its recent activity is its consideration of the 'no further use' withdrawal option (see Chapter 3), which led to a revision of section 6 of the Ethics and Governance Framework. Further information about the activities of the Ethics and Governance Council is available at <http://www.egcukbiobank.org.uk/>.

Similarly, it was originally intended that the Canadian biobank, CARTaGENE, once established, would have an independent Institute for Populations, Ethics and Governance (IPEG), which would be responsible for developing rules of ethics and responsible governance, ensuring those rules are respected, periodically publishing reports about those rules, organising and holding information and consultation sessions, providing opinions and advice about respect for the rules, ensuring monitoring of approved studies and ensuring responsible governance of orphaned biobanks to allow their optimal utilisation in the public interest (OECD Report, p. 109). However, as a result of recent restructuring of the research ethics evaluation process in the Canadian province of Quebec, including the creation of a multi-centre ethics review system, it was decided that an IPEG was unnecessary and that existing legislative and policy governance mechanisms provided sufficient oversight for biobank projects like CARTaGENE (Bédard et al, 2009).

In Iceland, the legislation prescribed three oversight committees: a monitoring committee; an interdisciplinary ethics committee; and a data protection commission (OECD Report, p. 107). The Estonian legislation requires the formation of an ethics committee and a scientific advisory board to assist the Supervisory Board and Management Board.

Policy documents support the need for such independent bodies. The German Biobank Opinion, for example, states that such bodies seem appropriate in view of the complex organisational structure of some biobanks (p. 63). As noted in the OECD Report, the composition and form of oversight committees vary across projects (OECD Report, p. 14). The German Biobank Opinion states that such a body should:

monitor observance of the ethical standards and legal requirements applicable to the handling of samples and data – for instance, the collection and subsequent use of bodily substances, or the processing of the personal data used in each case. This body should therefore be responsible for ensuring, for example, that donors' expectations, as recorded in their declarations of consent, are complied with; that the relevant conditions of access to the biobank are observed; that the limitations on the transfer of materials or data set by the research vocation of the biobank and by the declarations of consent are not exceeded; and, finally, that if the biobank is

closed down, its stored bodily substances and information are not misused. (German Biobank Opinion, p. 63-64)

Monitoring of ethics and governance by an independent body should not be seen as replacing ethical oversight of individual research projects by HRECs. It would still be necessary to go through the normal ethical review processes for each proposal for research involving the use of biobank resources (UK Biobank Ethics and Governance Framework, p. 15-16).

### ***Institutional governance arrangements***

While legal ownership of biobank resources may be vested in the biobank, it is widely recognised that the biobank still has responsibilities to participants with regard to their tissue and information. Various types of institutional governance arrangements may be utilised to ensure that these responsibilities are fulfilled.

#### **Custodianship**

The *National Statement* uses the language of custodianship in describing the duty to ensure that data are used responsibly and respectfully, and that privacy of participants is safeguarded (paragraph 3.2.5). The custodian is also responsible for contacting participants should it be necessary to re-identify data (paragraph 3.2.6) and for making decisions about whether to deny or restrict access to data when their use may be detrimental to people to whom the data relate (paragraph 3.2.8).

Custodianship has been described in the UK Biobank Ethics and Governance Framework as acting 'as the *steward* of the resource, maintaining and building it for the public good in accordance with its purpose' (p. 12, emphasis added). This notion of custodianship has also been adopted by other agencies. See for example, chapter 4 of the Irish Law Reform Commission's report, *The Establishment of a DNA Database*.

The National Cancer Institute Best Practices also use the language of custodianship, stating that 'Responsible custodianship requires careful planning and transparent policies to ensure the long-term physical integrity of the biospecimens while maintaining the privacy and confidentiality of research participants' (Best Practice C.1).

#### **Independent intermediaries**

In Australia, the ALRC/AHEC Report gives support to independent governance of biobanks, recommending that best practice in genetic research involving genetic databases requires the appointment of an independent intermediary between the researcher and the data and samples (a 'gene trustee') to protect the privacy of samples and information (Recommendation 16-1):

The value of this approach lies in the separation of any identifying information from all sensitive data and materials held in a database. No matter who obtains access to this material, they will be unable to identify it without contacting the gene trustee, who will be bound not to release any identifying information without the consent of the individual (ALRC/AHEC Report, p. 493).

The Report nevertheless recognises problems with this approach, particularly in respect of administrative costs. It notes that the approach will not be practicable in all circumstances, but is likely to have greatest value for large databases established for broad purposes (p. 493-494).

The *National Statement* points out that, in most situations in Australia, the custodian of the data will be the individual researcher or agency who collected the information or an intermediary who manages data from a number of sources. Nevertheless:

In some cases, an independent custodian may be necessary. For example, when coded data are stored in a databank, a custodian independent of both the data collectors and the researchers may be appointed to maintain the data in coded form... (paragraph 3.2.7)

A joint paper by the French and German national ethics councils also refers to the notion of trusteeship. However, the German Biobank Opinion cautions that Germany's Federal Data Protection Law requires the appointment of a data protection officer, who carries most of the functions of a trustee. The data protection officer is already subject to external oversight, both in the public and private sector, and 'Experience so far indicates that the establishment of a supervisory body with more extensive functions is unnecessary' (German Biobank Opinion, p. 64).

### **Institutional governance for large-scale biobanks**

The OECD Report notes that, with the exception of UK Biobank, few details are provided by the large-scale population biobanks on management-related matters (p. 109). In practice, most are managed by discrete entities.

For the large-scale population biobanks created and governed by statute, management obligations are devolved to particular bodies. The Estonian *Human Genes Research Act 2000*, for example, provides for management by an independent foundation, the Estonian Genome Project Foundation.

UK Biobank is managed by UK Biobank Ltd, a charitable company limited by guarantee. Members of the Board of UK Biobank act as charity trustees under UK charity law and they also act as company directors under UK company law. (UK Biobank Ethics and Governance Framework, p. 3). The Board is accountable to the members of the company (the Medical Research Council and the Wellcome Trust) and to the Charity Commission for England and Wales. The Board is responsible for ensuring UK Biobank policies and activities conform to the Ethics and Governance Framework, for institutional governance, and for direction, management and control of the biobank. It delegates day-to-day management to the CEO (UK Biobank Ethics and Governance Framework, p. 14).

The possibility of using charitable trust principles in the governance of large-scale biobanks has been raised in the academic literature (Winickoff and Winickoff 2003, p. 1180). The argument starts from the premise that, when a person agrees to donate tissue, the recipient has a responsibility to serve as trustee, or steward, of the tissue to ensure that the contribution is protected; therefore a more sophisticated trustee-type approach is required for worldwide collections of DNA:

The charitable trust is a promising legal structure for handling such a set of obligations, for promoting donor participation in research governance, and for stimulating research that will benefit the public.

Under a trust agreement, the tissue donor, or settlor, formally expresses a wish to transfer his or her property interest in the tissue to the trust. The permission form could be used for this purpose. The settlor appoints a trustee of the property who has legal fiduciary duties to keep or use the property for the benefit of a specified party, the beneficiary. In a charitable trust, the public acts as the beneficiary. (Winickoff and Winickoff 2003, p. 1181).

The institutional governance structure of UK Biobank adopts some features of the charitable trust model, although it has been subject to criticism for failing to provide donors with a representative role in institutional governance. Winickoff notes that 'True "partnership" would necessarily go beyond the idea of consultation to embrace forms of direct representation' (Winickoff 2007, pp. 452-453). This form of 'partnership governance', based on a corporate shareholding model, has, in turn, been subject to some criticism. Hunter and Laurie suggest that there are

practical and conceptual difficulties with this model and the language of stakeholding is more appropriate than shareholding (Hunter and Laurie 2009).

### **Case Study: Governance at the Breast Cancer Tissue Bank**

The Breast Cancer Tissue Bank (BCTB) was established in late 2004, following the award of an NHMRC Enabling Grant, with additional funding from the Cancer Institute New South Wales and the National Breast Cancer Foundation. The BCTB was set up to collect tissue, blood and clinical data from newly diagnosed breast cancer patients, to distribute biospecimens and clinical data to Australian researchers, and to establish and support a 'bench to bedside' research agenda.

Central project management is located at Westmead Hospital/Westmead Millennium Institute, with six individual collection centres at breast cancer treatment centres across NSW. The first donors were recruited in February 2006.

In developing its governance structure, the BCTB analysed the policies and governance models of biorepositories in Australia and overseas, consulted the literature on governance models, and obtained legal advice on aspects of these documents. The goal was a governance mechanism that is both robust and practicable, allowing ease of operation and maximising usage of the facility. The model established follows the requirements of the NHMRC, and it is proving to work extremely well.

Overarching management of the BCTB is by the Management Group, which comprises chief investigators (CIs) from the research grants supporting the BCTB; representatives from collection centres not represented by CIs; and the BCTB Project Manager. The Management Group is responsible for managing the agreements established with collection centres; custodianship of material; monitoring QA programs; auditing and regulatory compliance; endorsing applications for BCTB materials, monitoring progress of ongoing projects supplied with specimens, and ensuring researchers abide by BCTB conditions of use; managing the sharing of data and findings (ensuring wide dissemination); receipt of complaints; looking after financial obligations and developing methods to ensure financial viability; reporting on financial and activity status to the Advisory Panel; IP issues (under supervision of grant administrators); and endorsement of publicity proposals.

The day-to-day operations of the Tissue Bank are performed by an Executive Committee which is drawn from and endorsed by the Management Group.

The Independent Advisory Panel oversees the BCTB policies and procedures. It comprises the directors of four major Australian cancer tissue resources, a representative from a breast-cancer-related consumer group, an ethicist, a nominee from each of the three organisations funding the BCTB, one of whom is appointed as Chair, and a non-voting member from the Management Group.

The Advisory Panel receives an annual report from the Management Group that includes BCTB activity (including projects supported), ethical and regulatory compliance, budget and financial status, and details of complaints/disputes. The Panel is responsible for ensuring that the Management Group uses fair, equitable and transparent mechanisms; reviewing special cases (applications for material) referred by the Management Group; advising on scientific issues as requested; providing independent advice on conflict of interest issues; and advising in matters of dispute resolution and potential options for long term sustainability.

Project applications are independently reviewed by a Scientific/Peer Review Panel comprising experts in breast cancer and/or other scientific research. Individual membership fluctuates, with reviewers determined by their expertise in relation to the specific project under scrutiny. Whenever possible (considering the science of the project under review) reviewers are selected who are wholly external to the BCTB.

## **Chapter 6: Access to Biobanks for Research Purposes**

One of the defining features of biobanks, as identified in Chapter 1, is that they are established for sharing for research purposes. As noted in the German Opinion on Biobanks for Research, 'It is in the public interest for biobanks to be available for medical research. They should therefore be at the disposal of as large a group of interested researchers as possible' (p. 75). Access for research purposes should thus be facilitated as much as possible, while respecting any constraint imposed by participants' consent (discussed in Chapter 3) and protection of their privacy and confidentiality (discussed in Chapter 4).

This Chapter discusses principles, policies and procedures relating to access for research purposes.

### ***Principles of access for research purposes***

The OECD Report highlights the importance of access issues (p. 113), given that the main purpose of biobanks is to foster research. The main challenge is 'to strike an appropriate balance between freedom of researchers and the interests of participants and the public' (p. 113). Considerations include:

- from the participant perspective- welfare, respect for human dignity and justice;
- from the researcher perspective- scientific freedom and justice; and
- from the public perspective- welfare (health-care benefits), respect (community consultation) and justice (not being subjected to discrimination and stigmatisation) (OECD Report, p. 114).

Principles 7.A and 7.B of the OECD Guidelines reflect the importance of addressing these access issues:

7.A Access to human biological materials and data should be based on objective and clearly articulated criteria, and should be consistent with the participants' informed consent.

7.B The operators of the HBGRD should require that access requests include a scientifically and ethically appropriate research plan.

The NCI Best Practices state that: 'Access to human specimens and data for research purposes is crucial for fields such as genomics, proteomics, metabolomics, molecular imaging and nanotechnology'. The Best Practices recommend the formulation of guidelines that are clear, flexible, amenable and general enough to be applied to different kinds of biospecimen resources (Best Practice C.4).

Relevant issues that need to be considered in formulating access policies and procedures include:

- who has access – for example, public sector researchers only, or both public and private sector researchers;
- how should access be provided;
- whether access should be free or for a fee;
- what access should be given; and
- the purposes for which should access be given (see OECD Report, p. 113).

### ***Access to data***

Free exchange of scientific data is of paramount importance, and access arrangements for data in non-identifiable form should reflect this. Participant welfare, respect for human dignity, and justice are likely to be less pressing concerns in such circumstances than when access is sought to linked data or tissue.

International instruments recognise the importance of free exchange of scientific data; for example, UNESCO's *Universal Declaration on the Human Genome and Human Rights* provides:

States should make every effort, with due and appropriate regard for the principles set out in this Declaration, to continue fostering the international dissemination of scientific knowledge concerning the human genome, human diversity and genetic research and, in that regard, to foster scientific and cultural co-operation, particularly between industrialized and developing countries. (Article 18)

Similarly, Article 18 of UNESCO's *International Declaration on Human Genetic Data* states that international medical and scientific cooperation should be fostered and there should be fair access to human genetic data, human proteomic data and biological samples. This should be achieved by regulating cross-border flows of these resources in accordance with national laws and international agreements.

Wherever data are generated using public funding, the tendency is to classify them as research data that should be made publicly accessible. The HUGO *Statement on Human Genomic Databases* views human genomic databases as global public goods (Recommendation 1) and recommends free flow of data and the fair and equitable distribution of benefits from research using databases (Recommendation 3), and reciprocity and exchange of information with fair return (Recommendation 6).

The OECD *Principles and Guidelines for Access to Research Data from Public Funding* apply generally to research data, and also have relevance with regard to access to information stored in large-scale genetic information databases. The first three aims and objectives are to:

- Promote a culture of openness and sharing of research data...;
- stimulate the exchange of good practices in data access and sharing; and
- raise awareness about costs and benefits of restrictions and limitations on access to and sharing of research data from public funding. (OECD 2007, p. 11)

Relevant principles include openness, flexibility and transparency, taking into account restrictions resulting from legal requirements (which include national security, privacy and confidentiality, and trade secrets and intellectual property rights) (OECD 2007, p. 15-16).

Similarly, the International Council for Science (ICSU) *Report of the CSPP Assessment Panel on Scientific Data and Information* (2004) states that 'ICSU should continue to actively promote the principle of full and open access to scientific data' (p. 10, paragraph 33).

In Australia, the Prime Minister's Science, Engineering and Innovation Council Report, *From Data to Wisdom: Pathways to Successful Data Management for Australian Science* (2006) provides general guidance on data sharing obligations for publicly funded Australian scientists. It recommends:

That the principle of open equitable access to publicly-funded scientific data be adopted wherever possible and that this principle be taken into consideration in the development of data for science policy and programmes. (Recommendation 6)

The US National Institutes of Health (NIH) *Statement on Sharing Research Data* (2003) similarly affirms the NIH's support for data sharing in the translation of research results into knowledge, products and procedures to improve human health: 'Data should be made as widely and freely available as possible while safeguarding the privacy of participants, and protecting confidential and proprietary data'.

These and other similar policy documents emphasise the importance of distinguishing between raw data and research results, which should be made freely available, and technological innovations, which may need to be patented to provide



incentives for downstream product development. The ICSU Report notes the need to keep these two matters separate pointing out that:

Recent trends towards the appropriation of data, such as genetic information and the protection of databases under sui generis regimes, as well as limitations on the fair use of digitised data (e.g. anti-circumvention measures) pose serious obstacles to full and open access to data for scientific purposes. (p. 10)

In general, access arrangements for large-scale genetic information databases are open, as illustrated by the 'Bermuda Rules' for access to Human Genome Project (HGP) sequencing information. HGP participants signed up to the following commitments in 1996:

#### **Primary Genomic Sequence Should be in the Public Domain**

It was agreed that all human genomic sequence information, generated by centres funded for large-scale human sequencing, should be freely available and in the public domain in order to encourage research and development and to maximise its benefit to society.

#### **Primary Genomic Sequence Should be Rapidly Released**

Sequence assemblies should be released as soon as possible; in some centres, assemblies of greater than 1 Kb would be released automatically on a daily basis.

Finished annotated sequence should be submitted immediately to the public databases (Human Genome Organisation (HUGO), 1996).

Information relating to the HapMap Project is also in the public domain (see International HapMap Consortium 2004), as is information relating to the 1000 Genomes Project (<http://www.1000genomes.org/page.php?page=about>). The US NIH *Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS)* (2008) also states that datasets should remain available to all investigators, unencumbered by intellectual property claims (p. 12-13, Principle V). The NIH discourages the use of patents to prevent or block access to any genotype-phenotype data developed with NIH support, but encourages responsible approaches to management of intellectual property from downstream discoveries (p. 13, Principle V). Broader sharing of large reference data sets across the fields of biology and medicine was endorsed at a workshop in Toronto in 2009 (Toronto International Data Release Workshop Participants, 2009).

There are inevitable tensions associated with the imposition of data sharing requirements for institutions, researchers, participants, the public and those charged with oversight of access arrangements (Kaye et al, 2009). For example, the NIH GWAS policy is currently being reviewed because of privacy concerns relating to the release of data (as explained in the NIH (2008) *Background Fact Sheet on GWAS Policy Update*).

### **Access to biobank resources**

While there may be good reasons from the research perspective to adopt Human Genome Project-like rules for access to all biobanks, this may not be feasible for sharing biospecimens and potentially re-identifiable information: privacy and confidentiality are major legal and ethical issues, and biospecimens (unlike information) are finite physical resources (see US Cohort Study Report, p. 29; OECD Guidelines, Principle 7.E).

In striking an appropriate balance between freedom of scientific research, interests of participants and interests of the public, a distinction needs to be made between 'negative reasons' for refusal, focusing on potential for misuse, and 'positive reasons,' which require those wanting access to provide justification (OECD Report, p. 114). Decisions about whether or not to grant access will often require 'objective

assessment' of these positive reasons balanced against possible risks of harm; such assessment is best conducted by a professional review board (OECD Report, p. 114).

The OECD Report points out (p. 114-115) that, from the ethical perspective, access depends on the context; this includes the types of data, their linkability, the uses and users of data, and the general purpose of access. Access will always require prior approval of the project by a properly constituted ethics committee, and verification that the proposed research is within the scope of the initial consent. This is the context within which UK Biobank makes decisions regarding access, as made clear in its Ethics and Governance Framework:

UK Biobank will not proscribe any medical or other health-related research uses at the outset. However, all proposals will be reviewed by UK Biobank to ensure they are consistent with the participants' consent and this Framework, and that they have relevant ethics approval. All users, whether employed by universities, government, charities or commercial companies, will be held to the same scientific and ethical standards. (UK Biobank Ethics and Governance Framework, p. 12)

### **Small-scale biobanks**

For many small-scale biobanks, the operator will also be the researcher utilising the resource, and the question of access by external bodies for research purposes is unlikely to arise. In this regard, the *National Statement* notes that 'in most situations, the custodian of data will be the individual researcher or agency who collected the information' (paragraph 3.2.7).

Some small-scale biobanks do, however, provide access to other researchers. A study by Eiseman et al commissioned by the National Cancer Institute National Dialogue on Cancer, *Case Studies of Existing Human Tissue Repositories: "Best Practices" for a Biospecimen Resource for the Genomic and Proteomic Era* (2003), provides an insight into how access issues are dealt with by US tissue repositories focusing on cancer research. The Report makes the following recommendations for ensuring responsible use of resources:

The use of a tissue use agreement is a best practice. The tissue use agreements should contain language in which researchers agree that the specimens will be used only for the purposes cited in the application, no attempt to obtain identifying information will be made, no specimens will be sold or shared with a third party without the prior written permission of the repository, all specimens will be treated as potentially infectious, all personnel who will be handling the specimens will be properly trained, there is no implied warranty on the specimens, any publications resulting from the use of repository specimens will acknowledge the repository, and the researcher/institution using the tissue assumes responsibility for all risks associated with the receipt, handling, storage, and use of the tissue (p. 143-144).

The German Opinion on Biobank Research points out another important distinction between biobanks created by researchers for their own research purposes and the large-scale biobanks, generally established as shared research resources. It notes that:

research workers who have contributed preliminary work of their own to the setting up of biobanks may legitimately expect, in the initial period, to reap the fruit of their investment in time and labour and to enjoy priority of use for their own research. These interests can be taken into account by providing that the funding institutions set a period during which the researchers who establish a biobank have exclusive use of it. The funding conditions should specify the rights and obligations applicable to third-party access once this period has elapsed. (p. 76)

The Opinion notes further, with regard to privately funded biobanks, that the owners:

must enjoy sole rights to their use within the limits of the donors' consent. Compulsory opening up of a private biobank to other researchers – or commercial competitors! – would be equivalent to expropriation and hence impermissible without compensation. (p. 76)

## **Large-scale population biobanks**

Most of the large-scale population biobanks allow access for research purposes irrespective of nationality and sector, and most require those accessing the biobank to enter into an access agreement (OECD Report, p. 115). The OECD Guidelines recommend that a material transfer agreement or other appropriate agreement be developed for the purpose of access to specimens and samples (Best Practice 7.6).

The UK Biobank imposes further obligations, requiring that research findings be incorporated back into the biobank resource. In particular, UK Biobank contains in its Ethics and Governance Framework a strong statement on the need to build and add value to the biobank resource and ensure that the results of research using UK Biobank resources are in the public domain:

UK Biobank seeks to augment the value of the resource in order to ensure that the greatest potential benefit for public health may be realised from it. All research users will be required to put results from all analyses made on participants' data and samples, and any relevant support information, in the UK biobank's database so that they are subsequently available to all researchers with appropriate scientific and ethics approval.

There will also be a requirement on all research users to place the findings (whether positive or negative) from all research based on UK Biobank in the public domain so that people can benefit from them. Publication should be in the peer-reviewed scientific literature whenever possible. UK Biobank will also explore further strategies for dissemination of findings (such as through accessible electronic archives). (UK Biobank Framework, p. 7)

It remains to be seen how this will work in practice; there may be considerable practical problems.

Biobank policies recognise that while basic research findings should be made publicly available, follow-on innovation may need to be patented to encourage commercial development (see further the discussion on intellectual property in Chapter 7). While this may justify keeping research results confidential for a period of time to protect patentability, it is recognised that the timeframe for withholding the release of data should be kept to a minimum. This is reflected in the UK Biobank Ethics and Governance Framework, which prescribes that:

Researchers will only be permitted to keep results based on UK Biobank confidential for a limited and reasonable period ... (for example, while they prepare papers for publication, file patent applications or otherwise pursue reasonable competitive advantage for their efforts). This policy will apply to all research users, whether non-commercial or commercial. (p. 14)

## ***Recording access to biobank resources***

A major component of good governance arrangements for biobanks is a precise and reliable system for recording all requests for access to and release of information and biospecimens. Particular care is necessary where biospecimens are transferred, and many biobanks require that formal Material Transfer Agreements (MTAs) are executed prior to transfer. Generally these MTAs will specify: the parties to the transaction; the biospecimens to be transferred; conditions on transfer; destruction or return of residual biospecimens after use; restrictions on transfer to third parties and trans-border transfer; and intellectual property rights in resultant inventions (see Chapter 7). In addition, an important component of most MTAs is that they

include a mandated return of research results to the biobanks, within a given timeframe. A report by Eiseman et al (2003) on behalf of the US National Cancer Institute gives an indication of the core terms that should be included in arrangements for access for research purposes. The following terms might be considered for inclusion:

- Use should only be for the purpose specified in the application for access.
- No attempt should be made to obtain identifying information.
- There should be no transfer to third parties without prior written permission of the repository.
- Any publication resulting from use of the materials should acknowledge the repository.

### ***Charges for access to biobank resources***

It has been suggested in the national and international literature that administrative charges could be levied for access to biobank resources. One difficulty with this is that it is widely regarded as ethically inappropriate for there to be trade in human tissue for research purposes (see, for example, *National Statement*, paragraph 3.4.10). In general, the discussion of charges for access to biobank resources centres on cost recovery rather than profit-making. Another NHMRC document, *Ethics and Exchange, Sale of and Profit from Products Derived from Human Tissue: An Issues Paper* (2009) (hereafter, *Human Tissue Products Issues Paper*), provides valuable assistance in this regard. It suggests that bona fide cost recovery would not be ruled out by the prohibition on trading in the *National Statement* (p. 34). However, profit generation raises different considerations, which are discussed below in Chapter 7.

The human tissue legislation in each of the Australian states and territories also generally prohibits trading in human tissue. The legislation specifically allows for recovery of expenses associated with removal of tissue (for example, *Human Tissue Act 1983* (NSW) section 32(3)), but is silent on cost recovery for the expenses associated with maintaining the tissue. The prohibition on trading does not apply where tissue has been subjected to processing or treatment and sold or supplied for use for medical or scientific purposes (see, for example the New South Wales *Human Tissue Act 1983*, section 32(2)). The Acts are silent with regard to the definitions of processing and treatment. Subsection 32(4) of the New South Wales Act also allows the relevant Minister to approve a contract for the sale of tissue where this is considered desirable by reason of special circumstances. On this basis, it seems unlikely that administering a charge for access to biobank resources would be seen to contravene any prohibition relating to trading in human tissue, particularly if the resources accessed could be said to have undergone 'processing or treatment'.

The *Human Tissue Products Issues Paper* recognises that, in reality, cost recovery is common practice in the exchange of human tissue products, noting that:

In Australia, the exchange of human tissue products is generally for a fee which recovers the service costs associated with the product in order to perpetuate the business. For example, recently developed therapies that use umbilical cord blood typically recover costs for the collection, storage, processing and use of the underlying human tissue – with no cost being attributed to the tissue itself. Cost recovery also occurs in blood, bone marrow and eye banks and is the underlying principle applied to samples being obtained from research tissue banks. The organisations conducting this business are not-for-profit (p. 21).

One of the difficulties for biobanks is that they may be requested to do more than simply supply biospecimens and information, and questions arise as to whether the cost of undertaking these additional tasks can be recovered. As noted in the *Human*

*Tissue Products Issues Paper*, 'many biobanks are being asked to manipulate, or are offering services related to manipulation of, human tissue into usable human tissue products such as cell lines, DNA, RNA and protein extracts and tissue microarrays (TMAs)' (p. 35). It is unclear whether such activities would fall within the definition of 'processing and treatment' in the human tissue legislation.

These and other considerations led the Human Tissue Products Working Group to put forward the following preliminary view, prior to receiving feedback from public consultations:

- There is a gap between the existing guidelines and legislation for donated organs and human tissue, and the current practices of exchange, trade and commercialisation of human tissue products. The Working Committee has formed the view that, as a matter of some urgency, there is a need to provide guidance to those dealing with human tissue products, about when it may be ethically permissible and the restrictions that are needed to protect individuals and the common good.
- Extended forms of cost recovery (recovering costs for more than the handling, storage and distribution of human tissue products) challenge important values that are inherent in Australia's donor system, but also that cost recovery is required in order to maintain and build the availability of human tissue and human tissue products (pp. 37-38, *sic*).

### ***Differential charging structures***

In determining charges for access to biobank resources, it may be necessary to decide whether to distinguish between scientific and commercial access, and whether non-commercial users should have free access or be subject to lower charges than commercial users. One of the difficulties, as noted by the OECD, is that distinctions between 'commercial' and 'non-commercial' users may be blurred (OECD Report, p. 127).

The US Cohort Study Report (p. 29) suggests that charges should vary, depending on the intended research outcome. For example, academic or government researchers could be given access on a simple cost-recovery basis if they intend to place their discoveries in the public domain, while those who intend to patent their discoveries could be required to pay a higher charge or royalties (p. 29). This is unlikely to contravene the prohibition on trading in tissue because it relates to the development of downstream products rather than to tissue as such. Generally, no distinction is made between public and private researchers in terms of their access to biobank data and samples, the main focus being on the review of the science and ethics of the research proposed (OECD Report, p. 127).

The UK Biobank Ethics and Governance Framework also appears to support distinguishing between commercial and non-commercial users. It states that:

Access to data and/or samples will be granted under licence for scientifically and ethically approved research consistent with UK Biobank's purpose. Licences will be for specific uses under strict terms and conditions in standard access agreements, including compliance with the consent given, the provisions of this Framework and other policies.

Fees will be charged for licences, with the possibility of charges being higher for organisations that might be expected to derive financial benefit from use of the resource (p. 13).

The *Human Tissue Products Issues Paper* emphasizes that, whatever charge structures for cost recovery are ultimately implemented, these arrangements must be recorded and reported in a way that is transparent and publicly available; for example, on a website (p. 69).

## ***Access for non-research purposes***

The issue of access to biobank resources for non-research purposes is very controversial. The fact that potentially identifiable biospecimens are held may lead to interest in that resource from a range of external third parties such as insurers, employers or law enforcement agencies. Even if a biobank has a policy to refuse such access, it is not inconceivable that biospecimens held within the biobank could be the subject of a court order, for example, requiring release for use for forensic purposes. With this in mind, Principle 7.F of the OECD Guidelines states that:

Except when required by law, the operators of HBGRD should not make accessible or disclose participants' human biological materials or data to third parties (*e.g.* law enforcement agencies, employers, insurance providers) for non-research purposes.

As with other matters, it is important that biobanks have a clear and transparent policy with regard to access to the biobank for non-research purposes and that this is communicated to participants as part of the consent process. In the interests of protecting the privacy of participants, the clearest policy would be not to allow any non-research access, unless required to do so by law. For example, the UK Biobank Ethics and Governance Framework states that: 'Access to the resource by the police or other law enforcement agencies will be acceded to only under court order, and UK Biobank will resist such access vigorously in all circumstances.' (p. 13)

## Chapter 7: Commercialisation and Benefit Sharing

Throughout this Information Paper attention has been drawn to the public good rationale for the establishment of biobanks: to facilitate health and medical research and the translation of the outcomes of that research into real improvements in health care. This public good focus does not necessarily preclude the involvement of for-profit entities. Indeed, support from the private sector will almost invariably be required to bring health care products to the market. This chapter considers the legal and ethical issues associated with ownership of biobank resources, and commercial access to such resources for research and commercial development of new drugs, diagnostics and therapies (including intellectual property). Finally, benefit-sharing obligations are considered.

Further details on the issues discussed in this chapter can be obtained from the *Human Tissue Products Issues Paper*. At the time of writing, the *Human Tissue Products Issues Paper* is in the phase of public consultation. Although not yet in its final form, it provides valuable assistance in canvassing the issue of commercial involvement in biobanking and use of biobank resources. The Issues Paper provides an important reminder of the pivotal role of consent in biobanking and in the use of biobank resources in health and medical research and the development of new healthcare products. It states that:

Australians donate organs and human tissue without regard for material incentives. This “altruistic” donation is generally considered to be a strong part of Australia’s social capital. However, questions about an organisation’s funding model are rarely asked and an individual may question their donation if an organisation can be seen to profit from their donation when the donor themselves is prohibited from receiving remuneration.

This altruism is, in principle, protected by the need to obtain consent from donors prior to using human tissue for purposes that may involve commercialisation. However, unless consent is obtained for the entire chain of custody from collection through to processing, conversion into tissue-derived products, research, manufacture, exchange, sale and final use, it may be considered that the community interests are not being protected and that the key values of respect, justice and beneficence may potentially be compromised at some stage along the chain of custody (pp. 28-29, footnote omitted).

Later, the Issues Paper goes on to state that:

The Working Committee also believes that consent forms should ensure that tissue donors are informed of downstream commercialisation possibilities and the ethical guidelines that are in place to protect the interests of the community, maintain the integrity of the Australian system and to provide effective regulation of the commercial use of human tissue products (p. 38).

### ***Ownership of biobank resources and property in human tissue***

The *Human Tissue Products Issues Paper* notes at p. 16 that:

The life of human tissue products extends from collection through to processing, conversion, research, manufacturing, use and disposal. Custody can be transferred to another party more than once at any point within this lifecycle. Changing custody may occur in one of the following ways:

- Exchange – where custody is transferred without a fee being charged
- Trade – includes payment for a good or a service but may be no more than a fee being charged for the purposes of cost recovery (but not for the purposes of generating a profit)

- Commercialisation – trade where a fee is charged for the purpose of making a profit.

Invariably, the first stage in the transfer of custody of biospecimens, from donor to biobank, falls into the category of exchange.

Difficulties arise when the uses to which a donated biospecimen are put extend beyond those considered by the donor when the exchange was made. Inevitably questions of property in and ownership of human tissue will be raised in such circumstances, as exemplified by a series of court cases in the United States: *Moore v Regents of the University of California* 51 Cal. 3d 120 (Cal. 1990); *Greenberg v Miami Children's Hospital Research Institute, Inc* 264 F.Supp. 2d 1064 (Fla. 2003); and *Washington University v Catalona* 437 F.Supp. 2d 985 (Miss. 2006). In each case, the court rejected the notion that donors of tissue retain ownership rights in their tissue, without fully explaining the legal status of that tissue (Rao 2007).

The law in Australia with regard to property in human tissue remains unsettled (ALRC/AHEC Report, p. 527). Arguments that could be made about the status of human tissue include the following:

- there can never be full property rights in human tissue, but there may be more limited possessory rights;
- there can be some form of property in human tissue when it has undergone transformation (or processing or treatment, to use the wording in the Australian human tissue legislation), in which case ownership would vest in the person or organisation undertaking the transformation (this could be the researcher, the researcher's employer or the biobank);
- there may be ownership of human tissue by the person providing the tissue, but they 'abandon' any claims to ownership when they provide the tissue to the biobank or researcher; or
- the person providing the tissue has ownership rights in it and retains some of those rights, even after the tissue has been donated to the researcher or biobank.

These options are discussed in the ALRC/AHEC Report, p. 532-535. The Report concludes by recommending that full property rights in untransformed human tissue should not be recognised (Recommendation 20-1), essentially rejecting the third and fourth options. It would seem, however, that option two is not precluded in Australian law.

Issues relating to the first option have been canvassed more extensively in the *Human Tissue Products Issues Paper*, which introduces the concept of 'attenuation':

to describe the degree to which a donor is concerned about the use to which their donated tissue is put. A product is considered to be attenuated if a donor does not subjectively see the human tissue product as 'significant'. It may also be considered to have become attenuated in an objective sense if it has either lost that significance (such as genomic or cellular significance), to which importance may have been attached, or, the use to which it is put does not involve the significant properties that are considered important. (p. 15)

Internationally, Principle 9.C of the OECD Guidelines recognise the importance of dealing with this complex issue in the context of biobanking:

9.C The operators of the HBGRD should have a clearly articulated policy and explicitly indicate to participants whether they and/or the HBGRD retain any rights over the human biological materials and/or data and the nature of such rights.

In general, the large-scale population biobanks try to clarify this issue by informing participants that they are not entitled to ownership of samples or information held by the biobank. For example, UK Biobank states in its Ethics and Governance



Framework that it is the legal owner of the biobank and the sample collections, which allows it to take legal action against unauthorised use or abuse of the database of samples and the right to sell or destroy the samples. However, it goes on to state that it 'does not intend to exercise all of these rights; for example, it will not sell samples' (p. 12).

Vesting ownership of biobank resources in the biobank does not preclude participants from negotiating a right to access their personal information, or to withdraw from the project (see Chapters 3 and 4).

### ***Intellectual property rights associated with biobanks***

In addition to legal ownership or 'stewardship' (using the language adopted by the UK Biobank) of the collection of biospecimens and other tangible components of the biobank, intellectual property rights might also exist in the biobank itself (as opposed to intellectual property in research that utilises biobank resources, which is discussed below). For example, database protection may be available. The European Union Directive on the *Legal Protection of Databases* (96/9/EC) provides that the ownership of the intellectual property in the database vests in the 'maker' of the database, giving 50 years' protection in recognition of the work and costs in compiling, verifying and presenting data. The software that runs the database may be protected by copyright and/or patent.

The OECD Report notes that few of the large-scale biobanks have explicit policies relating to intellectual property rights associated with the resource itself (p. 124). The Icelandic legislation is silent with regard to ownership of intellectual property relating to the biobank itself, but the OECD Report argues that in this particular instance intellectual property rights would vest in the commercial licensee for the term of the licence (p. 124). The position is similar in Estonia (OECD Report, p. 125).

The UK Biobank Ethics and Governance Framework recognises that, in practice, it is unlikely that commercially valuable intellectual property will be associated with the biobank itself, stating that: 'UK Biobank is not expected in itself to lead to patentable inventions that return significant income either to researchers or UK Biobank, but it is expected to become a valuable common resource for research' (p. 18).

### ***Intellectual property rights arising from use of biobank resources***

In the Australian context, the *Human Tissue Products Issues Paper* acknowledges that the NHMRC has not yet provided guidance on intellectual property arising out of the use of human tissue (p. 56). While recognising the value of intellectual property in generating 'biotechnology opportunities', it cautions that:

The commercial use of intellectual property that contains identified or re-identifiable genomic information about a person or group of persons may be ethically permissible provided that:

- The nature of the arrangements ensures that those who have custody of the genetic information fulfil the requirements of the *National Statement* in relation to use of a person's genetic information or that of a group of persons.
- The person has been informed about the proposed commercial use of the information and has given consent to the commercial use including the possibility that those who develop and use it may make a profit from that use.
- No payment or any form of advantage to the donor is paid in exchange for permitting cells to be cultured from the original cells or permitting the commercial use of the latter. (p. 57)

In general, ownership of intellectual property arising out of use of biobank resources vests in the investigator creating it or his or her institution, rather than the biobank. In some circumstances it may be appropriate for the biobank to be a joint owner, depending on the relative levels of contribution (OECD Report, p. 126). Biobanks may claim joint ownership of intellectual property and a share of revenue from downstream commercialisation when the research is a collaborative endeavour.

Biobanks tend to support commercial development of research results arising out of the use of biobank resources, rather than prescribing limitations on commercialisation. For example, the UK Biobank's Ethics and Governance Framework acknowledges that research conducted using the resource could support the development of an invention that returns a profit, that:

The biotechnology and pharmaceutical industries can play an important role in realising health benefits in a practical sense by developing and improving the use of biomedical products. Commercial companies and other research endeavours that stand to make a profit will, therefore, be allowed access to UK Biobank if their proposal falls within the UK Biobank purpose and complies with the usual scientific and ethics requirements. (p. 18)

## ***Benefit Sharing***

The *Human Tissue Products Issues Paper* recognises that:

Commercial for-profit enterprises are necessary for the perpetuation of new and novel therapies, devices and other human tissue products, but the profit motive may undermine the spirit of altruism found in the Australian community, may contribute to increasing costs of health care and may decrease the equity of access to low cost, high quality health care. In order to maintain commercialisation but protect the key intrinsic values, the Working Committee believes that organisations should be required to prove a community benefit before they are authorised to profit from the supply of human tissue products. (p. 38)

One question raised in the international literature is whether there should be explicit benefit sharing obligations and, if so, what types of arrangements should be made and how they should be determined. Should they focus on general benefit to society as a whole or specific benefit to participants or their population groupings? Given the contentious nature of these issues, it is perhaps surprising that most biobanks do not have detailed commercialisation and benefit-sharing policies (OECD Report, p. 123). The relevance of these issues is also noted in the US National Cohort Study Report (p. 42).

The issue of benefit sharing is complex (OECD Report, p. 123). One problem is that it is not clear who should be sharing the benefits and what form of benefits should be shared. Should a national government receive compensation from a private entity in exchange for management of the biobank and, if so, how should such funds be distributed? Should participants be entitled to individual benefits? What forms of benefits should be considered other than financial benefits?

The need to address benefit sharing has found expression in a number of international instruments. UNESCO's *International Declaration on Human Genetic Data* is perhaps the most influential normative statement on benefit sharing in relation to biomedical research. It provides that:

benefits resulting from the use of human genetic data, human proteomic data or biological samples collected for medical and scientific research should be shared with the society as a whole and the international community. (Article 19a)

Notably, it adds that special assistance may be provided to the persons and groups who have taken part in the research (Article 19(a)(i)), but provides no specific

guidance as to the nature of this assistance, although it does discuss the forms that benefit sharing may take (Article 19(a)(ii)-(vii)).

The HUGO Ethics Committee *Statement on Benefit Sharing* provides more explicit guidance on the appropriateness of benefit sharing and the obligations it entails, both from the broad societal perspective and the more specific perspective of the biobank research participants and/or their social group. The statement recommends that:

- all humanity should share in, and have access to, the benefits of genetic research;
- benefits should not be limited to those individuals who participated in such research;
- there should be prior discussion with groups or communities on the issue of benefit-sharing;
- even in the absence of profits, immediate health benefits as determined by community needs could be provided;
- at a minimum, all research participants should receive information about general research outcomes and an indication of appreciation; and
- profit-making entities should dedicate a percentage (e.g. 1% - 3%) of their annual net profit to healthcare infrastructure and/or to humanitarian efforts.

The Statement sees benefit as more than just financial benefit. It is:

a good that contributes to the well-being of an individual and/or a given community (e.g. by region, tribe, disease-group...). Benefits transcend avoidance of harm (non-maleficence) in so far as they promote the welfare of an individual and/or of a community. Thus, a benefit is not identical with profit in the monetary or economic sense. Determining a benefit depends on needs, values, priorities and cultural expectations.

The OECD Guidelines recommend that biobanks address matters relevant to commercialisation in Principles 9.C and 9.D:

9.C The operators of the HBGRD should have a clearly articulated policy and explicitly indicate to participants whether they and/or the HBGRD retain any rights over the human biological materials and/or data and the nature of such rights.

9.D The operators of the HBGRD should have a clearly articulated policy that is communicated to participants relating to the commercialisation of its own resources, research results derived from those resources, and/or commercial products, if any, that may arise from research using its resources.

In relation to benefit sharing, Best Practices 9.1 and 9.2 of the OECD Guidelines provide that:

9.1 The operators of the HBGRD should have a clearly articulated policy regarding benefit sharing. This policy should address, inter alia, whether tests or products arising from research using its resources might be shared with the community and/or the general population, and how such sharing will be effected.

9.2 Where applicable, the operators of the HBGRD should negotiate benefit sharing agreements before a study begins, especially in the case of population-level studies where there may be vulnerable populations or unique concerns.

The Newfoundland and Labrador Department of Health and Community Services, in its Report, *Policy Implications of Commercial Genetic Research in Newfoundland and Labrador* (2003), recommends that the province should play a central role in negotiating benefit-sharing arrangements, which, it further recommends, should be required for *any* human genetic research with commercial potential.

Despite these statements in favour of benefit sharing, the incorporation of such considerations into biobank policies has been slow (see, for example, Knoppers and Sheremeta 2003).

UK Biobank (Webster et al 2008) and Generation Scotland (Haddow et al 2007, 2008) have undertaken public consultations with a view to elucidating public attitudes towards access to biobank resources and benefit sharing options. A survey of public opinion has also been conducted in Australia (Nicol and Critchley 2009). These consultations and surveys consistently illustrate that people care about benefit sharing and want to know what benefit sharing arrangements are in place before deciding to participate in biobank research.

### **Benefit to the nation and to the international community**

One form of benefit sharing is through payments to government. In Iceland, for example, while legislation is silent on benefit sharing as such, the licence agreement between the government and the operator of the biobank provides that the licensee will pay the government an annual fixed fee, which is earmarked for the promotion of health care and research and development, together with 6% of its profits, capped at ISK 70 million per year (OECD Report, p. 127). There are also various provisions with regard to reimbursement of the licensee should the government decide not to renew the licence.

The Statements of Principle relating to the proposed CARTaGENE biobank indicate that benefits could take a variety of forms, including access to medical care, future treatment or drugs; contribution to humanitarian organisations; and support of local needs, technological infrastructure or health services (RMGA Network of Applied Genetic Medicine 2000, 2003, OECD Report, p. 128).

The UK Biobank's Ethics and Governance Framework casts benefits in terms of long-term generation and dissemination of new knowledge for the benefit of public health in the UK and elsewhere (p. 17, Part III.C.1). Open dissemination of research results is a key feature.

The HapMap Project describes benefits in much the same way. In addition to the scientific benefits likely to arise out of rapid release of information:

It is hoped that the HapMap Project will eventually benefit the health of all people. Most of the benefits, however, will not be immediately apparent, and some might take years to materialize. So, in the short term, the main beneficiaries will not be sample donors, their families or their communities, but researchers, who will gain professional rewards, and companies, that will be able to develop drugs, diagnostic tests or other commercial products from research using the HapMap. (International HapMap Consortium 2004)

### **Benefits to individual participants and communities**

The issue of whether participants have the right to individual financial gain from participation is controversial, particularly given the prohibition on trading in tissue discussed earlier in this chapter as well as the more general prohibition on providing financial inducements to participants in research (see, for example, *National Statement* paragraph 2.2.10). In general, the large-scale population biobanks do not provide for sharing of profits with participants or fees for providing tissue or information. For example, the CARTaGENE Statements recommend that, while sharing of benefits should be discussed at the outset and might take a variety of forms, participants will not derive any personal financial advantage (OECD Report, p. 128).

While profit sharing with participants and their communities was discussed at the early stages of establishment of UK Biobank, this was rejected on the basis of the voluntary nature of participation, the scale of the project, and the long-term nature of the benefits that may accrue, suggesting that financial income would be better invested in the biobank itself.

The Australasian Biospecimen Network recommends that the donors of biospecimens should be provided with clarification as to their future entitlements

(or lack thereof) with regard to use of their samples. The Network recommends in its Biorepository Protocol Guidelines that the following (somewhat impersonal) information be provided to donors on commercial issues:

Our research is mostly directed to improving understanding of disease. Sometimes the research will lead to findings that result in the development of a commercial test or treatment that may be overseen by pharmaceutical companies. Australian law indicates that there is no financial reward or payment to you in such an event. (Australasian Biospecimen Network, p. 6)

This is not to say that the unique contribution made by certain donors should not be given due recognition, bearing in mind that privacy and confidentiality considerations may also be heightened in such circumstances and special care may need to be taken to protect participant identity.

Rather than profit sharing or other financial rewards, more indirect benefits could be provided to particular individuals and communities, such as preferential access to new healthcare developments, as well as genuine efforts to fully disclose all relevant information, particularly information about the process of commercialisation, and to explicitly recognise the input that sources have made. Some biobanks provide for other indirect benefits. For example, the Estonian biobank gives participants the right to access their data at no charge and the right to genetic counselling if they access their data (they are not given the right of access to genealogical information) (OECD Report, p. 128).

Where biobanks recruit from communities with particular cultural sensitivities, sharing the benefits with that community needs to be specifically addressed. The Canadian Institutes of Health *Guidelines for Health Research involving Aboriginal People* (2007) state that:

Research should be of benefit to the community as well as the researcher. Benefit sharing in research is an essential concern of Aboriginal communities. ... Benefit sharing involves fair reward for investments in research. Benefits can take a number of forms depending on the type of research being conducted. They may be immediate or longer term, tangible or intangible, and monetary or non-monetary, including but not limited to widespread community accessibility to the final results of the study. (p. 23, Article 9)

In some circumstances the uniqueness of a particular contribution and related cultural sensitivities may actually make it ethically unacceptable to allow commercial use. The Human Tissue Products Working Group expresses this viewpoint as follows:

In circumstances in which the tissue product has a value that is unique to its donor or their family, commercial use of the product could be seen as exploiting the uniqueness of the donor rather than being a novel approach or process. Commercialising and generating a profit from a tissue product with a unique value may also raise community concerns if people feel that the donor should share the profits. This would constitute material incentive and may erode community benefit and the altruistic nature of Australia's donor system if people start to withhold donations unless profits were made. For this reason the Working Committee is of the view that ethical guidelines should prohibit commercial use of human tissue products if the value of a product is derived from a characteristic that is unique to the donor. The Working Committee believes that such products may be exchanged and fees paid to recover costs but no profit should be obtained from such exchanges (p. 49).

However, it should be recognised that public funding of the costly process of product development is only likely to be available in exceptional circumstances.

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## **Relevant State and Territory Privacy Legislation**

### **New South Wales**

[Privacy and Personal Information Protection Act 1998](#)

[Health Records and Information Privacy Act 2002](#)

### **Victoria**

[Information Privacy Act 2000](#)

[Health Records Act 2000](#)

### **Tasmania**

[Personal Information Protection Act 2004](#)

### **Northern Territory**

[Information Act 2002](#)

### **Australian Capital Territory**

[Health Records \(Privacy and Access\) Act 1997](#)

## Glossary of acronyms and abbreviations

ABN	Australasian Biospecimen Network
AHEC	Australian Health Ethics Committee
ALRC	Australian Law Reform Commission
ALRC/AHEC Report	ALRC/AHEC Report 96, <i>Essentially Yours, the Protection of Human Genetic Information in Australia</i> (2003)
European Group Opinion, Tissue Banking	European Commission (1998). <i>Ethical Aspects of Human Tissue Banking</i>
<i>Genetic Register Guidelines</i>	National Health and Medical Research Council (2000) <i>Guidelines for Genetic Registers and Associated Genetic Material</i>
HBGRD	human biobanks and genetic research databases
HREC	human research ethics committee
HUGO Statement on Human Genomic Databases	Human Genome Organisation (2002). <i>HUGO Ethics Committee Statement on Human Genomic Databases.</i>
Human Tissue Products Issues Paper	National Health and Medical Research Council (2009). <i>Ethics and Exchange, Sale of and Profit from Products Derived from Human Tissue</i>
ISBER Best Practices	International Society for Biological and Environmental Repositories (2008) <i>Best Practices for Repositories: Collection, Storage, Retrieval and Distribution of Human Biological Materials for Research. 2<sup>nd</sup> Edn</i>
<i>National Statement</i>	National Health and Medical Research Council (2007) <i>National Statement on Ethical Conduct in Human Research</i>
NCI	National Cancer Institute (US)
NCI Best Practices	National Cancer Institute (2007) <i>Best Practices for Biospecimen Resources</i>
NHMRC	National Health and Medical Research Council
NIH GWAS Policy	National Institutes of Health (2008). <i>Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS)</i>
OECD	Organisation for Economic Co-operation and Development
OECD Guidelines	OECD (2009) <i>Guidelines for Human Biobanks and Genetic Research Databases (HBGRDs)</i>
OECD Report	<i>OECD (2006). Creation and Governance of Human Genetic Research Databases</i>
P <sup>3</sup> G	Public Population Project in Genomics
Singapore Report	Bioethics Advisory Committee (2002). <i>Report: Human Tissue Research.</i> Singapore.
UK Biobank Framework	UK Biobank, Ethics and Governance Framework

UPPs	uniform privacy principles
US Cohort Study Report	Report of the Secretary's Advisory Committee on Genetics, Health and Society (2007). <i>Policy Issues Associated with Undertaking a New Large U.S. Population Cohort Study of Genes, Environment and Disease</i>

## Appendix 1: Authors and Acknowledgements

NHMRC wishes to acknowledge the invaluable contribution of those listed below.

### Authors

**Professor Margaret Otlowski**

**Professor Dianne Nicol**

**Dr Mark Stranger**

Law School, University of Tasmania

### Biobanks Reference Group

**A/Professor Christine Clarke**

(Chair)

Westmead Institute for Cancer  
Research, University of Sydney

**Professor Peter Schofield**

Prince of Wales Medical Research  
Institute

**Professor Lyle Palmer**

Western Australian Institute for  
Medical Research

**Professor Simon Foote**

Menzies Research Institute, University  
of Tasmania

**Ms Lisa Devereux**

Peter MacCallum Cancer Centre

**A/Professor David Horsfall**

Australian Prostate Cancer  
BioResource, University of Adelaide

**Reverend Martin Robinson**

Member, NHMRC HGAC  
Rector, St Martin's Anglican Church,  
Killara, Sydney

**Dr Nikolajs Zeps**

Member, NHMRC AHEC  
St John of God Pathology  
Department of Radiation Oncology, Sir  
Charles Gairdner Hospital

**A/Professor Terry Dunbar**

Member, NHMRC AHEC and ATSIHRAC  
Charles Darwin University

NHMRC Human Genetics Advisory Committee, Australian Health Ethics Committee  
and Aboriginal and Torres Strait Islander Health and Research Advisory Committee.

### Peer Reviewers

Professor Graeme Laurie

Professor of Medical Jurisprudence, University of Edinburgh

Professor Tim Caulfield

Canada Research Chair in Health Law and Policy  
Professor, Faculty of Law and School of Public Health  
Research Director, Health Law Institute, University of Alberta

Professor Alastair Campbell

Chen Su Lan Centennial Professor of Medical Ethics  
Director of the Centre for Biomedical Ethics, Singapore

### NHMRC Staff:

Ms Nicole Craig, Dr Tanyth de Gooyer