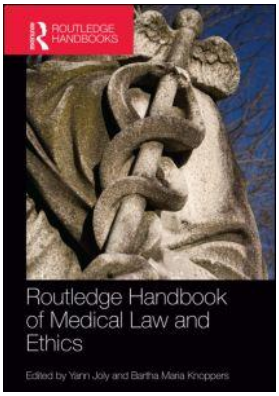

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Part IV
From bench to bedside

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17

Medical research

Future directions in the genome era

Don Chalmers[1]

Over a decade ago the National Bioethics Advisory Commission (NBAC) declared unequivocally that '[p]rotecting the rights and welfare of those who volunteer to participate in research is a fundamental tenet of ethical research' (2001a: i). This influential report went on to note that 'increasingly, the current system is being viewed as uneven in its ability to simultaneously protect the rights and welfare of research participants and promote ethically responsible research' (NBAC 2001a: i; Chalmers 2004). The first decade of this millennium saw an international reform effort to align the proper protection of human research participants with the accelerating expansion and pace of both academic and commercial research activity. There has been a sustained move to update research ethics and avoid the criticism that 'the philosophy of the state, its ethics – are always yesterday' (Brodsky 1987). This chapter will discuss the development of medical research ethics internationally, and the required future directions for the regulation of medical research and its ability to meet the challenges in the increasingly internationalised context of research in the 'Genome Era'.[2]

17.1 Background to the current governance of medical research

The traditional starting point for an account of the current principles of medical research ethics is the *Nuremberg Code* 1947 and the *Declaration of Helsinki* 1964. Both the *Code* and the *Declaration* were developed by reference to standards of medical ethics and, in the case of the *Code*, the complete failure to respect such standards. The fifth principle of the *Nuremberg Code* – that '[n]o experiment should be conducted where there is an *a priori* reason to believe that death or injury will occur' – derives from the central tenet of the *Hippocratic Oath* to do no harm to the

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2 A term coined by the current Director of the National Institute of Health (Collins 2010).

patient. This principle underlies the centuries of development of medical ethics (Baker 1995)[3] in different traditions (Mendelson 1998)[4] and finds expression in the current *Islamic Code of Medical Professional Ethics* (Universität Jena 1981). The *Oath* was restated in a modern form, reflecting the *Nuremberg Code*, in the World Medical Association's (WMA) *Declaration of Geneva* 1948: 'I will maintain the utmost respect for human life; … I will not use my medical knowledge contrary to the laws of humanity.' The *Declaration of Geneva* became the basis for the *International Code of Medical Ethics* the following year. However, the principles of medical ethics were largely directed to the doctor/patient relationship and the delivery of ethical medical services rather than research (Chalmers 2006).

Medical research was the core focus of the *Nuremberg Code*, which was a watershed in the development of modern research ethics. The *Nuremberg Code* was formulated as a direct response to the failure of professional and humane standards of medical experimentation, namely in the conduct of cruel, lethal and deadly experiments in Nazi concentration camps (Annas and Grodin 1992).[5] Similar revelations later emerged about Japanese atrocities in biological and chemical 'experiments' conducted on prisoners in Unit 731 in China between 1932 and 1945 (Nie *et al*. 2010). Unlike the German Nuremberg trials, many of the scientists in Unit 731 were not prosecuted or evidence was suppressed by US forces. Estimates of between 3,000 and 10,000 prisoners died during these unethical and lethal processes (Harris 1994). The *Nuremberg Code* dealt with universal standards for medical research and with 'matters of ethical significance to humanity' (Leake 1927: 57) in declaring ten principles for medical experimentation, as follows:

1. Voluntary consent of the human subject is essential.
2. The experiment should yield 'fruitful' results for the good of society, unprocurable by other means.
3. The experiment should be designed and based on the results of animal experimentation or natural history as such as anticipatory results justify the experiment.
4. The experiment should avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an *a priori* reason to believe that death or injury will occur.
6. The degree of risk should never exceed the humanitarian importance of the problem to be solved.
7. Proper preparations and adequate facilities should be provided to protect the subject against even remote possibilities of injury.
8. The experiment should be conducted only by scientifically qualified persons with the highest degree of skill and care in the experiment.
9. The subject should be at liberty to end the experiment where continuation is impossible.

3 See 'The Historical Context of the American Medical Association's 1847 Code of Ethics' (Baker 1995) and also 'Creating a Medical Profession in the United States: The First Code of Ethics of the American Medical Association' (Reiser 1995). This work assessed the work of Benjamin Rush in drawing up the American Medical Association's *Code of Ethics* 1847, which was influenced by the writings of John Gregory (1725–73) and Thomas Percival (1740–1804). Baker has quipped that the American *Code of Medical Ethics* was '… nothing more than self-serving professional etiquettes … to disguise organized medicine's attempt to monopolize medical thought so that, by driving homeopaths and other "irregular" competitors from the medical market place, it could ultimately monopolize medical practice.'

4 See also Rahman (1997).

5 See also Wikler and Barondess (1993).

10. The scientist must terminate an experiment where there is probable cause to believe that injury, disability or death will result to the 'experimental subject'.

(Nuremberg Trial 1949)

The WMA formally developed and adopted these ten principles in the influential *Declaration of Helsinki* in 1964. This *Declaration* has been regularly revised and updated, and establishes the *key pillars* for modern ethical review of medical research which echo the principles of the *Code*, namely:

1. Voluntary consent of the research participant;
2. Independent review of the research project;
3. Assessment of the risk to participants;
4. Conduct of the research by competent researchers of integrity; and
5. Demonstrated merit in the proposed research project.

(World Medical Association 2013)

The *Declaration of Helsinki* influenced national responses to research ethics with the introduction of codes governing ethical research practice (Furrow *et al.* 2000: 979).

Originally, impartial scientific peers were to undertake this ethical review. The idea of any ethical assessment by outside 'non-institutional' or non-scientific 'lay' members of the community had not emerged. Events in the United States were to have a profound and lasting impact not only on the development of modern medical research ethics in America but also on the independent review of human research projects around the world. The introduction of the American formal ethics review system was, in the 1970s, another important watershed in the development of medical research ethics. In America, a 'series of scandals of social science research and medical research conducted with the sick and illiterate underlined the need to systematically and rigorously protect individuals in research' (NBAC 2001a: i).[6] The Tuskegee Syphilis Study was one of the most widely publicised and egregious failures of proper human research standards (Furrow *et al.* 2000: 979). In response, the *National Research Act* 1974 established the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research and, importantly, required each institution conducting federally supported research involving human subjects to establish Institutional Review Boards (IRBs) (President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research 1983). The following year, the Department of Health, Education and Welfare issued the *Policy for the Protection of Human Research Subjects* (1975), which resulted in the establishment of IRBs in universities, medical schools and hospitals conducting research. This rapid expansion consolidated the IRB as the keystone of the national regulatory system for ethical review of research involving humans.[7] IRBs were required to confirm the voluntary consent of research 'subjects' (more usually now referred to as participants).

Critically, the *Helsinki Code* standard for 'independent review of the research project' was formalised in the IRB. The IRB required the appointment of '… at least one member who is not

6 See also Beecher (1966, 1968), Katz (1993) and Levine (1986).

7 The 'Common Rule' *Public Welfare*, 45 CFR, § 46.101 (a)–(f). The Food and Drug Administration (FDA) has correlative regulations paralleling the Department of Health and Human Services Policy.

otherwise affiliated with the institution' (*Food and Drugs* 21 CFR, § 56.107). This established, for the first time, a systematic procedure for this independent review and approval of research protocols. Monitoring and reporting requirements were also introduced for annual review, approval of changes to a protocol and strict reporting of any risk to participants. A 'light-touch' requirement was added to these procedures, making compliance and IRB approval preconditions for federal research funding. This is not to suggest that the introduction of IRBs was a seamless and uniform process; institutions reported variations, inter alia in professional composition, frequency of meetings, review procedures and access to records.

Reports of research impropriety were not only surfacing in American institutions. In New Zealand, following a Royal Commission into unethical research on cervical cancer patients, major reforms in the institutional basis for ethics committees were introduced (Dawson and Peart 2003). The formalisation of the American IRB system has been influential in the development of research ethics committees around the world and, arguably the most influential American legal export in the regulation of ethical review of research. In the decades following the *National Research Act*, IRB equivalents were introduced around the world in research-active countries. Essentially, research ethics committees were established to review and approve human subjects research for both the voluntary and informed consent of participants, and to ensure the expected benefits of the project did not supersede the interests and safety of the participants. In Australia, for example, the ethics review system traces back to the National Health and Medical Research Council's (NHMRC) ratification of the *Declaration of Helsinki* in 1967. The Council then introduced the *Statement on Human Experimentation*, establishing a system of ethical review for medical research projects and a system of Institutional Ethics Committees (IECs) based on the US model, in 1982. IECs were required to ensure compliance with the *Statement* and their ethical approval were made preconditions to research funding by the NHMRC. The *Statement on Human Experimentation* was replaced by the *National Statement on Ethical Conduct in Human Research* in 1999 (NHMRC 2007)[8] and was significantly revised in 2007.

There was a similar introduction of the research ethics committee system into other research-active countries. These research ethics committees (RECs)[9] were similarly composed of independent and non-affiliated lay members, where these IRB equivalents established a two-tier review system. The first tier continued the researcher's primary ethical and legal duties to the research subjects and the integrity of the project's design. The introduction of IRB/REC equivalents essentially established an independent second tier for the review and approval of research projects involving human subjects as a precondition for public research funding. Some countries have also established a third tier. The National Consultative Committee for Health and Life Sciences in France was a pioneer in its published reports on many aspects of bioethics and medical research. In 1992, the mandate of the Australian Health Ethics Committee (AHEC) set out not only to produce reports on medical research, but also to have sole responsibility for the formulation of guidelines dealing with medical research (NHMRC 1992, section 8),[10] and overseeing the developing national system of research

8 This statement was endorsed by the Australian Vice Chancellors' Committee, the Australian Research Council and the Learned Academies in 1999. It is a national research code of practice governing social as well as biomedical research.

9 'Research ethics committee' is used generically to refer to committees that provide ethical approval for medical and health research projects and that have the primary duty to protect the research participants. They have a variety of national designations: local research ethics committees (UK); human research ethics committees (Australia); institutional review boards (USA); institutional ethics committees (New Zealand).

10 However, these guidelines must be drawn up following a unique two-stage public consultation process under section 14.

ethics review committees. National committees under a variety of titles have been established worldwide to oversee or guide their national ethics review systems (Chalmers 2001a).

17.2 Future challenges in medical research review

17.2.1 Research governance

The governance agenda in research ethics review does not only focus on the central role of the committee, but also considers the wider issues of effective and proper management of research(ers) within the institution. Thus the agenda is a considerable challenge that includes consideration of certification standards for research facilities, risk management in the types of research conducted at the institution, insurance coverage and indemnity arrangements and research training (Chalmers 2001b). Governance borrows from the corporate model and follows the staged analysis of understanding, planning, modifying and implementing changes to improve the research endeavour. The introduction of the IRB system in the USA and its counterparts in other countries was *not* based on a centralised national system of bureaucracy. Essentially, institutions themselves were required to follow a set of general national standards of ethical review.

Perhaps unsurprisingly, different institutions followed the same 'common rule' of review and approval, but not always using the same procedural pathway. Different institutions developed idiosyncratic characteristics. The size of ethics review committees was varied and particularly over-representative of researchers and numbers 'affiliated with the institution' in relation to the non-affiliated members. They also varied in determining boundaries between the scientific and the ethical aspects of the project. In Australia, an inquiry in the mid-1990s noted these and other variations, including workload pressures, lack of scientific expertise, absence of training opportunities for committee members, issues of potential legal liability for ethics committee members, non-pharmaceutical company-sponsored clinical trials and lack of coordination between ethics committees dealing with multi-centre research and project monitoring by ethics committees (Commonwealth of Australia 1996).

Ethics committees were increasingly and commonly united in their complaints about the volume of paperwork to consider, particularly the length and complexity of participant consent forms and the accompanying project information sheets. Gradually, research ethics committees also began to consider social science research projects. The increased work volume of projects motivated procedures for *expedited review*, permitting some projects to be considered by the chair or a subcommittee rather than by the full committee. Research governance reform later introduced a *low-risk* classification for some research, permitting ethics committees to expedite and accelerate approval time of these types of applications while concentrating their expertise on more complex applications. There were continuing concerns, however, about 'excessive workloads for RECs, delays in carrying out reviews … and the risk of important problems being overlooked [in the context] of commercial imperatives and the reality of a global market' (Australian Health and Ministers Advisory Council 2006).

Ultimately, a reform agenda developed for research ethics committees. The international 'governance' (Leblanc and Gillies 2005) agenda for restructuring companies, government administration and civil society itself focused on ethics committees. This governance agenda recognised the centrality of participant consent in research and ethics committee approval, but extended beyond the ethics committee to the whole research endeavour within an institution. At the opening of the new millennium, the NBAC issued a two-volume Report (NBAC 2001a, 2001b) that heralded 'a time for change' in reform of the ethics review system to ensure protection of research

participants in the United States. The Report recommended a range of initiatives to improve the research review system including education for IRB members, accreditation of IRBs, independent risk-benefit assessment, investigator disclosure of interests, additional protections for vulnerable groups, compensation for participants suffering direct harm, review of multi-site research and reduced threats to privacy (NBAC 2001b). The NBAC concluded that 'a comprehensive and effective oversight system is essential to uniformly protect the rights and welfare of participants while permitting ethically and scientifically responsible research to proceed without undue delay' (NBAC 2001b, recommendation 2.2).

This Report noted the need for federal legislation to protect the participants in both publicly and privately sponsored research with: a single independent Federal Office for Human Research Oversight; requirements for education, certification and accreditation of committees; review of IRB membership with the inclusion of members who represent perspectives of participants unaffiliated with the institution; emphasising the informed consent process rather than editorialising documentation; improving and strengthening privacy; investigating the need for compensation programmes; and better resourcing of IRBs (National Bioethics Advisory Commission 2001b, recommendations 2.1–2.2, 3.1–3.4, 3.9–3.10, 5.1, 5.3–5.4, 6.6, 7.1).

These recommendations were echoed in reports from other research countries[11] and were followed by greater scrutiny and organization of ethics review processes. In the UK, for example, Health Authorities were responsible for establishing *local research ethics committees* that centralised guidelines in the Central Office for Research Ethics Committees within the Department of Health (UK Department of Health 2011). This process of continuing review led to a close examination of the regulatory and governance environment in medical research by the UK Academy of Medical Sciences. In their report, a number of recommendations were proposed to increase the speed of decision-making, reduce complexity and eliminate unnecessary bureaucracy and cost in carrying out health research (UK Academy of Medical Sciences 2010a). In this respect, the governance agenda accepted the efficiency as well as the safety aspects of research, although debates are ongoing regarding the use of consent waivers where there is a public benefit interest and the value of the research outweighs to a substantial degree the private interests of personal privacy (Organization for Economic Cooperation and Development (OECD) 2009).

Establishing procedures for single review of multi-centre research, without compromising proper ethical safeguards, is a continuing governance challenge. The Australian *National Statement* in 2007 allowed RECs to accept review by a single ethics review body (National Health and Medical Research Council 2007, chapters 5.3.1–5.3.2). The Harmonisation of Multi-centre Ethical Review is implementing an initiative to recognise a single ethical and scientific review of multi-centre research, which would ensure conformity to the researchers' national as well as local ethical standards of the country in which the research is conducted.

Efficiency may be the declared aim of streamlining ethics approvals systems. An Australian Report noted that a strong incentive for streamlining is the reduction in unnecessary duplication, transparency and consistency, but also acknowledged that these efficiencies could make Australia more attractive for international investment in commercial-sponsored clinical trials. The same Report stated that 'in a global market, it is important that processes for scientific and ethics review do not impede Australian … participation in clinical trials … [but] Sponsors speak of the Australian ethics review process introducing delays that tarnish Australia's reputation as a desirable location for the conduct of multi-centre clinical trials' (Australian Health and Ministers Advisory Council 2006: 14, 17).

11 In the UK see McLean (2004); in Canada, see Llewellyn *et al.* (2003).

The governance agenda is crucial in the face of increased research activity, which suggests enhanced regulation and accountability for the future evolution of the ethics review system that still relies substantially on volunteerism (Chalmers 2011).

17.2.2 The globalised research governance

The modern 'Genome Era' (Sulston and Ferry 2003), as described by Francis Collins and others, has seen an increasing globalisation of research with cross-border collaborations, data linkage and multi-centre clinical trials. In this new era, there has been a vast increase in the funding of medical and genomic research. Technologies, particularly whole genome sequencing (WGS), are becoming cheaper with increasing volume feasibility for large-scale data collection linkage. Increased research funding is not only driving expectations that breakthroughs in health outcomes are on the horizon, but also that these improved outcomes will increase wealth in developing economies. Many nations have adopted national biotechnology strategies to drive biomedical research and encourage private investment. As such, the Academy of Medical Sciences claims that '[t]he UK must grow and sustain its world-class biomedical workforce for our knowledge economy' (UK Academy of Medical Sciences 2010b, 2010c). Significant international collaborations, however, are driven by more beneficent motives. Innovative incentives[12] for multinational pharmaceutical companies to develop drugs in developing countries are being translated into public–private collaborations. Examples include the Medicines for Malaria Venture (MMV) Foundation[13] collaboration with Novartis and the Medicines for Malaria Venture that developed a prophylactic treatment through its collaboration (Novatis Global 2011).[14] Others still are facilitating large-scale research, such as the International Cancer Genome Consortium.

Greater activity and investment in medical research, particularly as international collaborations increase, confirms the need to review international regulatory frameworks. The current ethics review system remains focused on activity within institutions and within national borders. The challenge in the genome era is to develop a more harmonised international regulatory framework for research ethics review. An essential aspect of this challenge will be the development of procedures for the mutual recognition of IRB/REC approvals of cross-border research projects. An internationally harmonised system should be based on an 'equivalent protection' doctrine requiring that the highest standards of research ethics should apply where there may be differences in the ethical research standards between countries (Sugarman 2005; Chima 2006).

These international instruments may be divided into two classes: those of *direct* relevance to medical research; and those that have more indirect *referential* relevance (Pace Mason *et al.* 2010: 572). In the *direct* category, the International Conference of Harmonisation (originally the regulatory authorities of Europe, Japan and the USA) *Guidelines for Good Clinical Practice* were introduced to provide public assurance that the rights, safety and well-being of trial subjects involved in clinical trials are credible and consistent with the *Declaration of Helsinki*. At the regional level, the Council of Europe's *Convention on Human Rights and Biomedicine* 1997 sets out the broad general principles for human subjects research. Also of *direct* influence is the Council of Europe's

12 An idea championed by Thomas Pogge (2002).

13 The Medicines for Malaria Venture was funded through public and philanthropic donations from groups including the government of Switzerland, the UK Department of International Development, the government of the Netherlands, the Bill & Melinda Gates Foundation, the Rockefeller Foundation, US AID and the World Bank (MMV 2013).

14 In collaboration with international organizations, Novartis provides the anti-malarial medicine Coartem without profit for public-sector use in malaria-endemic developing countries.

Directive 2001/20/EC on Research Development for Medicinal Products, which emphasises good medical practice and the ethical and scientific quality requirements for designing, conducting and reporting clinical trials with human subjects. It assures 'that the rights, safety and well-being of prior subjects are protected, and that the results of the clinical trial are credible' (article 1(2); European Commission 2013).

In the *referential* category, the United Nations Educational, Scientific and Cultural Organization (UNESCO) undertook pioneering work in setting standards for human genetic research. Its *Declaration on the Human Genome and Human Rights* declared that '[n]o research … concerning the human genome … should prevail over respect for the human rights, fundamental freedoms and human dignity of individuals or … groups of people' (1997, article 10). The *Declaration* is non-binding but has been widely influential in the revision of some national codes of ethics, such as the 1999 version of the Australian *National Statement on Ethical Conduct in Human Research*. Similarly, the codes of good manufacturing practice issued by the various therapeutic goods administration organizations in different countries reference international standards. In 2011, the World Health Organization (WHO) developed the *Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants* in the way of this *referential* category. In the document, they acknowledge the *International Ethical Guidelines for Biomedical Research Involving Human Subjects* published by the Council of International Organizations of Medical Sciences (CIOMS) and the WHO in 1993. The CIOMS and WHO also collaborated in the publication of the *International Ethical Guidelines for Epidemiological Studies* in 2008. Apart from these, the myriad of international documents that are referred to and may be considered in revisions of national codes and international documents demonstrates a fair degree of national copycatting in setting research ethics standards. For example, the content featured in the 1999 version of the Australian *National Statement on Ethical Conduct in Human Research* was reflective of the United States *Code of Federal Regulations*, the Canadian *Code of Ethical Conduct for Research Involving Humans* (Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada and Social Sciences and Humanities Research Council of Canada 2010) and similar guidelines in the United Kingdom (Royal College of Physicians 2007).

New international collaborations in medical research have increased the need to assess existing ethics review standards and to consider further avenues for harmonising them. In this respect, there have been modest proposals for a framework and platform to facilitate research ethics discussion at an international level, enabling the ethics to catch up with the scientific collaborations that have made research an increasingly global endeavour (Kaye *et al.* 2012). More boldly, there have been proposals for an International Code of Conduct for global genomic research projects (Global Alliance for Genomic Health 2014).

17.2.3 Biobanks and research governance

In the genome era, human tissue and genomic data collection have become essential research tools and have allowed the translation of biomedical innovations to improve healthcare delivery. Biobanks are seen as flagships of the drive to personalised medicine (Chalmers *et al.* 2013). These collections have adopted the neologism of 'biobanks' (Chalmers and Nicol 2008) and depend on advances in sequencing, computational and information technologies. Biobanks are key drivers in new approaches to genomic science that now span large international collaborations of researchers in global networks, such as the International Cancer Genome Consortium (ICGC) (Hudson 2010), The Cancer Genome Atlas (TCGA) (National Cancer Institute 2013) and the Global Alliance for Genomic Health (2014). Large international collaborative cancer studies are

now feasible to identify genetic risk loci and somatic mutations using genome-wide association studies (Easton *et al.* 2007).

Biobanks also appear on governance agendas (Kaye 2011), but with greater urgency not only due to the scale of the endeavours, but also because of how their unique aspects have created new research ethics issues. Previously an individual-specific principle, the protection of research participants in biobanking often considers how the research protocol will benefit the public good. Secondly, consent to participate in one research project is now supplemented with consent for long-term data and tissue storage for future undefined research uses. This controversial idea of broad future consent has been widely debated (Kaye and Stranger 2009).[15] Third, ongoing and dynamic governance that factors in public interest more prominently has largely supplanted traditional institutional governance and accountability processes. Biobank research represents a distinct conceptual shift in research from a 'one project, one centre, one jurisdiction, one point in time' paradigm, to multi-centre group projects and research collaborations crossing national borders.

The proliferation of biobanks around the world encourages an equal proliferation in academic scholarship, debates about policy approaches, and strategies for ethics review and governance of biobanks (Kaye and Stranger 2009; Pascuzzi *et al.* 2013). Before its establishment, community engagement[16] has generally been undertaken and independent bodies established to administer and operate the biobank, such as the UK Biobank. It also requires an Ethics and Governance Council to address ethical concerns and 'to set standards for the project, and to ensure that safeguards are in place for scientifically and ethically approved research' (UK Biobank 2013). Biobanks have also had to develop more sophisticated consent processes that recognise the ongoing nature of participation in research. Similarly, biobanks have equally sophisticated data management and access procedure systems to facilitate research while safeguarding the privacy of participants and protecting confidential and proprietary data. In addition to key biobank governance issues of oversight, security and access, procedures are required in the unlikely case of discontinuing the biobank.

Biobanks have also promoted some reconsideration of the role of the ethics review committee not only as it relates to the institutional governance agenda, but also to wider considerations of the regulatory environment. The UK Biobank Ethics and Governance Council maintains a continuing role in public engagement. In this wider regulatory environment, Brownsword has cautioned that regulatory environments are varied and complex (2013: 43–4). Yet despite this complexity, there is a need to avoid two serious misunderstandings about the characteristics of the regulatory environment. The first misunderstanding, legal exclusivity, is to assume that the only signals in the regulatory environment are formal legal signals. The second misunderstanding, normative exclusivity, is to assume that the only signals in the regulatory environment are normative (that is signals that prescribe what ought, or ought not, to be done). It is easy enough to appreciate why lawyers might be tempted to jump to these conclusions, but why precisely are they in error? In the research ethics and biobank regulatory environment, it cannot be the role of ethics committees, much less lawyers, to police research projects; the ethics review governance system relies on the integrity of all involved in the governance processes and the researchers themselves (Chalmers and Pettit 1989).

15 See also Gibbons and Kaye (2007), Gottweis and Petersen (2008), Mascalzoni *et al.* (2008), Taylor (2008) and Hansson (2006).

16 In some cases this has involved conducting deliberative processes by engaging selected categories of individuals reflecting the 'community' to participate and deliberate on their preferences, judgments, expectations, concerns and values in relation to a proposed biobank (Australian National University 2013).

17.2.4 Privacy and data protection governance

Genetic research can uncover information, not only about the participants but also about their parents, siblings, children and relations. This prophetic potential has prompted many countries to develop codes of practice for ethical conduct in human genetic research. This potential is magnified in the context of biobanking. The research ethics committee must assess the consent aspects of a research protocol, but also the confidentiality and privacy issues of stored genetic information, proposed future research and communication of research results. Arguably, the greatest challenge for research and open genomic data sharing in the genome era is information privacy and security (Greenbaum *et al.* 2011; Global Alliance for Genomic Health 2014). This challenge is emphasised in the modern research regulatory environment in which the scientific community, research funders and governments have promoted and encouraged policies and practices of open access to genomic data for scientific research and medical progress (Greenbaum *et al.* 2011; Birney *et al.* 2009; Walport and Brest 2011). Open access is an accepted norm for large-scale, publicly funded genomic science projects.

At the national level, many privacy or data protection laws were based on the influential OECD *Information Privacy Principles* published in 1980. These principles[17] brought a measure of consistency to national privacy approaches by setting standards for the collection, storage, release, access and accountability for personal information. Later EU privacy directives, particularly the *Directive 95/46/EC* on data protection on trans-border data flow, maintained this principled approach.[18] Privacy or data protection legislation encompasses the collection, storage, release, access to and challenge to personal information.

In the increasingly globalised research environment, the key issue is privacy in trans-border data linkage, particularly in genomic research. Clearly, there are technical requirements for privacy enhancement technologies to shield participant information. In addition, some international projects adopt from the outset procedures to ensure approved access to data. For example, the Data Access Compliance Office (DACO) of the International Cancer Genome Consortium (ICGC) uses 'a tiered access system' (Joly *et al.* 2012) with access to separately classified 'open' and 'controlled' data. The 'controlled' data classification covers sensitive personal data, such as detailed phenotype and health outcome data and genome sequences files. This data, if released at all, requires the consideration and approval of the Data Access Compliance Office under the oversight of the International Data Access Committee. Like other data access processes, all applications for data access are documented, recorded and regularly reviewed. The individual project arrangements for data access and sharing within the ICGC have worked satisfactorily but are not necessarily a template for translation as a model for the future of more widespread data sharing.

There have been justifiable claims that privacy protection is the main challenge to open genomic data sharing (Greenbaum *et al.* 2011). The regulatory theorist Brownsword proposed a 'triple bottom line' test for the adequacy of the privacy and data protection regulatory environment for biobanks during their start-up period: '(i) that both participation and the use of participants' samples and data are based on free and informed consent; (ii) that the privacy, confidentiality, and fair data processing rights of participants are respected; and (iii) that the proprietary rights (if any) of participants are respected' (2013: 42). The latter two continue to apply throughout the duration of tissue and/or data storage (Knoppers 2007: 144).

17 Collection Limitation Principle, Data Quality Principle, Purpose Specification Principle, Use Limitation Principle, Openness Principle, Individual Participation Principle, Accountability Principle.

18 See also *Directive 2002/58/EC on privacy and electronic communications*.

Nevertheless, data sharing is expanding in the big-data genome era and concerns surrounding the actual security of stored data persist. The UK Academy of Medical Science expressed one such concern. It argues that the impact of 'data protection regulation in particular represents a serious impediment to medical research without apparently providing significant benefit to patients. Streamlining and improving current regulation represents a cost-effective approach to creating a more fertile and productive research environment.' There have been concerns within the genomics community that open access 'may not result in greater and more rapid scientific benefits' but may 'result in duplication of effort, cause problems in the peer review system and create incentives for generating more publicly inaccessible databases' (Foster and Sharp 2007).

The balance between open access and data protection is critical to address any privacy concerns participants and the wider community might have. The governance, sharing, design and implementation of revised data access and policies are major challenges in the genome era.

17.2.5 Research governance, conflicts of interest and public trust

Medical research is frequently conducted in a commercialised environment (Chalmers and Nicol 2004: 116). This environment has been supported and promoted by national biotechnology strategies that include medical research as one of the key drivers of commercial and knowledge-based economic development (Sakaiya 1991). Many small, start-up and spin-off companies have their genesis in symbiotic collaborations and partnerships with larger companies as a source for their research funding.

This growing commercialism raises issues of public trust and was the focus of a UK Parliamentary Select Committee. It discussed the crisis of trust in society's attitudes towards science and noted the particular challenges to scientific independence (House of Lords Select Committee on Science and Technology 2000). The Committee argued that 'the concept of independence has become problematic, particularly because of the increasing commercialisation of the research. In our view, scientists must robustly protect and vindicate their independence. Sponsorships and affiliations must be openly declared … [and] research output is submitted to peer review and published in the academic literature' (House of Lords Select Committee on Science and Technology 2000, paras 13–14). Later, the National Institutes for Health adopted a stricter – described as 'draconian'[19] – standard on conflicts of interest in their *Supplemental Standards of Ethical Conduct and Financial Disclosure Requirements for Employees of the Department of Health and Human Services* (2005, § 45.5501) addressing extracurricular activities and interests of their staff.

Detecting and avoiding conflicts of interest by ensuring full disclosure is important for maintaining public trust. In the early development of research ethics reviews, committees were placed in the invidious situation of checking on the ethical integrity of commercial research relations. Research ethics committees were required to examine any business, budget, contractual or other relevant relationships between the researcher and any commercial organization to identify any conflicts with ethical standards (NHMRC 1999, chapters 12.5–12.6).

The NBAC preferred to adopt a governance approach that placed responsibility for checking and auditing potential conflicts of interest on the institution and researchers themselves. The NBAC used the euphemism '*managing* conflicts of interests' (emphasis added) in recommending that sponsors and institutions should 'develop policies and mechanisms to identify and manage all types of institutional, IRB and investigator conflicts of interest. In particular, all relevant conflicts of interest should be disclosed to participants (NBAC 2001a, recommendation 3.8). The

19 These regulations were described as 'punitive and draconian' (Dutton 2005).

proper disclosure of any potential conflict of interest is the established norm[20] and is reflected in international statements.[21]

17.3 Conclusion

In the same year that the Human Genome Project consortium and Celera Genomics made their joint announcement for successfully sequencing the human genome (2001a, 2001b), the NBAC presciently announced a time for change in the regulation and governance of research ethics to meet the demands of the new genome era (NBAC 2001a: prologue). The primary role of the ethics review system remains the protection of the welfare and interests of research participants. In line with this view, the NBAC noted that 'a comprehensive and effective oversight system is essential to uniformly protect the rights and welfare of participants, while permitting ethically and scientifically responsible research to proceed without undue delay' (2001a, recommendation 2.2).

The proper balance between the values of scientific freedom and dignity of the individual research participant remains the dominant theme of research ethics. This theme has seen a shift to informational and privacy concerns in genomic research. In addition, greater international collaborations in research efforts emphasise these issues and the need for change in the proper governance of international projects. In this respect, the research governance agenda has widened the focus of research ethics beyond ethics committees to include researchers and institutions in the entire research endeavour. This is a fundamental requirement in the increasingly globalised research environment and particularly in genomic research. The philosopher, Peter Singer (2003, cited in Kirby 2003) observed the '… science is barrelling forward, but the ethics aren't … I don't want the science to slow down. I want the ethics to catch up.'[22]

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20 These include the Canadian *Tri-Council Policy Statement, Ethical Conduct for Research Involving Humans* (1998), the American *Federal Policy for the Protection of Human Subjects* (45 CFR 46) and the National Bioethics Advisory Commission's *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance* (1999).

21 For example, the Human Genome Organization (HUGO) Ethical, Legal, and Social Issues Committee, *Statement on the Principled Conduct of Genetics Research* (1996), HUGO Ethics Committee's *Statement on DNA Sampling: Control and Access* (1998), HUGO Ethics Committee's *Statement on Benefit-Sharing* (2000) and HUGO Intellectual Property Committee's *Statement on Patenting of DNA Sequences in Particular Response to the European Biotechnology Directive* (2000).

22 Professor Singer was talking about nanotechnology research but this equally applies to genomics.

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