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DOCUMENTED  
BRIEFING

# Guiding Good Research

Biomedical Research Ethics and  
Ethics Review

Observatory on Health Research  
Systems

Miriam Shergold

The research described in this report was prepared as part of RAND Europe's Health Research System Observatory Documented Briefing series, funded by the English Department of Health.

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Published 2008 by the RAND Corporation  
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# Preface

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This document is a thematic report that provides an overview of ethics and ethical review in biomedical research. Its overarching theme and international scope complements other, country-specific briefings within RAND Europe's Health Research System Observatory, funded by the English Department of Health.

The purpose of the document is to brief non-specialists on the key aspects of the evolution, and current debate, of biomedical research ethics and the assessment of proposed research by ethics committees or review boards. Ethical approval is now an almost universal requirement in the research process, and various national and international fora have formulated appropriate ground rules. However, practical interpretation of basic ethical principles, as well as the stringency and design of the review process, vary significantly from one location to the next. On the basis of desk research and expert interviews, this briefing highlights principal areas of consensus and tension, and outlines different approaches to the formal ethical scrutiny of proposed research. Its scope is international, with an emphasis on research intensive nations. It does not aim to deliver an exhaustive discussion of ethical principles, or take position regarding current controversies.

The report is organised in two parts. The first part provides an introduction to the history of research ethics, as well as key documents and current debates. The second part presents key aspects of the ethics review process, and describes different models currently in use.

The report will be of interest to government officials dealing with biomedical research policy, medical research councils, biomedical research charities, institutions hosting biomedical research projects, researchers, and patients.

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# Summary

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## Summary: Key Points

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- The codification of universal principles for ethics in health research is a 20th century achievement that has not, however, eliminated malpractice or dispute.
- Ethics guidance emanates from a range of different sources, resulting in a 'normative polyphony'.
- Agreement on basic principles does not guarantee identical or even similar decisions on the ethical acceptability of a specific practical research endeavour.
- There are multiple models for the review process to safeguard ethical research, including choice and authority of the reviewers.
- Reviewing the ethical aspects of a research proposal is a demanding task, which researchers find burdensome and which has led to a range of streamlining efforts.

Even though consideration of the ethical aspects of biomedical research is no new phenomenon, its systematic integration into the research process has lagged behind the progress of medical discovery itself. While governments and professional bodies have taken measures to uphold standards and protect the public, cases of malpractice have made clear the need to formulate basic ground rules to be followed by all those involved in research.

By its nature, ethics guidance seeks universality and authority, yet the world has no single body that can claim to have the last word on ethics. Rather, regulations, recommendations, statements, and comments are issued by a wide range of fora within and across countries around the world. For researchers, guidance translated into national legislation has the greatest immediate relevance. Public debate on ethics is an important influence on such legislation, including the opinion of 'ordinary' citizens who some countries consult on a regular basis.

Although there is universal consensus regarding core principles, such as patient autonomy, the task of determining whether a given piece of proposed research is acceptable requires the practical interpretation of such principles. This interpretation is guided by other personal and cultural values and other contextual parameters that can lead to different outcomes. Some researchers have been disconcerted at the discovery that whereas ethical approval is key to the realisation of research projects, opinions on what is ethical may vary.

Ethics review is conducted according to a set process, and by a group of suitably qualified individuals. Given that the consideration of the ethics of a research project requires both

expert and lay views, most countries and institutions opt for a combination of scientists and non-scientists. However, there is no obvious method for mixing or appointing members, and as a result, no two models appear the same. Main differences exist in the ratio of non-specialists participating, as well as in the choice of experts, such as lawyers, psychologists, or statisticians.

Ethics review committees have to give careful and unbiased attention to each research proposal before them, but researchers are frustrated by what seem to be unduly bureaucratic and burdensome processes. In particular, the time-consuming multiple approval routes of national and international multicentre projects have been highlighted. As well as trying the patience of investigators, delays in approvals diminish the attractiveness of a given research institution to investors. Driven by the desire to combine sound ethical scrutiny with facilitated processes, different countries have devised new approval routes, such as the use of standardised forms and single review points. However, the debate on the optimum path to facilitation continues.

# Acknowledgments

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The author is grateful for the interest and assistance of all those who contributed to this briefing. In particular, I would like to acknowledge the valuable input provided by the following individuals:

Dr Michael Fuchs, Institut für Wissenschaft und Ethik, Bonn, Germany;

Dr Bruce A Scoggins, Bruce A Scoggins and Associates Ltd, Auckland, New Zealand.

Within RAND Europe, thanks for ongoing thoughts and feedback is due to Observatory team members Edward Nason, Amanda Scoggins, Tom Ling, and Jan Tiessen. The briefing has furthermore benefited from the comments of Quality Assurance reviewers Jonathan Grant and Charlene Rohr.



# Introduction

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## Guiding Good Research

### A Documented Briefing on Biomedical Research Ethics and Ethics Review

Miriam Shergold

July 2007

Hippocrates famously required physicians to vow to “help the sick according to their ability and judgment and to refrain from harm and injustice.” The Oath, still widely in use today, aims to ensure that patients are cared for in the best possible way, but also to protect the patient from the professional’s power. Modern medical research has improved professionals’ ability to give help. However, the application of abstract ethical principles to this research increases the challenge of finding indisputable answers.

As our knowledge expands and our world shrinks, new questions arise about what to do when, in the search for more effective treatments, risks and benefits are hard to foresee and to balance, the implications of research activities need to be considered on a global scale, and new advances shake up core notions, such as life itself. In response, various institutional mechanisms have been developed to enable decision-making through ethical examination of the issues under debate.

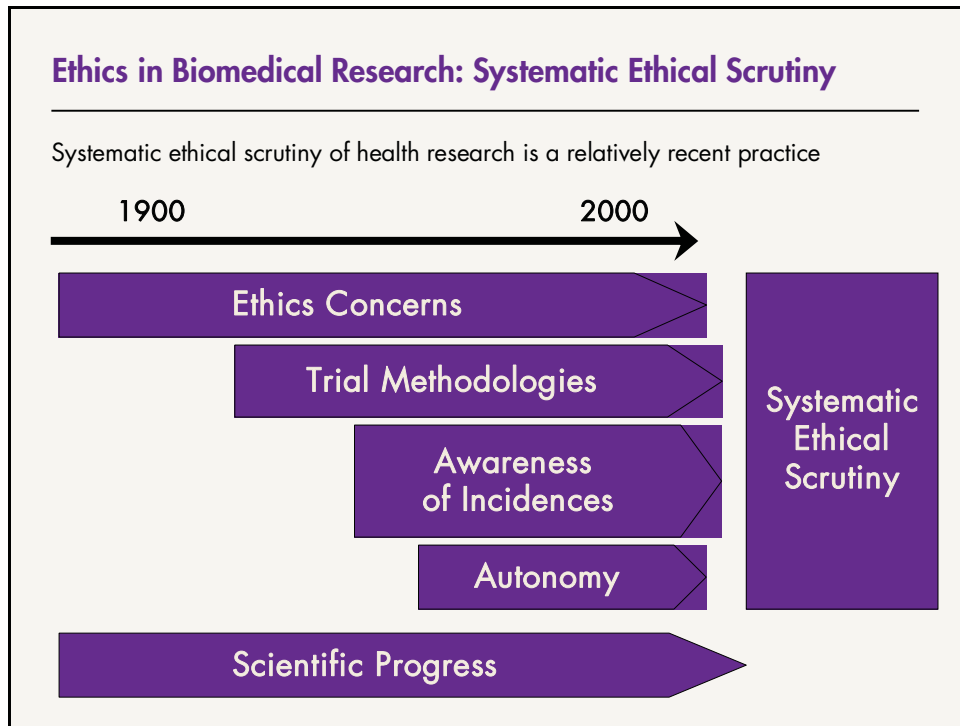
Ethics is the branch of philosophy that studies moral issues, aims to determine what is right or wrong, and evaluates human conduct accordingly. The terms ‘ethics’ and ‘morals’ are often used interchangeably, although various distinctions have been proposed. Ethical evaluations represent one form of value judgment, alongside other kinds of value judgments such as, for example, aesthetic or prudential judgments.

This briefing is concerned with the practical application of ethical principles to allow or forbid the conduct of biomedical research involving humans, that is, research to improve human health, cure diseases, and elucidate the functioning of the human body. The first

part focuses on the origins and development of ethical principles in research. The second part provides an overview of key issues in the practice of ethics reviews across different parts of the world.

# Ethics in Biomedical Research

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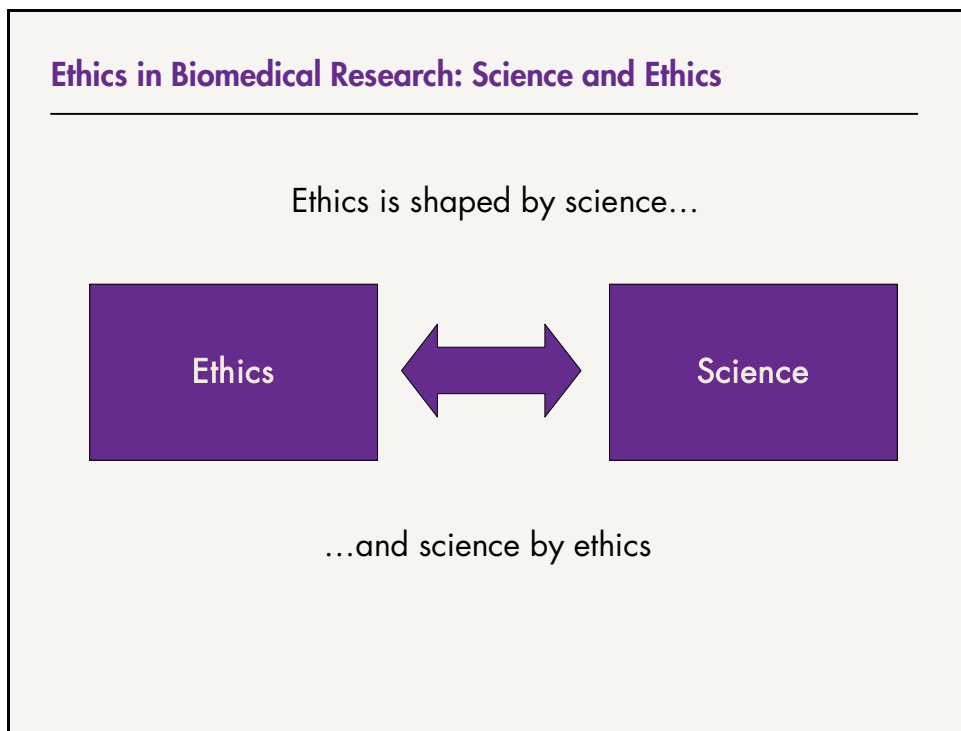
Throughout history, there has been some concern about the ethics of health care and health research, as evidenced by early codes of conduct for professionals, or oversight of drug sales (Moulin, 1998, p. 24). However, the prominence of such concerns has waxed and waned along with that of other, and sometimes competing, values. For example, in Western medicine, the ascendancy of science in the 18th century Enlightenment period led to the celebration of the freedom of the individual researcher from controlling outside influences. Against this background, ethics tended to be seen as a matter of personal judgment. However, by the late 19th century, the idea of adherence to intraprofessionally determined rules of conduct had grown more prominent (Waddington, 1975, p. 37).

The 20th century shift from self-regulation to externally codified requirements began to manifest itself through tighter state control of medical products, as exemplified by the United Kingdom's Therapeutic Substances Act and Therapeutic Trials Committee in the 1920s and 1930s. Although primarily concerned with the safety of substances for the general public, the development of formal protocols for drug trials began to bring the role of patients in experiments into sharper focus (Fuchs et al., 2005, p. 11). However, the shock of discovering harmful experiments on humans in Nazi concentration camps made clear the need to lay down fundamental and universally binding rules for the protection of patients in medical experimentation, subsequently published as the Nuremberg Code (1947).

The first principle of the Code established the necessity of free and informed consent on the part of trial participants. Although prompted by cases of extreme abuse, the concept of patient autonomy also challenged wider and deep-seated structures of medical paternalism. Over the subsequent decades, Western societies' growing emphasis on the individuals' right to self-determination, privacy, and confidentiality further promoted the principle of autonomy, and the debate on the nature of informed consent itself (Emanuel et al., 2004).

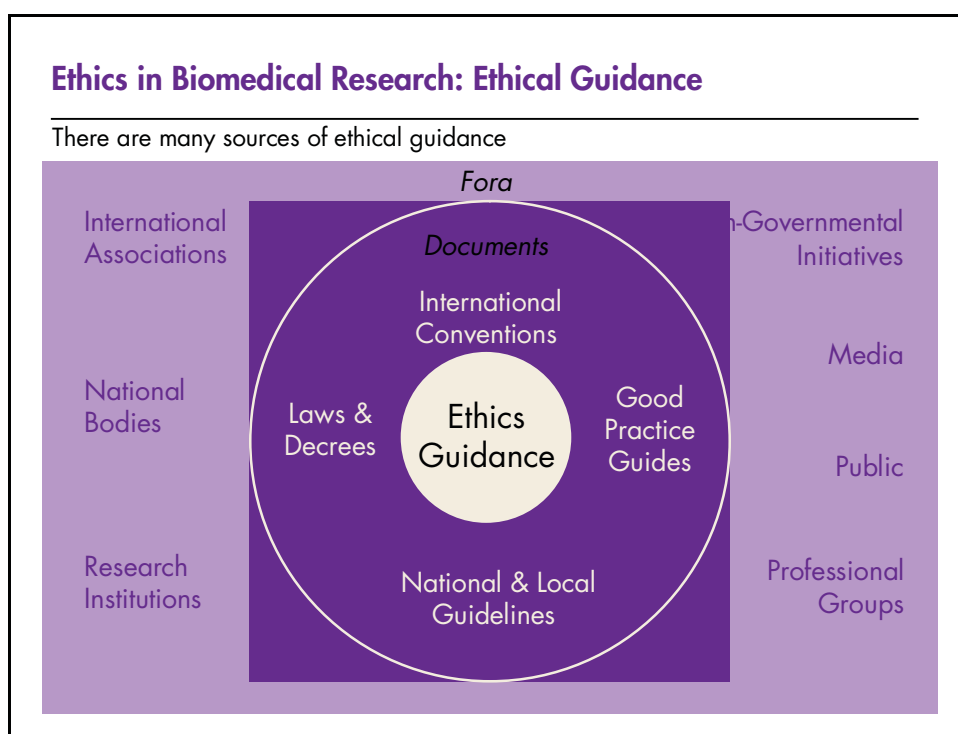
However important in itself, this first international Code did not eliminate unethical research at a stroke, partly because most professionals found it difficult to see a connection between abuses in concentration camps and their own work (Rothman, 1998). Rather, evidence of malpractice across different decades and different countries continues to demonstrate the need for close scrutiny of the conduct of health research. Prominent cases of research that violate key ethical principles include the following: the Tuskegee experiments, in which treatment was deliberately withheld from a group of syphilis sufferers in the United States; the marketing of the poorly investigated drug thalidomide; and, more recently, the unauthorised use of stored human tissues at Alder Hey Children's Hospital in the United Kingdom.

The perennial need for the ethical scrutiny of research, as well as scientific advances, has influenced the further elaboration of guidelines, exemplified by the successive versions of the World Medical Association's international code on research ethics, the Declaration of Helsinki (1964). With particular relevance to this briefing, the 1975 amendment of the Declaration required the submission of clinical trial protocols to an independent commission, and the regular use of ethics reviews.



Today, ethics is part of most health research systems. However, ethics and medicine do not necessarily evolve in synchrony. In certain cases, such as organ transplantation, ethical deliberations have needed to catch up with scientific feasibility. In other fields, such as assisted reproductive technology, fundamental rules and limits have been established before certain interventions could be attempted. Mechanisms for scrutiny have become increasingly thorough and, as a result, laborious. At the same time, there is political will to minimise obstacles to scientific innovation as a path to health and wealth in any particular country. For example, some critics have warned that the European Union (EU) Directive on Clinical Trials' streamlining of processes may encourage the prioritisation of economic interests over the interests of trial participants, and certain ethics committees in Africa have been condemned for giving approvals to attract investment (Kass et al., 2007).

Thus ethics is bound to remain a fertile field of debate. On the one hand, new questions will arise from medical research; on the other, old questions of balancing risks, benefits, and rivaling principles will continue to pose puzzles to professionals and the wider public alike.



Research ethics concerns everybody: patients, researchers, policy makers, investors, and members of the general public. It is relevant at different organisational levels, from the international stage down to the individual institution that is hosting the research, or the individual household. The objectives of discussions held at these different levels may vary: for example, an international association may be seeking consensus, and an individual patient may be pondering whether to participate in research. However, there are significant overlaps regarding the basic principles and processes for decision-making.

The parallel existence of various bodies concerned with ethics represents different perspectives, interests, and heritage. In many countries, professional groups were the first to instigate codes of practice. More recently, national ethics councils have been created, either by law, like the pioneering Comité Consultatif National d’Ethique pour les Sciences de la Vie et de la Santé in France in 1983, or through private initiative, such as the UK Nuffield Council in 1991 (Fuchs, 2005).

None of these entities can claim a direct mandate by the electorate, and none can claim precedence. They have different claims to authority, expertise, and representation, and they have different strengths and weaknesses:

- International bodies such as the World Health Organization or the World Medical Association, although elite groups, have the strongest claim to representing a single international voice and laying down agreed ground rules;
- National ethics councils serve as a differentiated and independent source of advice to legislators;
- Research institutions take a direct interest in the conduct of local research;

- Professional groups' self-regulation reflects first-hand knowledge of research;
- Non-governmental initiatives vocalise concerns in specialist areas; the media stimulate public debate and publicise incidences of malpractice; and
- The public offers the widest base of ethical opinion finding.

However, all these fora have specific weaknesses in terms of effectiveness, accountability, and objectivity (European Observatory on Health Care Systems, 2002).

### Key International Guidance on Ethics in Research

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- ***Declaration of Helsinki***  
by the World Medical Association
- ***International Guidelines on Biomedical Research Involving Human Subjects***  
by the Council for International Organizations of Medical Sciences
- ***Operational Guidelines for Ethics Committees that Review Biomedical Research***  
by the World Health Organization
- ***Statement on the Principled Conduct of Genetics Research***  
by the Human Genome Organisation

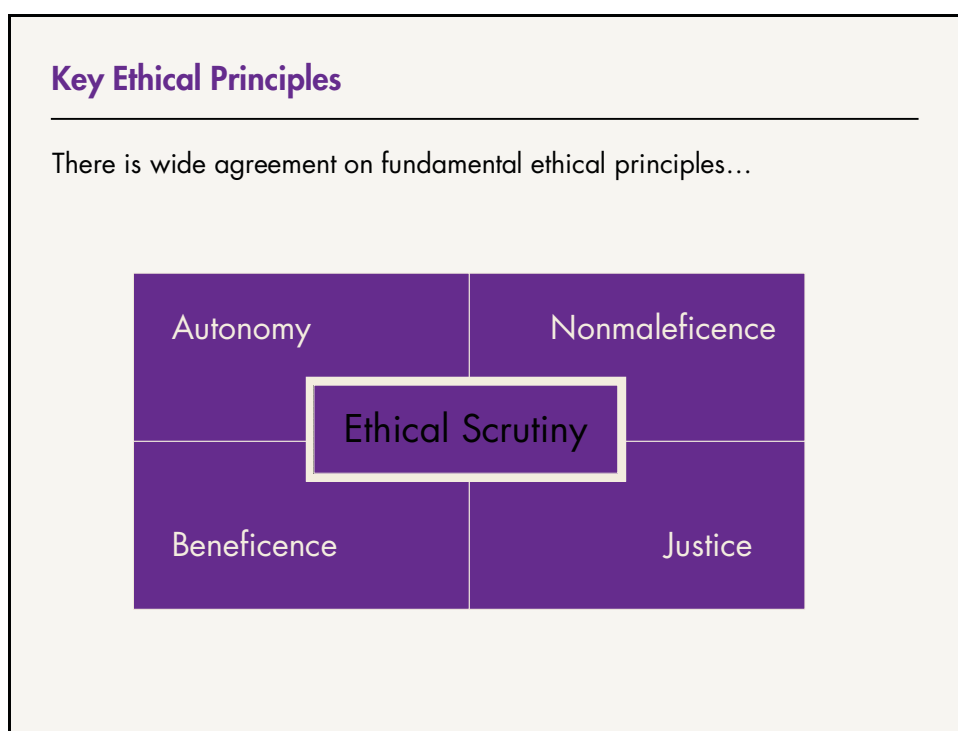
The activities of the different fora have resulted in a range of guidance documents, some of which, as shown above, focus on specific geographical spheres, audiences, and scientific fields. These documents command different degrees of legal authority, ranging from the expression of principles in Declarations, to Conventions that bind the signatories under international law and require them to translate the agreement into national law.

Laws at national level are issued as a result of international or multinational commitments, or internal political decisions. Examples of such national laws can be found across the world, for example in India, Thailand, Uganda, and Australia, or the EU state's adaptations of the EU Directive on Clinical Trials. The scope of activities governed by national level laws can vary. For example, the U.S. Federal Policy for the Protection of Human Subjects, or Common Rule, concerns the specific area of federally funded research (Emanuel et al., 2004). In China, regulations issued in 2003 required all hospitals undertaking clinical trials to set up institutional review boards, but preclinical research on cells from living humans was not covered (Döring, 2003).<sup>2</sup> Internationally, there is substantial variation in the definition of research involving humans, such as the categorisation of psychological studies. In addition to overarching legal instruments, professionals are often required to observe guidelines drawn up by their institution, as well as recommendations generated by good practice initiatives at the international, national, or intraprofessional level.

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<sup>2</sup> Jia, H., "China to Release Tougher Rules for Research Ethics," Science and Development Network, 16 August 2006, <http://www.scidev.net/News/index.cfm?fuseaction=readnews&itemid=3045&language=1> (as of April 16, 2007).

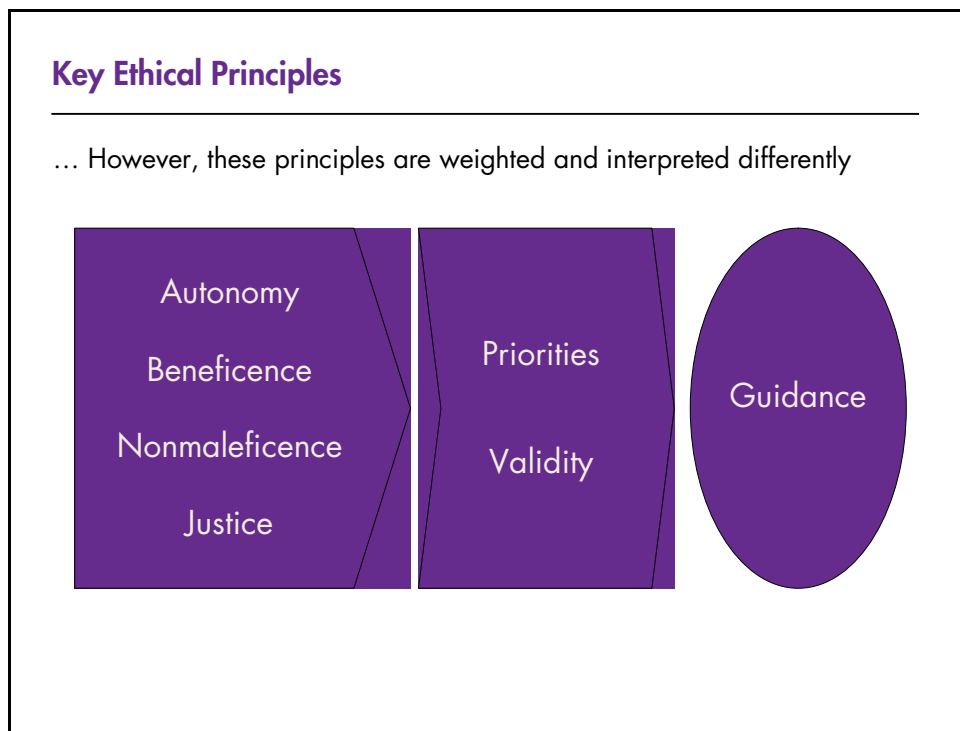
The result of this overlapping guidance has been termed a ‘normative polyphony’ (Fuchs et al., 2005, p. 19). Clearly, some guidance is more influential than others, such as national legal frameworks and the international consensus expressed by the World Health Organization and Council for International Organizations of Medical Sciences guidelines. However, the many-voiced chorus of rules and recommendations highlights both the relevance of ethical decision-making to different groups, and the complexity of ensuring ethically sound research.



All of the ethics guidance described, however diverse in form and content, has at its core the aim to protect humans in the context of research, and to safeguard the quality of that research. In a more differentiated perspective, four key clusters of principles (Beauchamps and Childress, 1994) commonly form the cornerstones of ethical scrutiny:

- **Autonomy** recognises the individual's right to make their own choices free from coercion or undue outside influence. In the context of biomedical research, this means that the free, informed consent of the patient, or the patient's lawful representative, is a precondition for involving the patient. The principle implies protection of vulnerable groups, such as children or prisoners.
- **Nonmaleficence** serves to protect the patient by requiring that, all other things being equal, the proposed research does not harm the patient's health or interests.
- **Beneficence** guards the patients' interests by requiring that, all other things being equal, the proposed research benefits the patient.
- **Justice** demands the fair and equitable distribution of goods and services to patients with the same medical needs.

Due to their abstract and universal nature, these principles lend themselves to a basic consensus on ethics. However, their practical interpretation reveals great potential for conflict and diverging interpretation.



The challenge of applying abstract rules to practical situations is recognised beyond the field of ethics. In the case of the four basic ethical principles, decision-makers may face conflicts that require certain criteria to be weighted more heavily than others. For example, it can be difficult to reconcile the principle of autonomy with that of justice: vulnerable groups, such as children or intensive-care patients, may not be able to give free informed consent, but have nevertheless the same rights as other patients to have their health needs addressed by research. Some guidelines explicitly acknowledge this fact: the UK Research Governance Framework states that the assessment of risk may require judgment and interpretation. Room for flexibility, a “framework for action rather than prescriptive protocols,” has been highlighted as an important element of good governance structure (Shaw and Barrett, 2006; Slowther, Boynton, and Shaw, 2006). At the same time, flexibility in interpretation also harbours the potential for conflict.


Ethical judgments in research reference universal principles, but are firmly grounded in the context of time, place, and beliefs. Concerns have been voiced that in the current practice of ethical scrutiny, there is a bias towards the principles of autonomy and nonmaleficence, with the overall priority of protecting the research subject from harm. As such, biomedical research is examined first as a potential threat to patients (Goodyear-Smith et al., 2002). As a result of this perception, some scientists have demanded that patients should be better informed about the scientific cost of opting out of research, and that ethics committees should allow for more risk-assessment competence in participants, even by the inclusion of certain vulnerable groups (Hewison and Haines, 2006; Edwards, Kirchin, and Huxtable, 2004; Terry et al., 2006). Cultural context also seems to determine how principles are weighted, with countries that have a tradition of communalism placing a comparably greater value on the potential common good (Gross, 1999).

Competing priorities are not the only cause of variety in guidance documents. They have differing validity in terms of definitions, type of research, and disciplines covered. Capturing the meaning of basic concepts is the first challenge. To regulate research on humans, there must be a clear and shared understanding of what constitutes human life, as well as what is meant by research. Across the world, and between guidelines, the research covered varies substantially, as exemplified by the treatment of studies based on questionnaires and interviews. Some countries, like France, take an encompassing view covering all research involving humans. Others, like the Czech Republic, Estonia, Hungary, and Poland have no such overall rule, but specifically include questionnaires and interviews (Coker and McKee, 2001). A third group of guidance documents, like the U.S. Common Rule, only regard research funded by state agencies, or, like the European Directive on Clinical trials, focus exclusively on clinical trials (Fuchs et al., 2005, p. 14). Some of these differences are historical, or are due to the parallel existence of several complementary pieces of guidance; in other cases, however, gaps remain. For example, in the United States, there is no federal regulation on further research into approved drugs or surgical interventions not testing a device (Lenrow and Chou, 2002). Further questions have been posed by the often blurred boundaries between biomedical research and clinical practice audits (Saunders, 2004; Glasziou and Chalmers, 2004).


In addition to differences in scope, there remain grey areas, and points of dispute. This is exemplified by debates surrounding the World Medical Association's initiative to clarify and update the Declaration of Helsinki for the new millennium. Different positions have been taken regarding the question of whether it is acceptable to neglect the principle of giving research participants the absolute best standard of care in favour of validating inferior, yet locally implementable, treatments in developing countries (Schuklenk, 2004).

## Ethics in Biomedical Research: Ethical Acceptability


Controversial and new research areas show the difficulty of defining ethical acceptability




**ABC Western Australia**  
Hollywood loves an evil scientist madly cloning humans  
Tuesday, 24 October 2006




**BBC NEWS WORLD EDITION**  
Nanotech may spark fierce ethical row  
A mini-sub cruises an artery (Image: Science Photo Library)




**LE FIGARO · fr**  
La révision de la loi de bioéthique en débat  
Les premières rencontres parlementaires destinées à réfléchir à la révision de la loi du 6 août 2004 ont eu lieu hier.



**SciDev Net**  
Science and Development Network  
China cracks down on malpractice in fertility industry  
Heping Jia  
10 April 2006  
Source: SciDev.Net  
[BEIJING] China has tightened its rules on how researchers and clinicians can use reproductive technologies such as in-vitro fertilisation.  
The new rules, issued by the health ministry on Friday (7 April), are intended to eliminate unethical practices.  
Only 64 approved Chinese institutes are no



**ZDFheute.de**  
magazin  
Gericht stärkt Schutz menschlicher Embryonen  
Umstrittenes Stammzellen-Patent teilweise aufgehoben  
Das Bundespatentgericht in München hat den Schutz menschlicher Embryonen gestärkt. Der 3. Senat des Gerichts erklärte am Dienstag ein Patent von 1999 zur Tiefgefrorene Probe m

**Each stored embryo is a stem cell debate** 

With every day that passes in the world's laboratories and studies, we are brought closer to new avenues of biomedical intervention. Some of these prospects reopen the question of where to draw the line between what is possible, and what is possible and acceptable. Individual positions taken can reflect cultural values, religious attitudes, or past experiences, such as Germany's past experiences of misconduct in medical experiments. In many research-intensive countries, the debate of such questions has been institutionalised in the form of ethics councils (Fuchs, 2005). Although their status and relationship with the legislation varies, these bodies serve to provide independent and reasoned advice to their country's government in drawing up legislation on ethical research.

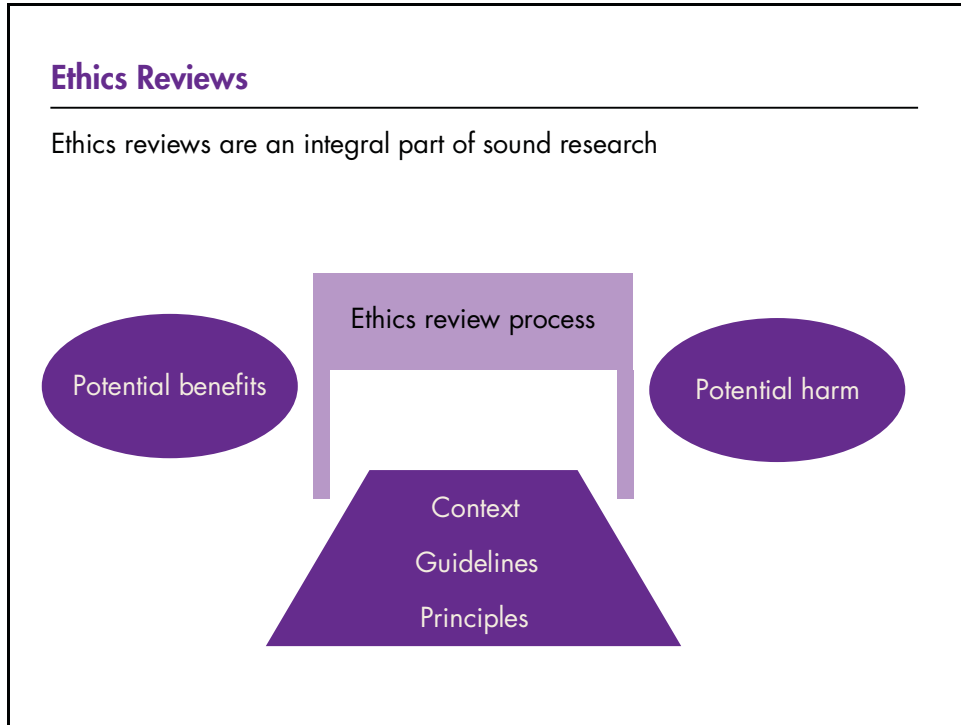
In recent years, such controversy has concentrated in particular on the boundaries of acceptability of research that uses stem cells and reproductive technologies. Much of this debate has hinged on different definitions and interpretations of human life, along with its associated rights and dignity. It has also exemplified the difficulty of weighing up such concerns against the potential development of treatment for a range of serious conditions. Other debates concern the legal and economic implications of research, such as rules for patents in biotechnology, and the boundaries between invention and discovery in this area. As it becomes increasingly possible to store and exchange individual health data, limitations to the use of such information, too, is being discussed.

Some new questions are on the horizon. These include the boundaries of performing modifications to human brains, and more generally, the permissibility of human enhancement, ranging from interventions in adults to germline engineering to create 'designer babies'.



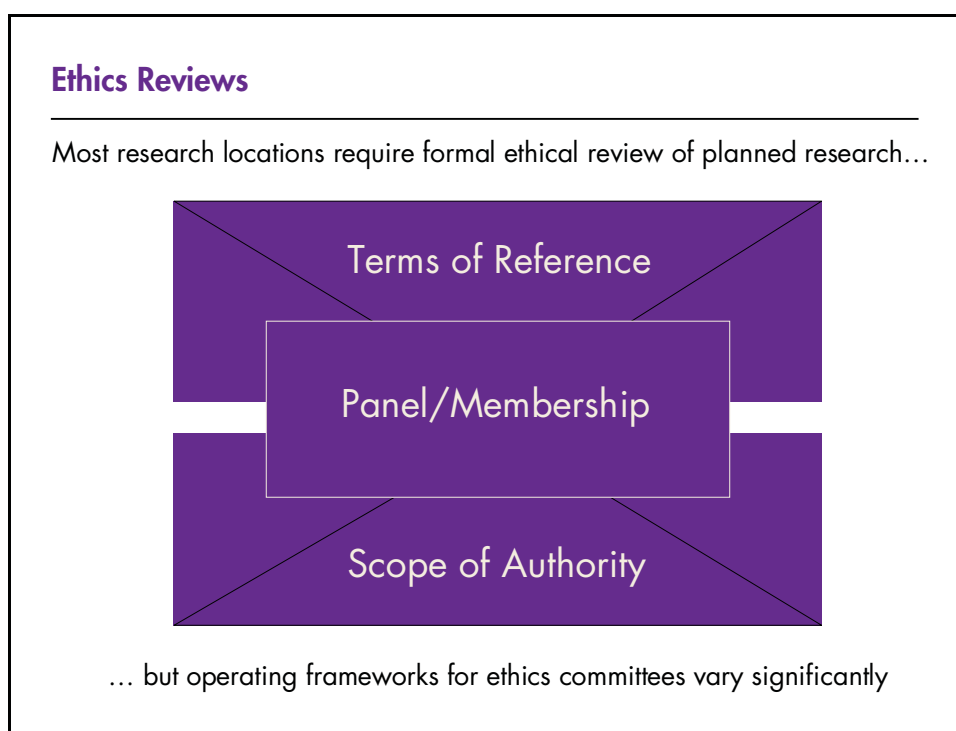
# Ethics Reviews

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It is against the background of multiple guidelines, gaps, uncertainties, newly emerging questions, and unsolvable conflicts of the ground rules that researchers prepare research proposals, and ethics committees examine them. In established systems of ethical scrutiny, this process is demanding for all involved, and often frustrates researchers. However, in some less established systems, uncritical approval practices call for more rigorous analysis and better training of committee members.

To borrow the famous adage attributed to Einstein, the ethical review of proposed research should be as simple as possible, but not simpler. Across the world, different systems have been designed to meet this challenge. The manifold differences between systems along this spectrum are outlined in the second part of this briefing.



Most biomedical research is now required to undergo ethical review, either through national laws or as a condition of funders, host institutions, research partners, or publishers. As with basic ethical principles, across the world there is strong consensus on the essential functions and functioning of ethics committees. According to this consensus, biomedical research involving humans should only be allowed to proceed if its compliance with ethical standards has been verified by a suitably qualified group of individuals. Broadly, this requires the following steps:

- The principal investigator and his team submit a detailed research protocol and related documents, including information for research subjects, which is examined and discussed by a knowledgeable panel.
- This panel approves the project or requires modifications and re-submittal, unless the project is rejected outright.

In some research-intensive countries, such scrutiny has been practised for many decades. In other regions, ethics committees have only emerged in recent years. For example, several African countries, such as Kenya and the Democratic Republic of Congo, have established such bodies in the past five years (Kass et al., 2007).

However, this commonality needs to be qualified by certain other facts. The belief that the ethical dimension of research must be examined furnishes no obvious guidance as to who is best placed to judge such issues, and how. Accordingly, a range of ethics committee models has emerged. Every configuration has its own strengths and weaknesses: for example, the local level is good at accountability, but weak on coordination, whereas self-regulators are strong on specialist knowledge, but weak on accountability (European Observatory on Health Care Systems, 2002). There are disparities between the principles and practice of

ethics review, and further complications if committees are not sufficiently resourced, trained, or objective.

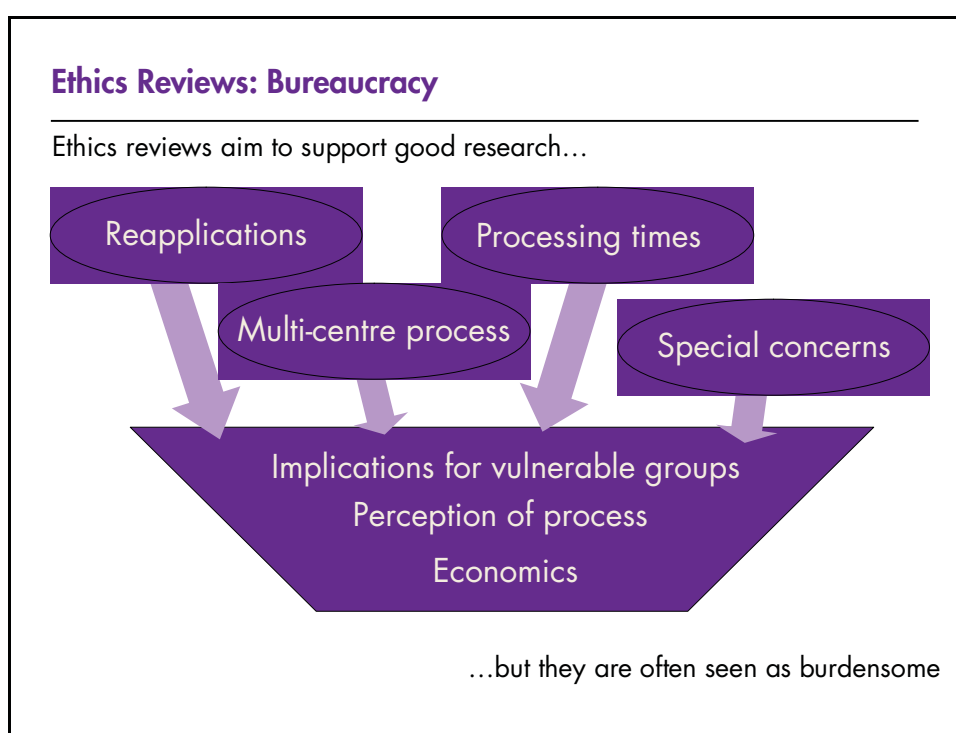
As with guidance documents, the scope and impact of committee authority can vary substantially. Not only do committees cover different areas (e.g. as a regional, institution-based, or multicentre committee), but their responsibilities vary. An interesting point of diverging aspiration and practice is the continued tracking of research activity once approved. This has repeatedly been described as a desideratum or even a requirement: in the words of the EU Directive on Good Clinical Practice, “a clinical trial may be initiated only if the Ethics Committee [...] comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored” (European Parliament and Council of the European Union, 2001). The monitoring of responsibility also featured in a new section to Australia’s ‘Processes for research governance and ethical review’, and is part of the official activities of ethics committees in Albania, Bulgaria, Croatia, Estonia, and Hungary (Anderson, Cordner, and Breen, 2006; Coker and McKee, 2001). However, practice in much of Europe and the United States shows that close and regular scrutiny of ongoing research, for example through site visits, goes beyond the resources of already burdened panels.



Diverse answers have also been found regarding the question of who should make up an ethics committee. To examine the acceptability of a research project, committee members must, on the one hand, be able to understand the scientific value of the research. On the other hand, they need to be able to assess whether a member of the general public would be able to make an informed decision on participating in the planned work (Lenrow and Chou, 2002). With very few exceptions, such as in Albania where ethics committees are comprised entirely of scientists, panels are therefore made up of a combination of health professionals and laypersons. The ratio of the two groups ranges from an equal balance in New Zealand and the Netherlands, to a minimum of one outsider in Institutional Review Boards in the United States (Scott, 2004; Lenrow and Chou, 2002).

Most ethics committee guidelines also require certain experts to be represented. Of these, theologians, bioethicists, and lawyers are most common, but the range of relevant professions is wide and can also include nurses, patient representatives, statisticians, economists, or psychologists (Fuchs et al., 2005; Gillam, 2004). Depending on a country's heritage, certain population groups are also represented. For example, ethics committees in New Zealand include two Maori members. Appointment processes vary: in most cases, members are invited or appointed, either at committee level or by an external authority (Scott, 2004). Committee members thus do not generally have a direct democratic mandate. Given the influence of committees, this lack of publicly assured legitimacy has been challenged. However, it has also been pointed out that the independence of members from any obligations toward a voting public is highly valuable (Edwards, Kirchin, and Huxtable, 2004; McNeill, 1993). By the same token, the objectivity of 'insider' panel members who belong to the institution hosting a proposed study, as is common in the

United States and Canada, has been called into question (Emanuel et al., 2004; Downie, 2006).



Although it is widely acknowledged that ethics reviews should be as thorough as necessary to appreciate the implications of each piece of planned research, a vocal group of scientists in research-intensive countries believe that reviews have become overly time and labour intensive. One investigator in the United Kingdom, for example, summarised his experience of a trial based at 51 centres as requiring over 25,000 pieces of paper and 62 hours of photocopying (Al Shahi and Warlow, 1999). Many other researchers have also voiced their frustration on the issue of the bureaucracy of ethics reviews, to the point of suggesting that the system has degenerated into a self-sustaining ‘machinery’ with a vested interest in complications (Gilman and Garcia, 2004).

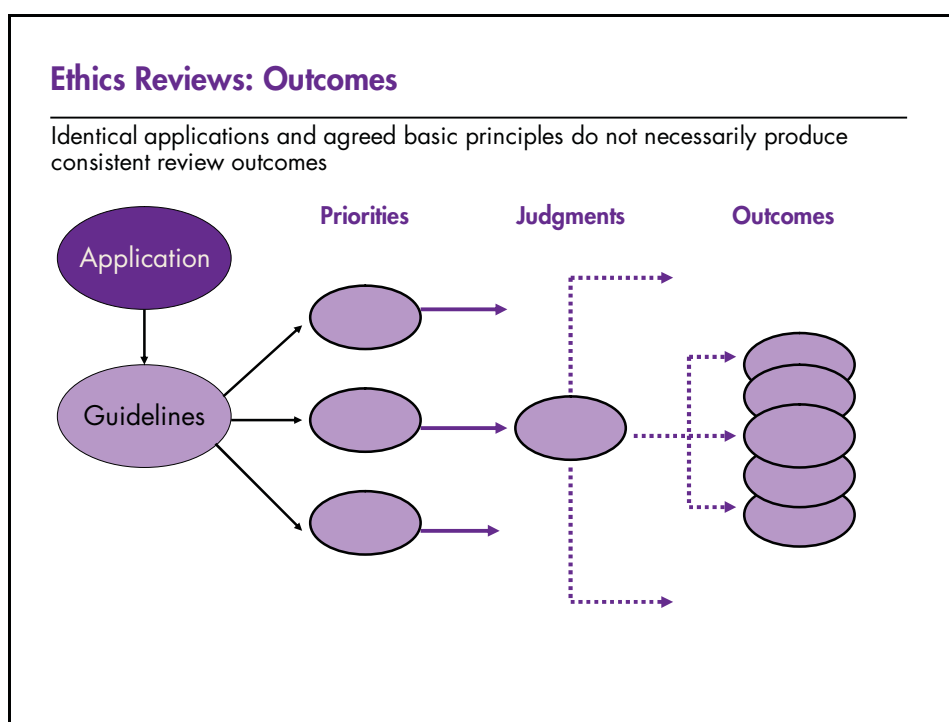
Multicentre studies are a particular target for criticism because the involvement of the various local committees involved necessarily multiplies the administrative requirements. This is all the more relevant if research centres use different documentation and application protocols, and if the study is being carried out in various national settings. As one leader of a multicentre study in the developing world describes, “even the most benign study must navigate a maze of committees, setting the research process back months and even years. For example, a simple village survey study over a 5-year period could require 40 separate IRB [i.e. Institutional Review Board] approvals (or renewals)” (Gilman and Garcia, 2004; Glasziou and Chalmers, 2004). A recent comparison of the outcomes of multicentre-study applications has also highlighted the time-consuming nature of ethics reviews as a universal problem (Edwards, Stone, and Swift, 2007).

The combination of burgeoning research activity, detailed multiple examination requirements, and the often limited time available to ethics committees can lead to delays in the processing of applications. This too can frustrate researchers, especially when there are implications for health treatments. For example, delayed recruitment of patients to the

Second International Study of Infarct Survival (ISIS-2) in the United States has been directly linked to 10,000 unnecessary premature deaths (Shaw and Barrett, 2006; Collins, Doll, and Peto, 1992). A further point of conflict between researchers' desire to minimise delays and interruptions, and the need for regular ethical approval, is the issue of modifications to the proposed study protocol after the submission of the original application. The need for such modifications to optimise the study outcomes may arise as the protocol is put into practice; however, the formal requirements for resubmission can be prohibitive (Fuchs et al., 2005, p. 25).

Apart from upsetting the researchers' morale and research progress, the bureaucratic aspects of ethical approval have economic implications, because lengthy or complicated processes deter research partners and investors. This deterrence was observed in Austria after cumbersome requirements were introduced in the 1980s, and has also featured as a concern in the United Kingdom (Fuchs et al., 2005; Hearnshaw, 2004). Indeed, the attraction of investment is the very motive attributed to ethics committees that carry out less than thorough reviews. Hence, finding an appropriate balance between conscientious examination and a streamlined and speedy process is one of the key challenges of ethics review practice.

An additional challenge is the treatment of proposed research that involves individuals who are disadvantaged in giving free informed consent, such as children, prisoners, people in the developing world, or intensive-care patients. Given the difficulty of safeguarding the autonomy principle in such cases, committees tend to be especially wary of possible harm done by involving these groups in research. This can lead researchers to feel unjustly demonised for what they perceive as a beneficial undertaking; one researcher involved in studies in the developing world summarised this as "a basic presumption of guilt" (Gilman and Garcia, 2004). It has also been pointed out that well-intended safeguards for vulnerable research subjects can indirectly discriminate against these groups, because their specific medical problems, such as prisoners' exposure to tuberculosis in Peru, are less likely to be investigated (Gilman and Garcia, 2004). A group of prisoners in the United States has even contended that their exclusion from trials under the regulations of the Food and Drug Agency violated their right to serve as research subjects (Edwards, Kirchin, and Huxtable, 2004).



There is ample, if anecdotal, evidence for variation in ethics committee decisions, both within countries and internationally. These experiences have shown that, within a multicentre study, the same proposal may on occasion meet with the unreserved approval of one panel, request for modifications by another, and rejection by a third.<sup>3</sup> For example, of 24 applications in a British multicentre study done in the mid-1990s, 14 were given unconditional approval, and three were rejected (Redshaw, Harris, and Baum, 1996).

Variation in outcomes can be due to differences in national regulations and local application criteria, such as the definition of research that requires committee scrutiny. For example, a recent study on childhood sexual abuse that used questionnaires needed no approval in Israel, but met with many restrictions in New Zealand (Goodyear-Smith et al., 2002). Similarly, cultural factors play a role. As has been claimed for the Pacific Island and Asian nations, as well as Israel (Gross, 1999; Goodyear-Smith et al., 2002), emphasis has traditionally been placed on the welfare of the community rather than on the individual.

At the case level, outcomes pivot on panel members' ability to weigh up possible harm and potential benefits. This is likely to lead to differing judgments, as risk evaluations have been shown to be socially determined and context dependent rather than universal or objective (Kimmelman, 2004). Assessment of the potential harm or good to be expected from research is all the more difficult in the case of novel methods, such as gene transfer, for which the implications cannot be reliably predicted (Shaw and Barrett, 2006).

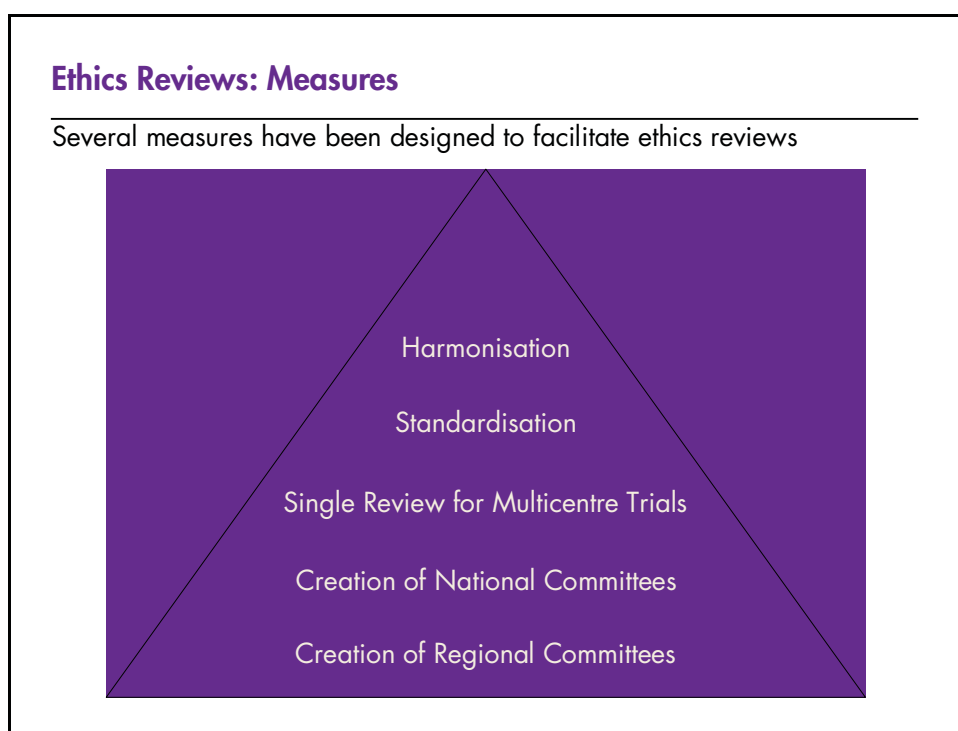
<sup>3</sup> Variations reported by researchers were recently discussed by Edwards, Stone, and Swift (2007). Recent publications include the following: Silverman and Hull (2001); Stair et al. (2001); Hirshon et al. (2002); McWilliams et al. (2003); While (1996); Tully et al. (2000); Dal-Re, Espada, and Ortega (1999); Goodyear-Smith et al. (2002); Glasziou and Chalmers (2004); Hearnshaw (2004).

For scientists used to the desideratum of repeatability in experiments, diverse outcomes can be difficult to accept. As one UK researcher reasoned, “if all countries are meeting the principles of the Declaration of Helsinki, then the striking variations mean that we are too careful in some countries and too lax in others” (Hearnshaw, 2004). However, provided that due processes and objectivity are observed, such inconsistency is not universally perceived as problematic. Rather, it has been pointed out that because ethics committees do not have access to a single moral truth, differing judgments are acceptable and even desirable (Edwards, Ashcroft, and Kirchin, 2004; Edwards, Stone, and Swift, 2007).

The granting or withholding of ethical approval decides whether a given research project can be realised, at least within the relevant ethics committee’s sphere of influence. Ethics committees thus have power. However, committees’ internal processes of decision-making have been likened to a ‘black box’, and the soundness of judgments has been questioned in Australia, the United Kingdom, and the United States (Anderson, Cordner, and Breen, 2006; Lenrow and Chou, 2002; Grob, 1996; Emanuel et al., 2004; Advisory Committee on Human Radiation Experiments, 1996; Kass, Dawson, and Loyo-Berrios, 2003). Indeed, there is a scarcity of systematic evaluations of ethical reviews in any country. Nevertheless, this area is recognised as important. In Ireland, one of the working groups of the national ethics council, the Irish Council for Bioethics, is dedicated to examining the workings of ethics committees, and the Health Research Council of New Zealand is currently undertaking an expert-based study of ethics committees in other countries with the aim of drawing out good practice.<sup>4</sup>

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<sup>4</sup> Oral communication: Bruce Scoggins (Bruce A. Scoggins and Associates Ltd, Auckland, New Zealand), 17 January 2007.



Depending on local or national context, different steps have been taken to ensure that proposed research is reviewed more reliably, and with as little disruption as possible. In less research-intensive regions, the creation of (more) ethics committees has been a fundamental step, even if the effectiveness of some of these committees can be further improved on (Kass et al., 2007; Williams, 2006).

Within established review practice, several national systems, including New Zealand and the United Kingdom, have tackled the particular burden of multiple applications and multiple outcomes for multicentre studies by focusing the process on a single committee; this system has also been called for in the United States (Scott, 2005, p. 2; Emanuel et al., 2004). There are different ways of accomplishing this, either by choosing the principal investigator's local committee, or by referring the application to a national level body. However, time savings have not always been as significant as hoped: for example, in the experience of one UK researcher, the continued reference to local committees still required several thousand pages to be produced and copied by researchers (Glasziou and Chalmers, 2004; Tully et al., 2000). National level committees are in place in many European countries, and the system has been piloted in the United States. However, critics are concerned that such bodies may have too little flexibility and specialist knowledge. In addition, the question arises as to what appeal institution is available for national body decision, which was pointed out as a flaw in the U.S. pilot (Emanuel et al., 2004; Downie, 2006).

Efforts have been made in several countries to standardise application documents and processes. Standard forms are in use in the United Kingdom and Austria. Austria also operates a forum for committees to discuss further harmonisation (Fuchs et al., 2005, p. 18). However, standardisation is not universally seen as a path to improvement, as

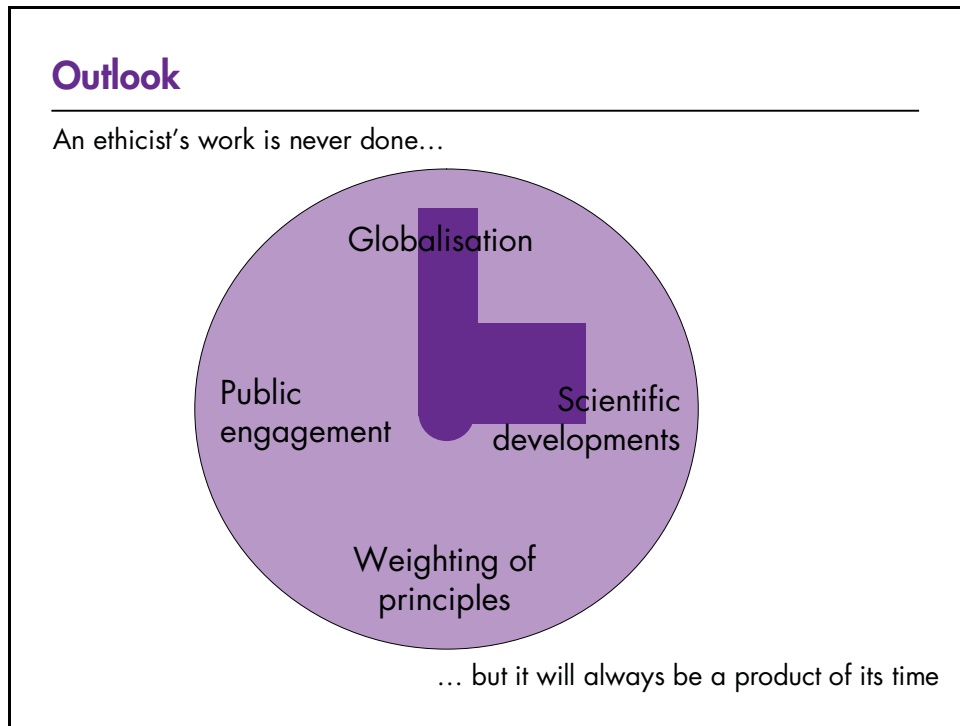
exemplified by protests against the 'one-size-fits-all' approach to ethics review by Australian health research ethics committees (Anderson, Cordner, and Breen, 2006). Since May 2003, independent ethics committees have had a statutory role under EU legislation on drugs trials, whereas plans for a European-level body were abandoned in favour of a culture of pluralism (McLaren and Hermerén, 2000). Internationally, harmonisation initiatives have been driven by the desire to make multinational studies easier to do, leading to an increasing adoption of the code of practice of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Subjects as the international standard for clinical drug trials involving human subjects (Fuchs et al., 2005; Hirtle, Lemmens, Sprumont, 2000).

Novel proposals for the facilitation of ethics reviews include the abandonment of local issues review, an opt-out system for trial participants, and the psychiatric testing of trial participants to assess competence in judging the risks of participating in research (Edwards, Kirchin, and Huxtable, 2004).



# Outlook

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*Globalisation and marketisation of biomedical research will increase pressure on ethics reviews, as well as international agreements.*

Investors will be tempted to go wherever ethics review is 'quick and easy' or non-existent, although there are considerable reputational risks involved (Macilwain, 2006). This will generate economic pressure on the approval of controversial types of research. Despite harmonisation efforts, the system of national ethics councils and laws is essentially pluralistic. Ethics judgments are culturally determined, therefore certain differences between countries is inevitable. This opens up the question of how national values and economic interests this will in future be balanced by cooperation-driven consensus and standards.

*Shifts in health needs and cultural values may lead to a re-balancing of basic ethical principles.*

Autonomy, often seen as the currently dominant principle, has been linked to a focus on the individual, which is characteristic of Western and Westernised nations. However, like other priorities in history, this is a time-bound cultural value that may recede in importance in the future. Hypothetically, large-scale problems, such as pandemic disease, may sway the balance to put greater emphasis on beneficence instead.

*Ethical scrutiny will only go some way in containing controversial science, and the resulting use of new interventions.*

Scientific investigations are set to proceed on a larger and more international scale than ever before. As in previous decades, this will include some unethical research, either because ethical guidelines are not enforced in the research location, or because individual researchers ignore them. In either case, as opportunities and needs evolve, societies around the world will have to redefine their positions on existing research areas, and find new positions on novel advances. In particular, breakthroughs achieved in more permissive settings may offer benefits on a scale that prompt other countries to review their reservations regarding the use of certain types of research (e.g. proven successful stem-cell therapy for Alzheimer's disease).

*Involvement of the general public is likely to play an increasingly important part in defining positions on research ethics at national level.*

The past decade has seen a significant shift towards involving the general public in debating a nation's position on fundamental questions of research ethics. Although the great majority of ethics panels around the world now include lay members, this movement aims at a broader and in some respects 'more lay' decision base. Consensus conferences with citizens debating ethics positions are routinely used in Denmark, and have also taken place in the Netherlands, the United Kingdom, and Germany (Fuchs, 2006). In France, the 'road shows' of the Comité Consultatif National d'Ethique have encouraged the participation of the interested public. Even if the effective influence of such initiatives may have been weak and limited to a relatively small group of countries, the emphasis on engagement is of wider significance. For example, in Japan, a strategic plan was launched in 2002 to stimulate the debate between scientists and the public (Fuchs, 2005, pp. 17–80). Given the great challenges posed by future ethics judgments, the trend to legitimise decisions through a wide public basis, as well as specialist expertise, may grow stronger in the future.

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