Original Article

Challenges for ethics committees in biomedical research governance: illustrations from China and Australia

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Abstract

In this paper, the evolution of the ethics committees for health research, their history, membership, and function in China and Australia is described. Investigators in each country compared the history and governance of their ethical systems based on the published evidence rather than personal opinions. Similarly, examples of challenges were selected from the literature. In both countries, the aim was to maximize the social benefits of research and minimize the risk imposed on the participants. Common challenges include maintaining independence, funding and delivering timely ethical reviews of the research projects. These challenges can be difficult where research ethics committees rely on voluntary contributions and lack a strong resource base. They must adapt to the increasingly rapid pace of research as well as the technological sophistication. Population health research can challenge the conventional views of consent and privacy. The principles of the sound ethical review are common in both countries; governance arrangements and operational procedures, however, can differ, reflecting the cultural values and norms of their host countries and in respect of legal environments. By studying the evolution and function of ethics committees in the two countries, we established the differences in the governance and health systems, while similar ethical objectives helped sustain collaborative research.

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Introduction

Ethics committees play a vitally crucial role in the governance of the ethical conduct of biomedical research by minimising any potential risk to the research participants. Consequently, the anticipated research benefits for society justify any risks. The committee structures, composition, and procedures have similarities worldwide; some differences, however, exist due to the customs, norms, and legislative environments of their host countries. With increasing international collaborative research, it is important to analyse the differences in the ethics review in different countries. This ensures the social benefits of research while minimizing the risk imposed on the participants.

The collaboration between the researchers from Australia and China in the cancer epidemiological research revealed the historical development of the ethical review process and the approach to the challenges they faced to differ in these two countries. China and Australia have vastly different cultures and political structures. This has provided a unique opportunity to compare the history, use, and contemporary challenges of ethics committees in two very different countries, aiming to illustrate their commonalities, differences in the approaches, and challenges.

Methods

The researchers from both countries reviewed the literature on the development, structure, and role of the research ethics committees in their respective countries so that the comparisons would be made based on the published evidence rather than personal opinions. The researchers were familiar with the challenges faced by their ethics committees and selected published examples on the solutions, in order to be helpful for the other countries.

International History of the Ethics Committees

The recognition of the necessity for having independent ethics committees for human research arose after World War II with the 1947 Nuremberg trials of the Nazi doctors. They were found guilty of subjecting prisoners to research procedures, causing torture and death in their valueless experiments. The subsequent Nuremberg Code established the principles for human experimentation, including the requirement for voluntary informed consent (1,2). Other examples of unethical research included the Tuskegee study by the U.S. Public Health Service which left black American males untreated to observe the natural course of syphilis (3). They were given poor and even misleading information about the nature and duration of the study.

In 1964, the World Medical Association adopted a set of ethical principles for medical research by adopting the Declaration of Helsinki. This Declaration was written by the doctors planning self-regulation (4). However, following the Declaration, reports revealed unethical research practices in both the United States of America and Great Britain. Henry Beecher published a paper in the New England Journal of Medicine citing 22 examples of unethical research in 1966 (5).

In 1967 Maurice Pappworth, a British clinician, published a book outlining examples of unethical research (6). Such cases provided the impetus for the formation of research ethics committees (7). A major change in the 1975 revision of the Declaration of Helsinki was the requirement for a research protocol describing the experiment to be presented to a research ethics committee before the experiment could proceed.

Historical Development of Ethics Committees in Australia and China

China

In China, medical ethics committees were introduced in the 1980s. It was in response to the emerging ethical challenges in medical treatment, research, and the recognition of more formalized ethics review processes required to protect the legal rights of patients and research participants. The ethical challenges of the new developments in medical practice and research in China are similar to those encountered in many other countries. Examples include questions around the withdrawal of life support for terminal patients, priorities in the allocation of rare human organs for transplantation, and the extent of treatment provided to newborn babies with major birth defects. Additionally, research into the new medical technologies, whether on animal or human participants, are often ethically sensitive, and formalized reviews of the research activity is required to protect the rights of the participants (8).

Medical Ethics Committees developed in various stages. In Stage 1 (1987-1996), an Ethics Subcommittee of the Chinese Medical Association was initially proposed by a group of academics with a special interest in biomedical ethics. Its purpose was to promote good ethics by monitoring ethical issues in clinical practice, research, and discussing the findings with the government and professional leaders.

Stage 2 (1997-2006) was developmental and characterized by increasing international collaborations and the emergence of national biomedical-related regulations and codes (9). The number of ethics committees increased markedly during this stage throughout China. Nearly 400 hospitals established ethics committees, responsible for ethical review of specific studies, education, training, and broader policy research. The key developments included the establishment of the “Biomedical Research Review Committee of the Ministry of Health” and the “Health Ministry Biomedical Ethics Committee of Experts” in 1998 and 2000, retrospectively (10). Since 2001, four key sets of regulations were introduced, relating respectively to “Human Assisted Reproductive Technology Management”, “Human Sperm Bank Management”, “Prenatal Diagnosis Technology Management”, and “Human Organ Transplant Regulation”. These along with other initiatives provided an essential framework for regulating biomedical ethics applications. Subsequent developments included the establishment of a specialized

drug clinical trial committee, a new biomedical technology committee, a productive medicine committee, and a human organ transplantation committee. These committees were attached to the relevant biomedical institutes.

In Stage 3 (from 2007), the medical ethics committees benefited from the implementation of the biomedical regulations in China. In some respects, these were stronger than the international standards. They were supported by the publication of two national landmark documents, namely: the "Biomedical research ethics regulations" which were released by the Ministry of Health and revised in 2007 and 2016, retrospectively. The "Guidelines for Ethical Review of Drug Clinical Trials" were released by the National Drug Administration in 2010 (11). In addition to these national foundation regulations and guidelines, complementary regional regulations such as the Shanghai ethics regulations were established (12) and published by the Beijing Municipal Health Bureau in 2015 and 2018, retrospectively (8). These regional regulations gave specific direction to the development of detailed functions, procedures, and the composition of the local medical ethics committees.

Australia

The Australian medical research focused on bacteriology and parasitology in the 19th century (13, 14). The first medical school was established at the University of Melbourne in 1862. In 1936, the National Health and Medical Research Council (NHMRC) was established to support discovery research by focusing on the translation of the findings for the community benefits (15).

The current ethical guidance document, the National Statement on Ethical Conduct in Human Research 2007, was developed by the NHMRC, Australian Research Council (ARC), and the Australian universities and revised in 2018. It was a successor to the first code of ethical conduct issued in 1966 (16,17). The first guideline for the use of animals in the research was also published in 1966 and was updated in 2013 (18). These followed guidelines of the NHMRC Statement on the Scientific Practice (1990), the Australian Vice-Chancellor's Committee's Guidelines for the Responsible Practice in Research, and the Problems of Research Misconduct (1990) (19). There is also a rolling review of the National Statement conducted by a subcommittee of the Australian Health Ethics Committee of the NHMRC.

Although in the Australian federated structure, the institutional research ethics committees are the states' responsibility, the NHMRC sets out the certification standards. The NHMRC published a handbook for the National Certification Scheme of Institutional Review Processes Related to the Ethical Review of Multi-Centre Research in 2012 (20). Several states have created committees for this purpose to improve the efficiency and the cost-effectiveness of the review of the multicentre trials without compromising the quality or paralleling the international experience (21).

In Australia, the National Health and Medical Research Council Act 1992 (NHMRC Act) established the NHMRC as a statutory body that requires human research guidelines to be developed by the Australian Health Ethics Committee (AHEC), one of the Principal Committees of the NHMRC. Ethics committees throughout Australia are required to provide an annual report on their activities to this committee before they can be re-certified.

A private Australian health research ethics company (Bellberry) that complemented the state-run ethics committees, was formed in 2004. Bellberry Limited is a national, not-for-profit company designed to provide an ethical review for the research conducted in the private sector, although its services are extended to include several public sector institutions. It encompasses new clinical drug studies, social sciences, and observational studies (22). Bellberry HRECs provide a turn-around time of 20 working days by using an online e-Protocol system and multiple committee meetings weekly. The paid reviewers are expected to deliver timely reviews. Bellberry's Committees are also NHMRC certified, like all the other institutional ethics committees in Australia.

Membership of Ethics Committees

China

The composition of the ethics committees, based on the publication of updated ethics regulations, evolved between 2001 and 2016. The changes included the national ethical codes for human-assisted reproductive technology, human stem-cell research, human organ transplantation, drug trials, and biomedical research on humans (23).

These regulations specified the composition of the corresponding medical ethics committees and indicated standard eligibility criteria, selection processes, and tenure. For example, the human stem-cell research ethical regulation describes in the 9th code that the ethics committee must include researchers and managers in the fields of biology, medicine, law, or sociology. An ethics committee for human organ transplantation research must comprise experts in medicine, law, and medical ethics as stated in the 11th code. An ethics committee for the pharmaceutical trials must be a multidisciplinary team consisting of at least five members with gender balance from pharmacology and non-pharmacology departments, lawyers, and an independent individual. An ethics committee for the biomedical research on humans should have at least seven members, selected in the areas of biomedical sciences, ethics, law, and sociology, and the membership of a non-institutional community. An ethics committee in the areas with minority ethnicities should include members from the respective ethnic communities. Committee members are selected for a five-year term with the possibility of an extension. The committee is managed by a committee director and several vice directors selected by the committee (8).

The ethics committee structure is a branch of the government with vertical management from the national, provincial, and municipal levels. It is obliged to follow the Chinese ethics review regulations, as well as the International Ethical Guidelines for the Biomedical Research Involving Human Subjects, and the Helsinki Declaration. A national ethics expert committee is responsible for guiding or monitoring the provincial ethics review procedures and reviewing the performance of leading national biomedical researchers. The provincial ethics expert committee facilitates the standardized implementation of the regulations and provides training and consultative input into ethics review.

At present, the major hospital centres for diseases control, blood centres, and medical research institutions in the main cities of China have established such ethics committees.

Australia

The National Statement sets out a minimum membership of a health research ethics committee (16). It specifies that there should be an equal number of men and women in the committee along with a suitably experienced chairperson. However, it was found that the Australian ethics committees do not play an active role in monitoring gender equity in the research (24).

At least a third of the members should come from outside of the institution for which the HREC is reviewing the research. There should be two laypeople, a man, and a woman, on the team. Lay in this context means not engaged in medical scientific, legal, or academic work, nonetheless, these people should be interested in the research ethics. One member should understand professional care or counselling (e.g., a nurse or allied health professional). Another one should perform pastoral care in the community, such as a minister of religion, and one should have legal expertise. Two members should be researchers in a field of relevance to the submitted research proposals. If specific expertise for a proposal does not exist within the committee, it should be accessed from outside the committee. At least one of the ethics committee members should have ethics expertise. Appointments should be made based on a transparent process, reflecting individual expertise not because individuals are representatives of any group or organization with ethics expertise. (Table 1)

Understanding the impact of research practices on vulnerable populations and specific ethnic groups is a global challenge for the ethics committees. In Australia, this is exemplified by research involving the Aboriginal and Torres Strait Islanders. They often cite inadequate community consultation and lack of demonstrable community benefits among issues reflecting exploitation born in colonialism and indicating an entrenched "Western" approach to research (25). Ethnically diverse populations in most countries raise the challenge of providing patient information in a diversity of languages and ensuring culturally appropriate decisions. It can be problematic when the ethics committees do not reflect multiculturalism. This, however, can be addressed in larger groups.

Nowadays, there are separate Aboriginal ethics committees for studies involving Aboriginal communities in Australia. existing since birth, may develop and change under the influence of environmental factors (e.g., family, society, culture, and religion) and during the process of personal growth.

Table 1: Comparison of Ethics Frameworks in China and Australia

	China	*Australia*
Membership	*Differs by research field*	*Minimum membership categories set by NHMRC*
Gender	*Equity*	*Equity*
Governance	*Vertical from national to provincial government*	*State-based with national guidelines*
Role	*Review research protocols using standard operating procedures with code of conduct*	*Review research protocols guided by National Statement of NHMRC*
Alternate Committees	*No private ethics committees*	*Private fee for service ethics committees*
Certification of Committees	*Mandated using third parties*	*NHMRC certified*
Challenges	*Finance of committees*	*Finance of committees*
	Workload	*Workload*

In China, they have accommodated international ethics review practice in clinical research and traditional Chinese medicine ethical review practice (26). In 2014, the first Chinese Accreditation Program of Ethics Review System for CM Research (CAP) was established conjointly by the State Administration of Traditional Chinese Medicine and the ethics committee of the World Federation of Chinese Medicine Societies.

Both countries have urbanised and sparsely populated rural areas (27, 28). It is important to ensure that all population sectors are adequately represented in the population health and health services research. Although, this can raise significant costs and logistical challenges. Modern telecommunication and information technologies are increasingly being used to reach remote populations so that the population health research results would be relevant to their needs (29).

Roles of the Ethics Committees

China

The major role of the Chinese ethics committees is to review and evaluate the rigor and broader scientific merit of medical research proposals, and their ethical conduct

with the protection of privacy, dignity, and safety of study participants (30). This includes checking the proposed research complementary to clear objectives of the past research and employing a rigorous methodology including well-defined processes for subject recruitment, informed consent, and privacy. Proposals are expected to avoid harm and promote maximum benefits. As proposed therapeutic agents could extend the survival of cancer patients, due consideration is given comparing likely benefits to adverse impacts on patients' quality of life, research costs, and cost-effectiveness.

The committees required the research to provide satisfactory responses to the questions about the proposals. Approved researches undergo ongoing monitoring for compliance with approved protocols, research conduct, and adverse events as well as for risk/benefit (10,30,).

The committees follow the Standard Operation Procedures (SOPs) to ensure independence and transparency for reviewing ethics applications for biomedical research. SOPs cover comprehensive codes of conduct in the daily administration and workflow of the review process (31). These codes include mode of the review (e.g., meeting reviews, emergency meeting reviews, rapid reviews, etc.), review of the procedures (initial screening, follow-up reviews, conclusive reviews, etc.), time frames, outcome options for the review decisions (e.g., approval, approval after modification, rejection, and termination of research), protocols for on-site visits, application inquiries, and documentation (23). For example, the codes for an ethical review of the drug trials clearly explain regulations and governing processes for maintaining confidentiality, declaration and management of conflict of interest, training of new reviewers, the selection of independent external reviewers, and procedures for storage and distribution of applications. Regulations for the human biomedical ethics committees state that an application should be approved by more than half of the relevant members of the ethics committee at regularly scheduled review meetings.

Australia

Likewise, in Australia, most of the institutional research ethics committees guide researchers through the nature of the ethics approval process. They also aim for timely assessment of the research protocols. They enter into dialogues with researchers to ensure the risks or benefits to the research participants are minimised as they are fully informed. They monitor the progress of the research by considering amendments, possible ethical issues, or protocol violations that may have occurred (32).

Research ethics committees meet in fixed intervals, often monthly, and set forms for submitting research protocols. In Australia, several committees submit protocols through the NHMRC online Human Research Ethics Application (HREA) form collecting detailed information about the proposed research study (33). Generally, each committee appoints a spokesperson to present a summary of the proposal to the committee in order to make a collective decision on the study. Committees can

approve the study, return the study for amendment, re-review, or reject the study. A key performance indicator for a committee is the timeliness of the review. Increasingly, mutual recognition of the decisions made by other ethics committees is encouraged to avoid duplicated efforts and possible delay by having to be reviewerd by multiple ethics committees. Major differences in the decisions made between similarly constituted ethics committees are unlikely.

For the very-low risk studies (e.g., student surveys), several committees have altered the mechanisms of the review to the Chair or a subgroup with later ratification by the full committee. The best committees are willing to engage with the researchers who may have queries before the submission or who wish to discuss amendments prior to resubmission. Frequently, the scientific aspects of the study are scrutinized by a separate committee or experts who inform the committee in specialised research areas. Research governance issues are usually and separately considered by the administering health unit.

Committees also have active processes for following the approved studies. Many committees require the investigators to submit at least annual reports. A further aspect of the ongoing review is to assess adverse event reports and therefore the ethical viability of the project.

Challenges for Ethics committees

Research ethics committees across the world face similar challenges

Independence and funding

A challenge for the health research ethics committees is to maintain independence irrespective of whether they are government-sponsored or depend on an institutional structure for their finances or governance. Regularly, the key members come from the management ranks of the institutions in China (34). There may be limited financial support outside of the levies for the review of applications. A survey of 14 Fujian ethics committees did not find any stable financial support (30).

In Australia, there is an ever-increasing workload for the research ethics committees and with limited financial support it makes sense to have a single committee review multicenter trials and the other committees accept that decision. The NHMRC allows mutual recognition of decisions of ethics committees but with Australia's federated political structure this has only occurred to date within state borders and not nationally. High workload pressure in China makes it difficult for the committees to maintain standards (30, 34). Some ethics committees lack sufficient professional ethics membership, forcing the limited ethical experts to hold membership in 5 to 6 committees at the same time. It is not compulsory to have academics in ethical or legal sciences on the committee, although the required composition of a human-based biomedical ethics committee is clearly stated (31).

China has established local ethics committees to improve the overall performance. Major municipal cities (Beijing and Shanghai) and provinces

(Shandong, Sichuan, and Guangdong) have set up their regional committees, following a government announcement in 2017. More developmental efforts are required to reinforce the regional committees, their composition, and SOPs (30). In China, the ethics review process is being reinforced by the legislation based on the international codes such as 2001/20/EC, 2005/2B/EC, British "Human Drug (clinical trials) Codes" and the US Federal laws (35). However, the legislation needs flexibility as research evolves over time.

In Australia, in the case of research on mitochondrial replacement therapy, current laws stating that the embryos must be produced from two sources of DNA have to be revisited (36).

As previously indicated, one of the NHMRC functions is to approve the third-party certification of the ethics committees introduced under the Chinese law, the recommendations of the Strategic Initiative for Developing Capacity in Ethical Review (SIDCER), and the Association for the Accreditation of Human Research Protection Program (AAHRPP) for the existing international 3rd party practice (37,38). This is expected to improve the procedural standardization of ethics committees and their independence of practice.

Providing education for the researchers and potential ethics committee members would have been an important role for ethics committees as most of them are not resourced to do so. In Australia, the NHMRC has no resources for educating ethics committees beyond providing written guidelines on the ethical conduct of research through the National Statement and special guidelines for emerging research areas such as assisted reproductive technology and organ and tissue transplantation (39).

Ethics committees can aid researchers in reducing the number of required amendments by publishing acceptable wording for the standard sections of the patient information and the consent form if they were poorly worded.

Timeliness of the review process

A common challenge for the ethics committees is the review process timeliness. Most research ethics committees rely on the member contributions freely given without any charge. This was successful at the beginning; it, however, became more difficult with the increasing demand over time. When the committee secretariat is poorly resourced, additional pressure and lengthened turnaround times hinder timely and productive research. Increasingly, the committees have performance standards on the processing time to address this issue.

Solutions include creating single ethics committees for multicentre trials to reduce the duplication of efforts, and private committees where timely reviews are part of the contractual obligation of the reviews (21, 22). However, a more difficult issue is the timeliness of the parallel governance process where individual institutions want to work on their own due diligence and being reluctant to allow a centralised process to review and yet have not set timelines in parallel with those of the ethics review committees. The performance indicators for the governance reviews of the protocols are required.

The ethical challenges of evolving research capabilities

New research capabilities challenge traditional ethical ideals as the digital world and social media have created new problems. Large databases and registries can be linked, and special issues are faced in balancing the privacy of information against the importance to the community and policymakers. Ethical reflection on big data and the application of artificial intelligence and machine learning, regardless of it being a genomic dataset, biobank, or epidemiological research data, will determine if additional ethical considerations are needed to be considered over the use of older data for research (40).

An issue with social media is the easy dissemination of information to the public. Ethics committees ensure the balance and accuracy of the information provided to potential trial participants in the consent forms while not applying sponsored online information. Social media has also spawned the participant-led research of the virtual communities, raising the need for new methods to assess the ethical standards of consent, privacy, and way of sharing intellectual property (41).

Issues of consent

Consent has always been an issue with minors or incompetent patients who require substituted consent (42). With genetic testing, the results may reveal information about the health of the relatives. One question always remains regarding the incidental finding of abnormalities in the genes other than the ones being tested (43). In the field of xenotransplantation research, the greatest concern is the transplanted organ that triggers a human epidemic due to harbouring a zoonotic infection. If the research receives the required permission, the subjects should be monitored and close relatives or contacts need to be informed of the risk. This would challenge two of the traditional statements in the consent form such as the participant being able to withdraw at any time and their confidential participation (44).

When dealing with a large population of patients whose data will be analysed anonymously, this is considered low-risk research, and it would not be practical or appropriate to ask for everyone's consent. In between a waiver of the consent and individual consent can be so-called opt-out consent (45). The group of potential participants is informed of the study and given a mechanism to opt-out if they wish. The ethics committees assess the research that uses registries and other large datasets. Such datasets which need to have as complete a sample as possible to be confident of the accuracy of the outcomes may prefer an opt-out option of obtaining consent rather than a waiver of consent where no information is given to potential participants. Alternativly, quality assurance activities are often granted the waivers of consent.

Conclusion

By comparing the evolution and the function of ethics committees in two countries with

distinctly different government and health systems, we have established the similarity of the objectives of the research ethics review processes. These goals include maximizing the social benefits of research while minimizing potential harm to the research participants and so collaborative research was sustainable. Both countries face similar challenges; they, however, have often addressed them in different ways, reflecting the cultural values, norms, and legal environments of the countries. This unique comparison has produced insights into a range of solutions available for the challenges faced by research ethics committees.

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Conflicts of Interests

The authors have no financial or other conflicts of interest to declare.

Abbreviation

National Health and Medical Research Council (NHMRC)

Australian Research Council (ARC)

National Health and Medical Research Council Act 1992 (NHMRC Act)

Australian Health Ethics Committee (AHEC)

Chinese Accreditation Program of Ethics Review System for CM Research (CAP)

Standard Operation Procedures (SOPs)

Human Research Ethics Application (HREA)

Strategic Initiative for Developing Capacity in Ethical Review (SIDCER)

Association for the Accreditation of Human Research Protection Program (AAHRPP)

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