Australian Government

National Health and
Medical Research Council

Challenging Ethical Issues in Contemporary Research on Human Beings

INVESTING IN AUSTRALIA'S HEALTH

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December 2006

ISBN Print: 1864962933

Online: 1864962992

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The Hon Tony Abbott, MP
Minister for Health and Ageing
Parliament House
Canberra ACT 2600

Dear Minister

In accordance with your request, I am pleased to present you with this report on ethical dilemmas arising from consideration of research proposals involving human participants.

The report is focussed on health and medical research and the ethical issues that researchers and Human Research Ethics Committees (HRECs) must consider and resolve when research proposals are being considered. The research proposals discussed in the report are case studies that were identified by participating HRECs as interesting and challenging by virtue of the ethical issues they raised.

Key issues identified by HRECs and researchers were:

- Consent – what should be done when free, informed and prior consent cannot be attained from participants?
- Scientific merit – can innovative research that does not involve participant risk but is of uncertain merit be justified?
- Conflict of interest – how to resolve conflicts of interest arising from involvement in research and the product of research.
- Risks versus benefits – when can the potential benefits of research justify the possible risks to participants?
- Protection of vulnerable people – what measures should be put in place to protect vulnerable research participants?
- Disclosure of information to participants and their families – when is it ethical to either withhold or disclose to participants and their families, information about them derived from research?
- Privacy – what safeguards should accompany the collection of participant information derived from research?
- Confidentiality – are there circumstances which justify providing confidential participant information derived from research to third parties?

The report clearly shows that the public interest is being well served in two important respects: research involving humans is being subjected to careful prior review, and research quality is being promoted.

The report reflects the key issues emerging in the consideration of health and medical research proposals. I believe the report demonstrates that members of HRECs take their role very seriously and give careful consideration to each research proposal coming before them. Thorough consideration of proposals requires adequate time, and this may sometimes delay the commencement of research. Being a member of an HREC is a significant commitment and, in giving freely of their time, members of the public and other HREC members bring dedication and a strong sense of responsibility to their work.

The NHMRC thanks the contractors, Denis Muller & Associates, for their work in preparing the report. Most importantly, thanks must go to the HRECs involved in the report, and especially to the Chairs, members, executive officers and researchers at the twelve sites visited. This informative report would not have been possible without the reflective, insightful and open responses provided by those interviewed.

Yours sincerely

Professor Warwick Anderson
Chief Executive Officer
December 2006

Professor Colin Thomson
Chair, Australian Health Ethics Committee
December 2006

PREFACE

In Australia, all health and medical research projects involving humans must be approved by a Human Research Ethics Committee. Of the 230 committees across the nation, most are based in universities and hospitals. In considering research proposals, Human Research Ethics Committees refer to the guidance developed by the Australian Health Ethics Committee, a principal committee of the National Health and Medical Research Council on best-practice standards of ethical conduct for research involving humans.

At the NHMRC's National Ethics Conference in May 2005, I asked the Australian Health Ethics Committee to prepare a report on "challenging and interesting" ethical issues arising from consideration of health and medical research involving humans by Human Research Ethics Committees.

I can now provide a report that illustrates the careful and rigorous consideration that these Committees give to research proposals before they are allowed to proceed. I look forward to public comment on this document and on the quality of the Ethics Committees' work. Depending on the level of public interest, the CEO will consider a regular report along similar lines.

Human Research Ethics Committees tackle some very complex and sensitive issues. Some of the key difficulties involve consideration of participant consent, patient safety and welfare, privacy and disclosure, and the scientific merit of research proposals. The issues are getting more complex because medical science is opening up possibilities that have not previously existed. And the breadth of research has widened to include more behavioural, attitudinal and sociological components. Details of the kinds of dilemmas faced are contained in the ten case studies included in the report.

The work of the Committees involves volunteered time by hundreds of members including counsellors, lawyers, Ministers of religion and members of the public. The system would not work without the significant commitment and contributions of members. In addition to giving of their time, Committee members bring dedication and a strong sense of responsibility to their work.

The quality of Australia's health and medical research effort is recognised worldwide. The public interest is well served by Human Research Ethics Committees which continue to play a key role in ensuring that such research meets the highest ethical standards.

I wish to thank the Committees who provided information for inclusion in the report, especially the Chairs, members, executive officers and researchers at the sites visited.

Hon Tony Abbott MP
Minister for Health and Ageing

EDITORIAL

HUMAN RESEARCH ETHICS COMMITTEES – WHAT'S NEEDED NEXT TO PROTECT PARTICIPANTS AND ADVANCE HEALTH?

Over the last half century all countries that have a developed health and medical research effort have established human research ethics review systems. These vary between comprehensive centralised governmental systems (e.g. in New Zealand and Scandinavia) to more localised systems such as Australia and the USA.

Australia's system of human ethics review is well regarded internationally. National standards were first developed and promulgated by the National Health and Medical Research Council (NHMRC) in 1966 and there have been two major revisions and several updates to the guidelines in the ensuing 40 years, to take account of international ethical and scientific developments. The most recent version has just been released by the NHMRC (*National Statement on Ethical Conduct in Human Research*). As previously, it sets the overall parameters for Human Research Ethics Committees (HRECs) (e.g. membership, operations, special considerations for specific populations, clinical trials, privacy).

This publication outlines how several HRECs addressed a wide range of research questions. The dilemmas vary from concerns about whether consent to involvement in research is informed and voluntary, to the privacy implications of new technologies such as gene therapies which involve collection of genetic information now for use and disclosure in the future. Each HREC consists not only of researchers and people with expertise in ethics, law and counselling, but also a person who performs pastoral care and at least two lay people (a man and a woman) not currently engaged in medical, scientific, legal or academic work. This range of membership ensures that a variety of views are taken into account for every research proposal reviewed. The dedication of HREC members to this task, many hundreds of people who donate their time, is very impressive. Without their commitment the system would not work!

There are currently 230 HRECs registered with the NHMRC. The establishment and proper support of a HREC requires considerable resources from a research institution (hospital, University, medical research institute, company). The amount of work involved can be huge, with some of our larger Universities examining around 1000 applications per year. As this document shows, there is little doubt that considerable care and attention is given to the initial consideration and approval/rejection processes by the HREC. But, as we move into this century, a number of questions have been raised about the system that should be examined. Is it adequate for the complexities of research, the size of the community's investment in medical research, and the community's expectation that all HRECs will continue to have the capacity and resources to protect the interest and safety of participants in research?

1. Monitoring of the conduct of research? Are all HRECs aware of deviations from the approved protocols or of problems that might arise during the conduct of the approved research (e.g. unexpected problems with recruitment, complaints or concerns of the research subjects). An exception is that larger clinical trials have independent monitoring in place so that as soon as it becomes clear that the "treatment" being trialled is significantly effective, or significantly harmful, the trial is stopped. NHMRC sponsors the Australian Clinical Trials Registry at its University of Sydney Clinical Trials Centre. This allows anyone to see what trials are being conducted in Australia.

2. Are HRECs adequately resourced? HRECs may be overloaded and under supported as they may be sometimes required to take on other functions (e.g. clinical or professional ethics, grant administration, research governance generally).

3. Who monitors the HRECs? The only formal reporting of the operations and functioning of HRECs is by the NHMRC and this only applies to those HRECs that have registered with the NHMRC. These committees are asked to complete an annual questionnaire about compliance with the provisions of the *National Statement on Ethical Conduct in Human Research*. Compliance with provisions of the *Privacy Act 1988* is also checked and reported to the Federal Privacy Commissioner. These questionnaires give a snap-shot of compliance but beyond this there is no other external audit or inspection of the work of HRECs.

4. Do we need a formal complaints mechanism? Currently, there is no formal complaint system at either the State/Territory or national levels. The *National Statement* requires institutions to investigate complaints, but such a system of self regulation may have served its time. NHMRC receives complaints about researcher and research conduct or HRECs from time to time. The NHMRC's legislation does not provide a statutory capacity to investigate complaints. However if the research is funded by NHMRC, we can suspend or cancel the research if there is evidence that research, even if approved by an HREC, is not in accord with the conditions under which it was funded, or with NHMRCs, *National Statement on Ethical Conduct in Human Research*.

5. More and more, research is collaborative and conducted with multiple investigators and across multiple centres, across State and Territory boundaries, and also across international boundaries. Is there a better system for multi-institutional research, and can the current excessive time that is sometimes taken to review such research be reduced? Whilst the NHMRC has been encouraging mutual recognition of the ethics approval granted by one HREC, institutions and HRECs have been slow to take up the opportunities this affords. Most cite concerns about insurance, indemnity, and monitoring as their reasons for seeking to give individual approval. This situation is becoming untenable, creating inefficiency in the system, delays in approving and commencing research, and most of all increased work for researchers and HRECs alike.

To help, NHMRC has worked with jurisdictions to introduce the National Ethics Application Form (NEAF) as a means of creating comprehensive and consistent information for HRECs. We are now also working to gain agreement from all jurisdictions for a national system of single ethics review based on mutual recognition. An implementation plan will be developed over the coming months and implementation is planned from late 2007.

WHERE TO FROM HERE?

First, it is essential to ensure that the diligent work of many hundreds of Australians that serve on HRECs is maintained and acknowledged. No system will work without their energetic contributions. The current system has evolved to suit Australian circumstances and in general has worked well to protect research participants under local conditions.

However, improvements are needed. These might include:

1. Mandatory registration and accreditation or credentialing of HRECs.

2. A reliable method of monitoring compliance by researchers and HRECs with the *National Statement* and related guidelines.

3. A formal complaints process.

As ever, the promotion of best practice and awareness of the ethical implications of research, by researchers, HREC's and research institutions, remains the cornerstone of any ethical review system. NHMRC is proud of the system of human research ethics that it has nurtured, with its partners (ARC, AVCC) over the last half century. We are keen to continue its development to ensure that the system is suited to the 21st century, and that it protects those who selflessly contribute to the better health of humankind through participation in research projects. It is time to take the next steps in the evolution of the Australian System.

Warwick Anderson,
Chief Executive Officer,
National Health and Medical Research Council

PART I METHODOLOGY

BACKGROUND

Human Research Ethics Committees (HRECs) play a central role in the Australian system of ethical supervision of research involving humans. HRECs review proposals for research involving humans to ensure that the research is soundly designed, and is conducted according to high ethical standards such as those articulated in the National Statement on Ethical Conduct in Research Involving Humans 1999 (the *National Statement*). Many other countries have similar systems.

There are more than 200 HRECs in institutions and organizations across Australia, mainly in hospitals and universities. Organizations establishing HRECs are responsible for adequately resourcing them and for ensuring that they operate in accordance with the *National Statement*. While HRECs primarily fulfill a guardian role, an often overlooked secondary purpose set out in the preamble to the *National Statement* is to "facilitate research that is, or will be, of benefit to the researcher's community or to humankind". Thus HRECs are seen as having a role in promoting good research and good ethical practice, as well as guarding against poor research and poor ethical practice.

In June 2005, the Minister for Health and Ageing, the Hon Tony Abbott, MP, requested that the Australian Health Ethics Committee (AHEC) prepare a report on ethical dilemmas arising from research proposals involving human participants. Under the guidance of AHEC and a small Steering Group comprising the AHEC Chair and National Health and Medical Research Council (NHMRC) officers, contractors - Denis Muller & Associates of Melbourne[1] (DM&A) - were engaged to assist in preparing the report, to avoid any bias that might be perceived to arise from either the interests of AHEC or those of the HRECs that it supports. Work commenced in May 2006.

THE APPROACH

A qualitative, case-study approach was adopted for the following reasons:

1. The tender brief indicated that a qualitative approach was preferred
2. There were many complex questions to be asked. Reducing them to the types of questions used in quantitative analysis would have been an affront to those complexities and to the subtleties of thought required to resolve them.
3. The sizes of the populations being studied were not large enough to provide a useful basis for quantification, particularly if wide variety was desirable, as it was.

[1] Denis Muller & Associates (DM&A), policy and social research consultants - Dr Denis Muller, Principal, in collaboration with Dr Prasuna Reddy and Associate Professor Erica Frydenberg of the University of Melbourne.

The case-study approach seemed most likely to provide answers to the main questions posed by the brief:

- What were the interesting and challenging ethical issues?
- How were they resolved?
- What was the nature of the interactions and the relationships between the HRECs and the researchers?

Given the number of HRECs in Australia, it was necessary to develop criteria for selecting the HRECs that would be asked to participate in the project. Noting the Minister's primary interest in health and medical research, the criteria focused on HRECs dealing with health and medical research, that is, HRECs that advise either hospitals or health and medical research institutions. From this group, the HRECs that reviewed the greatest number of proposals, based on the most recent statistics provided in annual reports, were selected.

In order to keep the numbers manageable, 50 HRECs were selected with a view to obtaining the widest possible range of examples for the report. These 50 were invited to participate and 33 accepted.

These 33 were then asked to submit brief synopses of two cases which they regarded as challenging and interesting. No definition of this term was prescribed: it was left to the HRECs to determine by reference to their own experiences. HRECs were advised of the kinds of factors to be considered in deciding which HRECs would be interviewed for the report. These included: the research subject area; the ethical issues raised; the discipline(s) covered; the social setting(s) covered; the location of the research (with a view to wide geographical spread befitting a 'national' report); and the availability for interview of the HREC Chair, members and the researcher whose work was the subject of the case.

Of the 33, 21 HRECs furnished synopses and it was from these that 12 HRECs were chosen. The final selection was made by a working party consisting of the NHMRC Project Steering Group, and the three DM&A team members.

As may be inferred from criterion 6, it was proposed to interview the Chair of each HREC, a selection of other HREC members, and the researcher whose project had produced the interesting and challenging ethical issues.

Each of these interviews was to be conducted by two DM&A team members in person at the institution in question or at some other place convenient to the respondents. For logistical reasons, two sets of interviews had to be conducted by one interviewer, but on all other occasions two interviewers were present.

The selection of the HREC members to be interviewed was left in the hands of the Chair and Executive Officer of each HREC, with a request that they attempt to get as broad a range of members as possible, with a special emphasis on ensuring that a lay member was included.

In the event all 12 HREC Chairs were interviewed. At one site the former Chair, who had occupied that position at the time the case had been dealt with, attended with the present Chair. At five sites, the Executive Officer also sat in, but did not participate in the interview except to provide additional factual information when requested by the Chair.

At all sites, the Executive Officer was asked to provide basic data about the number of cases handled in the most recent year, and the proportion rejected.

At three sites the interviews with the Chair and the HREC members were conducted as one. This was done at the request of the institution because of time constraints.

A breakdown the 41 HREC members interviewed shows that they came from a wide range of disciplines or backgrounds, as the list below indicates.

Medical practitioner or researcher	12
Lay person	8
Nursing	7
Minister of Religion	5
Hospital staff	5
Lawyer	4

It should be noted that these are not categories of HREC members as prescribed by the *National Statement*. They are the disciplines or backgrounds from which the interviewees were drawn. Concerning the composition of HRECs, the *National Statement* requires:

The minimum membership of an HREC is seven members, being men and women, comprising:

(a) A chairperson
(b) At least two members who are lay people, one man and one woman, who have no affiliation with the institution or organization, are not currently involved in medical, scientific or legal work, and who are preferably from the community in which the institution or organization is located;
(c) At least one member with knowledge of, and current experience in, the areas of research that are regularly considered by the HREC (eg. health, medical, social, psychological, epidemiological, as appropriate);
(d) At least one member with knowledge of, and current experience in, the professional care, counselling or treatment (eg. medical practitioner, clinical psychologist, social worker, nurse, as appropriate);
(e) At least one member who is a minister of religion, or a person who performs a similar role in a community such as an Aboriginal elder; and
(f) At least one member who is a lawyer.

Of the 12 researchers whose work was the subject of discussion, 10 were interviewed. Of the two not interviewed, one was involved in a case not subsequently included in this report. Descriptions of this and one other case are not included because, when asked to comment on the interview reports, the parties involved declined permission for their inclusion.

Interview schedules for Chairs, HREC members and researchers were drafted by DM&A and, once they had been approved by the Steering Group, were sent in advance to all respondents. The interview schedules used are provided in Appendix I to this report, as is the consent form.

All interviews were audio-taped on condition that the quotations used would not be attributed, that the case would not be identified, that the recorded material would not be used for any purpose other than this project, that no one other than the contractors would hear them, and that they would be erased at the end of the project.

All fieldwork was conducted between 8 August and 7 September 2006. The study was carried out at sites in Queensland (two), New South Wales (two), Victoria (five), South Australia (two), and Western Australia (one). One of the Victorian sites was in a regional centre; all the others were conducted in metropolitan settings.

PART II THE CASE STUDIES

MENTAL HEALTH PROFESSIONALS WORKING IN RURAL COMMUNITIES – CASE STUDY A

INTERVIEWS

Interviews were conducted with the Chair and the executive officer together, and then with three members of the HREC. One was a psychologist, another was a former schoolteacher who sat as a lay member, and the third was a minister of religion.

The researcher whose case was the subject of the discussions was also interviewed.

DESCRIPTION OF THE RESEARCH PROJECT

The researchers proposed to explore the relationship between mental health professionals and people in rural communities, focusing on the "dual relationships" that may exist in rural communities where everyone knows everyone else socially as well as professionally.

The research consisted of personal interviews with psychiatrists, psychologists and other professionals who provide services to the mentally ill, as well as with patients.

The objective was to discover how commonplace the "dual relationship" issue was, and how these various parties coped with the effects of "dual relationships".

ETHICAL ISSUES IDENTIFIED BY THE HREC

- Confidentiality versus reporting of possible misconduct
- Treatment of a vulnerable population

THE COMMITTEE'S VIEW

Two main ethical questions arose. The first was, what happens if a patient interviewee says that one of the professionals has exhibited inappropriate (including sexually inappropriate) behaviour towards the patient?

> *If it came out in the interviewing for this research that someone said, "That psychiatrist raped me during my consultation", what is the researcher going to do about it?*
>
> *If it's a child, it is clear: mandatory reporting. If it's an adult, you have these dilemmas: Is it the truth? What do I do about it?*
>
> **— HREC Chair**

The second was, in a small community where there are few independent qualified persons available to investigate the allegation, to whom should this be reported, bearing in mind the need to be fair to both parties – the patient and the professional?

> *Is it appropriate for the researcher to make a complaint, for example to the Psychologists Registration Board? If the researcher is also an employee of [this institution], is it appropriate to report this allegation to the practitioner's supervisor [who might also be an employee of this institution] ?*
>
> **— HREC member**

To complicate matters, this was a particularly vulnerable population of patients, but also a population who by the nature of their illness might hold perceptions that are at variance with reality. Moreover, the research itself might have an impact on them by causing them to bring up issues that had led them to seek professional help in the first place, but in circumstances where the interviewer had no specific responsibility to provide assistance.

> *There is the impact of the questioning on the subject. How do you counsel them afterwards? They go to your study, they realise their mother has always hated them, and then you say, "Thanks very much, now I'm going to have lunch." It comes up repeatedly: what support. We don't deal with that adequately.*
>
> **— HREC chair**

> *We were also concerned about the researcher who has inadvertently found out this information. And I don't think the researchers had seen that at all.*
>
> **— HREC member**

Furthermore, there was concern on the part of the ethics committee that the researcher might feel bound to act in what he or she thought was the best interests of the interviewee but in doing so pursue the matter further or more vigorously than the interviewee might wish.

> *I have personal experience of this and I would certainly not have thanked someone for rushing in and saying, "I'll report it for you". People might think they're helping, but it's always much more complicated.*
>
> **— HREC member**

THE RESEARCHER'S VIEW

The researcher had a background in sociology and public health, and had been conducting research in the field of mental health for about six years. She spoke in some detail about the difficult balances to be struck when conducting research among people with mental illness.

> *In mental health, there's a tension between the vulnerability of our clients and not putting them at risk, and balancing that with shedding light on important issues.*
>
> *There is a quite big power imbalance between participants and researchers [but] if we don't do this work, vulnerable groups don't get acknowledged.*

She also revealed a perception that ethics committees were particularly sensitive to the ulnerability of such people, and that this led them to challenge the research more closely than might otherwise be the case.

> *It's good because these people are vulnerable, but sometimes it seems a bit adversarial. You get a sense they're going through it looking for every little problem and don't see the overall benefit of the project. It's more risk management.*
>
> *Some researchers self-censor and say, "There's no point in doing that because you won't get it past the ethics committee".*

In the case under review, it was clear that initially at least, the researcher and the committee had diametrically opposite perspectives on the ethical difficulties.

> *When we took [the proposal] to the ethics committee we emphasised that we wanted to look at everyday interactions, not interactions of an improper nature. But that is exactly what they focused on, and they wanted to know what we would do if a client revealed a relationship with a clinician that was suggestive of misconduct by the clinician.*

And yet there seemed to be common ground between the researcher and at least some members of the committee on how far the researcher should go in helping someone make a complaint of improper conduct in the event of some such allegation coming to light.

> *Our response was, we would give people information on how to make a complaint, but that was as far as we could go. Ethics wanted us to act on the information but we couldn't do that because a client may make an accusation -- and mud sticks – or the client may not want to take it further, and we just felt it in a small community it wasn't our role to ride up on a white charger . . .*

Overall, the researcher expressed satisfaction with the way the matter had been handled, but had clearly learned from the experience that obtaining expert ethical input when the research was being designed would have saved time and trouble later.

> *We had a person with a good knowledge of ethics. If it hadn't been for her, I would've been pretty stumped as to where to go. So I guess access to that kind of information is important.*
>
> *It would be much better to have the ethics input at the start of writing your submission rather than at the end.*
>
> *It did make us reflect on an issue we hadn't seen as an issue. We might yet thank our lucky stars we have thought about this thoroughly.*

HOW THE QUESTIONS WERE DECIDED

The ethics committee decided that in the event of such a disclosure or allegation emerging during an interview, the researcher would inform the interviewee of his or her rights in relation to reporting the matter to the appropriate authorities, but that the researcher would be restrained from taking any further action on the interviewee's behalf.

The limitations inherent in this decision left a lingering unease among some members of the committee because they felt that vulnerable people were even less likely to report sexual misconduct than were the population generally, and that some further support or follow-up would have been desirable.

We know the majority of people who are sexually abused don't report it. So the chances are quite small, particularly in a small community where they might have other social contacts with the psychiatrist.

I took this to a lot of ethicists and other practitioners and no one really had a good answer.

The researcher nominated somebody independent, who was actually the new head of the psychiatry department, to whom the person could be referred.

The researcher had to give [respondents] the protocols and contact details for all the different reporting systems that they could follow, and [tell them] where they could get support.

It went ahead, but everyone still felt a little queasy, that we hadn't quite got there. What we did was roughly adequate, but if the same thing came up next week, I think we'd still feel concerned.

I phoned Canberra and [two hospitals in Melbourne] and nobody could give me a better approach: "You're dealing with adults, you give adults the information, and that's what we consider ethical".

— HREC chair

My view is that if the interviewee is a competent consenting adult, they should be given information about how to make a complaint, but it should be their choice whether to do so. But there were different views around the table.

DM&A: Was the fact that the interviewees were competent consenting adults built into the research design?

Yes.

— HREC member

IMPACT OF LONG DISTANCE AIR TRAVEL ON PEOPLE WITH LUNG DISEASE - CASE STUDY B

INTERVIEWS

The HREC Chair, the executive officer, and three HREC committee members were interviewed together.

The Chair had occupied that position for six years, and previously had been a member for five or six years. He was a consultant in rehabilitation medicine and a former chair of a state health ethics committee.

The three members were a clinical nurse consultant who had just joined the committee at the time the research project was reviewed, a retired registered nurse sitting as a lay member, and an anaesthetist on the hospital's staff who had done the scientific review of the case.

The executive officer was also manager of the research office at the hospital, and had occupied the position for five years.

The researcher whose case was the subject of discussion was also interviewed.

DESCRIPTION OF THE RESEARCH PROJECT

People travelling on commercial aircraft are exposed to cabin pressure equivalent to an altitude of between 6000 and 8000 feet. In people with normal lung function, that presents no hazard: their oxygen level will fall but they will suffer no ill-effects. But the question has often arisen, especially for people in Australia who travel long distances, whether that is safe for someone with underlying lung disease.

The Aerospace Medical Association, among other international bodies, has produced guidelines about the type of people who should be tested for their capability to cope with prolonged exposure to reduced oxygen pressure. The guidelines have two thresholds. The first threshold concerns the quality of a person's lung function. If the function is below a certain level, the person is then tested for capacity to cope with exposure to cabin pressure. The results of the test represent the second threshold. If the test result shows incapacity to cope, the person should carry and use oxygen on aircraft.

For a long-distance flight -- for example, between Australia and the United States -- oxygen would cost a passenger several hundred dollars, and some carriers do not accept passengers who need oxygen. This is because of the associated risks, including the risk of having to make a diversion in the event that the passenger falls ill. Therefore, the ability of these people to travel can be curtailed.

The researcher was a highly experienced research physician specialising in lung-function at altitude. He was not convinced the existing Aerospace Medical Association guidelines were accurate, and wished to explore this matter. It was considered by the ethics committee to be a research project of high scientific merit.

The population to be tested consisted of middle-aged to elderly people with smoking-related lung disease who had undergone the first test but had not triggered the need for the second test. In other words, the first test had not revealed their lung function to be so impaired as to require the second test. Thus in the ordinary course of events, they would be able to fly without oxygen or any other form of assistance, and indeed many had done so.

In the research project, they were to be exposed to a simulated cabin altitude of 6000 feet for a certain period of time, during which they would be asked to walk short distances, as if they were walking to the toilet on an aircraft. This was a completely novel element in the research. The objective was to see whether their oxygen levels fell when they exercised and whether they needed to be given particular advice as a result.

ETHICAL ISSUES IDENTIFIED BY THE HREC

- Participant safety
- Disclosure of participant information to the participant

THE COMMITTEE'S VIEW

Initially, the primary concern of the ethics committee had been the safety of the participants, all of whom were known to have at least some degree of lung-function impairment and who were described by committee members as "a bit on the frail side".

> *You have people with reduced lung capacity and reduced oxygen levels and you're going to subject them to a simulated low-oxygen environment with an exercise test. We had to have careful supervision and careful monitoring, and in case of emergency there was a crash cart very close by with people who were trained in CPR, and a cardiac physician.*
>
> *The research was a very good idea and it dealt with very interesting questions, but we had to make it safe.*
>
> **— HREC chair**

With those precautions in place, the ethics committee gave approval for the research to proceed. However, it was not long before a further ethical question arose: should the researcher disclose to the participants their test results when they showed the patient would have failed the standard test?

> *I'm always for disclosure generally, but I thought that if these people had a particular condition the insurance company would have asked them these questions anyway. And I thought it wouldn't make a blind bit of difference.*

DM&A: Was that because the results of the trial were not evidence of a pre-existing condition?

Yes.

— HREC member

We had an experiment that was trying to reflect reality but it was not reality, but I thought the physician had a duty of care to any who he thought shouldn't fly.

DM&A: So there are grounds which make withholding information reasonable?

The ground for withholding is that it may not be meaningful. It may not give them accurate information about whether they could or could not fly. It was a simulation.

And it was an experiment. Any anxieties might or might not be groundless but they are anxieties that we could not calm down because we didn't have the information.

Even though we said there wasn't a general need to disclose, where they went past a certain threshold we said they should disclose, but this was left to the clinical-researcher to decide if the person was likely to be in danger and we felt very confident the researcher could make that judgment.

The other thing was that we look after a lot of people in this hospital who have chronic lung disease and our experience is that they don't have as much trouble as the text books would suggest. A lot of these patients are habituated to poor lung function, and they seem to get by.

— HREC member

THE RESEARCHER'S VIEW

It became clear early on that a lot of people who, under the existing guidelines, would not even require the first test, showed oxygen levels falling below the level at which they required oxygen.

So there was a paradox. Under the current guidelines, they didn't even require the test, but they had consented to do the test and most of them failed, particularly when they walked. Their oxygen fell below the level that required oxygen.

What do you do with that information?

Further complicating that was the fact that 80 per cent of them had flown without having a problem, so in the absence of their participating in this experiment, they would have just happily got on the aircraft and been fine.

This was when we started a conversation about this with the ethics committee.

The researcher put it to the ethics committee that the fact that they had failed the oxygen test should be withheld from the participants unless, in the clinical judgment of the researcher, they were likely to be genuinely at risk if they flew. He adduced two reasons for this:

The primary basis was, we didn't know, and we couldn't prove, that that was an important result of which the patients needed to be informed for their own safety.

We were seeing low oxygen levels in people who the current guidelines would not require testing upon. They'd only done the testing to help us understand this. So they would not have required the test according to the consensus guidelines.

Second, many in the group had actually flown without an adverse event. We thought to deny these people the opportunity to fly was not appropriate and the best way to avoid that was to simply not tell them.

DM&A: So you made a judgment about the risks against the potentially disabling effects of knowing?

Yes.

DM&A: What obligations of disclosure would that have placed on those participants had they been told? Would they have had to declare that to insurers, for example?

I'm not a legal practitioner but I can imagine that it might. And anyway, these were decent hardworking people and if they were filling in a form for travel insurance they would probably wish to fill it in honestly.

DM&A: Did you take that into account?

Yes. And I didn't have any reason to believe this was a high risk.

However, if we saw someone who did show distress in association with low oxygen levels, we would recommend they use oxygen in flight, and I would disclose to them. That was the compromise. And that was a judgment call for the clinician-investigator.

And in the guidelines we are trying to work up, that is now our arbitrary clinical distinction.

— Researcher

HOW THE QUESTION WAS DECIDED

Ultimately the approach proposed by the researcher was accepted by the ethics committee. It was decided that the data from the experiment would be withheld from the participants unless, in the opinion of the researcher, the results suggested a real risk to the welfare of the individual if he or she were to fly without oxygen.

The reasons for the decision were as described by the researcher: the data were from a simulation; their veracity was untested; these people had flown previously without incident; disclosing it to them might create inhibitions and barriers which would be a form of disability when, on the evidence, this was not warranted.

SEXUALLY TRANSMITTED DISEASES - CASE STUDY C

INTERVIEWS

At this site the chair, members and executive officer of the HREC were interviewed together at their request because of the difficulty of arranging alternative times.

DESCRIPTION OF THE RESEARCH PROJECT

It was proposed to establish a State-wide network of sentinel clinics for the surveillance of HIV, chlamydia, syphilis and hepatitis C cases among young women. The purpose was to understand disease transmission.

ETHICAL QUESTIONS IDENTIFIED BY THE HREC

- Consent
- Privacy

THE COMMITTEE'S AND RESEARCHER'S VIEWS

A threshold issue was whether the project fell within the definition of "research" or "surveillance". If it were surveillance, consent of the young women would not be required. If it were research, consent would be required.

Complicating this was that fact that it was a multi-centre project, and opinions differed among the ethics committees in these centres about the definitional issue. Some frustration was expressed by both the HREC and the researcher over this distinction.

> *In the original submission the investigators said they didn't see any ethical dimensions to the proposal, and yet here we are having it identified as one in which there are considerable ethical issues to be addressed. So it's a perspective thing.*
>
> **— HREC Chair**

> *We put it to the ethics committee that we were setting up a surveillance system, and you don't need ethics clearance for a surveillance system. But for research you do. So you have this convoluted process where you're collecting the same information you might collect six months later, but if it's for research you need ethics approval and if it's standard surveillance you don't.*
>
> *And then you have this discussion with multiple ethics committees because you're using eight or nine sites and each committee's interpretation on the consent issue varied from those who said, "Why are you even asking us? This is surveillance", to those who said they needed written informed consent in a way which was entirely impractical for a surveillance project. Others said you must give them a thing to read prior and if they say okay, it's verbal consent.*
>
> *When does a surveillance system no longer require ethics approval? This is a question not answered by anybody.*

Then the question came up: If I'm collecting data from someone, what level of consent do I need from that individual to collect that data?

— Researcher

At the institution visited, the ethics committee had taken the view that the project clearly fell within the definition of "research". This then led to an ethics review of the project, focusing on issues of consent and privacy.

The first question arose over the fact that some of the young women would be minors (aged between 16 and 18). Therefore, should consent be obtained from parents or guardians? And what consent would be required from the young women themselves?

If consent were to be sought from the parents, then a privacy issue arose because of the sexually-related nature of the diseases being observed.

A further issue concerned the way in which consent would be obtained – verbally or in writing. This was a large study, and given the numbers involved, it was necessary to streamline data collection as much as possible, consistent with maintaining standard consultation procedures.

HOW THE QUESTIONS WERE DECIDED

It was decided that seeking consent from parents would be an unacceptable breach of the young women's privacy, so this would not be sought.

In those circumstances, it was recommended that only young women aged over 16 would be recruited into the study.

It was further decided that, given the size of the study, the subject-matter, and the clinical context within which the research would be carried out, verbal consent would be appropriate.

EMERGENCY TREATMENT OF CARDIAC ARREST - CASE STUDY D

INTERVIEWS

The former Chair, who had been Chair when the case under review was dealt with, was interviewed, along with the present Chair, and the executive officer.

The former Chair, a neo-natal paediatrician, had occupied the position for 12 years. The new Chair, who had a long career in renal research and clinical practice before his retirement four years ago, had taken over only a few months before this interview took place.

The executive officer had been in her position for two years.

Four members of the HREC were interviewed. One was a clinical nurse and manager of patient risk management and for this reason sat on the committee. She was also a representative of an associated institution, also served by the committee.

Another member was a clinical nurse manager in coronary care with a PhD, part of which was on informed consent for participation in clinical trials by acutely ill people. She had been on the committee for 11 years and had been deputy chair until 18 months before the interview. This person was a university lecturer, but at the time of the review was a clinical nurse manager in the coronary care unit.

The third was a lay member, with a background in social work and counselling. She also was involved in active lobbying for palliative care. She had been on the committee for 11 years.

The fourth was the nursing director of the associated institution, and had been on the committee 10 years. She had studied ethics as part of Bachelor's and Master's degrees, and was now deputy chair.

DESCRIPTION OF THE RESEARCH PROJECT

The principal investigator in this project had a PhD in bio-chemistry and renal physiology, and worked as a paramedic in an ambulance service.

A Norwegian study had shown that three minutes of CPR before electric-shock defibrillation in out-of-hospital ventricular fibrillation (VF) cardiac arrest made a big difference in the rate of survival to hospital-discharge. The standard treatment at the time this research started was to apply electrical current straightaway.

It was proposed that the paramedic crews who attended these patients would randomly assign patients to Group A or Group B – standard treatment or the proposed treatment. The randomising process consisted of opening an envelope on the way to the scene and following the treatment prescribed inside.

The rate of survival to hospital-discharge is poor in cardiac arrest – the researcher estimated it at perhaps not more than five per cent and probably closer to one per cent. His view, therefore, was that even a small improvement would mean the saving of proportionally a lot of lives.

The Norwegians had found that with normal procedures there was a 15 per cent survival to hospital-discharge. With three minutes of CPR applied before electric current, this rose to 22 per cent, a 50 per cent increase.

In the Australian location where this research was being done, there were about 100 VF cardiac arrest cases per year, of whom it was estimated that about eight survived to hospital discharge, so a 50 per cent increase on that would mean the saving of four more lives each year.

The researcher also cited considerable laboratory-based evidence that CPR primed the heart and made it more receptive to being shocked.

In the city where the research project was carried out, the average response time for an ambulance in reaching a cardiac arrest case was eight minutes. In general, this left a window of about two minutes before the patient was irretrievable.

If, in that window -- so the laboratory studies and some earlier studies indicated – CPR was applied and oxygenated the heart, the fibrillation became more coarse. The greater the coarseness in the fibrillation, the more chance that when an electric shock was given, the heart would resume a steady beat.

The objective of the research was to reproduce the Norwegian study to see if it was correct. The researcher had one particular question about the Norwegian data. This concerned the average response time, which had reportedly been 12 minutes, well beyond the point at which a patient could usually be retrieved.

The researcher had questioned the Norwegian researcher directly but had not obtained an answer.

The research proposal was submitted first to the ethics committee of the State department of health for approval to carry out the in-field research - the randomised use by ambulance paramedics of the standard and experimental treatments on out-of-hospital cardiac arrest patients. This approval was necessary because the ambulance service came under the control of the department.

It was also necessary to obtain the medical records of VF cardiac arrest patients from the hospitals to which they were taken so that a connection could be made between the type of

treatment given initially and the ultimate outcome for the patient. For access to these records, approval needed to be obtained from the ethics committees of each of the three main public hospitals to which most cardiac arrest patients in that city were taken.

However, the researcher submitted to the hospitals the entire research protocol, not just the part of it pertaining to access to patient records.

Two of the three hospitals approved the research, as did the departmental ethics committee. The third hospital, however, did not initially approve it – indeed retains profound reservations about it -- and provided the case study for this report.

ETHICAL ISSUES IDENTIFIED BY THE HREC

- Consent in circumstances of a life-threatening emergency
- State power and the rights of individual patients
- Avoidance of distress to surviving relatives
- Offering of potentially sub-optimal treatment to an acutely ill person
- Quality of the background science

THE COMMITTEE'S VIEW

> *The difficulty was that we did not agree that this was an ethical project. The consent was to be obtained post hoc from survivors or family.*
>
> *After the event you go along and say, "Mrs Jones, I'm sorry your husband died. He was actually involved in a research study. He had treatment A. Now he has died, so he may have contributed to proving that treatment B was more effective. Would you please sign the consent form?"*
>
> *We perceived that to be a very weak negotiating position with family members, and had no credibility.*
>
> **— Former chair**

Members of the committee had further objections, one being the power of the state to override an individual's right to give or withhold consent, another being the risk of offering sub-optimal treatment to an acutely ill person, a third being doubts about the quality of the hypothesis being studied because of the anomaly over response times and some concerns about the risks associated with CPR.

> *The fact that the state can override ethical issues raised by this hospital is outrageous. If we had taken the line taken by [another of the city's hospitals] and said this is only about access to case notes – well, that's not how we work.*
>
> *Second, this is experimental treatment. There is nothing out there. It's not in the standards of the Australian Resuscitation Council. Neither treatment [standard or experimental] has overwhelming benefit for the patient. So how can you justify a random trial? If you hold one*

out as being possibly a better treatment, you're going to be accused of offering sub-optimal treatment.

DM&A: Do I take it that when you are making judgments about treatment of the acutely ill, that the level of comparative benefit is a relevant consideration?

Yes. We have to weigh risk and benefit where patients can't consent themselves.

In my role in primary care, I have been involved in resuscitation and some of the information being given in the first protocol we looked at was against current knowledge. Also they quoted three or four studies that really didn't offer any support to the position they were taking. If people can't consent, and there is no indication that this may be a potential benefit, and it may be a further risk . . .

The second protocol they put forward had a Norwegian study that did come up with some data.

DM&A: Was consent an issue for you?

If you said you have to have consent for everything, you would never do acute-care research. You would never make improvements in resuscitation. I think there is acceptance among the committee that there will be research where you can't obtain consent prior to the treatment. That means that while you can't take back what has been done, you don't have to take part further.

DM&A: So what are the issues for consideration for you when you are making decisions about people like this? What do you want to see in place before you are satisfied that the consent criterion has been met?

That it has some reasonable benefit.

There has to be some belief that what is proposed will be of benefit to the patient.

That it will pose minimum risk.

The advice from the Department about the concept was to some extent quite justifiable. They said they did not need to get retrospective consent from people whose relatives had died. Also that they did couch the consent form in words that I thought were reasonable. It looked to me as if they had taken the NHMRC guidelines into account, so you couldn't really fuss about that. But CPR is pretty rough stuff, and the person could get broken ribs and pneumonia and die as a result of the CPR.

That's an important point. Probably the foremost US authority on resuscitation at the time was very much against CPR because of the risk of traumatic injury and thought that there wasn't a place for this sort of study.

And working in cardiology I am aware of the effects of delay to treatment, and that concerned me as well.

— HREC members

The present chair sat in on this interview. He had not been on the committee at the time the case was dealt with, and took the opportunity to become acquainted with it. At this point he interposed a question to the lay member, the answer to which led to a re-opening of the debate about the issue of consent and the impact on bereaved people:

Can we just draw [lay member] on her view about consent in relation to the deceased. You were supporting that position? You were happy for the family to be not told?

— Present chair

Yes, on balance, the family would be more distressed than informed by something like that. You have to take into account the amount of distress that could cause. I feel the distress would far outweigh any good that could be obtained from getting consent about the data.

— Lay member

When we allow people to tell us it is going to upset people if you tell them the truth, can you see where we might go the next time and the next time?

— Another member

Yes I can. But I still worry terribly about the person whose relative has died.

— Lay member

And that sums up all that was wrong with this proposal.

I think this was the biggest dilemma we had – the ones that were unsuccessful whatever the treatment was. There could have been people who had had the standard treatment and still died.

— Another member

THE RESEARCHER'S VIEW

The Department approved it. The ethical dilemma we had was that when you go to a scene and somebody's on the floor dead, and you randomise one of two treatments and that person ends up dying, do you tell the family what you've done? But you haven't had time to get consent from the family because it's a time-critical situation.

I rang the NHMRC and got some advice and because it was time-critical research we could get it under one particular rule. The opinion of the Department's ethics committee was that if we did our randomisation patient-selection, we didn't have to tell the family we had enrolled them in a study, because they were happy that the new treatment arm was no more detrimental than the current treatment and might be better.

The only concern of theirs was the letter to the family if the patient got to hospital. They were just concerned about the wording and making it too complicated.

DM&A: And so you then had to go to the hospitals?

One debated it very little. One had a bit more to-ing and fro-ing but not much.

DM&A: What happened at the third hospital?

I told the Department we had a problem with [the third hospital] over not telling the families about the trial, and they came back and said, "That's fine with us".

DM&A: Your argument was that [telling the families] would cause unnecessary distress to the families?

Yes. And it was an occupational health and safety issue for our people at the scene because Granddad's dead, there was a 90-odd per cent chance that was going to be the outcome

anyway, the treatment we wanted to try is no worse than our current treatment. But the family would be looking for somebody to blame. It's a point of grief and they might lash out. So it was a matter of safety for our crews.

What we do in the field is none of [the hospitals'] business. It's the Department's business, because we're not bringing that person to hospital. So I was a little bit miffed that they had that issue, but they were entitled to raise it.

What they wanted us to do for those who made it to hospital, to ICU, was to give the family a consent form and an information sheet about the study, which was fair enough, because they could then have the situation explained to them in a controlled environment.

DM&A: So it was retrospective consent?

Yes. And that conforms with the rules of the NHMRC.

DM&A: And it was retrospective consent to use the data?

Yes. It was to give our medical person in the hospital access to that patient's data.

DM&A: And did the Department overrule the [hospital]?

No. I wrote to the chair of the hospital ethics committee advising him that the Department had ruled that we are not required to notify the relatives of those who are declared deceased on the scene about their inclusion in this study. I wrote:

> "Of course we are notifying the relatives of those who survive to hospital. "Interestingly, [the chair of the ethics committee at one of the other hospitals] agreed with you on this, but was happy to let the [Department's] ruling stand because it's not a hospital issue.
>
> "What are your views given this ruling? I can fully understand both sides of the argument."

The response was:

> "The fact that [the other chair] shares my views, even if he has agreed to let you proceed, increases my concerns. At present I am not going to give you an approval. I will consult some of my committee members to see if they are prepared to let you go ahead at [this hospital]."

So that was denying us access to the patient data, essentially.

Once he'd consulted his colleagues on the committee he wrote:

> "We are unanimous in our opinion that we cannot approve this study in its present form. It is felt it would be only a matter of time before the relatives of patients who do not survive become aware of the study and that their relatives have been enrolled without their knowledge and given ineffective treatment.
>
> "We agree that the study has merit. . . The sub-group of the committee discussed ways in which it might be possible for the study to proceed. It was thought that

> it would be impossible to obtain any form of consent at the resuscitation scene and that the only satisfactory process would be to make public announcements, television, print media and talkback radio, to present the issues to the public at large.
>
> "I feel that any feedback is likely to be variable but that there is likely to be general support for undertaking the study."

DM&A: What was the final outcome from [this hospital]?

[Reading from the ethics committee letter]

> "The following documents have been reviewed and approved: application form, media release" -- which is what we did to satisfy the concerns – "and the patient information sheet and consent forms."

So we got approval.

DM&A: What was the media uptake of the release?

There were two small things in the [daily newspaper], I don't know about talkback radio, but there wasn't a huge response.

DM&A: If you wanted to do another study like this, what would be a better way to handle ethical approval?

I don't know – and I knew you were going to ask! Because you want individual patient records you have no option but to go to the individual ethics committees, unless there could be standardised ethics procedures so you could go to one and send that to the others.

We'd still have to go the Department, so you'd still have two applications. But I had to write five different approvals for this using five different formats. And I was at the point last year of saying, "Forget it". But if it does work the way the Norwegians think it does, it'll be good.

Separately from the study, the national resuscitation guidelines have changed. Our study was looking at getting there, giving them three minutes of CPR and then shocking them. Under the new guidelines, we shock them once, do two minutes of CPR. So in a sense this has already crept in.

HOW THE QUESTIONS WERE DECIDED

The central issue this committee was to resolve was that of consent. They acknowledged that it was impractical to obtain consent before treatment and they thought it was unacceptably hard on bereaved relatives to obtain consent *post hoc* in cases where the patient had died.

The committee proposed a program of media publicity to raise public awareness about the trial and to give the public an opportunity to debate these matters before the trial began. The committee's view was that a house-to-house letterbox drop was impracticable, but that some effort should be made to arouse public awareness so that there might exist some general

knowledge in the public mind about what would happen in the event of a family member suffering a heart attack and being attended by the ambulance service.

As a result, the ambulance service issued a media release to this effect, the media take-up of which was unrecorded but on an anecdotal basis was described as limited.

However, the stand taken by this ethics committee did lead to a more substantive modification of the consent process. It was agreed in the end that the families of patients who died would not be informed about the research; only the families of patients who survived to hospital would be told. These families would also be asked to give retrospective consent to the patient's being recruited, and prospective consent to the researchers' gaining access to the patient's records.

As can be inferred from what some HREC members said, the committee remains concerned about the use of executive power in deciding ethical questions. Some HREC members said that in this case State power had been used unjustifiably to override individual rights to give or withhold consent.

The presentation of the Norwegian data allayed some of the concerns about the underlying science, and the fact that the protocol conformed to the *National Statement* on research involving acutely ill people satisfied some, though not all, of the committee members.

PSYCHIATRIC DISORDERS AND GENETICS - CASE STUDY E

INTERVIEWS

Interviews were conducted with the Chair, in the presence of the executive officer, and with five members of the HREC, as well as with the researcher whose project was the subject of our discussion.

The Chair was a clinical psychiatrist with 25 years' experience and about 20 years' experience on ethics committees.

The members were:

- An Anglican priest who had worked with homeless people, alcoholics and drug addicts, and as a prison chaplain. He had a background in social research and had been on the committee since the beginning of 2006.
- A barrister who had joined the committee to replace a former legal member, eight years ago.
- A lay member, retired, with a PhD in history. He had been a member for six months.
- A clinical psychologist, mainly working in research, who had remained on the committee after an amalgamation of the previous two separate committees, science and ethics. He had worked for two years on an ethics committee in the US.
- A hospital-based pharmacist who had joined just over a year ago.

The researcher whose case was the subject of discussion was also interviewed.

DESCRIPTION OF THE RESEARCH PROJECT

The case discussed here was representative of a class of cases increasingly coming before this ethics committee, because it belonged to what the researcher described as one of the great new frontiers in psychiatric research. It was based on the premise that major psychiatric disorders such as schizophrenia and bi-polar disorder have a very strong genetic basis. Unfortunately, unlike Huntington's Disease, they are unlikely to be caused by a single gene but by a number of different genes in some way interacting with the environment.

The capacity to identify those genes was extremely limited because of the number of genes, and each gene had multiple mutations. To solve this problem, the researchers thought they could try to break down a disorder like schizophrenia into its component pieces. Schizophrenia had multiple symptom domains – psychotic symptoms, negative symptoms, cognitive dysfunction.

If the researchers collected DNA from patients as well as comprehensive clinical information on each of these symptom domains in people with schizophrenia, they could examine the DNA for specific gene mutations which might be strongly correlated with very specific symptoms.

Obviously that cannot all be done at once, so the researchers were looking at mutations in one particular receptor in one system to see if it correlated with one particular deficit.

What they would like to have the capacity to do in the future is to look at another receptor, another deficit. So they want to collect lots of DNA from lots of different patients because they don't know which genes are related to which symptoms, and will need a large pool of DNA to do these analyses.

The other important area of research in this field concerned treatment. It was known that treatments were effective for some patients but not for others with what appeared to be the same disorder. It would be beneficial to be able to work out why some people responded and others did not, because treatments could then be targeted according to clinical response.

It was for these reasons that the researchers applied to the ethics committee to hold DNA and clinical data on the same people.

ETHICAL QUESTIONS IDENTIFIED BY THE HREC

In this particular case:
- Informed consent from people with mental illness
- Unspecified future use of DNA

In this class of case, but not in this particular case:
- Potential identification of participants, even from de-identified data
- Loss of jurisdiction over DNA material
- Motive for collecting DNA in the first place

There was broad agreement between the researcher and the ethics committee on the nature of the ethical questions.

Two of the issues concerned consent in different ways.

> *First, how is informed consent obtained from people who have a psychiatric disorder which at times may impair their decision-making ability, or who may have been detained and treated involuntarily?*
>
> *Second, is it possible to obtain informed consent at all in relation to the storage of people's DNA material, when it is not yet possible to know what it may be used for in the future?*

Two more issues concerned the storage of DNA:

> *Could individuals be identified by looking at the DNA and clinical information together, even where the clinical information had been de-identified?*

What happened to the DNA when it was collected as part of an international drug trial, and was then sent for storage overseas where its fate and usage would be beyond the reach of the ethics committee?

A further issue raised by a member of the HREC, concerned the motive behind some of these cases – though not the present one. This HREC member drew attention to the fact that the committee needed to be convinced that the stated reason for collecting genetic material was genuine. In this person's view, motive could be deduced by reference to scientific merit.

THE COMMITTEE'S VIEW

In relation to consent, the starting point for this committee was that patients with a psychiatric illness were able to make decisions about their involvement in a research project, so long as certain safeguards were in place.

For the majority of our patients, we would expect that the patient makes the decision. Even if you're paranoid it doesn't mean you can't make informed consent. But it means you have to have someone able to sit down and ethically talk you through what the research protocol involves and to respect the patient's wishes.

We're looking for researchers to be sound in this area, and they mostly are.

— HREC Chair

But in common with virtually every ethics committee member interviewed for this report, the HREC members expressed serious reservations about the length and complexity of the patient information sheets.

If you wave one of these long plain-language statements in front of a person with a mental illness, they are likely to say, "Oh well, this person seems trustworthy", and won't read it.

We work with people to try to make them shorter, but the language is still complicated.

— HREC members

Unspecified future uses of DNA was also something that deeply troubled this and other committees.

People in laboratories have a set of functional ethics, but a lay person like me is looking at the effects on the world outside, and sometimes it's not even the same language. For example, anything touching on the genetic area: new things can be done with genetic material and we have to make decisions that have very long-reaching ramifications.

— HREC member

The question of genuine de-identification of data was a further issue causing deep concern.

> *When you do research on genetic material, it isn't of any value without the clinical picture. If you want to see if there is a genetic element in depression, you need to know a lot of clinical information about that patient so you can match it to the genetic material and identify certain characteristics of the clinical picture that may be related to a genetic marker.*
>
> **— HREC Chair**

The fourth question concerning the shifting of DNA material offshore did not apply in this particular case, but had applied in others of the same class, and the committee had previously withheld approval because of it.

This had led to considerable confrontation with researchers because if they could not deliver the DNA to the international drug companies sponsoring the research, the sponsorship funding might cease. This did not impress the committee at all.

> *Sometimes we're very unhappy with that, particularly if we don't believe that the researcher is reliable. We will say we're not happy for you to do that component of it. You can do the rest, but we're not going to approve the data base.*
>
> *The people on the committee see themselves as representing the patients and their families. And if we were unhappy that would be the end of it, regardless of the money.*
>
> **— HREC Chair**

> *If the scientific merit of the core research project has the appearance of being really subsidiary to the collection of this genetic material, and the real purpose is to build up a repository of genetic material for future use, it could be seen as an ulterior motive.*
>
> *So the technical excellence and value and benefit of the research, we as a committee thought it would have to pass that.*
>
> **— HREC member**

THE RESEARCHER'S VIEW

The researcher trained as a psychiatrist and held a PhD about the possible biological bases of psychiatric disorders. He had 15 or 16 years' experience as a researcher and had served on an ethics committee for about three years.

He and the ethics committee broadly agreed on what the ethical issues were in his study exploring possible correlations between the incidence of certain psychiatric disorders and genetic characteristics.

Concerning consent, he said this:

> *There is the issue of patients not believing they have a mental illness, not having the insight that they are ill and so not consenting to treatment. So that presents unique challenges.*

Some of these patients are detained under the Mental Health Act and are treated involuntarily, so they are treated against their consent, and that presents a second set of unique challenges.

DM&A: How do you overcome that?

We present ourselves as being distinct from the treating team, as not being involved in their being detained. We are trying to understand these illnesses better. If the person says no, that's the end of it. We don't compel them in any way.

In psychiatry, all current treatments are standard treatments, so any trial treatment is not going to represent a material advantage so we're not compelled to trial a new treatment which might be "life-saving". So we're not faced with that ethical dilemma.

We do have treatments we think are better – and that's the one we're trialling – but we make the assumption that any advantages we think may be there are not outweighed by the compulsion.

DM&A: And that holds even if you make the clinical judgment that the refusal is coming out of the illness, not out of the person?

Correct.

DM&A: What's the general attitude of patients and next of kin to research in this area?

They are generally very keen to participate. We find the greatest resistance coming from non-research or clinical staff, and that comes from the custodial or paternalistic approach to patients. So we have quite a lot of resistance from staff which takes a lot of working through.

Over many decades there has developed a culture which understands mental illness through non-biological frameworks. In the last 20 years, biological research has re-emerged in psychiatry and that has engendered resistance. There are lots of mental health professionals who believe the biological component is oversold.

The third area, not unique to psychiatry, is the issue of obtaining tissue for future research which we don't know about yet, for unknown projects. That is a new challenge.

The storage and future use of DNA also had implications for consent:

How can you validly obtain informed consent to something neither they nor I know what it may involve. We can talk about current possibilities but we can't project three or five years into the future.

It should be noted, however, that any subsequent use of the tissue would need ethics committee approval.

De-identification of data presented a further set of ethical complexities. The researcher was frank about the limitations of the de-identifying process, and about what should be done with information that might be discovered that had implications for the welfare of the patient and his progeny:

At one level we can rigorously de-identify people from their clinical records, but we also need to retain the link between the two [the DNA and the records]. So we're sort of saying we're going to de-identify, but we're not really.

Then what if something major turns up? We find there is a gene that causes a cognitive deficit in young people with schizophrenia and if you develop this then in 25 or 30 years you're going to have a ten-fold increased risk of developing Alzheimer's Disease or will be at a much increased risk of suicide. What happens when you obtain information which is highly clinically relevant, not necessarily for that individual but for their progeny? How do we deal with that information? What do we do about disclosure to the patient, to clinicians, to progeny?

DM&A: How did these play out at the committee?

They were discussed at great length. These issues are not new to other branches of medicine, and the type of research is not particularly new, but it is new to psychiatry. So we used the arguments used in other branches of medicine, that we are obtaining consent and in the process will discuss these issues with the person who is consenting, in particular the issue that we may not have any further contact with them, that the material is being stored in a de-identified form and the implications.

If we did find something seriously abnormal we would not have a way of coming back to the patient and telling them they had a particular problem. And similarly that would apply to their progeny. Although these issues are real, they are not necessarily going to be confronted by the individual or the researcher.

Those arguments the ethics committee could understand and they worked through them. There was a lot of consternation the first time one of these projects came up, and a lot of time was spent discussing what might happen over the lifetime of the project.

The reality is that the science is well behind the ethical dilemmas that we're talking about. It is going to be a long time before we find anything substantive. That obviously excludes serendipity. Assuming that doesn't apply, I think we're years, decades, away from finding these critical gene mutations.

HOW THE QUESTIONS WERE DECIDED

The Chair and members of this committee set out a number of criteria that they used to decide the first consent-related question, which concerned the competence of the patient to make an informed decision. These criteria included the *bona fides* of the researcher, and the independence from the research team of the person approaching the potential participant.

We have a particular role of ensuring that all the researchers present to us in person, and we use that time to judge whether they are bona fide, whether they understand the delicacy of dealing with someone who may have impaired cognitive function as a result of their illness.

We get the researcher to spell out in great detail what is to happen.

They have to declare any honorarium from the drug company, or any money per patient.

We require that the person obtaining consent is not a member of the research team. We can have the research team inform the patient about the process, but we require that someone else be the one who actually gets the yes or no. It's usually a person at a clinic our people are attending, a case manager, not necessarily a treating doctor or nurse or other professional.

The person who gets the final consent is independent and is a confidant of the patient.

Our patients have a right to participate in research, so our concern is just to ensure that they are given time to work through the issues before deciding on consent. If they say no, that is the end of it.

If they say yes, but their level of decision-making isn't to the informed-consent standard, we go to the next of kin, and if you can't find next of kin, the treating doctor can obtain procedural authorisation so long as it is not to the detriment of the person, and a range of other issues.

And that clinical person wouldn't be part of the research team. We're very clear about that.

— HREC Chair

The term "procedural authorisation" refers to an administrative process. In the State concerned, this authorisation had been in the hands of the State's administrative appeals tribunal, but had recently reverted to the hospital executive. The appeals tribunal had relied heavily on the original assessment of the ethics committee, the patient had not been represented at the hearings, and so in large measure these proceedings had been reduced to a rubber stamp.

The second consent-related question proved ultimately to be insoluble, since it was impossible for anyone to say what future uses the DNA might be employed for. The committee considered, however, where the tissue would be held and who would have access to it. Where the tissue was to remain within the jurisdiction of the committee, it was more likely to give approval than otherwise.

The question of genuine de-identification of data was resolved in this case by the committee's accepting that the material would not leave the jurisdiction, and so access to the data would remain within the purview of the committee. Thus any attempt to link DNA material with records identifying the person would come before the ethics committee.

DM&A: The ethics committee approved the research on the basis of de-identification. Were there other bases for their decision?

No. The important issue was that there was a two-phased consent process. The patient consents to the study in question, and the next consent is for the storage of their DNA to be used in subsequent research. So the patient is absolutely clear that participation includes two processes and they can consent to either.

I would think any subsequent application based on this would sail through using the principles that were developed.

— Researcher

CONSENT ISSUES SURROUNDING ACUTELY ILL PATIENTS - CASE STUDY F

INTERVIEWS

The Acting Chair of the ethics committee was interviewed, along with the institution's ethics manager.

The Acting Chair was Nurse Director, Corporate Nursing Research, of the hospital. She had been a member of the ethics committee for four years. The ethics manager's position was part-time (one day a week), occupied by a biologist specialising in oncology research. He had a particular interest in ethics arising from the use of human tissue for molecular diagnostics in cancer.

Two members of the HREC were interviewed together. One was a clinical nurse consultant in research who had been a member of the nursing scientific sub-committee for three years, medical research sub-committee for four years and the ethics committee for 18 months. She was doing a PhD based on an epidemiological study of elderly patients presenting at emergency departments.

The other was a medical practitioner and deputy executive director of the hospital group. She exercised a medical director role in the hospital and had executive responsibility for clinical governance. Sometimes this person acted as Chair of the HREC. This was her first time on an ethics committee, and she had been a member for just under a year.

DESCRIPTION OF THE RESEARCH PROJECT

This case study is based on a class of cases, not one particular case. The facts are drawn from two cases.

The hospital has an established research tradition in the area of intensive care (IC). The two cases under discussion involved the proposed use of drugs on unconscious ICU patients, one to counter septicaemia and the other to stop clotting.

In neither case was there conclusive evidence that the proposed treatment was likely to be better than the existing treatment. However, in the case of septicaemia there was doubt that the existing treatment had any beneficial effect at all. However, it did no harm and as a result had been used as a matter of routine for many years.

In the case of the proposed anti-clotting drug, there was a known risk of stroke, but it was not known whether it was likely to save more people than it harmed. The alternative treatment was to do nothing.

Designing a research experiment in these circumstances was made more complicated by an established ethical practice forbidding sub-optimal treatment to an acutely ill person. The ICU patients were by definition acutely ill. The difficulty arose from there being no prior knowledge about whether the existing treatment or no treatment was better or worse than the experimental treatment. It follows that it was impossible to say which treatment was sub-optimal, but in experimental research both had to be given – one to an experimental group of patients and the other to a control group.

A further issue raised by the committee – though not strictly relevant to these two cases – was the issue of consent when an ICU patient is competent but desperate. The example given was that of a mother dying of cancer who wished to do anything to prolong her life so as to be with her young children.

On top of this, a recurring dilemma facing the ethics committee in this institution arose from the fact that the jurisdiction within which it operates makes no legal provision for next-of-kin to give consent to the involvement in research of unconscious or otherwise incompetent ICU patients.

ETHICAL QUESTIONS IDENTIFIED BY THE HREC

- Consent for incompetent patients in the Intensive Care Unit and Emergency.
- Consent in circumstances where the patient's condition is desperate.
- Avoiding sub-optimal treatment for acutely ill people in the absence of data on the efficacy of available treatment options.

THE COMMITTEE'S VIEW

The central ethical issue was framed in these terms by the ethics manager:

> *The ethical issue for us is, how do we establish that the trial's design and intent, and the integrity of the researchers, was directed towards the best interests of the patient, as opposed to advancing some idea in medicine?*
>
> *We then have to consider the beneficence and maleficence arguments. What's in the best interests of the patient can be a difficult call at times.*
>
> *People who are highly dependent on medical care may be exposed to severe threats to their lives, so that recruiting them seems unfair, but the other side is they should be entitled to be involved in research that may be to their benefit or provide a benefit to humanity.*
>
> *So we have to balance the justice to the individual on both arms.*
>
> **— Ethics manager**

For members of the ethics committee, the issue was framed more directly in terms of patient safety.

Many patients were at the end of life, and in ICU. They had septicaemia. There was a drug that was used when all else failed, but there was no research to say that it was any better than not giving anything. The existing drug is just given just because we have always given it and because there is no alternative.

Then a new drug became available.

DM&A: You have no idea whether the new drug will be better, worse or no different from the drug you already don't know anything about?

Generally, yes, although the researchers may have a little additional information from the drug companies saying that preliminary trials show x, y and z.

We have to give this patient some treatment or no treatment. What can we do? I know the National Statement says that if it is deemed to be reasonable that this treatment could enhance the patient's quality of life or welfare, from a medical perspective they can give it. But when you add that it is for research, that's when people become more sensitive.

DM&A: Because research carries the connotation of doubt?

Yes. It solidifies that and it also unravels unless you can ask this patient and explain to them that the drug may have no benefit and may even hasten their death.

So you have a vulnerable patient, you have a very novel treatment. We can't use next-of-kin [because of legislative inadequacies].

— HREC members

THE RESEARCHERS' VIEW

The two researchers interviewed were of the view generally that the ethical considerations had become transformed into legal issues, and were now a threat to the future of research in this field.

Both were senior and experienced Intensive Care specialists. One had started doing a law degree because of his frustrations with the legal minefield surrounding his medical work. The other was himself a member of an ethics committee.

There are a lot of difficulties doing research in this area and getting it through the ethics committee and I think that's a deterrent to younger staff. A lot of paper work, and the requirements seem to be increasing.

There is a difference in understanding, as well, between the medical profession and legal profession and ethics people on requirements. We seemed to have started with a common purpose but diverged. The purpose of the regulations seems to have got lost in the detail.

Most of the requirements seem to be legal, rather than protecting the patients from exploitation, which is where it should be. So people see complex consent forms as a protection for themselves as a researcher rather than a way of communicating with patients and protecting them.

— Researcher 1

We think pretty much along the same lines. And certainly the legal requirements for the consent of the incompetent patient is providing a lot of problems. The current framework and the interpretation of it is getting to the stage where it's going to halt all research in intensive care, virtually, unless the patients are conscious, and we don't have too many of those.

— Researcher 2

We haven't got options to obtain consent when a patient is incapacitated. We can't get direct consent from most of our patients.

DM&A: And the law prevents you getting consent from next-of-kin?

It is legal for treatment but not for research.

DM&A: Where is the HREC at in clearly identifying the issues and in having some kind of agreed criteria for deciding them?

All the parties have agreed there's a problem. We now have to find a way to solve it.

— Researcher 1

They have gone to the length, on one occasion, of saying, go ahead with the research and get consent from the relatives to embark on the research but that if, when the study was completed we then couldn't go back and get consent from the patient, we would have to disqualify all those results from those patients, which automatically completely collapses the trial, because anyone who has died or hasn't recovered mental competence has to be eliminated.

DM&A: And that would be a high proportion?

It could be. And would completely invalidate any results that were meaningful.

— Researcher 2

HOW THE QUESTIONS WERE DECIDED

The ethics committee broke these conundrums by the application of established scientific method, and by confronting the researchers starkly with their responsibility for the patients' welfare, including the question, "Would you give this to your mother?"

With the patient comatose and the law silent on whether next of kin could give consent to research, the issue of consent was side-stepped and the HREC's decision rested on two other criteria – patient safety, and risk and beneficence. The safety issue was dealt with by requiring the researchers to provide literature reviews on the proposed treatment with a particular emphasis on side-effects. The risk-and-beneficence issue was dealt with by asking the researchers to draw up a risk matrix.

We asked the investigators to draw up a risk matrix. And the National Statement says you can do this kind of research without consent but it must be minimally invasive. That can be very difficult if a trial involves an intervention – say, one antibiotic over another. We need to know whether the literature supports that intervention in this new setting, whether the basis for the hypothesis is adequate.

We then have to consider the beneficence and maleficence arguments. Looking at those with the risk matrix, if the risk was low, helped us in our deliberations.

DM&A: You are obliged not to give ICU patients anything that was regarded as sub-optimal treatment, but that you couldn't know which was sub-optimal?

Yes. So going back and doing meta analyses of several reports of outcomes from one intervention versus another, which have been empirically chosen by departments or treating physicians – what we think might work. The meta analyses establish a pattern of care which we consider to be best practice. The question is, how then do you establish whether a new treatment is any better or harmful?

For instance, a researcher here has been looking at anti-thrombolytic drugs and seeing whether giving them is better than not. Now, there is a side-effect to these but no one's done a test to see whether it's going to save more lives than it harms. And you can manage the side-effect.

Preventing clotting is very important, but if they then suffer a stroke there's a major side-effect.

So we're guided by the researchers. We've discussed having the researchers come and describe to us the intent of their program.

The researchers hold ultimate responsibility for the conduct of the trial. The ethics committee is giving an opinion, and we have to establish what our legal liability is in terms of giving negligent review. If we have satisfied ourselves through all the various points on the checklist and we can't see any reason why the trial should be thought unethical on the basis of the National Statement, then we have acquitted our duty.

We push back on them the research-merit and integrity question. That's quite a good litmus test. I said to one researcher, "Would you give it to your mother?" And if they can't convince themselves that they would, then they have no business offering it to anyone else.

— Ethics manager

DM&A: As an ethics committee how do you decide this?

The issue becomes patient safety. It may or may not benefit the patient. The researcher needs to persuade the committee there is some merit to the drug and inform the committee about any interpretation of side-effects.

As a committee, if the side-effects are too vast, or there is a high probability of side-effects which minimises potential benefit, then on that basis we may say no.

DM&A: I understand also that it is unethical to prescribe a treatment for a vulnerable person like an ICU patient which is in any way sub-optimal. Is that right?

Yes.

DM&A: But if you don't know the comparative merits, how do you make a judgment about sub-optimality?

That's a hard question. In the past we've asked for a literature review to be done on the issue so that we are better informed to make the decision. We also rely on the researcher, and how the proposal conforms to our requirements for patient information sheets and application forms.

— HREC members

TRADITIONAL CHINESE MEDICINE - CASE STUDY G

INTERVIEWS

The HREC Chair was interviewed, as were two members of the HREC, and the supervising researcher who was responsible for the project under discussion.

The Chair was a kidney transplant specialist and immunologist. He had been Director of Research of his institution for six years. He was chair of one of the HRECs at the time the case was reviewed.

One of the HREC members had a background in science, and had done some research, though not involving humans. He sat as a lay member.

The other member was a solicitor, and sat as the lawyer member. He worked for a private health legal firm, mainly on compliance and insurance and commercial work. A mentor in the legal profession had sat on the committee and, when he retired, had encouraged this person to join.

The researcher was a general practitioner who worked partly in clinical practice and partly as a senior lecturer in the department of general practice at a major teaching institution. Her research interests were women's health and complementary medicine.

The case under discussion was being conducted under her supervision by a medical science student doing his full-time research year.

DESCRIPTION OF THE RESEARCH PROJECT

The central research question was to establish whether any correlations existed between the appearance of the tongue, which plays a large role in Traditional Chinese Medicine (TCM) diagnosis, and any disease diagnosed by Western techniques. The researcher explained it thus:

> *The concepts are quite difficult because both systems of medicine use similar language but they mean different things. If we are talking about the liver in Western medicine, we are talking about an organ that we can see and do tests on. If you talk about liver in Chinese medicine, they have meridians of energy through the body and there would be a liver channel but it doesn't mean this liver. Disease occurs when the energy flow in the meridian is disturbed.*
>
> *So we were interested in the tongue, which is pretty neglected in Western medicine, and whether what could be identified reliably from the tongue in the abnormal group-- spots or fur or other signs -- were much more common in a group with a known disease than in a normal group.*

The researcher was advised to seek out a hospital specialising in liver failure because this condition was very specific. It also was clearly diagnosable using Western techniques, and it

was possible that using TCM techniques the condition could be diagnosed by examining the tongue.

The group with known liver failure would be recruited from this hospital's hepatitis clinic, and the "normal" group from people coming to the hospital's pathology laboratory for blood tests.

Each participant's tongue would be photographed twice, and the diagnosis of liver failure or no liver failure would be made on the basis of an analysis of the photographs.

The results of this analysis would then be compared with the Western diagnosed condition of the participants to see if any correlation existed between the two.

THE ETHICAL QUESTIONS IDENTIFIED BY THE HREC

- Scientific merit
- Application of Western ethical principles to Traditional Chinese Medicine

THE COMMITTEE'S VIEW

For the Chair, the overriding ethical question was scientific merit, a consideration he weighed against any risk to the patients.

> *You had the university trying to find a project for someone. They put together a project which basically said the Chinese people have for years been looking at people's tongues. So they thought, let's take something that's got a really hard end-point, say terminal liver failure. Stick your tongue out and let me see if I can tell you you've got liver failure. They were going to take a whole lot of photographs of the tongue.*
>
> *So for about 10 minutes the committee said, "'Do we really think this is worth doing?"*
>
> *The next question was: "Let's say it is okay. Is it going to do anyone any harm? Is there a risk? Someone who has volunteered is asked to stick their tongue out and someone is going to have a look at their liver-function test in their medical records. Is anyone going to get hurt by this?"*
>
> *The short answer was no.*

One HREC member was inclined to agree with the Chair that the whole proposal was not good science, but the other was inclined to be critical of what he saw as a too narrow approach to medical research.

> *It was bad science. That was the issue.*
>
> **— Member 1**

> *I didn't necessarily agree. It's often the clinicians that lead the discussion and I don't think that's always a good thing. They are very sceptical of something that is an alternative therapy. They were trying to establish whether there was a correlation between what they use traditionally to look at an unwell liver, and what scientists use. I'd be interested in finding out.*
>
> **— Member 2**

DM&A: So you have raised the question whether the ethics committee was open-minded enough to give fair consideration to the case?

There's no reason why something can't be evidence-based, whether it's alternative, complementary or conventional medicine. But if it's the clinicians who always present the studies, sometimes I think they can create a problem because you're always coming from one part of the committee.

Now it's changing. There's a lay person being designated as the return point for comments on the patient information sheet and that is allowing the lay person the capacity to comment on the overall proposal. That is balancing things to some extent.

— Member 2

THE RESEARCHER'S VIEW

It emerged that there was some misunderstanding between the researchers and the HREC over exactly what was originally proposed. The matter was further complicated by the fact that the institution where the research was to be carried out was different from the institution where the researchers were based, and the researchers were unknown at the research site.

I spoke to a friend who is a full-time clinician and acupuncturist who said he had always wondered, particularly with Traditional Chinese Medicine, whether there are any correlations between the appearance of the tongue, which is a really important part of examination in TCM, and anything in Western medicine.

A lot of people mix and match a little bit of TCM and Western medicine. So I thought, what a great idea. We needed something that was do-able without much money. The student thought it was a great idea.

We were advised to go to [a hospital specialising in liver failure] where they had a much higher rate of abnormalities than is normally found these days.

I approached the head of gastroenterology at [this hospital] and he was a bit bemused. He seemed not to think much of Traditional Chinese Medicine, but he agreed to go along because it was low-risk and wouldn't interfere with the running of his clinic.

So I was in this position of having to apply to an ethics committee at a different hospital from my own, supervising a very inexperienced researcher, and at the same time I was trying to finish my own PhD.

It also emerged that there was a misunderstanding about what the central ethical issue was. The committee chair and members had been clear: the primary issue was scientific merit. However, the supervising researcher said the main issue had concerned recruitment of participants.

The main ethical issue was in the recruitment of patients because we were relying on the doctors to say, "Would you mind helping this student out?" It was very low-risk. We wanted to take two photographs of their tongue and have access to their file to get confirmation that they had chronic hepatitis, and a little more problematic was a normal group. And the student wanted

to recruit through people coming in to have blood tests relating to something other than liver function, so we could take photos of their tongues as well.

The issues were not being coercive in recruitment, and when doctors involved in treatment are asking them to be involved there's always a problem. And maintaining confidentiality of patient records.

I don't think the ethics committee understood what we were trying to do. Traditional Chinese Medicine doesn't have a correlation in Western medicine. We weren't trying to say that hepatitis diagnosed here was the same as hepatitis diagnosed there. They don't meet up at all, and I think the ethics committee got a bit hung up on exactly what it was we were trying to do.

HOW THE QUESTIONS WERE DECIDED

The committee's approach was to look at patient safety. Would anyone be harmed by being asked to put their tongue out and have it photographed (the rest of the face was to be masked)? Would anyone be harmed in these circumstances whereby the researcher would be able to see from their clinical records whether or not they had liver failure?

The answer to both questions, in the words of the HREC chair, was "probably not". The procedure was not invasive. Measures were in place to protect patient identity. The patients were not going to be asked to give more than a minute or two of their time. They would already be in the hospital. The procedure would not cause discomfort or pain. No resources of the hospital would be used.

On the positive side, it was conceivable that something might be learnt if the methodology were adjusted, and it might help the researcher, a medical student, get through his course.

The HREC chair and members retained profound reservations about the scientific merit of the proposal, but against all those other considerations allowed it to proceed, having insisted upon changes to the research design to try to provide at least some likelihood that useful data might emerge from it.

We didn't think the science was particularly outstanding. But let's try and turn it into a study that is scientifically analysable. That's largely what the discussion with the researcher was about.

So instead of getting them to diagnose liver failure, we said, "What does looking at their tongue tell you?" We knew that this guy has liver failure and this guy hasn't, and we got them to tell us what they found.

If in the end they can say those seven people will be dead in six months, you get some value out of it. So if it proved to be predictive in some way, you might think, well, this is useful adjunctive therapy.

They had to look at various parts of the tongue and score them according to a particular scale based on their Chinese experience. But they were people who were trained in Western medicine as well as traditional medicine.

— HREC Chair

After this somewhat sceptical description, the Chair went on say that the exercise had not been without benefit to the ethics committee, even if the scientific benefits were marginal at best.

> *One of the positive things is that it made us think perhaps we shouldn't be such damned cynics and proud of our way of doing things.*

The HREC members expressed similar views.

> *I thought it'd be good to consider it. All right, the methodology needed to be fixed up, but there was no reason we couldn't do that and make it evidence-based, to show that some of these things work and some of them don't.*
>
> *This project came closer than any other we have had to being rejected out of hand. The scientists on the committee are very straight-down-the-line.*
>
> *This wasn't going to be invasive and had the potential to yield some meaningful work. We accepted that there had been no research on Traditional Chinese Medicine and liver diagnosis. So we didn't just want to say no.*
>
> *The best decisions can be made with an open mind.*
>
> **— Member 2**
>
> *It was a very non-invasive procedure. They were just going to photograph the tongue.*
>
> **— Member 1**

It is clear from these comments that the question of recruitment, if it played a part at all, was certainly not central to the decision to allow the research to proceed.

GENE THERAPY - CASE STUDY H

INTERVIEWS

The current Chair of the HREC was interviewed, as was a member of the committee.

The current Chair was a paediatric gastroenterologist who had occupied the position for nearly four years, after having been a member and then chair of the scientific sub-committee. He had not chaired the meeting which dealt with this specific case, however. He will be referred to as Chair A. The Chair at the time will be referred to as Chair B.

The HREC member had completed an ethics courses at the Monash bio-ethics centre, the Plunkett Centre, and the NHMRC. She described ethics as her "main love". She had been involved with this ethics committee since her appointment ten years previously, and had held the position of secretary for seven years, during which time this case was considered. Two years ago she employed a lawyer as a dedicated Research Ethics Manager and as secretary of the HREC, as her role as Research and Development (R&D) Manager had expanded. As R&D Manager she was responsible for providing resources to the committee and, for twelve months after the appointment of the Research Ethics Manager, continued to be a member of the HREC.

The researcher whose project was the subject of discussion was also interviewed. He was a medical and bio-medical graduate with a special interest in biomedical research, and had completed his paediatric training. He had a PhD in molecular and cellular biology, and had undertaken post-doctoral studies abroad. For the past 10 years he had been running this hospital's pre-clinical research in this area, trying to translate laboratory progress into outcomes in the clinic.

DESCRIPTION OF THE RESEARCH PROJECT

This research project was at the forefront of world research into the application of gene therapy for clinical purposes. It was part of a study taking place in three countries, and the researcher was one of only a few international experts in his field.

These factors themselves tended to complicate the ethical review process because no one outside these few experts fully understood the science, even though the scientific sub-committee consisted of several other researchers who were leaders in their own fields.

The objective of the research was to find a gene-based alternative therapy for children with a condition for which the standard treatment was a bone-marrow transplant.

Bone-marrow transplants are long-established, having been introduced in 1968, but patients have high mortality and morbidity rates because 80% of them receive marrow from matched unrelated donors. The mortality rate in these patients is 30% or higher, and the morbidity rate higher still. This treatment, then, is considered sub-optimal.

The optimal treatment is received by the other 20% who obtain matched bone marrow – that is, from a sibling, where as many as 95% might succeed in reconstituting at least some immune cells. Even among these patients, however, 30 to 40% may need ongoing immuno-globulin therapy, which carries risks of infection.

Altogether, then, bone-marrow transplants remain a risky and usually sub-optimal option, but there is no established alternative.

This joint research project involving scientists from Europe and Australia was aimed at developing a gene-based alternative.

In this therapy, bone-marrow cells are taken from the patient's body and genetically repaired by inserting a healthy copy of the faulty gene using a retrovirus carrier or "vector". These cells are then re-introduced into the patient, where they return to the bone marrow and reconstitute the patient's ability to produce certain types of white blood cells that were previously missing from the patient's blood.

ETHICAL ISSUES AND HOW THEY WERE DECIDED

- Safety of the participant
- Risk/benefit balance
- Consent
- Response to an adverse effect

The European researchers, working in two different countries, had treated a total of about 12 children, but when the project came before the ethics committee at this site, the treatment had never been previously attempted in Australia.

THE COMMITTEE'S VIEW

The first issue was patient safety.

> *The ethical issue revolved around what was the major risk to the patient? There had been four children done in [one European country] and we knew they had regeneration of their immune cells. So we knew about efficacy. But was this gene therapy absolutely safe for the child?*
>
> *The unknown side-effects were the things people were concerned about. To do gene therapy you have to insert a fragment of DNA in cells and then put the cells into the body and you need a retrovirus to do that. They used one that had been tried in the US and had proved to be the most effective, with the virtual absence of side-effects.*
>
> *The other things is, could something adverse happen with the insertion of the gene? There didn't appear to be any problems at all initially.*
>
> **— HREC Chair A**

Consent was an issue insofar as the committee was concerned that parents in such a desperate situation were prepared to do anything that might save their child.

When you've got a patient in such a desperate position, the parents are also desperate. You have to see it to believe it. If you present something to them, they say, "Just do it". So there is an element of coercion and you have to be careful how it is presented to them.

I think the investigator handled this very well. The investigator talked with the committee and described the balancing act and how he would explain that even if the gene therapy was not successful they could do a bone marrow transplant, but that this was a far better and less invasive procedure.

Putting it that way, they said OK, we take the gene therapy option.

— HREC Chair A

The researcher told us that in fact the parents had approached the hospital, having read about the European trial on the Internet.

The family arrived at this hospital asking whether we could treat their children by gene therapy. They had read what had happened overseas on the Web. It happened that that family were highly intelligent people and they arrived with a fairly solid grasp of what it was about. So it could be explained adequately without losing the integrity of the message.

— Researcher

HOW THE QUESTIONS WERE DECIDED

On the basis that four cases appeared to have been carried out successfully in Europe, it was decided that the safety issue would be considered by reference to the risk/benefit balance.

Given the sub-optimality of the established treatment – bone-marrow transplantation – and the lack of alternatives for a child whose prognosis was very poor, it was considered that on the basis of what was known from the European experience, the benefits outweighed the risks. The HREC member spoke of the need for the committee to restrain itself from becoming carried away by the novelty and quality of the research. She also revealed the extent to which the committee had to rely on the researcher in making its assessment of the risk and benefits.

It was very exciting. This was a breakthrough moment for us in research. Ethically we had to be very careful not to be too excited by the knowledge and science and lose sight of what was best for the patient.

We relied on the researchers to give us background about standard treatment so we could assess known versus possible. We were heading right into the unknown but knowing it was probably better than the standard treatment.

We also had to assess the risks associated with the standard therapy, which were pretty horrendous, but knew only from the northern hemisphere what the risks were of the new therapy.

We were given an overview of the success rate elsewhere, and we had to rely on the integrity of that data [from the researchers].

It wasn't such a leap for us to trust the researchers, because we had built up a relationship with these people over many years. The committee knew the work they had been doing, that the science wasn't dodgy, the results weren't skewed.

If it did work, it could cure the patient.

— HREC member

The issue of consent was resolved by the committee discussing a process with the researcher for obtaining parental consent. The advantages of the gene therapy would be presented to the parents, along with a clear explanation that it was experimental. The parents were told that if it failed, the child would be given the standard treatment – a bone-marrow transplant.

THE ADVERSE EFFECT, AND THE RESPONSE

About one year after the Australian patient had undergone the gene therapy, the researcher in one of the European countries reported that one of 10 patients treated there had developed leukaemia. Subsequently, a further two treated patients developed leukaemia and died from this complication.

It appears that there was a small fragment of the gene that had either stimulated the [leukaemia] cells to reproduce or had produced some inhibitor that allowed the cells to reproduce at will. So that was the unexpected finding. That didn't affect our patient.

— HREC Chair A

This confronted the committee and the researchers with a new ethical dilemma. The Australian patient had not done very well and the researchers had come to the view that one reason for this might have been that he had needed a larger application of the gene therapy.

So the question of a top-up arose -- but by now the European country where the leukaemia cases had occurred had put the trial on hold.

The child we treated partially reconstituted his immune system but he didn't get robust reconstitution. He got some neurological problems and he needed a top-up. But at this time the [European country] had put their trial on hold.

In the event, we decided what we had done was experimental, part of the trial was on hold and this child should be offered the available conventional therapy, a matched unrelated donor bone marrow transplant. He ended up dying from the complications of that conventional treatment.

If I'd asked, the [Europeans] would probably have provided us with some additional vector to top him up, but I thought we were stepping on to difficult territory. It's not only what you do but the perceptions about what you do. We'd given this child a shot with experimental therapy. That shot had failed.

There are people out there who are critical of genetic techniques for whatever reasons, not always logical. Given that the trial was on hold in one country -- and we were part of that trial -- and there had been children with leukaemia, we would have been making a decision to

top up the child up with a less clear vision of what the real risks were in relation to insertional mutagenesis, and I felt we didn't have enough facts available to do that.

You could perhaps rightly become the target of criticism for heading off down that path. Yet it would have been very hard to criticise us for offering conventional therapy.

It's an example where the personal ethics of the investigators are influencing how they behave, but in a positive manner. It is not as though they've pushed the science at the expense of the children. They've become more cautious.

— Researcher

It should be noted that in the second European country the trial continued, and no leukaemia cases had been reported. The researcher was coming to the view that subtle differences in the vector used might account for this, and he was considering adopting the second country's approach when embarking on another gene therapy trial for which he was preparing.

The committee and the researcher were soon to confront many of these issues again, since the researcher was about to put forward an even more complex proposal for using gene therapy as part of the treatment regime for brain tumours.

HAND HYGIENE IN HOSPITAL HEALTHCARE WORKERS - CASE STUDY I

INTERVIEWS

The HREC Chair, the Executive Officer, and a committee member were interviewed together. In addition, a second HREC member, a research nurse, responded to the questionnaire in writing because she was unavailable on the day.

The Chair had occupied the position for about a year, and before that had been a member of ethics committees at another hospital in her role as director of the hospital pharmacy.

The executive officer had been in the position for one year. She had an undergraduate degree in science, and a Masters degree in moral philosophy. She was also doing a law degree.

One committee member was a pharmacist who had a joint appointment with the university and the hospital for ten years. She had been on the HREC committee for five years.

The second was a registered nurse with 15 years' experience, who specialised in emergency nursing. She had sat on the committee for three years, and had a particular interest in the ethics of research.

It was not possible to interview the researcher.

DESCRIPTION OF THE RESEARCH PROJECT

The study was a continuation of the researcher's current work on improving hand-washing hygiene among the hospital's staff. There had been staff education programs and a project focusing on hand hygiene at the bedside, but it was not clear how effective these had been in conveying the message about the importance of hygiene and the extent to which people were complying with the hygiene rules. The study proposed to establish the critical elements of a program which would lead to sustained compliance.

From the research work already undertaken by the researcher, the optimal way to conduct this study was by covert observation in a single medical ward. It was proposed to conduct covert observation of nursing staff in the ward over 24 hours, divided into three observation periods, to obtain rates of hand hygiene activity and the level of inherent and elective hand hygiene behaviour. After a further six months, covert observation would occur again to assess any potential improvement in practices. During the interim six month period, staff would be given education and other hand hygiene assistance designed to increase compliance.

Covert observation would be carried out by independent professional observers in the ward. Staff would be given minimal disclosure about the presence of these observers and told that they were collecting data on "workplace practices of nursing staff within the ward".

ETHICAL QUESTIONS IDENTIFIED BY THE HREC

- Covert observation
- Risk to participants' welfare

THE COMMITTEE'S VIEW

The Committee acknowledged the importance of the need to improve hand hygiene in healthcare workers.

> *It is one of the biggest issues in medical problems that people don't wash their hands.*
>
> **— HREC Chair**

The Committee was also aware that the researchers were prominent in their field, and that any objections from the Committee might be viewed as obstructionist.

> *The researchers are very well respected. They are national spokespersons on infection management. They have a very big presence and reputation. Their persona is very large and out there. And they are absolutely passionate about trying to reduce the infection rate.*
>
> **— HREC Chair**

The first issue was whether the study had to be done using covert observation methods. A related concern was whether it was justified to withhold informed consent from potential participants.

> *We were observing people without informing them. Was the need for a covert observation strong enough that this was necessary to be done?*
>
> **— HREC Chair**

Was there sufficient reason to see this study as an "exceptional circumstance" where the information could not be obtained in any other way than the use of covert observation?

> *The thing was that if they [participants] knew they were being watched, they still won't wash their hands anyway – they do their best but they still make mistakes. The research would still have value. But they [the researchers] wanted the covertness because it would have a lot more value.*
>
> *— HREC Chair*

The second issue was whether there were any risks to the participants as a result of the covert observation. Was it possible that participants could be identified or stigmatised?

> *They had done a previous project that was published. It was completely de-identified. No one who was observed could be identified. But a second study that they did was pulled because someone found out about the covert issue. It was the deception they were worried about. That project did not get completed. They had to stop the research.*
>
> **— HREC member**

Another member was also concerned about the effect on staff:

> *As only one ward was to be studied, if the results were poor it would potentially impact on the professional reputation of the unit involved. It was unclear what feedback would be provided to the staff.*
>
> **— HREC member**

HOW THE QUESTIONS WERE DECIDED

The ethics committee asked the researcher to provide more information justifying the use of covert observation.

> *How are you going to do the covert observation? Does it have to be covert? Is there any other way that you can do it? We agreed that you would get some useful data if it was not covert. But the researcher put up a good argument for making it covert. [The researcher] gave a good scientific reason for doing it this way.*
>
> **— HREC Chair**

The committee noted that under the proposed research method, "prospective information about the study could not be given to subjects as it would influence their hand washing behaviour" and asked the researcher to address what procedures would be put in place to ensure that "all staff will be completely de-identified."

> *[The researcher said that] the covertness would be carried out by market researchers who would hang around the ward and note down what they observed, marking down how many people washed their hands, when and how. They [the observers] did not know the names of anybody. It was totally de-identified. They [the participants] were told that the marketers were there to monitor health practices – very broad and general, very vague [about what was being observed].*
>
> **— Executive Officer**

The committee also asked for information from the researcher about how participants would be debriefed.

> *[The researcher] provided quite good information back to those queries. [The researcher] had consulted with the nurse manager and she was supportive. We had asked for and they agreed that the nurse in charge of the ward would be responsible for some feedback to the nurses involved. They [the participants] would find out afterwards that it was covert observation. They [the researcher] did tell them they were doing the study but not when they were doing it.*
>
> **— Executive Officer**

One HREC member described what she called a long discussion about this project.

> *The researchers were asked to comment on the potential impact on the ward's reputation and on the potential for significant harm. There was no discussion of feedback and the committee asked the researcher to provide information about how they planned to feed back to the participants. The researchers made clarifications to assure the HREC that the data were in no way identifiable.*

The researchers satisfied the committee's concerns through a strong communication and supportive relationship with the management of the clinical area.

— HREC member

The committee was satisfied that covert observation was necessary to the proper conduct of a research project that had genuine scientific merit, and that, by stopping short of deceiving the staff about what the observers were doing, a reasonable balance had been struck between maintaining the integrity of the research and informing those who were being observed.

HEALTH STATUS OF CHILDREN OF DRUG-ABUSING MOTHERS - CASE STUDY J

INTERVIEWS

The Chair, who had held that position for only three months, was not present for the case under discussion, and spoke from files at the interview. She had seven years' experience on ethics committees elsewhere. Her background was in clinical and physiological research. She had been R&D manager for a hospital, and had extensive experience in the management of research governance.

Two members of the HREC were also interviewed.

One was a general paediatrician with a special interest in child protection. She had been a physician for 20 years, working largely at a children's hospital, one of the sites where the study was being conducted.

The other was a lay member with a background in chemistry and biology, now retired, but whose working life had been spent teaching in tertiary institutions.

The researcher whose case was discussed was also interviewed.

DESCRIPTION OF THE RESEARCH PROJECT

This was a retrospective cohort study of information collected by health facilities in the State on notifications, referrals, attendances and immunisations of children of drug-abusing mothers.

The researcher sought approval to waive consent on the basis of the potential importance of determining the use of health facilities, the abuse risk of children and the extent to which preventative measures, such as immunisation, were taken up by mothers.

Because of the anticipated difficulty of obtaining consent from mothers, the researchers specifically asked for approval to access children's health records without parental consent. The researchers argued that the project met the pre-requisites for the guidelines approved under the Privacy Act. The researchers wanted to see records from two hospitals, a government department of child safety, the Child Protection Information System and the Australian Childhood Immunisation Register.

ETHICAL QUESTION IDENTIFIED BY THE HREC

- Waived consent

This was a retrospective study. Data were to be obtained through the registers of external agencies, and patients would not be informed.

THE COMMITTEE'S VIEW

The Chair pointed out that the proposal had first been submitted as a "quality assurance" project. These are generally easier to get through an ethics committee because they are considered a form of audit rather than research. However, the HREC wasn't buying this, as the Chair said:

> *Clinicians everywhere will do everything they can to convince everyone that it is really only a quality-assurance project. But it was the privacy issue, the confidentiality issue, the use of information for a purpose for which it was not originally collected. And consent for that use, and for use of information about a child. And not only were they not going to the child, but they weren't going to the parent.*
>
> *The basis for that was that there was a risk that they would refuse, which of course is never a reason not to seek consent.*
>
> *The previous chair was not happy with this. Even if it was quality assurance, the principle of consent applies.*
>
> *So it was knocked back as a quality-assurance project and had to go to the full committee and to the Director-General of Health for permission not to seek consent.*
>
> *So it went to the full committee and there were concerns about whether it was of sufficient value to warrant not seeking consent and to breach confidentiality.*

There were discussions with the government health department, facilitated by the chair of the HREC of another hospital. The Chair noted that there had been previous situations when information had been released from registers without parental consent because it was in the interests of public health or safety.

> *He indicated that there had been incidents of governance in council recommendations that this type of information could be provided if it was deemed to be in the public interest. He had precedents with other cases over the years, such as drownings and needing to access other information such as pool fencing. It was also used for seatbelts and accidents.*

The Chair suggested that the researcher obtain a governor-in-council order.

The HREC also wanted to see if the research could be done any other way. When it became clear that this was not possible they balanced private and public interests:

> *We asked a lot of questions and asked the researchers to come and talk to us. We decided that, first, there was really no other way to collect the information because it had to be identified so the researchers could go to the different databases. There was no way of coding them. You had to have the names.*

The justification was that it was important [research data] to know and they would feed the information back into the systems. So there was a public interest justification. They convinced us that the public good was sufficient to make it okay to go ahead without consent.

— HREC member

There was also the question of what was in the long-term interests of the children, compared with the possible effects on the mothers:

It was very much that these were "bad" people. We were marking them out as bad parents and we were spying on what they do and marking them as different. But if the kids are at risk, what are you going to do? Step in or just stand back and watch?

— HREC member

THE RESEARCHER'S VIEW

The researcher appreciated the difficulties:

From the [government health department] point of view, and the restrictions around research and NHMRC guidelines, it would be inappropriate to be seeking the sort of information we were seeking without consent from the patient, which in this case would be the mother because the maternal case is the index. We are tagging on the child as a subsequent case. They [the HREC] were concerned that we were not able to seek consent from the parent.

Given the nature of the study, it would be highly unlikely that either the case or control groups would be comfortable with our seeking information from the central register for child protection notifications. Also, the more pragmatic problem of being able to locate parents, particularly substance abusing parents, because of what we know to be high mobility.

DM&A: If you had gone to the mothers and asked for their consent?

I don't think the research would have been able to be done. They [the mothers] would not give consent. Because of the stigma attached. It would not be feasible to do the study.

We believed there was value in doing the study principally because we see it as a high risk group where there is little information.

The attempt is to see whether these infants of substance using mothers had a higher incidence of child protection risk than the general population.

The researcher was surprised to find that the government department was supportive.

Information sharing had been high on the legislative agenda and awareness. In this area of child protection [there is] an ability to share information between departments. In clinical cases. The clinical setting has been put in place. In the research area they might not be addressed.

They [the government department] were quite keen to support this kind of initiative. They provided the directive to be used: an approach to the Governor-in-Council. The Director-General had to sign off on it.

HOW THE QUESTION WAS DECIDED

After some deliberation, the HREC felt the research should proceed on the basis that the public interest in keeping track of at-risk children outweighed the interest of the mothers in controlling the consent process.

After submission to the Director-General and Governor-in-Council, via the Chief Health Officer, the researchers were granted approval to release the information under the provision of the Health Act.

> DM&A: Was it the view of the ethics committee that this was a worthwhile project?
>
> *Yes. But it was difficult to judge whether it was worthwhile enough to warrant waiving consent. That was the balance. That was the difficulty.*
>
> *It was referred for legal opinion about the non-consent issue, and the advice was that a written submission should go to the Director-General for permission to access the records without the consent of the patients.*
>
> *It was deemed to be important enough to support the research.*
>
> **— HREC Chair**

The HREC reflected that the traditional structures and skills available to ethics committees might not be sufficiently wide to allow a properly informed assessment of this kind of case, which was sociological as well as medical.

> *In this area of social research we need to learn a lot more. We have now a professor of nursing on the committee and this is much more her field. It is a totally different field. It's not the kind of research we have done and know and are comfortable with.*
>
> *It's only recently that this kind of research is moving into hospitals. It's very valid, important and interesting research.*
>
> *As a physician, I have a commitment to my patient and I'll be completely honest with that person. So research where people go behind people's back – that's a different model.*
>
> *So it's probably our need to move.*
>
> **— HREC member**

PART III: DISCUSSION OF ETHICAL ISSUES ARISING FROM THE CASE STUDIES

INTRODUCTION

Contemporary ethical dilemmas in the field of research on humans are many and complex.

In their fundamental nature, the dilemmas have been present for a long time, and may be broadly grouped under headings which ethics committees from any era would find familiar:

- consent
- participant safety
- scientific merit
- conflict of interest
- risks versus benefits
- protection of vulnerable people
- disclosure of information to participants and their families
- privacy
- confidentiality.

What creates today's complexity are the new and various ways in which these questions now arise. These are what make the "interesting and challenging" ethical dilemmas which were sought and which are the focus of this report.

Four main factors contribute to this increasing complexity.

- First is the advancement of medical science, opening up possibilities that have not previously existed.
- Second is the increasing breadth of human research, spreading well beyond conventional drug trials and experimental treatments into fields of behavioural, attitudinal and sociological research.
- Third is the globalisation of research, with implications for local ethics committees in respect of the long-run consequences of their decisions.
- Fourth is the level of scientific specialisation required to assess some of the work being proposed.

Advances in medical science have led ethics committees to re-balance their calculations about risk and benefit, and make the giving of truly informed consent by participants acutely problematic. Added to this is the issue of increasingly complicated participant information sheets, which are regarded by some ethics committees as written more for the purpose of risk-management than genuine patient information.

The expanding breadth of human research is causing ethics committees to recruit from a wider range of backgrounds so that they have sufficient expertise across the new range of proposals they are being asked to review. Traditionally, medical research has been dominated by large quantitative studies involving well-established and tightly-designed experimental procedures such as treatment and control groups where outcomes can be statistically validated. Increasingly researchers are presenting projects that involve qualitative methods where measurement is more difficult and outcomes more hypothetical.

Globalisation of research, while conferring many benefits, raises many problems. One is the power of large pharmaceutical companies to exert financial pressure on institutions to conform to a research design, and to agree to despatch overseas the human tissue collected as part of the local research. Once the tissue is gone, its fate and usage are beyond the reach of the institution, the local researchers and the ethics committee. This is considered to be a particular problem in the field of genetic research, which has created the demand for large tissue banks..

The level of scientific specialisation has created real difficulties for even highly expert committees to make well-informed independent assessments of research proposals. This means that committees must depend more heavily than otherwise on the *bona fides* of the researcher, who in some cases may be one of a tiny group of international experts who understand all the elements of the relevant science.

In many cases these four factors interact to create ethical decision-making that requires either an entirely new approach or an integrated approach of a kind the particular committee has never before confronted. Some of the case studies in Part II of this report show how this can play out.

In this part of the report, each of the ethical issues listed above is discussed, and a synthesis produced of what was learnt about them from all 12 of the committees and from the 10 researchers interviewed. Where relevant, cross-references are provided to one or more of the case studies where the playing out of the issue is illustrated.

Before doing so, however, a few general observations are made about the way the 12 HRECs approached their task.

First, it was obvious that everyone – Chair, members and executive officers – took the role of the ethics committee with the utmost seriousness. This was clear both from the way they spoke and from what they said about the prodigious commitment of time involved.

They conveyed a strong sense of guardianship in respect of participant welfare, as well as a sense of responsibility for facilitating research. Strong-mindedness was characteristic. Debates on the committees were frequently described as “robust”, and in the interviews it was easy to see why. These were people of ideals and conviction as well as intellect. They were not easily intimidated. They did not mind indicating when they had had disagreements, but were proud of their capacity to reach a consensus.

It was common to hear that more than a day's reading was required in preparation for a meeting. Agendas of 1000 pages were spoken of. In one institution the documentation was so voluminous, members were not permitted to carry it because of concerns about occupational health and safety: the documents were brought in on trolleys. HREC members nonetheless worked their way through this material diligently.

Second, there was a widely held view that ethics committees should more actively discharge the positive function of facilitating good research. In several institutions this was leading to a more pro-active consultative process with researchers in an effort to solve issues before the proposal came before the committee.

Third, they were conscious of the need to deal with cases expeditiously, and the vast majority of cases were dealt with in no more than two meeting cycles – typically two months. Few proposals were rejected, but many were modified, and HRECs everywhere were looking for ways of streamlining the modification procedure. Some were adopting an open consultative approach with the researchers, as mentioned earlier. Others had appointed as executive officers people with high-level scientific expertise who were able to perform a kind of triage function. Others were doing both.

Finally, they were frank. They had put themselves forward to participate in these interviews knowing they were going to be asked about the really difficult cases. By definition, these were cases where they had had to struggle for a solution. This had involved considerable debate, sometimes among members of the HREC, sometimes between the HREC and the researchers. They spoke about these issues freely and without mincing words. In all cases but two, they had already found their way to a resolution. As it happens, these were the two cases that subsequently had to be withdrawn from this report.

From the HRECs visited, the impression gained was that the public interest was being well served in two important respects: research involving humans was being subjected to serious prior review, and research quality was being promoted. The Australian community is fortunate to have people of this calibre carrying out such a vital function.

CONSENT

The *National Statement* describes the high principles upon which the necessity to obtain consent rests.

These high principles are:

- Each human being must be recognised as having inherent value, and
- Each human being has the right to autonomy – to determine his or her own path in life.

It follows that a person's involvement in research must be grounded in that person's consent to be involved, and that the consent must be free, informed and prior.

Free consent is not forced, coerced or obtained by improper inducements.

Informed consent is based on an understanding of what is to be done, why, and what will happen to the results.

Prior consent is obtained before the research is begun.

This is the ideal. The *National Statement* recognises, however, that it is not always possible to attain to the ideal. Therefore it provides guidance on how decisions about consent should be made when the ideal is unattainable. Many of the "challenging and interesting" ethical decisions confronted by the Human Research Ethics Committees interviewed for this report arose from circumstances in which the ideal was unattainable.

Free consent can be infringed in many ways. In Case E, for example, researchers had recruited into their study psychiatric patients, some of whom had been detained in hospital involuntarily because they were deemed by the appropriate authorities to be a danger to themselves or others. It does not, of course, follow that their subsequent recruitment into the research project was involuntary. Indeed this was not the case. But the opportunity to recruit them arose as a result of their having been involuntarily detained. Does this matter?

The answer – at least in the State concerned – is no. The hospital authorities there have the legal power to compel such people to participate in a trial, and to receive either a treatment or a placebo. Until recently the use of this power was reviewable by an administrative appeals tribunal, but changes to the law placed it back in the hands of the hospital. The tribunal process had depended entirely on the deliberations already conducted by the ethics committee, there had been no provision for patients to be represented and the process had been reduced to a rubber stamp.

Where the patient's own consent could not be obtained – and regardless of whether the patient had been voluntarily or involuntarily admitted to hospital – assent by next-of-kin was sufficient.

This situation imposed a large responsibility on the HREC.

Its approach to all research proposals – whether they were to involve voluntary or involuntary patients or some combination – was essentially the same: that is, that psychiatric patients are generally competent to give or withhold consent.

The HREC started from a position that psychiatric patients in general should have the right to be involved in research, and were on the whole competent to decide this question for themselves. The HREC took the view that many psychiatric illnesses are episodic in their effects and that between episodes patients are generally competent.

However, this HREC had as a standard procedure something seen nowhere else – the appearance before it of the primary researcher for every case. This appearance was used

not only to ask questions about the research but also to gauge the researcher's attitude to the consent question. A lacking in the requisite delicacy of understanding, or in respect for the patients' wishes, provided ground for the HREC to not approve the research. While the HREC considered that most researchers exhibited the requisite qualities, some did not, and their work had not been approved as a result.

As a further safeguard, the approach to the patient was made by a person who was independent of the research team and usually independent of the treating clinician as well: a case manager or somebody well-known to the patient and whom the patient would trust.

The researcher – whose work had been approved -- advised that, when approaching the patient after consent had been obtained, he and his team would go out of their way to distance themselves from any process of involuntary detention.

Their experience was that patients and next-of-kin generally were keen to give consent. However, the custodial staff of the hospital tended to be protective of the patients and there was some tension between them and the researchers over the recruitment of patients into research. This had a tendency to complicate the consent process.

Free consent can also be compromised by factors that have nothing to do with the way the researcher approaches the patient, but by the desperation of the patient's illness. The desperation of the circumstances creates emotional pressure which researchers and the HREC alike think of as a kind of coercion. Against that, when a prognosis is appalling, how does one ethically withhold treatment which might be the patient's only hope, even if it is experimental? This was vividly illustrated by Case H.

Case H involved an infant with a rare fatal disorder treated conventionally with a bone-marrow transplant. Fifty to sixty per cent of cases are genetically based.

The investigator running the gene therapy unit at the hospital in question had been working in collaboration with researchers at two hospitals in Europe who were the first to use gene therapy on people with this condition.

The parents of the child had read on the Internet about the gene therapy and asked if it might be made available to their child. The coercive pressure resulting from the circumstances was clear to the HREC and the researcher alike.

The standard treatment for this condition was a bone-marrow transplant. While this was a well-tried procedure, a high proportion of patients died from complications or required extended medication to combat infections or graft-versus-host disease. These problems were especially acute when – as in this case – the bone marrow would come from a matched unrelated donor.

So not only was the child desperately ill, but the standard treatment was sub-optimal.

The view of the HREC chair was that the investigator handled the consent issue well. The investigator talked with the committee, described the treatment options and how he would explain to the parents that if the gene therapy was not successful a bone marrow transplant would be done as a fallback. He would also explain that while the gene therapy was a less invasive procedure, it was experimental.

Having had those options put to them, the parents consented to the gene therapy.

For reasons described in the case study, the gene therapy was not successful and the patient was given a bone-marrow transplant from a matched unrelated donor. He died of complications from that procedure.

A form of coercive pressure can also arise from the desperation of a dying patient. Patients with terminal cancer, for example, who have small children, sometimes will do whatever it takes to buy a little more time.

In a couple of trials at one hospital, there was an overwhelming view by the committee that if the patient were given all the information possible and he or she made a decision, then that decision should be regarded as informed, even though the patient might at least appear to be coerced by the desperate state of his or her health. However, a lay person on the committee abstained because he felt very strongly that these people were just too vulnerable and he did not believe they could make an informed decision.

Related to the coercion arising from desperation is the coercion arising from emotional pressure to help a family member. For example, if a family member is asked to donate a kidney for transplant or a sister is asked to donate an egg for fertilisation, does the emotional pressure overwhelm free consent?

The response by one HREC was to keep the clinician at arm's length from the consent process, and to see that potential donors had independent counselling from a psychiatrist or psychologist to discuss with them the possible short-term and long-term issues.

A third source of infringement upon free consent was the use of inducements. The HRECs interviewed showed considerable reserve on this whole question of inducements. In the minds of many HREC members it was closely associated with what they saw as the inappropriate influence of some pharmaceutical companies who offered inducements to hospital staff for the purpose of recruiting patients into trials. In one case the inducement was to take the form of vouchers for medical books. This committee was still wrestling with the issue.

Informed consent raised by far the most widespread challenge for HRECs. It arose mainly from the impossible length and complexities of so-called "plain language statements" or participant information sheets.

Many HRECs felt that some participant information sheets had less to do with informing the participants than with protecting drug companies, researchers and institutions from legal action or insurance claims.

One HREC member expressed the view that the swamping of the participant with incomprehensible information was symptomatic of a paternalistic attitude among medical people, rather than of excessive risk-management. However, this was a uniquely held view.

Concern about the impenetrable nature of plain language statements was not confined to HREC members. A researcher pointed out that it opened the way for researchers to manipulate the consent process. Patients unable to comprehend or too ill to try, commonly asked the investigator to explain what was being proposed. This researcher's view was that inevitably the explanation would be given from the perspective of the investigator and that this would be done in an unrecorded, unvalidated, informal conversation.

It was noted during many interviews that the plain language statements for clinical drug trials – which make up the vast bulk of medical research proposals coming before ethics committees – came directly from the pharmaceutical companies and were usually part of large multi-centre trials. Any changes made to the statement by one ethics committee would then have to be circulated to all the other centres involved, creating a whirlwind of paperwork and long delays.

The companies therefore discouraged ethics committees from making changes. This was just one part of a large and related problem: how to handle ethics clearances for multi-centre trials more efficiently.

Different problems arose from plain-language statements produced by local researchers. These tended to be inadequate because they did not cover the ground set out in the *National Statement*, and were sometimes so jargon-laden as to be considered incomprehensible to ordinary people.

Much HREC time was spent on these matters, and much goodwill between HRECs and researchers was jeopardised in the process.

Another major issue concerning informed consent arose from the potential future use of participants' DNA for unforeseen purposes. This was a particular issue in Case E, but it troubled many HRECs.

The central question was: How could participants give informed consent to the future use of their DNA when the uses could not be predicted? Many HRECs were taking a strict line on this, refusing approval until it had been made clear to potential participants what was being measured, what would happen to the tissue, whether it would be used for any other purpose, and what conditions would be attached to its use.

Open-ended and simplistic consent forms were being rejected.

Informed consent in this area was made more difficult still by the fact that genetics was seen by HRECs as an inherently complex subject which many participants could not be expected to understand.

In addition, there were concerns about whether a single individual was really in a position to consent to the future use of his DNA when he shared it with other people whose lives could be affected by the disclosure of information about what the DNA contained.

There also was concern at what many perceived to be pressure to accumulate DNA so it could be banked indefinitely by pharmaceutical companies for unforeseen purposes.

The need for informed consent presented obvious problems where the potential participant was not competent or able to give consent. This was an issue in Cases D, E, and F. In each case the cause of incompetence was different. In D, patients were in acute cardiac arrest; in E patients suffered from psychiatric disorders; in F they were comatose patients in intensive care.

The issues in Case E have been dealt with already. Case D will be dealt with under "prior consent" later.

Case F dealt with a class of cases all essentially alike for the purposes of this discussion. These cases presented a challenge peculiar to the jurisdiction, where there was no law allowing next of kin to give consent on behalf of an incompetent patient to involvement in research.

Specialists in an intensive care unit (ICU) wanted to try on comatose patients a new drug to combat septicaemia. The existing drug had been given for years without any evaluation of efficacy, but at least it was known to have no harmful side-effects. It was administered as a matter of course rather than from certainty that it would do good.

However, with the patient comatose and the law silent on whether next of kin could give consent to research, the question was how the issue of consent could be resolved.

In fact it was side-stepped and the HREC's decision rested on two other criteria – patient safety, and risk and beneficence. The safety issue was dealt with by requiring the researchers to provide literature reviews on the proposed treatment with a particular emphasis on side-effects. The risk-and-beneficence issue was dealt with by asking the researchers to draw up a risk matrix.

Prior consent can complicate already difficult dilemmas concerning informed consent, as was shown by Case D.

In this case it was proposed to recruit heart-attack patients into a randomised trial of two emergency treatments. These treatments would be performed by ambulance crews responding to emergency calls. Given their eight-minute average response time, typically they would have not much more than two minutes to re-establish a heart rhythm before the patient was beyond

retrieval. In these circumstances, obtaining informed consent either from the patient or the family prior to giving treatment was obviously impractical.

In favour of the research was the fact that only a tiny proportion of people – one to five per cent -- who had heart attacks in these circumstances survived under the standard treatment. There was some evidence that the experimental treatment might be better, and it was certainly considered no worse. Coming from such a low threshold, the saving of even a few lives would make a large proportional difference to the survival rate.

On this basis, and in conformity with the relevant provisions in the *National Statement,* the State health department's ethics committee had approved the research. However, approval was also needed from the public hospitals where heart attack patients were taken in order to allow the researchers to obtain access to subsequent patient records. An impasse ensued when one of the three big hospitals involved refused approval because of issues arising from the failure to obtain informed prior consent.

The sticking point was this: in the overwhelming majority of cases where the patient died, what, if anything, should the bereaved families be told about the experiment?

The hospital ethics committee eventually relented after obtaining some assurances that there would be some publicity to alert the public generally to the existence of the trial, and certain modifications made to the consent form.

However, the stand taken by the ethics committee also led to a more substantive modification of the consent process. It was agreed in the end that the families of patients who died would not be informed about the research; only the families of patients who survived to hospital would be told. These families would also be asked to give retrospective consent to the patient's being recruited, and prospective consent to the researchers' gaining access to the patient's records.

Some members of the hospital ethics committee were not noticeably placated by this, and retained a strongly expressed view that the power of the state had been exercised wrongly to limit the right of individuals to consent or not consent to involvement in medical research.

The final consent-related issue to emerge in the course of this report arose from three projects in two of which the researchers wanted to waive participant consent, and in the third to conduct covert observation of participants.

These issues arose in Cases C, I and J.

In Case J, the researcher wanted to compare notifications, referrals, clinic attendances and immunisations of children of drug-dependent mothers with those of the general population of children.

The researchers anticipated having trouble getting consent from these mothers to see the children's records, so they asked to be able to see them without obtaining consent.

The HREC accepted that it might indeed be hard to get consent for this kind of research from mothers who might understandably think they were being portrayed as bad mothers. However, this was not enough on its own to justify waiving consent.

It asked the researchers to look for other ways in which this information might be obtained but eventually accepted that there were none. The HREC also accepted that de-identification was not practicable either, if a reliable comparison was to be made.

The final decision came down to a balancing of the public interest against the individual mothers' interests.

It was considered that there was a strong public interest in finding out whether this cohort of children were at risk from not being immunised and not attending clinics, and that the public interest in tracking the welfare of at-risk children outweighed the consent rights of the mothers. On this basis the research was allowed to proceed, with the endorsement of the State's director-general of health who had final responsibility for giving access to patient records.

In Case C, it was proposed to establish a State-wide network of sentinel clinics for the surveillance of HIV, chlamydia, syphilis and hepatitis C incidence among young women. The purpose was to understand disease transmission.

The first question arose over the fact that some of the young women would be minors, and therefore should consent be obtained from parents or guardians? It was decided that this would be an unacceptable breach of the young women's privacy, so this would not be sought.

In those circumstances, it was recommended that only young women aged over 16 would be recruited into the study. However, the issue of consent in this case was complicated by the fact that it required multi-centre approval. Some centres took the view that, since this was surveillance, consent was not required. Others took the view that it was research and that consent therefore was required. There was some frustration expressed by both the HREC and the researcher over this distinction.

Case I involved covert monitoring of hand-washing by hospital staff to see if various educational and other measures designed to improve hygiene were working. A previous research project on the same topic at the same institution had foundered because it was discovered by the staff being monitored that they had been deceived. This time it was decided that no deception would be employed. The staff would be told monitoring was taking place but that it would be covert and directed at hospital practices generally.

This open-ended description, without specific mention of hand-washing, was considered to be honest enough to get around the deception problem without being so specific as to ruin the research design.

PATIENT SAFETY AND WELFARE

The *National Statement* deals with the issue of patient safety under the broad rubric of risk. It describes risk as a potential for harm and acknowledges that there are various kinds of potential harm in research on human beings: physical, psychological, social, economic and legal.

The *National Statement* does not disqualify research simply because it may be risky. Instead it provides guidelines on how risk is to be handled. These guidelines are grounded in the values upon which the *National Statement* is based – research merit and integrity, justice, beneficence, and respect.

The guidelines require that risks be identified and evaluated as part of any ethical review of a research proposal. This evaluation is required to consider the extent to which the risks can be minimised and how they weigh in the balance against the potential benefits of the research. The evaluation is also required to consider two dimensions of risk:

- The probability or likelihood that harm will occur, and
- The magnitude of the harm, including its consequences.

The issue of patient safety and welfare is therefore a consideration in all cases, but in four of the Cases, A, B, F and H, it confronted the HREC with particularly challenging dilemmas.

Case A involved an examination of "dual relationships" in small communities, where professionals and patients commonly meet in situations outside the clinical setting. The research was looking at how both parties coped with this. The issue of participant welfare arose over what the researchers ought to do in the event that the patient in the relationship made an allegation of misconduct, including sexual misconduct, against the clinician in the relationship.

The matter was made more complicated by the fact that in a small community, it was difficult to find an independent person in a position to investigate these allegations.

The committee decided that where the patient was a minor, the law was clear: the matter had to be reported by the researcher to the relevant authorities. However, where the patient was an adult, it was decided that the researcher should draw the patient's attention to the various means of redress available, but take no further action.

The committee retained a sense of unease about this. The members accepted that it was not for the researcher to become an advocate or champion of the patient, but at the same time recognised that these were often psychologically vulnerable people who might be even less inclined than the population as a whole to report misconduct, particularly if it were sexual.

Case B involved research by a highly experienced respiratory physician who wished to explore the effects of aircraft cabin pressure on people with impaired lung function, because he was not convinced the existing safety guidelines used by the aviation industry were accurate.

The guidelines have two thresholds. The first threshold concerns the quality of a person's lung function. If the function is below a certain level, the person is then tested for capacity to cope with exposure to cabin pressure. The results of the test represent the second threshold. If the test result shows incapacity to cope, the person should carry and use oxygen on aircraft.

The population to be tested consisted of middle-aged to elderly people with smoking-related lung disease who had undergone the first test but had not triggered the need for the second test. In other words, the first test had not revealed their lung function to be so impaired as to require the second test. Thus in the ordinary course of events, they would be able to fly without oxygen or any other form of assistance, and indeed many had done so.

In the research project, they were to be exposed to a simulated cabin altitude of 6000 feet – common in commercial aircraft -- for a certain period of time, during which they would be asked to walk short distances, as if they were walking to the toilet on an aircraft. This was a completely novel element in the research. The objective was to see whether their oxygen levels fell when they exercised and whether they needed to be given particular advice as a result.

The research was considered by the ethics committee to be of high scientific merit. Against this, however, was the potential risk that a participant would collapse and possibly die during the experiment.

Because of the researcher's expressed doubts about the accuracy of the aviation safety guidelines – and the fact that many of these people with known lung impairment had flown without incident -- assessing the probability of this risk was, for practical purposes, impossible.

The magnitude of the risk, however, was clearly very high, with death a real possibility.

The HREC resolved the issue by allowing the research to proceed on condition that a "crash cart", a cardiac physician and a CPR team be stationed at the site of the experiment whenever a simulation was being conducted. A "crash cart" is a trolley bed with resuscitation equipment.

Case F presented an acute dilemma. The patients here were all in intensive care. Many were comatose; some were at the end-stage of terminal illness.

It is a cardinal principle of caring for such people that they should never be subjected to sub-optimal treatment, for the obvious reason that both the probability of harm and the magnitude of harm are great, given their perilous condition.

Yet it is also recognised that intensive-care patients should not be denied the right and the opportunity to participate in research, especially when it may benefit them.

Research, by definition, involves an exploration of the unknown. The efficacy of an experimental treatment is unknown. It might be better, worse or no different from the standard treatment. How, then, can the right of intensive care patients to be involved in research be

reconciled with the principle against giving them sub-optimal treatment when the comparative optimality of the two treatments is unknowable without the experimentation?

If the experimental treatment turns out to be better, then patients on the standard treatment have been given sub-optimal treatment; vice-versa if the experimental treatment turns out to be worse.

In Case F, intensive care specialists wanted to try a new drug to combat septicaemia. The existing drug had been administered for years without any evaluation of its efficacy. It might do good; at the very least it had no side-effects and did no harm. Septicaemia, of course, represents a severe risk to anyone and is often fatal in acutely ill people.

The HREC in question broke through this dilemma by having the researchers do two things.

The first was to present a meta-analysis of several reports of outcomes from one intervention versus another, which had been empirically chosen by departments or treating physicians, to establish a pattern of care which the HREC was able to identify as best practice.

The second was to draw up a risk matrix. What is the probability of side-effects? How severe are those side-effects like to be? Can they be managed? How do the answers to these questions compare with the evidence of best practice which had emerged from the meta-analysis?

It should be added that in this case – for reasons already set out in the section on consent – patient safety became the threshold determinant for the inclusion of patients in the research, since consent was unobtainable.

The trial of the septicaemia drug was allowed to proceed on the basis that the risk-benefit calculus was favourable to the trial.

Case H raised a highly complex patient safety issue. This case involved the experimental use of gene therapy in an infant with a rare and fatal disorder.

The standard treatment for this condition was a bone-marrow transplant, an invasive and sub-optimal procedure with high mortality and morbidity rates, particularly – as in this case – when the donated bone marrow came from a matched unrelated donor. Gene therapy, by contrast, was far less invasive and good results had apparently been obtained overseas. For those reasons the initial risk-versus-benefit test was not especially difficult.

In this therapy, bone-marrow cells are taken from the patient's body and genetically repaired by inserting a healthy copy of the faulty gene using a retrovirus carrier or "vector". These cells are then re-introduced into the patient, where they return to the bone marrow and reconstitute the patient's ability to produce certain types of white blood cells that were previously missing from the patient's blood.

The Australian case was part of a trial being carried out in two other hospitals, both in Europe, where a total of about 12 patients had been treated.

Approval was given for the Australian trial to proceed, and the gene therapy was administered. The patient did not reconstitute his bone marrow as vigorously as had been expected, and the researchers were considering a top-up of the modified gene when a report came in from one of the European countries that one of 10 patients treated there had developed leukaemia. Subsequently, a further two treated patients developed leukaemia and died from this complication.

The cause of the leukaemia was not known, but it was suspected that the modified DNA might have contributed, either by stimulating the leukaemia cells to reproduce or by producing some inhibitor that allowed the cells to reproduce at will. That did not occur in the Australian patient.

So the researcher and the HREC were confronted by a new risk-versus-benefit calculation. In the face of the report from Europe, should the top-up proceed?

The answer that both researcher and HREC came to was no. The gene therapy had been embarked on with a clear idea of the risks and benefits it offered when compared with the alternative – a bone-marrow transplant. But now the risk of leukaemia had to be added, and nothing conclusive was known about its cause. Therefore, a decision to carry on with the experimental gene therapy would be made on the basis of incomplete knowledge about the real risks involved. This was considered unethical by all involved.

The alternative treatment -- a bone-marrow transplant -- was given, and the patient died of complications arising from it.

From the HREC's point of view, the safety calculations were especially difficult because only the researcher and his two colleagues in Europe really had a complete grasp of all aspects of the relevant science. This demonstrated to the HREC the importance of having confidence in the *bona fides* of the researcher. Yet when we spoke to them, the chair and members were still expressing anxiety about the inadequacies of their capacity to evaluate very advanced and complex science, even though many of the HREC members were distinguished specialists in their own fields.

The same researcher was about to present them with an even more complex proposal concerning brain tumours and the committee were undecided about how to proceed. They were debating the merits of finding someone to give them an independent evaluation, but there was only a tiny group of international experts to choose from.

DNA AND TISSUE BANKS

Aside from the issues of consent arising from the taking and storing of people's DNA, dealt with under Consent above, many HRECs were confronting a range of other issues arising from this aspect of research.

One issue – which was raised in Case E – was the linking of DNA materials with clinical records, including data that could identify the patients.

The concern was, fundamentally, that this could lead to genetic information about identifiable individuals falling into the hands of people who had no connection with the research. Such information might then be used in ways that were against the patient's interests.

For example, if it were to fall into the hands of law enforcement authorities or insurance companies or prospective employers, what might the consequences be for the individual if the material showed a genetic predisposition to a condition which the individual did not in fact suffer from?

Lack of legislative control over tissue banks was another matter of concern to HRECs generally. This was a concern when the material was to be banked within the HREC's jurisdiction. The concern was heightened when the material was to be sent overseas – as most of it was – to places where the HREC neither knew, nor would be able to control, what it was used for or who had access to it.

Intellectual property and ownership rights over DNA material was also a matter of concern on equity grounds: ordinary people were providing their DNA and others were set to reap large profits from it without the original providers benefiting in any way.

Even in hospitals where this had not been an issue in the case under review, questions about the collection and storage of DNA was seen as a major ethical issue. It was mentioned in nearly every institution visited.

CONFLICT OF INTEREST

A subtle conflict-of-interest issue arose in Case Study H, involving the use of gene therapy in an infant with a rare and fatal disorder. When interviewed, the HREC reflected on the fact that the then Chair of the HREC was involved generally in the same area of research as the protocol the committee was dealing with. He had declared this, and having declared it continued to sit. The committee members, however, now wondered whether that had been quite appropriate, and were of the view that, in the future, they would probably ask a person in that position not to participate in the discussion.

Another member of the HREC, who sat *ex officio* as research manager of the institution, also questioned whether she ought to have disqualified herself on the grounds that as manager of research she had a vested interest in seeing such ground-breaking research proceed. Her concern was that in such circumstances she may not have brought a completely open mind to the discussion.

PRIVACY AND DISCLOSURE OF PARTICIPANT INFORMATION

In what circumstances, if any, might it be ethical to withhold from participants information about them derived from research?

This became a complex question in Case B.

In Case B, people with impaired lung function were placed in an environment which simulated aircraft cabin pressure at 6000 feet. This approximated the pressurisation used in commercial aircraft. They were then asked to perform a small amount of exercise to simulate walking to an aircraft toilet.

The Aerospace Medical Association, among other international bodies, has guidelines about the type of people who should be tested for their ability to function safely under these conditions. The guidelines have two thresholds. The first threshold concerns the quality of a person's lung function. If the function is below a certain level, the person is then tested for capacity to cope with exposure to cabin pressure. The results of the test represent the second threshold. If the test result shows incapacity to cope, the person should carry and use oxygen on aircraft.

The population to be tested consisted of middle-aged to elderly people with smoking-related lung disease who had undergone the first test but had not triggered the need for the second test. In other words, the first test had not revealed their lung function to be so impaired as to require the second test. Thus in the ordinary course of events, they would be able to fly without oxygen or any other form of assistance, and indeed many had done so.

The research indicated, however, that several participants would have failed the second test, had they been required to undergo it. These included people who had flown without incident.

The question arose: should they be told?

If they were told, they might be inhibited from undertaking further air travel, even though they had coped with it in the past. They might also have then been required to notify travel insurance companies and this might have resulted either in their having to pay high premiums or in their not being able to obtain insurance at all. Furthermore, the cost of carrying oxygen runs to several hundred dollars for long-haul flights, and not all airlines are willing to take passengers in this condition.

Altogether, then, there were considerable potential penalties involved for the participants.

On the other hand, if they were not told but later collapsed while flying, the consequences of not having been told would obviously have been serious.

The HREC decided that, in general, the participants should not be told the results. The exceptions would be cases where the clinician conducting the research came to the view that the participant's data were so poor that disclosure was essential for the participant's safety.

The decision to otherwise withhold the information was based on a number of factors.

First, the data had come from an experiment in a simulated environment. The overall findings of the experiment were not known at this stage and so knowledge was incomplete. This did not warrant discouraging or perhaps preventing people from flying.

Second, it was well established at this hospital – which specialised in respiratory ailments – that patients with impaired lung function adapted to the impairment in ways that enabled them to cope in circumstances which the text books predicted they could not. This, coupled with the fact that many had flown without incident, suggested a low risk to the patient's safety if they did fly.

Third, the participants had been under no obligation to participate in the research. They had done so voluntarily. They had not failed any of the standard tests imposed by the aviation industry. It was considered unfair that they should face the possibility of penalties arising from their altruistic participation in the project, on the basis of unproven data.

SCIENTIFIC MERIT

It is an axiom that research lacking scientific merit or methodological rigor is unethical if for no other reason than it wastes time and resources.

It was a threshold criterion, therefore, in all our case studies, but only in Case G was it the central issue.

Case G involved a proposal to use a diagnostic method from Chinese Traditional Medicine (TCM) to identify people with liver function impairment. The research would be conducted among a group of patients already diagnosed with liver disease using Western diagnostic techniques, and a "normal" group, not diagnosed with liver disease.

Participants from both groups would be asked to allow their tongue to be photographed, and their clinical records to be seen by the researcher. A comparison would then be made between the diagnostic outcomes of TCM and Western medicine as they related to liver function.

This proposal, which came from outside the HREC's institution but nonetheless from a large and well-established medical school, confronted the HREC with a serious question about scientific merit. Indeed it presented a challenge to the HREC's whole concept of what scientific merit might consist of, since it was a complete departure from the evidence-based approach of Western medicine.

Its response was to look at patient safety. Would anyone be harmed by being asked to put their tongue out and have it photographed (the rest of the face was to be masked)? Would anyone be harmed in these circumstances by the researcher being able to see from their clinical records whether or not they had liver failure?

The answer to both questions, in the words of the HREC chair, was "probably not". The procedure was not invasive. Measures were in place to protect patient identity. The patients were not going to be asked to give more than a minute or two of their time. They would already be in the hospital. The procedure would not cause discomfort or pain. No resources of the hospital would be used.

The HREC chair and members retained profound reservations about the scientific merit of the proposal, but against all those other considerations allowed it to proceed, having insisted upon changes to the research design to try to provide at least some likelihood that useful data might emerge from it.

APPENDIX I INTERVIEW SCHEDULES AND CONSENT FORMS

NHMRC – HUMAN RESEARCH ETHICS PROJECT 2006 INTERVIEW SCHEDULE FOR CHAIRS

1. Before we get on to the specific case we have come to talk with you about, would you please give us a little background information about you and your involvement with ethics review work:
   - What is your own professional background?
   - How did you first become involved in ethics review work?
   - Why did you become involved?
   - How long have you been involved?
   - When did you join this HREC, and when did you become Chair?

2. Thinking generally, from your experience what are the most challenging ethical issues confronting people involved in designing, reviewing or conducting human research these days, and what is it that makes these issues challenging?

3. Are these issues new, or have they been with us for a long time?

4. How would you describe the climate within which your HREC works at the moment? For instance, how would you describe the attitudes of researchers, in general, to the HREC processes that you follow? And how would you describe the general social climate as it affects your work in reviewing human research?

5. Do these factors change over time? If so, what effect, if any, does this have on the way your HREC approaches its work?

6. Thinking now about the specific case we have come to talk about. Just take us through it, if you would:
   - Background to the case:
   - Was there any prior communication with the researcher before the HREC meeting?
   - Did you have prior knowledge, if any, of researcher and researcher's work and did you take this into account in reviewing the proposal?
   - What do you recall were the aim and methods of the research proposal
   - What were the ethical issues that the committee identified, how were these described, and what was sought from the researcher in your response? How was the response given, by letter or conversation?

7. What was particularly challenging about those issues, and why?

8. How did the HREC go about dealing with those issues?

    - What were considered to be the relevant considerations to be taken into account in coming to a decision?
    - Was there general agreement within the HREC on these, and on the way the issues should be approached and on how the researcher should be approached?
    - What was the nature and quality of interaction between the HREC and the researcher?
    - Ultimately, what was the HREC's decision and reasons?
    - What was the researcher's response?
    - If all the issues were resolved to the committee's satisfaction, how was this achieved? If they were not, do any issues remain outstanding?

9. Did the HREC think it learnt something from this case which might help it in future cases, including anything about the nature and quality of interaction between the HREC and researchers?

10. What, if anything, did it reveal to you about the strengths of the HREC process as it operates here?

11. What, if anything, did it reveal to you about the weaknesses of the HREC process as it operates here?

12. Were there lessons from this case which you think might be of benefit to HRECs more generally?

13. To sum up, what do you think are the characteristics of best practice in reviewing human research from an ethical perspective?

NHMRC – HUMAN RESEARCH ETHICS PROJECT 2006 INTERVIEW SCHEDULE FOR HREC MEMBERS

1. Before we get on to the specific case we have come to talk with you about, would you please give us a little background information about yourselves and your involvement with ethics review work:

    - What are your own professional backgrounds?
    - How did you first become involved in ethics review work?
    - Why did you become involved?
    - How long have you been involved?
    - When did you join this HREC?

2. Thinking generally, from your experience what are the most challenging ethical issues confronting people involved in designing, reviewing or conducting human research these days, and what is it that makes these issues challenging?

3. Are these issues new, or have they been with us for a long time?

4. How would you describe the climate within which your HREC works at the moment? For instance, how would you describe the attitudes of researchers, in general, to the HREC processes that this HREC follows? And how would you describe the general social climate as it affects human research?

5. Does this climate change over time? If so, what effect, if any, does this have on the way this HREC approaches its work?

6. Thinking now about the specific case we have come to talk about. From your point of view what were the ethical issues that it involved and the HREC needed to address? Why?

7. What was particularly challenging about those issues, and why?

8. How did the HREC go about dealing with those issues? In particular:

    - What were considered to be the relevant considerations to be taken into account in coming to a decision?
    - Was there general agreement within the HREC on these, and on the way the issues should be approached and how the researcher should be advised?
    - What was the nature and quality of interaction between the HREC and the researcher?
    - What was the HREC's decision?
    - What was the researcher's response?
    - If all the issues were resolved to the committee's satisfaction, how was this achieved? If they were not, do any issues remain outstanding?

9. Do you think you learnt something from this case which might help in future cases, including anything about the nature and quality of interaction between the HREC and researchers?

10. What, if anything, did it reveal to you about the strengths of the HREC process as it operates here?

11. What, if anything, did it reveal to you about the weaknesses of the HREC process as it operates here?

12. To sum up, what do you think are the characteristics of best practice in reviewing human research from an ethical perspective?

Thank you very much for your time. It is greatly appreciated.

NHMRC – HUMAN RESEARCH ETHICS PROJECT 2006 INTERVIEW SCHEDULE FOR RESEARCHERS

1. Before we get on to the specific research project we have come to talk with you about, would you please give us a little background information about you and your research work:

    - What is your professional background?
    - How long have you been working in this particular field of research?

2. Thinking generally, from your experience what are the most challenging ethical issues confronting people involved in your area of human research these days, and what is it that makes these issues challenging?

3. Are these issues new, or have they been with us for a long time?

4. How would you describe the general social and professional climate within which researchers like you are working at the moment?

5. Do these factors change over time? If so, what effect, if any, do you think this has on the way HRECs approach their work?

6. How would you describe the approach by HRECs to assessing research projects from your area of human research?

6. What were the origins and aims of the research proposal you took to the HREC?

7. From your point of view, what were the ethical issues associated with the research? Were they challenging and , if so, how?

8. To what extent did your identification of the ethical issues accord with those identified by the HREC?

9. Take us through the process with the HREC.

    - Did you have any discussions with the secretary before the application was submitted?
    - What was the nature and content of the initial response from the HREC?
    - What was your view of this and how did you respond?
    - What was your view of the final outcome, e.g. of any modifications that you agreed to make?
    - Do any issues remain outstanding or problematic?

10. Thinking about this particular case, what, if anything, did it reveal to you about the strengths of the HREC process as it operates here?

11. What, if anything, did it reveal to you about the weaknesses of the HREC process as it operates here?

12. To sum up, what do you think are the characteristics of best practice in reviewing human research from an ethical perspective?

Thank you for your time. It is greatly appreciated.

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NHMRC ETHICS PROJECT – STATEMENT OF PURPOSE AND PROCEDURES FOR INTERVIEWEES

Thank you for agreeing to be interviewed for this project. This short statement:

- sets out the purpose of the research;
- gives guarantees concerning anonymity and confidentiality;
- sets out the basis on which the researchers seek your permission to audio-tape the interview, and
- gives an undertaking to allow a review of the draft report by the participating HRECs.

PURPOSE OF THE RESEARCH

The purpose of the research, as set out by the National Health and Medical Research Council and agreed by us, is:

> Provide the Minister for Health, by the end of 2006, with a well-written report which highlights the role of Human Research Ethics Committees (HRECs) in reviewing research proposals involving humans, that present particular ethical challenges. (Request for tender, B2).

GUARANTEES OF ANONYMITY AND CONFIDENTIALITY

Interviewees, their institutions, and the research projects will not be identified in our report and, where necessary, special steps will be taken to mask potentially identifying information in ways that do not mislead the reader.

Any information imparted to us in confidence will not be used in the report, and the confidences will be respected absolutely.

AUDIO-TAPING

We ask your permission to audio-tape your interview with us on the basis that the above guarantees are respected, the tape is heard only by the three lead researchers, is erased at the conclusion of the research project, and is not used for any other purpose.

REVIEW

The draft report will be sent to each participating HREC for review of the accuracy and fairness of the description and analysis of that HREC's case, and for a general comment concerning the report as a whole.