



**Australian Government**

**National Health and Medical Research Council**

# **Inter-jurisdictional Forum**

**Towards timely, efficient and effective review  
of multi-centre clinical trials**

**Friday 4 February 2005**

**9am to 4pm**

**Carlton Crest Hotel**

**Port Jackson Room**

**169 - 179 Thomas Street Sydney**

**Forum papers and outcome of discussions**



# INTERJURISDICTIONAL FORUM

## Towards timely, efficient and effective ethical review of multi-centre clinical trials

Friday 4 February 2005  
9.00 am to 4.00 pm (NSW Summer Time)  
Carlton Crest Hotel, Port Jackson Room  
169-179 Thomas St. Sydney

### FORUM PAPERS, DISCUSSION NOTES AND OUTCOMES

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**FORUM AGENDA**  
**Moderator: Dr Norman Swan**

8.30 Registration: tea and coffee

**Session 1: setting the scene**

9.00 – 9.05 Welcome  
*Professor Michael Reid, Director-General, NSW Ministry for Science and Medical Research*

9.05 – 9.45 Multi-centre clinical trials: issues around ethical and scientific review  
*Dr Kerry Breen, Chair, Australian Health Ethics Committee*  
(20 minute paper: 20 minute discussion)

9.45 – 10.25 Multi-centre review in Australia: barriers and possible solutions  
*Dr Nik Zeps, WA Health*  
(20 minute paper: 20 minute discussion)

**10.25 – 10.45 Morning Tea**

**Session 2: current developments in Australia and New Zealand**

10.45-11.15 NSW Health Pilot Shared Scientific Assessment Scheme  
*Ainsley Martlew, Senior Analyst, Research Ethics, NSW Health*  
*Deborah Frew, NSW Ministry for Science and Medical Research*  
(15 minute paper: 15 minute discussion)

11.15 – 11.45 Queensland Health: move to a mutual acceptance model  
*Dr Jane Jacobs, Principal Advisor, Qld Health*  
(15 minute paper: 15 minute discussion)

11.45 – 12.20 Mutual acceptance of HREC review of cancer trials in some Victorian Hospitals  
*Carole Alt, Chief Operating Officer, Cancer Trials Australia*  
Victoria: a project for streamlining ethical review of multi-centre research  
*Jane Southwell, Project Officer, Special Projects, Biotechnology and Ethics, Department of Human Services, Victoria*  
(20 minute papers: 15 minute discussion)

12.20 – 12.45 New Zealand experience  
*Dr Bruce Scoggins, Chief Executive, Health Research Council of New Zealand*  
(15 minute paper: 10 minute discussion)

**12.45 – 13.45 Lunch**

### **Session 3: developing solutions**

13.45 – 14.45 Group working session 1 and discussion: Principles of a system for ethical review of multi-centre clinical trials

14.45 – 15.30 Group working session 2 and discussion: Testing the principles: models for consideration

15.30. – 16.00 Practical ways forward

## FORUM DELEGATES

### Commonwealth

#### *Commonwealth Department of Health and Ageing*

Prof John Horvath, AO      Australian Government Chief Medical Officer

#### *National Health and Medical Research Council*

Cathy Clutton      Executive Director, Centre for Health Advice, Policy and Ethics

Jane-Ann Jones      Director, Health Ethics

Francine Kelly      Asst Director, Health Ethics

Assoc Prof Colin Thomson      Consultant, Health Ethics

#### *Australian Health Ethics Committee*

Dr Kerry Breen      Chair

#### *Therapeutic Goods Administration*

Jon Rankin      Drug Safety Evaluation Branch

#### *Australian Institute of Health and Welfare*

Dr Kerry Kirke      Board Member

Tony Adams      HREC Member

Dr Anny Stuer      Head, Business and Information Management Division

Margaret Fisher      Head, Executive Unit

### Australian Capital Territory

#### *Department of Health and Community Care*

Daniel Coase      Deputy Director, Office of the Chief Health Officer

Elizabeth Grant      Chair, ACT Health Ethics Committee

Joan Jensen      Secretary, ACT Health Ethics Committee

### New South Wales

#### *NSW Ministry for Science and Medical Research*

Prof Michael Reid      Director-General

Assoc Prof Maree Gleeson      Director, Medical Research

Deborah Frew      Senior Principle Policy Officer

Lisa Eckstein      Policy Officer

#### *NSW Health*

Dr Greg Stewart      Chief Health Officer, Deputy Director-General, Population Health

Dr Louisa Jorm      Director, Centre for Epidemiology and Research

Ainsley Martlew      A/Senior Analyst, Research Ethics

#### *Cancer Institute NSW*

Prof Jim Bishop      Chief Cancer Officer

Carmel Edwards                      Director, Research Programs  
Rodney Eccleston                    Ethics Manager

## **Queensland**

*Queensland Health*  
Dr Gerry Fitzgerald                      Chief Health Officer  
Dr Jane Jacobs                            Principal Advisor, Research and Ethics Unit, Office of  
the Chief Health Officer

## **South Australia**

*Department of Human Services*  
Andrew Stanley                      Director, Strategic Planning and Research, Chairperson,  
Department of Health HREC

## **Victoria**

*Department of Human Services*  
Ellen Kittson                            Manager, Biotechnology Safety and Ethics Program  
Jane Southwell                          Project Officer, Special Projects, Biotechnology and  
Ethics

*Cancer Trials Australia*  
Carole Alt                                Chief Operating Officer

## **Western Australia**

*Department of Health*  
Dr Nik Zeps                                Research Manager, Radiation Oncology; Director, WA  
Research Tissue Network; Chairman, Human Research  
Ethics Committee, Sir Charles Gardiner Hospital

## **New Zealand**

*Health Research Council of New Zealand*  
Dr Bruce Scoggins                      Chief Executive

## **Organising Committee**

Dr Kerry Breen, Deborah Frew, Ainsley Martlew, Francine Kelly, Dr Nik Zeps

## The current system of ethical review in Australia for clinical trials

The *National Statement on Ethical Conduct in Research Involving Humans* requires all such research to be reviewed by a properly constituted Human Research Ethics Committee (HREC).

There are currently 226 HRECs registered with the Australian Health Ethics Committee: 37% of those are in the public health sector; 18% in the private health sector; and 24% in the University sector.<sup>1</sup>

The conduct of clinical trials in Australia is governed by the Therapeutic Goods legislation. Under that legislation, all clinical trials must be reviewed by an HREC. The HREC is responsible for reviewing the scientific and ethical aspects of a clinical trial. Most clinical trials in Australia are conducted under the Clinical Trial Notification Scheme. Many clinical trials are conducted at more than one centre in Australia. Generally, such trials will be reviewed by an HREC at each centre, leading to multiple reviews of the same trial.

In 2003/4, 2387 clinical trials were conducted under the CTN Scheme in Australia. Of these, approximately 340 were single sit trials. Approximately 225 were multi-centre trials conducted at over 2037 sites (an average of 9 sites per protocol).<sup>2</sup> The Pharmaceutical Industry Action Agenda Report estimates that R&D investment of the pharmaceutical industry in Australia is approximately \$300 million per annum.

Many of the clinical trials undertaken in Australia have already undergone ethical and regulatory review overseas.

The issues related to ethical review of multi-centre clinical trials are well-known and include the following:

### For sponsors and researchers

- Administrative burden of applying to and dealing with several HRECs.
- Different HRECs making inconsistent requests for amendments to the trial protocol.
- Time delays in commencing trials caused by multiple review processes.

### For HRECs/institutions

- Difficulty in accessing sufficient scientific expertise to review complex trial protocols.
- The volume of work involved in assessing a large number of clinical trials, which leads to high administrative costs and difficulty recruiting and maintaining members.
- Lack of knowledge and communication of the decisions made by other HRECs reviewing the same trial.

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<sup>1</sup> HREC Bulletin, Issue 13, July 2004, NHMRC

<sup>2</sup> Figures provided by Medicines Australia

For governments, university and private sector generally

- Duplication of effort by multiple HRECs, leading to non-optimal use of resources.
- Limited scientific resources being used in the least efficient manner.
- Maintaining safety of participants in these circumstances.
- Maintaining the viability/competitiveness of Australia as a place to conduct clinical trials.

## Multi-centre clinical trials: issues around ethical and scientific review

Dr Kerry J Breen: Chair, Australian Health Ethics Committee

### Historical background to the Australian system

Australia was one of the first countries to establish national ethical guidelines for medical research with the issuing of the first *Statement on Human Experimentation* by the National Health and Medical Research Council (NHMRC) in 1966. Although many institutions conducting human subject research subsequently established independent<sup>3</sup> research ethics committees, it was not until 1985 that the application of the principles laid down in the *Statement on Human Experimentation*, by appropriately constituted ethics committees, became ‘mandatory’. In that year the NHMRC determined that release of NHMRC research funds was to be conditional on (a) the research proposal being prospectively reviewed by an ethics committee and (b) that all other proposals for research involving humans in that institution were similarly subject to such prospective review.

In the early years of the application of the *Statement on Human Experimentation* (which was further revised in 1976, 1985, and 1992) most clinical research, including clinical trials, was conducted in single institutions. Thus the establishment of ‘institutional ethics committees’ (IECs, as they were then called) was appropriate. The local remit of these IECs was very clear as the following extracts of the 1992 *Statement*<sup>4</sup> indicate:

1. *All research projects involving human subjects and relating to health must be considered and approved by a committee constituted in accordance with this Supplementary Note (1).....*
6. *Application of Functions*  
*In carrying out these functions, an IEC shall:*
  - (i) *.....*
  - (ii) *Give its own consideration to projects that involve research in more than one institution.*

Thus the *Statement on Human Experimentation* can be seen to have strongly influenced the culture and attitude of IECs when asked to examine studies proposed for more than one institution. The only concession made as a footnote to the 1992 *Statement* was that

*An IEC is free to discuss a project with other IECs if it chooses, with due regard to confidentiality.*

In 1992, amendments were made to the Therapeutic Goods Act 1989 and its regulations which resulted in the establishment of two distinct schemes for the trial of unapproved therapeutic goods, that is, the Clinical Trial Notification (CTN) scheme and the Clinical Trial Exemption (CTX) scheme. The CTN scheme allowed clinical

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<sup>3</sup> For ethical oversight independent of the researcher who proposed the research.

<sup>4</sup> NHMRC *Statement on Human Experimentation and Supplementary Notes* 1992, NHMRC, Canberra

trials to be commenced upon notification to the TGA that an IEC had approved the protocol and undertaken to monitor the trial. These changes increased the responsibilities and perceived legal exposure of ethics committees by removing the requirement for review of the trial by the TGA and resting all responsibility for review on the IEC. In the absence of any national ‘system’ to address the increased responsibility, IECs responded by strengthening the emphasis on their institutional status, as is clear from the NHMRC *Report on Legal Liability, Insurance and Indemnity Arrangements for Institutional Ethics Committees, 1995*<sup>5</sup>

However “times were a changing”. Driven by the increasing awareness of clinical researchers of the need to recruit research participants in numbers sufficient to provide statistically convincing evidence for or against the null hypothesis, the needs of the pharmaceutical industry to accrue data regarding new drugs as quickly as possible, and the de-regulation of clinical trials in Australia, the 1990’s saw an enormous growth in multi-centre trials, both nationally and internationally. The proportion of trials conducted under the CTN scheme compared with the CTX scheme also increased. The frustrations of researchers facing submission to multiple IECs became clear in the mid 1990s. Thus pressure mounted for action to simplify the ethical review of research at multiple sites. However, this was balanced by objections from institutions faced with losing control of the review process.

The frustrations of researchers were identified in a 1996 report to the Federal Minister of Health<sup>6</sup> by a working party asked to conduct a review of the role and functioning of IECs. That Report noted that it was the “usual practice for the assessment of multi-centre research proposals for each IEC to consider separately, usually in isolation from other IECs considering the same proposals”. The Report noted that this posed problems for researchers and IECs, leading to delays, inconsistencies and increasing workloads for IECs.

The 1996 Report made several relevant recommendations including:

- the need for improved communication and cooperative arrangements between IECs;
- the acceptance by IECs of a single assessment of the scientific and safety/privacy aspects of a proposal
- the encouragement of administrative consistency among IECs

These recommendations were picked up in the revision of the *Statement on Human Experimentation* conducted over 1996-99.

When the NHMRC issued the *National Statement on Ethical Conduct in Research Involving Humans* (NS) in August 1999 it contained a chapter devoted to multi-centre research. The content was directed at researchers and HRECs<sup>7</sup> and included the following key points :

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<sup>5</sup> NHMRC *Report on Legal Liability, Insurance and Indemnity Arrangements for Institutional Ethics Committees, 1995*, NHMRC, Canberra

<sup>6</sup> *Report of the review of the role and functioning of Institutional Ethics Committees: Report to the Minister for Health and Family Services, 1996*, Commonwealth of Australia, Canberra.

<sup>7</sup> The new term “Human Research Ethics Committee” (HREC) replaced the previous IEC.

1. Researchers were encouraged to come to a prior agreement with one HREC that it would take the primary role in the ethical and scientific assessment of a protocol (NS para 3.5).
2. The principal researcher was required to inform each HREC of all the other Australian sites at which the research is being proposed or conducted (NS para 3.7).

Paragraphs were also directed primarily at HRECs which :

1. Encouraged HRECs to avoid unnecessary duplication of ethical review by seeking to ascertain if the same protocol has been reviewed elsewhere (NS para 3.3);
2. Permitted HRECs to communicate with, and give advice to, or receive advice from any other HREC (NS para 3.4);
3. Permitted HRECs to accept scientific/technical assessment by another organisation (NS para 3.4); and
4. Allowed HRECs to review and adopt the reasons for ethical approval/disapproval of another HREC in reaching its own decision (NS para 3.4).

In hindsight, it needs to be acknowledged that these changes failed to recognise that the responsibility of deciding that an external HREC's review of a proposals was a satisfactory substitute was that of the institution and not the HREC. The changes also took insufficient account of the previous seven years of IEC concern about legal exposure in clinical trial review and of the increased independence of institutions. By 1999, three decades of a robust tradition of independence, exacerbated by seven years of strengthened institutional autonomy in clinical trial review, left HRECs in major medical research institutions deeply resistant to devolving or sharing any of their responsibilities for ethical review.

### **What has happened (in Australia) since the release of the 1999 National Statement?**

The Australian Health Ethics Committee has tried to encourage the uptake of the opportunities offered in the 1999 *National Statement* for HRECs to rationalise the ethical review of multi-centre research proposals in a number of ways (so far it must be added without any discernable impact, perhaps for the reasons outlined above). First, via annual regional 'training' workshops and regular Bulletins to HRECs, AHEC has continually urged HRECs to grasp these opportunities. Second, AHEC has actively and constructively supported initiatives in several States which have been undertaken to achieve the same aims. Third, being aware of a major UK NHS initiative in this area, AHEC made multi-centre review a central part of the program at the first National Conference on Ethics in Human Research held in Canberra in 2003 and invited the leader of the UK reform process, Prof Terry Stacey to be a speaker at that conference. The conference drew an attendance of approximately 600 delegates, the vast majority being HREC members.

AHEC also embarked upon the development of a common HREC application form (in electronic format), believing that widespread use of such a form would at least simplify the task of making multiple HREC submissions and might also encourage HRECs to communicate more readily amongst themselves. This project is nearing completion. AHEC now recognises that some of these efforts might have been better

directed at the leadership of those institutions involved in multicentre research rather than just at HRECs.

AHEC has also sought to analyse the reasons for the failure of HRECs and institutions to use the new provisions of the *National Statement* regarding multi-centre research and has identified the following obstacles (real or perceived) :

1. Legal obstacles: Just as directors of corporations have legal duties of due diligence and as institutions and directors have duties under common law to exercise reasonable care, members of HRECs may have similar legal duties. These duties were recognised in the 1995 Legal Liability Report, which acknowledged that the likelihood of legal proceedings was remote “provided members perform their function in good faith, with all due reasonable care in accordance with relevant NHMRC guidelines”. As a consequence, institutions may perceive there to be a risk of liability should a research participant be injured and it be shown that the institution’s HREC had not made its separate independent assessment of the research proposal. With such a perception, an institution might question whether it would fulfil its duties to research participants where it adopted the approval of another HREC or its HREC had adopted the decisions, and reasons for those decisions, of another HREC.
2. Indemnity obstacles: The *National Statement* provides that HRECs are to be satisfied that adequate compensation arrangements are in place for participants in clinical trials (NS para 12.7). During the period from 1992 until now, indemnity arrangements, especially for pharmaceutical company sponsored clinical trials, were usually institution specific ie. they assumed the HREC approving the trial was established by the institution conducting the trial and this was reflected in the language of the indemnity agreement offered to the institution by the company. Institutions perhaps perceived a gap in insurance cover if they did not insist on their own HREC reviewing the research proposed.
3. Monitoring obstacles: The *National Statement* requires that appropriate monitoring be decided upon by institutions and their HRECs but does not give specific guidance on how the monitoring of multi-centre research (where one HREC accepts the decision of another HREC) might be achieved. The TGA regulation requirement that an HREC undertake the monitoring of a clinical trial further discouraged the sharing of HREC review.

### **And so where does AHEC see the future lie?**

In its efforts to encourage institutions and HRECs to accept the provisions of the 1999 *National Statement* and in its examination of what is happening in other countries, AHEC has:

1. recognised that under the NHMRC Act 1992, neither AHEC nor the NHMRC has the power or the authority to force the uptake of mutual acceptance or centralised (ie. single HREC) review.
2. accepted that if more efficient ethical and scientific review of multi-centre research in Australia is to be achieved, this needs to be sought actively by institutions, researchers and by research sponsors and must be pursued by

Federal and State and Territory governments (preferably via a uniform national arrangement).

3. decided to continue to explore a voluntary system for centralised review of multi-centre public health and epidemiological research.
4. attempted to address the issue more clearly in the revised *National Statement*, a first draft of which was issued in December 2004 for its first round of public consultation<sup>8</sup>.

The first consultation draft states the obligation of institutions to ensure that research is reviewed by an HREC and to reduce or avoid unjustified duplication of review. It actively encourages institutions to establish clear policies for the efficient review of multicentre research proposals with an emphasis on separating the research governance issues which require local consideration and the ethical issues which could be undertaken by any properly constituted HREC.

### **And can we learn from other countries?**

Circulated separately to this paper is a valuable summary of the approaches being taken to multi-centre clinical trials in several other countries. It is noteworthy that nations with a federal system of government (USA and Canada) are labouring under the same handicap as Australia. It is also noteworthy that the single most important initiative in Europe has come via legislation (a Directive of the European Parliament as described in the separate paper on overseas systems). However, significant reforms had been put in place in the UK well prior to the implementation of the European Directive (which became operative on May 1, 2004). These reforms are probably the most relevant to the Australian context.

Until the late 1990s, ethical review of clinical research undertaken in UK NHS hospitals (and their affiliated universities) was conducted by institutionally based Research Ethics Committees, which followed guidelines issued by the NHS Central Office for Research Ethics Committees (COREC). In response to complaints over delays from clinical researchers, COREC introduced a system of centralised review, establishing 5 regionally based RECs in England, 2 in Scotland and one each for Wales and Northern Ireland. Any clinical research proposal involving more than 2 sites was referred automatically to a central REC. Local RECs retained the power to consider local issues.

Although care was taken to establish the membership of the new committees by drawing on members of existing RECs, the new system met with considerable antipathy from long established LRECs and the “settling in period” took nearly 5 years. However, towards the end of this time, Prof Stacey observed that the antipathy had changed to a feeling of respect, with LRECs at times turning to the centralised RECs for advice. With the advent of the European Directive, this existing model was readily adapted to meet the new requirements. In addition COREC introduced an electronic registering, allocation and lodgement system, such that workloads could be spread evenly across the central committees. In passing it should be noted that the centralised RECs have maintained a philosophy of meeting with researchers wherever

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<sup>8</sup> Consultation draft on *National Statement on Ethical Conduct in Research Involving Humans*  
[www.nhmrc.gov.au/issues/natstrev.htm](http://www.nhmrc.gov.au/issues/natstrev.htm)

this is desirable, using telephone hook ups and/or face to face meetings. Of additional relevance is to note that RECs in the UK are NOT asked to take responsibility for monitoring research.

### **Are there obvious ways forward for Australia?**

No simple readily implemented mechanism to achieve effective and efficient review of multi-centre research has emerged to date. Hopefully this meeting can identify the necessary criteria for such a mechanism and find practical means for its implementation. AHEC has recently suggested (in a submission to the TGA/NHMRC review of the CTN/CTX clinical trials scheme) that an amendment to the Therapeutic Goods legislation be considered for this purpose. This legislation is already used as a means of ensuring the legal requirement that no CTN trial may proceed without prior review by a HREC which is registered with AHEC/NHMRC.

The proposal envisages that some HRECs would be ‘licensed’ or ‘accredited’ by the TGA for the purpose of reviewing clinical trials of unregistered therapeutic goods and that a condition of any licence would be a requirement that multi-centre studies be reviewed once only. HRECs would still be required to ‘register’ with AHEC and to report annually upon their compliance with the *National Statement*. Although not an essential component of this particular reform, the opportunity could also be taken to address three other current weaknesses of the HREC system: viz

1. Making the use of a national common application form a condition of the licence,
2. Ensuring that monitoring and adverse event recording and analysis was centralised and rationalised, and
3. Making the establishment of an adequate complaints system also a condition of any licence.

## Multi-centre clinical trials: issues around ethical and scientific review: Discussion

Issues that arose from delegates questions and discussions in relation to this paper were as follows.

- Dr Breen noted the need for State, Territory and Commonwealth Governments to move ahead with reform in relation to ethical review of multi-centre clinical trials, as AHEC and the NHMRC had exhausted their “moral authority” to effect change.
- Dr Breen noted that the UK experience of reform was not directly applicable to Australia, because the UK has a single national government and is not a federation. Reform is more difficult in the latter situation. However, the UK experience does show you can change the mindsets of local ethics committees.
- Dr Breen advised that the UK resource their central committees through the general NHS funding model.
- There was discussion about whether amendments to the Commonwealth Therapeutic Goods legislation were feasible and whether this would assist in achieving reforms. The importance of an agreement by all States and Territories was noted in this regard.
- The issue of monitoring was raised and Dr Breen advised that the UK ethics committees do not monitor research; rather, the institutions do. As long as someone (i.e. the institution) has the role of monitoring, it need not be the responsibility of the HREC.
- It was noted that the National Statement does not distinguish between clinical trials and other research requiring ethical review. It was questioned whether any system developed through this forum should also apply outside the ambit of clinical trials. Dr Breen agreed that it could be preferable to have one system; however, he suggested that within this forum it might be more beneficial to concentrate purely on the problem of clinical trials.
- The problem of adverse event reporting swamping ethics committees was raised. It was suggested that it may be useful to have a centralised model to deal with adverse events. The Cancer Institute NSW noted that oncology is one area where this could be trialled in a bite-sized way, particularly because of the importance of adverse event reporting in cancer trials.
- The question was raised whether the new draft *National Statement* went far enough to accommodate reform of ethical review of multi-centre research. Dr Breen noted that there are to be 2 rounds of consultations on the draft *National Statement*. However, for the moment it is still drafted in the permissive sense. Delegates were encouraged to make submissions to the review.
- There was discussion about how institutional responsibility for monitoring could be achieved, rather than HREC responsibility. It was noted that, at present, ethics committees see themselves as being the accountable body, rather than the institution. There was discussion as to how this situation could be dealt with.



# Multi-centre review in Australia: barriers and possible solutions

*Dr Nik Zeps: Research Manager, Radiation Oncology, Sir Charles Gardiner Hospital, WA*  
*Deborah Frew: Senior Principle Policy Officer, NSW Ministry for Science and Medical Research*  
*Francine Kelly: Assistant Director, Health Ethics Section, NHMRC*

## Introduction

Ethical review of medical research entails consideration of the scientific, ethical and legal aspects of undertaking that research. While Human Research Ethics Committees (HRECs) have no statutory basis in Australia, the regulatory authorities overseeing medical research, including clinical trials, require ethical review of research and, in practice, no clinical trial is undertaken without such a review.

In Australia, the Therapeutic Goods Administration (TGA) follows the ICH GCP<sup>9</sup> guidelines for clinical trials and under section 4.4 of their comments on ICH GCP state that approval from an Institutional Review Board (IRB) or HREC is required before a trial may be opened. Similarly, most funding bodies in Australia strictly adhere to the NHMRC National Statement on Ethical Conduct in Research Involving Humans (NS)<sup>10</sup>. Chapter 1 of the NS, “Principles of ethical conduct”, states: “research projects involving humans must be reviewed by an HREC and must not be undertaken or funded unless and until approval has been granted”.

While the ICH GCP sets out guidelines for all aspects of the conduct and reporting of a clinical trial to an HREC, it makes no comment on who that HREC should be, nor does it set out any requirement that it needs to be based at the institution conducting the trial. Similarly, although the NS envisages HRECs being established by institutions, it does not specifically require that the institution in which the study is being conducted carry out the ethical review.

Nevertheless, there is a firm belief amongst the majority of the 200+ HRECs in Australia and their parent institutions that they alone must conduct ethical review for the institution to which they are affiliated. This belief is largely based on the practice of institutions which, on the whole, bundle the separate issue of ethical consideration in with the administrative ‘governance’ type requirements of clinical trial conduct. This paper sets out to illustrate why and how this bundling occurs. It also proposes that it may be possible to unravel ethics and governance in a way that permits a more streamlined approach to HREC operations.

## Responsibilities for conducting medical research in Australia

Both the host institution and the researchers are jointly responsible for ensuring the following conditions are met for a clinical trial:

1. Ensure the proposed study is GCP compliant and that there are mechanisms for checking continued compliance.

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<sup>9</sup> <http://tga.gov.au/docs/pdf/euguide/ich/ich13595.pdf> (last accessed 10-1-2005)

<sup>10</sup> <http://nhmrc.gov.au/publications/pdf/e35.pdf> (last accessed 10-1-2005)

2. Ensure that necessary legal indemnities and insurances are specified and
2. obtained.
3. Ensure there are suitable facilities to conduct the trial.
4. **Ensure the proposed study is scientifically and ethically sound.**

Only the last of these is specifically an issue for an HREC. All the others can be taken together under the auspices of “clinical governance” and are issues for the administration of the institution.

Despite these separate roles, however, most hospital based HRECs are established by the medical executive as a part of the institution’s administration. Indeed, the membership of many HRECs often reflects this, as the terms of reference require that the HREC include members of the medical executive. Moreover, the terms of reference can often require that directors or heads of clinical units be represented on the HREC in addition to the core membership outlined by the NS. This raises issues with respect to the independence of the HREC, especially if institutional employees are predominant. In addition, it automatically introduces a tacit understanding that the committee will consider more than just the ethical issues. As a result, both during HREC meetings and in the HREC executive officer’s duties, there is a disproportionate amount of time spent on what are essentially clinical governance issues as opposed to the consideration of specifically ethical issues.

Frequently these governance considerations are beyond the expertise of the non-institutional members of the HREC. This begs the question of whether such members should be required to consider those issues at all.

This paper will examine each of the aspects of trial conduct described above and will identify: how their consideration and implementation is presently carried out by HRECs; the issues this gives rise to; and finally propose some tentative solutions for streamlining ethical review by unbundling these different roles.

### **1. Good Clinical Practice (GCP): Whose responsibility?**

Many hospitals have involvement in ‘research’ as part of their mission statement and, as such, have an obligation to provide the infrastructure to support research and develop a culture of research activity. The ICH GCP provides a set of clear guidelines for the conduct of medical research by employees of an institution as well as by the institution itself, and requires that these guidelines be strictly adhered to. Unfortunately, HRECs are often regarded as a means to ‘prove’ compliance with ICH GCP when, in fact, the HREC has no direct legal responsibility for the conduct of the study.

The question may be asked as to why conduct of a clinical trial is any different in its requirement to follow GCP than standard medical treatment. Investigators need to be aware that the trial sponsor or TGA/FDA may require more detailed clinical notation of the patient’s progress and treatment, but the fundamentals of working to clear guidelines of acceptable practice fall more generally under the auspices of clinical governance. If this is true, then the conduct of a trial is in essence a continuation of this and is an obligation for the hospital, not the HREC.

Importantly, most HRECs are not funded or staffed in any way that permits routine examination of the conduct of a trial and, instead, the system requires that the researchers self-police and notify the HREC of any deviation from the protocol. It is therefore the institution's responsibility to provide adequate training for research staff in GCP and any monitoring of their conduct to ensure compliance.

## **2. Indemnity and Insurance**

Institutions and HRECs often believe that there are legal requirements which obligate them to undertake ethical review "in-house" (that is, by an HREC established by that institution). They believe that legal liabilities may arise if they rely on the ethical review of another HREC.

It is important to unbundle the legal liabilities that can arise from a clinical trial, and realise that it is not necessarily the law itself which causes problems for the concept of non-institutional review.

Generally, liabilities from a clinical trial can arise in two ways:

- Product liability: that is, an unsafe product (drug or device) causes injury; or
- Negligence: where a party's negligence causes a participant of a trial to be injured. In clinical trials, there are three major parties who can be negligent and cause damage to a participant: the HREC, the person(s) who designed the trial; and the individual(s) who conduct the trial (the investigator(s)).

### Product liability

Responsibility for product liability sits with the manufacturer of the product, and it makes no difference to this liability at law which HREC reviews the trial, or which institution established that HREC. Product liability does not pose a barrier for non-institutional ethics review.

### Negligence

An HREC can be negligent if they do not review a trial with due care and, consequently, approve a trial which is dangerous and causes damage to participants. (This liability is a theoretical one, as there have been no cases of this kind against an HREC in Australia). It is important to note that this liability flows to HREC members (and therefore to the institution which established the HREC and indemnifies its members) regardless of whether the HREC is located in the institution which conducts the trial, or elsewhere.

A researcher can be negligent in designing a trial. This may lead to a dangerous trial, and to participants suffering injury. This liability rests with the persons(s) who designed the trial or their employer. It makes no difference at law which HREC reviews the trial.

An investigator can be negligent in conducting a trial, and this will be the responsibility of the investigator or their employer (often the institution conducting the trial). Which HREC reviewed the trial makes no difference to liabilities that flow as a result of the negligence of the investigator(s).

So, it is necessary for HREC members to be indemnified against liabilities which arise from their own negligence; and it is necessary for manufacturers, designers of trials and investigators to have insurance and indemnity arrangements to cover their potential liabilities. Why is this an obstacle to separating ethical from institutional responsibilities?

There are two major obstacles. First, if an institution has convened an HREC, that institution is required to cover that HREC's liabilities. The institution might be prepared to cover those liabilities where the HREC is reviewing research being conducted in that institution. However, the institution may not be so happy to cover liabilities of the HREC if it is reviewing research which is being undertaken at another institution. In other words, the institution might not wish to take on perceived potential liabilities because its HREC is generous enough to review research for other institutions. This is sometimes the case even though there are many HRECs that readily review research on behalf of unaffiliated organisations and/or researchers which do not otherwise have access to an HREC.

To overcome this problem, institutions or other bodies which convene HRECs need to see themselves as part of a system and recognise that it is part of their role to review research which may be taking place elsewhere. Further, they should recognise the extremely small risk which attaches to HREC review and take a practical, rather than a theoretical approach to this risk.

Second, there can be issues relating to insurance and indemnity arrangements. The parties offering insurance or indemnity (either insurers or, in some states, self-insurance arrangements) do so on certain conditions, and these conditions have grown up around an institution-based HREC system. Some problematic conditions imposed by insurers or indemnifying bodies are:

- Cover will only be provided to an institution for the liabilities arising from the conduct of a clinical trial if the trial was reviewed by that institution's HREC (that is, the insurer links review of the trial with conduct of the trial).
- Cover will only be provided for the liabilities of the HREC when it is reviewing research taking place in that institution.

Insurance and indemnity cover are provided under contract or other arrangement and are therefore not set in concrete. They are negotiable, and problematic clauses, such as those noted above, could be re-negotiated in line with the implementation of a new system, if there was proper understanding by the insurers and indemnifying bodies of the needs of the institution and the wider health system.

### **3. Suitability of the institution**

An examination of the core membership of an HREC as set out by the NS suggests that, in practice, the core members alone will not have the expertise or inside knowledge required to determine whether the institution is able to adequately host the trial. In practice, researchers are often required to obtain the signature of the relevant departmental head of the institution to confirm that the department has adequate resources to accommodate the trial. It is not possible for the HREC to corroborate

these confirmations as this would require that each departmental head was interviewed and required to demonstrate a business case to support the application as not impacting on the normal function of the institution. It is therefore clear that this responsibility exists primarily as one for the institutional administration and not the HREC.

While institutions have gotten around this by bundling this responsibility into the HREC process, it is plausible that it could be delegated solely to the host institution and that ethical review would simply ensure that an appropriate person has provided assurance of the suitability of the host institution before conduct of the study would be found to be ethically sound.

#### **4. Ethical review**

According to the NS section 1, an HREC must consider each study and be satisfied that the study design and conduct are appropriate. In a clinical trial, scientific review entails a careful evaluation of the investigator's brochure detailing the safety profile of the trial medications, the statistical power of the study to deliver a result and comparisons with alternative strategies or work already undertaken that conclude that the study in question will answer an important and relevant question with a potential to lead to improved healthcare. An HREC must also consider from where the patients are being recruited, issues of respect, justice and beneficence to the patients as well as consider the appropriateness of all documentation such as patient information sheets, consent forms and questionnaires/diaries that may be used.

#### Expertise of HRECs

These scientific and ethical considerations require a depth of comprehension about the intended study that is often beyond the majority of the members of most HRECs in Australia. For this reason HRECs are able to delegate aspects of the review process to external experts, or as is the case in an increasing number of instances, the institution creates expert sub-committees to the parent HREC. Regardless, the threshold of expertise remains highly dependent on the frequency of reviewing trials of a particular nature, which together with a moderately high turnover of volunteer members, means that for many HRECs it is next to impossible to establish any sort of corporate knowledge base upon which to draw.

The development of differing levels of expertise between individual HRECs is often put forward as one of the main obstacles to accepting the review of another institution. That is, although establishing an HREC under the NS is possible for any institution in Australia, there is no system of benchmarking the ability of any to adequately consider and give an authoritative approval to any study. The establishment of such a system may be one way to ensure that HRECs that review clinical trials are appropriately resourced to do so.

#### **Proposal: Separating ethical review from institutional responsibility**

Many of the issues related to acceptance of a non-institutional model of ethical review are based on the current confusion of an HREC's duties which should only be to carry out ethical review of a study, as opposed to the institutional role which should be

conducted by the institution's research administration. This paper proposes a model whereby ethical review can be separated from institutional responsibility.

### **The concept**

This "separation of roles" model proposes that HRECs can operate independently of institutions that conduct research. Research institutions seek advice, as required, from an HREC regarding the ethical acceptability of a research project prior to the institution giving approval for the research to commence. Obtaining this advice is one of a number of responsibilities that a research institution should fulfil prior to undertaking a research project.

Under this model, not every institution is required to have its own HREC and therefore, the number and type of HRECs could be determined by the demand. As a result a smaller number of HRECs would be established and they could be adequately resourced and their members adequately trained. Each could operate in accordance with a comprehensive set of policies and procedures in accordance with the National Statement. The workload of each HREC could be sufficient to enable it to build up its expertise but not so large as to be unmanageable.

HRECs could be specialised so that a humanities project was allocated to, for example, 1 of the 12 suitable committees and a clinical trial was allocated to 1 of the 10 clinical trials committees, ART/embryo research to 1 of the 2 HRECs suitable to review these proposals. Some HRECs could undertake a number of specialist roles and there would always be more than one HREC capable of reviewing a particular project. This latter feature would ensure that there was always an HREC available to review the project and that no HREC operated in a 'monopoly'.

This model would enable each research project to be reviewed once only. HRECs could operate on a fee for service basis and the fees could pay for the operation of the HRECs.

Research organisations currently engage the professional services of external organisations, for example, legal advice, auditors, risk assessments. Purchasing ethical advice should be considered similarly and not pose insurmountable legal liability issues.

### **Advantages of the model**

- One study, one review.
- It would be efficient in terms of workload, expertise and resource balance.
- HRECs with small workloads, which are often under resourced and lacking in expertise, would no longer exist, so the total number of HRECs would be reduced, thus reducing overall operating costs.
- Specialist HRECs would be more efficient due to familiarity with the research, availability of experts and scientific review processes.
- Research projects would be allocated to an available HREC and so the time between submission and review would be consistently low.

- HRECs advice would be independent.
- Ethical review would be available to all researchers whether institution or non-institution based for example, medical specialists in private practice, community based researchers.

### **Issues raised by the model and proposed solutions**

- Issue: The role of HRECs in providing ethical review would need to be clearly separated from the other research administration roles that HRECs often undertake on behalf of their institutions. Solution: Institutions would need to establish other mechanisms to undertake these functions.
- Issue: Some current insurance and indemnity arrangements may require an institution to have its research reviewed by its own committee. Solution: Re-negotiate problematic insurance and indemnity arrangements in light of the new structure.
- Issue: Institutions would need to be able to “trust” the HREC from which they are obtaining advice and be assured that its advice was reliable. Solution: An accreditation system or some other independent quality assurance “benchmark” for HRECs.
- Issue: Processes and operating policies between HRECS would need to be standardised. Solution: Use of a national application form and standardised operating procedures and policies.
- Issue: Universities may need to have specialised HRECs for certain kinds of research. Solution: Universities may choose to have an institution based HREC to review student and local, low risk research but all other research and all hospital based research would be reviewed within the non-aligned HREC system.
- Issue: HRECs would need to be centrally coordinated but geographically dispersed. Solution: There could be an overall “administrative” body which coordinates the allocation of multi-centre research proposals.
- Issue: High levels of scientific expertise would still be required. Solution: Scientific review processes would draw from the national pool of expertise, as there would be fewer HRECs vying for limited scientific expertise.
- Issue: HRECs still need to be established by someone and be physically located somewhere. Solution: HRECs might physically operate in existing research institutions such as hospitals and universities, and those institutions might even be responsible for constituting and maintaining those HRECs, but conceptually the HREC would be non-aligned.
- Issue: The system needs to be funded: Solution: The financial structure would take into account the usage of the system by research organisations but also the contribution to the system made by research organisations, for example, provision of staff as committee members or expert reviewers.

## **Multi-centre review in Australia: barriers and possible solutions**

### **Discussion**

Issues that arose from delegates questions and discussions in response to this paper were as follows.

- Much of the discussion in this session revolved around the concept of “unbundling” ethics review responsibilities from the responsibilities of the institution regarding research governance, as the main theme of Dr Zeps paper was the need to achieve this aim in order to successfully streamline ethics review.
- It was discussed whether the effect of unbundling would be that institutions become the bottleneck, rather than the HREC. Dr Zeps noted that if an institution wishes to enhance its research opportunities, it is in its interest to invest in the requisite framework which allows institutional issues to be dealt with efficiently. It was noted that State health systems can play an important role in assisting their institutions to deal properly with research governance.
- The position of universities was discussed. There was some discussion and debate on the extent to which university HRECs reviewed clinical trials (ie whether they conducted a full review as the HREC for the host institution does, or a lesser level of review, or relied on the review of the host institution). In any event, it was noted that universities may need to retain their own institutional ethics review processes for student and psycho-social research.
- It was noted that many ethics committees have an element of ownership associated with their procedures, for example their consent forms. It was questioned whether this could provide a block to uniform systems. It was noted that any uniform system should be informed by wide community consultation. It was further noted that cultural issues will need to be addressed, and changes should be made both top down and bottom up.
- It was noted that, even if ethics committees were separated out from institutions, the institution still has tasks that it needs to do. Previously these tasks were performed by the HREC as a part of the institution. With unbundling, how will these be done? It was noted that the existing administrative framework at the institution could be maintained and enhanced. It was noted that the EU Directive had resolved this problem in Europe to some extent, because hospitals under that system needed to accept research governance tasks as part of their role. It was also noted that the UK system includes a site-specific assessment on local issues, with a 25-day time limit, which assisted in specifying the institution’s responsibilities.
- It was noted that the principal motivation of government reforming ethical review was to enhance the protection of research subjects, and that this primary aim of ethical review was not to be compromised by the desire to foster research. The merits of “unbundling” had to clearly address this primary aim.

## **NSW Health Pilot Shared Scientific Assessment Scheme**

*Deborah Frew: Senior Principal Policy Officer, NSW Ministry for Science and Medical Research  
Ainsley Martlew: A/Senior Analyst (Research Ethics) NSW Health*

A scheme established by the NSW Health Department to provide a single scientific review for multi-centre clinical drug trials being reviewed by NSW Health Human Research Ethics Committees

### **Aims of the Scheme**

- To eliminate duplication in scientific review
- To achieve a more efficient utilisation of limited resources
- To decrease inconsistencies in scientific review across HRECs
- To be timely

### **What the program entailed**

- A 12 month pilot project which included 22 trials, followed by an evaluation
- The establishment of a central Shared Scientific Assessment Committee (SSAC) and an expert panel to review the scientific aspects of multi-centre trials
- All trials yet to be reviewed by 3 or more HRECs were eligible
- Submission to the Scheme was voluntary: sponsors/principal investigators chose whether or not they wished to submit protocols to the Scheme for review. HRECs could choose to submit protocols received by them to the Scheme.
- The SSAC provided a final report to the applicant dealing with all scientific issues which the applicant could make available to all reviewing HRECs

### **What aspects of the program worked and why**

- Reduction in HREC workload when trial reviewed by SSAC
- Provided scientific support to HRECs lacking such expertise
- Quality of scientific review high
- Generally considered accessible and easy to use by applicants

### **What aspects of the program were problematic and why**

- Resistance from some sectors of industry – do not support a “2 step” process
- During pilot, Scheme under-utilised compared to expectations
- Initial administrative difficulties
- Data obtained in review could not make conclusions about timeliness
- Inability for SSAC meetings to synchronise with HREC meetings

### **Where to from here**

- Continue with SSAS and enhance its utilisation
- Reduce eligibility criteria to trials yet to be reviewed by 2 HRECs
- Resolve administrative difficulties and improve timeliness
- Integrate with other NSW initiatives regarding multi-centre research

## NSW Health Pilot Shared Scientific Assessment Scheme: Discussion

Issues that arose from delegates questions and discussions in response to this paper were as follows.

- It was confirmed that SSAC members were not paid, and that they met face to face (it was not a mere paper based review). With the expansion of the Scheme, Ms Frew noted that the need to pay members would be carefully monitored, although the idea of paying both SSAC members and HREC members had been met with concern at a recent meeting of NSW Health HREC chairs and executive officers.
- Dr Scoggins noted that industry did not oppose separate scientific review in New Zealand, as SCOTT has been operating there for several years and industry has never raised issues with that system. It was noted that one difference with SCOTT was that it conducted its reviews in parallel with the ethical review, whereas SSAS involves the scientific review being done before ethical review. It was noted that SCOTT does not conduct a full scientific review, in the sense that HRECs are required to carry out scientific review in Australia. Ms Martlew advised that SSAS takes, on average, eight weeks to finalise a report (although much of this time is attributable to applicant delays); SCOTT takes, on average, 15.6 days. It was noted that the NZ Medicines Act specifies the number of days in which review must be done. Dr Scoggins advised that SCOTT members are paid a nominal fee.
- It was noted that many of the multi-centre trials that are done in Australia have been reviewed overseas. The extent to which this may be used to inform Australian scientific review was discussed. It was suggested that, at a minimum, a copy of a review report would be needed and a description of the nature of the review undertaken. However, it was generally remarked that Australia should not depend on the systems of other countries, some of which were not entirely satisfactory. Some delegates had noted aspects of clinical trials which had been accepted overseas which were totally inappropriate to Australia. Nevertheless, there is no reason why Australia could not conduct just one scientific review for clinical trials which HRECs could accept.
- It was suggested that different types of trials (eg phases I, II, III) might warrant different levels of scientific review.
- The meeting questioned whether NSW Health envisaged SSAS remaining limited to scientific review, or whether it would be extended to complete ethical/scientific review. Ms Edwards advised that at the time that SSAS was developed, ethics committees appeared willing to agree to a shared scientific review, but there was more resistance to any shared ethics assessment. The model that was adopted had to take into account the extent to which the system was willing to accept change.
- It was questioned whether SSAS could in the future become mandatory in NSW. Ms Frew advised that this would presently be unacceptable to industry and that, at present, the thinking was that SSAS could not be made mandatory until there is a system of streamlined ethical review to complement it.
- More information about SSAS, including the final report of the pilot, is available at [www.health.nsw.gov.au/healthethics](http://www.health.nsw.gov.au/healthethics).

## Queensland Health: Move to a Mutual Acceptance Model

*Dr Jane Jacobs: A/Principal Advisor, Research and Ethics, Office of the Chief Health Officer, Queensland Health*

In November 2004, Queensland Health launched its research management policy after a 12 months of consultation and review with researchers, HREC administrators and other key stakeholders. A number of historical, strategic and accountability factors were key drivers in bringing about a uniformed approach to research management in the state's public hospital sector. The outcomes of this process has produced a policy that clearly articulates the:

- roles and responsibilities of researchers;
- ethical review and regulatory requirements;
- financial management requirements for research projects;
- indemnity for Queensland Health employees;
- insurance and indemnity for fee-for-service research & research for non-profit or collaborating organisations; and
- principles for Queensland Health research contracts and agreements

The next step to improving the efficiency and effectiveness of research conducted in Queensland Health facilities has been to investigate the most suitable model for ethical review of multi-centered studies.

### **Aim of the scheme: on a broad level**

- demonstrate to government and industry QH commitment to the "Smart State" strategy and support the Department of State Development and Innovations 'Clinical Trials Network';
- facilitate more rapid and efficient review processes for multi-centre/site research; and
- makes QH nationally & internationally competitive in attracting clinical trials

### **What the programme will entail**

- a lead committee taking responsibility for the ethical review of multicentre trials;
- procedures for lead and accepting committee to process a quality review in less than 60 days.

### **Where to from here**

- proceed with consultation – reporting back from this meeting will inform this process

### **Where will Queensland Health be in 5 years**

- embedded & fluid procedures with > 60 day turn around for protocol reviews
- A Web based records for potential patients to view
- 20-25% of the clinical trials market in Australia (this is a x4 more then current market share) held by Qld

## Queensland Health: Move to a Mutual Acceptance Model : Discussion

Issues that arose from delegates questions and discussions in response to this paper were as follows.

- More detailed information was sought on how the mutual acceptance model would work. Dr Jacobs noted the model currently under consideration was still subject to consultation which had recently commenced, and that many details would be finalised in response to information that arose from this meeting and that consultation. Generally, the model would be based on a lead committee taking responsibility for the ethical review of a multi-centre trial.
- Dr Jacobs noted that Queensland had previously trialled a central scientific and ethics review committee for the entire state for multi-centre studies, but that this system had not been successful particularly in relation to clinical drug trials, mainly due to concerns that local requirements weren't being sufficiently considered and that funds for scientific review were diverted to a central committee.
- Dr Jacobs advised of the possibility that, within the proposed model, certain committees would build up specific areas of expertise. Non-lead HRECs would have the right to accept or to reject the study, but not to make changes to the study protocol.
- How the lead committee will be chosen is currently being negotiated. A number of lead committee selection options are being considered.
- General ideas:
  - Single site scientific and ethics review;
  - Integration of a multi-centre review system for all multisite research, i.e. not just clinical trials.
- Committees working closely together eg combined training and education and meeting regularly to build trust and communicate issues about mutual acceptance.

More information about the progress of the model can be provided by the Research and Ethics Unit in Queensland Health and information on the Research Management Policy for Queensland Health can be found on: [www.health.qld.gov.au/ethics](http://www.health.qld.gov.au/ethics).

## **Mutual Acceptance of HREC review of cancer trials in some Victorian Hospitals**

*Carole Alt: Chief Operating Officer, Cancer Trials Australia*

Mutual Acceptance Program (MAP) – A process whereby the review and approval of a multi-centre clinical trial protocol by one Human Research Ethics Committee (HREC) may be accepted by other HRECs (Based on Section 3.4 of the National Statement on Ethical Conduct of Research involving Humans).

### **Aims of the program**

- Reduce time to approval for multi-centre clinical trials
- Reduce duplication of effort in ethical review
- Remove barriers to clinical research in Victoria

### **What the program entailed**

- A pilot project period of 13 months consisting of 18 multi-centre clinical trials
- Four hospital HRECs
- Project manager with funding from Victorian Department of Human Services
- A stakeholder steering committee
- A randomisation process to determine ‘Primary’ and ‘Accepting’ sites
- Management infrastructure to coordinate randomisation, submissions and data collection
- Report and communication of results to stakeholders

### **What aspects of the program worked and why**

- Communication between HRECs initiated and maintained
- Improved processes agreed
- Submission to approval timelines reduced by 25%
- No perceived reduction in ethical or scientific rigor
- Randomisation process for ‘primary’ site seen as fair and equitable
- No loss of income for HRECs
- Executive signoff by “accepting sites”
- Engaged insurers, secretariats, industry, lawyers and government in addressing the issues and finding solutions
- Interest from other HRECs in participating

### **What aspects of the program were problematic and why**

- Lost momentum after pilot completed – needs dedicated central resourcing to roll out to other sites and maintain momentum
- Increased approval timelines post-pilot due to extended legal review time and accepting site approval processes
- HRECs ‘forget’ agreed text and processes
- Industry resistance - saw less work being done for the same cost

### **Where to from here?**

- CTA has identified ethics approval timelines as one of three focus areas in 2005

- New initiatives to overcome barriers identified in MAP 1 incorporated into MAP 2
- CTA has applied to DHS for funding to conduct 'MAP 2'
- "Trust and Confidence" paper published Dec 2004.
- Meeting to discuss benchmarking ethics approval timelines held between CTA HRECs, DHS, Victorian Managed Insurance Agency (VMIA) and DHS in Dec, 2004.
- Update on progress will be advised during this session

*CTA gratefully acknowledges the support of the Victorian Department of Human Services for the Mutual Acceptance pilot project.*

## Mutual Acceptance of HREC review of cancer trials in some Victorian Hospitals: Discussion

Issues that arose from delegates questions and discussions in response to this paper were as follows.

- Questions were raised about the duplication that was present during the pilot, that is, some HRECs continued to do their own review in addition to the review done by the lead committee. Ms Alt noted that this was a choice by the individual HRECs and did not form part of the pilot programme. As the pilot progressed and trust was built up between committees all HRECs chose to discontinue this practice.
- Ms Alt advised that some indemnity issues had arisen in the course of the pilot, but that the adoption of the Medicines Australia standard indemnity throughout Victoria had assisted with these.
- In respect to extending the MAP program, additional funding has been requested to a part time administrative assistant for each participating HREC. This would enable data to be collected on time lines and act as an incentive for HRECs to achieve agreed performance targets.
- There was discussion as to whether this system had made participating committees more likely to be amenable to central review. Ms Alt noted that local matters would still need to be resolved.
- There was discussion about this system, and its role of giving responsibility of accepting the lead committee's review to the participating institution's HREC versus the institution itself. There was discussion about this model not effectively meeting the "unbundling" aim discussed in Dr Zeps paper. This led to discussion about how the *National Statement* could more effectively impose duties on institutions, rather than on ethics committees.
- It was noted that the *National Statement* does not currently preclude the acceptance, by an institution, of ethical review from an external committee.



# Victoria: a project for streamlining ethical review of multi-centre research

*Jane Southwell: Project Officer, Special Projects- Biotechnology and Ethics, Dept of Human Services, Victoria*

## **Aims of the project**

- To identify impediments inhibiting efficient ethical review and other processes associated with multi-centre research in Victoria;
- To consider methodologies for improving efficiency in the ethical review of multi-centre research;
- To examine models for streamlining ethical review processes for multi-centre research operating in Australia and internationally and evaluate their application in Victoria;
- To facilitate problem solving discussion amongst relevant stakeholders.

The development of a model for multi-centre review is only one part of a number of possible wide-ranging solutions. The ideas for a specific model that are being evaluated for application in Victoria are as follows:

## **What the proposed model entails**

- A central body (eg. State Govt/DHS) establishes approx 4 central HRECs to initially handle all multi-centre research (including clinical trials and epidemiological/public health research).
- Agreements established between all participating institutions and the central body/HRECs by which the central HREC is appointed as the “HREC of Record” for the purposes of ethical review of all multi-centre research (ie. decision of central HREC stands without adoption by institutional HREC).
- Appointment to central HRECs be by public advertisement to attract members of appropriate skills and competencies; participating institutions invited to nominate HREC members for central HRECs.
- Each central HREC has a core membership plus may call on individuals from an “expert panel” depending on the nature of research to be addressed at each meeting.
- Central HRECs’ meetings staggered ie. scheduled for a different week of each month (ie. HREC A meets 1<sup>st</sup> week; HREC B meets 2<sup>nd</sup> week and so on).
- A Central Office is staffed as the secretariat to the central HRECs and:
  - receives and allocates applications to the next available meeting date and consults with the Chair of relevant HREC concerning members of the expert panel to be invited to each meeting;
  - forwards single copy of application to participating institutions for local feasibility assessment.
- Local feasibility to be considered and signed off by institutional representative and notified to central HREC within a 21 day timeframe. Study cannot commence until satisfactory local feasibility received.
- Central HREC to be responsible for ongoing monitoring and annual review (copies to institutions).

### **What aspects of the model overcome issues and why?**

- Limits ethical review to occur only once by one HREC and not multiple review by multiple HRECs.
- Enables well structured research to proceed within a reasonable timeframe without unnecessary delays.
- Reduces duplication of paperwork, individual time and effort and resources.
- Improves HREC meeting scheduling so ethical review is not delayed unnecessarily.
- Eases the burden of heavy workload and increasing complexity on institutional HRECs.
- Central HRECS offer complete “independence” and will attract membership of strong competencies.
- Honours existing institutional HREC system for single-centre studies and education within institutions.
- Takes leadership in addressing an issue which is unlikely to resolve itself quickly and comprehensively.

### **What aspects of the model are problematic?**

- Funding, location of central HRECs and resourcing.
- Local feasibility assessment by institutional representative or the Institutional HREC?
- Initial increase in number of HRECs, however, over time, central HRECs will accept applications for single centre studies and smaller institutional HRECs with low demand may pass over all studies.
- NHMRC National Statement will require amendment to allow an institution to appoint an alternative HREC (ie. other than the institutional HREC) as the HREC of record and to remove the requirement that the institutions own HREC “adopt” or “accept” another HRECs approval or disapproval.
- Coordination of legal review/insurance issues related to clinical trials.

### **Where to from here?**

- Address remaining issues and ideas for methodological improvements eg. establishing standard operating procedures for HRECs and streamlining details of the model.
- Consult further with stakeholders in respect of proposed improvements, including above model.

## **Victoria: a project for streamlining ethical review of multi-centre research: Discussion**

Issues that arose from delegates questions and discussions in response to this paper were as follows.

- It was noted that a core feature of this model was that there would be a number of central ethics committees (four were used as the example), each with the capability of dealing with any kind of research. Each HREC would have a core membership and could access additional members from an expert panel.
- There was a suggestion from delegates as to whether central committees could be defined by a clinical area (rather than being generalist), thus enhancing their expertise. However, this gave rise to the further question of whether specialist HRECs could be established to provide for all clinical areas that are the subject of multi-centre research.
- It was noted that the clear advantage of generalist committees was the minimisation of cycle time. Possibly both of these goals could be achieved through a national system.
- The model still faces the questions of who resources and who indemnifies, and Ms Southwell advised that this will be further discussed in the consultation that will be taking place regarding the model.
- It was suggested that the consultation process might be aided by commencing with heads of institutions and then progressing to HREC members and secretariats.
- It was questioned whether a system for expedited out-of-session review had been considered. Ms Southwell advised that this had not yet been considered in detail.
- In relation to institutional HRECs, it was noted that the role of an HREC within an institution would continue in respect of single site research as well as for any educational and other clinical ethics roles within the institution.

It was noted that institutions will still need to keep their administration for locality assessments and monitoring etc, but that the system would effect “unbundling” of the HREC’s ethical responsibilities and other institutional governance responsibilities.

Further information may be obtained by contacting [jane.southwell@dhs.vic.gov.au](mailto:jane.southwell@dhs.vic.gov.au).



## Multi-centre ethical review: the New Zealand experience

*Dr Bruce Scoggins (Health Research Council of New Zealand)*

### Introduction

This paper discusses the recent changes in the framework for ethical review in New Zealand with a focus on the review of multi-centre trials.

### The old New Zealand framework for review of multi-centre trials (pre-December 2004)

- i) Proposals received a primary review from the principal investigator's local regional ethics committee (one of 14 EC).
- ii) Secondary reviews were conducted by all other participating regional ethics committees. Their comments returned to primary committee who provide response to investigator.
- iii) For many ethics committees in the smaller regions their principal role was as a secondary reviewer.
- iv) Transaction costs were high but all proposals received rigorous 'local' input into the ethical review process.
- v) Review conducted by Prof Don Evans (University of Otago) in 2003 established that with very few exceptions the multi-centre process worked efficiently and well.

### Rationale for the new framework<sup>11</sup>

- i) Advantages in having committees established on a statutory basis with increased public accountability.
- ii) Reduction in transaction costs for investigators (only a single application) and for ethics committees (only a single review).
- iii) Locality assessment is best conducted by the host institution not an ethics committee.
- iv) Provision for an appeals process (NEAC) to complement the existing second opinions process (HRC) and complaint process.

### The New Zealand framework for ethical review (post-December 2004)

- i) In late 2004 the Minister of Health made key changes to the ethical review system. Key changes were:
  - provision of statutory authority for committees with public accountability;
  - reduction in the number of committees from 15 to 7 (6 regional and 1 multi-region);
  - establishment of a multi-region committee, and
  - introduction of an appeal process.
- ii) The major change is that any proposal will only receive a single ethical review measured against the National Operational Standard.

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<sup>11</sup> A review of processes for ethical review of national and multi-centre research was a recommendation of the Ministerial Inquiry into the Under-Reporting of Cervical Smear Abnormalities in the Gisborne Region (2002)

- iii) The six regional committees will review multi-centre studies in their region.
- iv) Locality assessment will be conducted by the organisation conducting the study, on all proposals to check:
  - investigator is appropriate at each location;
  - that resources (not research funding) and facilities are appropriate and available;
  - lack of conflict with resource use for health services;
  - cultural and any other specific locality issues have been addressed, and
  - local contact details are on participant information sheet.
- v) HRC's SCOTT (Standing Committee on Therapeutic Trials) will continue to have a role in providing recommendations to the Ministry of Health on clinical trials seeking an exemption under Section 31 of Medicines Act 1981 until establishment of the new Trans-Tasman regulatory agency. At that time the role of SCOTT will be reviewed.

**Possible risks associated with the new framework**

- i) The locality assessment becomes a second tier of ethical review.
- ii) Perception that ethics committees are now less independent.
- iii) Reduced attendance of investigators at ethics committee meetings due to cost of travel.
- iv) Local Maori and Pacific issues not adequately addressed.
- v) Review of responsiveness to Maori becomes an additional tier of review.

## **Multi-centre ethical review: the New Zealand experience: Discussion**

Issues that arose from delegates questions and discussions were as follows.

- The meeting questioned whether piloting had been done for the new scheme now operating in New Zealand. Dr Scoggins advised that no piloting as such had been undertaken, however the scheme drew heavily on work that had been done in other jurisdictions.
- The role of SCOTT was discussed. Generally SCOTT and ethics committee review are done in parallel in NZ, although the ethics committee might defer their decision until they had heard from SCOTT. The review conducted by SCOTT is a quasi-regulatory review rather than a scientific review as conducted by the NSW Shared Scientific Assessment Scheme.
- The appeals mechanism was discussed by the meeting. Until now, New Zealand has only had a second opinion process. A formal appeals mechanism has now been instituted, carried out by a sub-committee of NEAC. It is likely that a principal researcher will have to have gone through the second opinion process before getting access to an appeal.
- It was noted that the HRC have established a data safety monitoring board. A protocol review system is also being set up. It is anticipated that this will be especially relevant to biotech start-ups.



## Notes on Session 3: developing solutions

Delegates were asked by the moderator to develop a set of operational rules which would characterise a timely, efficient and effective system of ethical review of multi-centre clinical trials.

Through a moderated process, the Forum developed the following principles.

1. Every trial is ethically and scientifically reviewed only once with a single submission point for applications.
2. All committees conducting ethical/scientific review have been through a process demonstrating competency.
3. Time from submission to time of approval (or rejection) shall be no more than 60 days (stop clock may apply).
4. National policy & infrastructure (including application form).
5. Committees are responsible for ethical/scientific review and not research governance (monitoring etc.). This is the responsibility of the institution (unbundling). HRECs may be independent of institutions.
6. Substantial community input into the development of the system.
7. Clear accountability, responsibility and transparency of system (roles and lines relative to others).
8. Proper resources must be ongoing for system set-up and maintenance.
9. The system shall include mechanisms to ensure natural justice/fairness. This may take the form of an appeals process.

It was noted that it is not the intention of the group for there to be a separate system for the review of multi-centre research; rather, these principles should apply to a unitary system of ethical review.

The meeting then applied these principles to four different models of ethics review:

- **Model A: Devolved review.** Institutions that conduct research establish an HREC and all research for which this institution is responsible is reviewed by that HREC (the status quo).
- **Model B: Mutual acceptance: HREC to HREC.** The HREC of an institution which conducts research agrees to accept the review of an HREC at another institution.
- **Model C: Mutual acceptance: HREC to institution.** The research institution agrees to accept the review of another institution's HREC, instead of its own HREC, as one aspect of the decision to allow research to be conducted.
- **Model D: Centralised review.** The research institution agrees to accept the review of a central HREC instead of its own HREC, as one aspect of the decision to allow research to be conducted.

The meeting agreed that none of the four models by themselves captured all nine principles. Models A and B were unanimously dismissed. It was generally felt that some combination of models C and D would be most beneficial. Whilst model D was broadly considered to be the 'gold standard' model, elements of model C may be necessary in order to take into account the history and traditions of Australian ethics committees.

Delegates then discussed how reform could be progressed at a national level. It was suggested by Dr Breen that the Australian Health Minister's Advisory Council (AHMAC) was the only appropriate inter-jurisdictional body which could progress this issue. Ms Frew suggested that the Forum co-sponsors could write to the Commonwealth Department of Health and Ageing informing them of the outcome of the Forum, and suggesting that the matter be placed on the AHMAC agenda. This letter could be circulated to forum delegates to brief their Directors-General/CEOs.

*For the record, it is noted that delegates did not attend the Forum in a representative capacity, or have the authority to endorse decisions on behalf of their respective agencies. Agreements reached by Forum delegates represent discussions by interested individuals working in the area, and participating agencies would need to be briefed by their delegates in order to reach a formal position. Thus, none of the agreements or views of Forum delegates should be taken to necessarily represent the final views of the participating agencies or jurisdictions, or to bind those agencies or jurisdictions to any position or course of action.*

# Reference Paper: ethical review in overseas jurisdictions

*Lisa Eckstein: Policy Officer, NSW Ministry for Science and Medical Research*

## Overview

The issue of multiple ethics committees reviewing multi-centre research proposals is not unique to Australia, with many countries struggling to establish more efficient review mechanisms. A number of jurisdictions have initiated schemes aimed at streamlining the process of obtaining ethics approval for multi-centre trials. These have typically involved the separation of discrete aspects of the review process. For example, Singapore shifted the onus of obtaining a valid scientific assessment of the research proposal on to the investigator. As such, a researcher can only seek ethics review once this certificate of validity has been obtained. In contrast, the United Kingdom requires that a 'lead' research committee be designated, taking on primary responsibility for the ethical review. The other sites where the research will be carried out conduct only a limited locality assessment.

This paper briefly describes the systems of ethical review that exist in a representative sample of countries: France; The Netherlands; The United Kingdom; Singapore; New Zealand; Canada; and the United States of America.

## The EU Directive

In 2001, the European Union put out their Directive 2001/20/EC on clinical trials. As this Directive has considerably altered the way in which ethics reviews are conducted across Member States, the primary requirements have been summarised below.

Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medical products for human use (The EU Directive) was published in the Official Journal of the European Communities on 1 May 2001. Member States were required to draw up legislation implementing the Directive by 1 May 2003, with application of the requirements by 1 May 2004.

The Directive requires Member States to place specific responsibilities on ethics committees. These include:

1. A 60-day time limit for decisions.<sup>12</sup> It is envisaged that ethical review and requisite Licensing Authority authorisation will take place in parallel. Specific extensions to this time limit are in place for clinical trials of gene therapy, somatic cell therapy and medicinal products containing genetically modified organisms. No time limit is imposed on ethics committees for consideration of xenogenic cell therapy trials.

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<sup>12</sup> Article 6(5)

2. Within the 60-day period, the ethics committee may send a single request for information supplementary to that already provided by the applicant. The time period is suspended until this information has been received by the committee.<sup>13</sup>
3. For multi-centre clinical trials being conducted within a single Member State, a procedure is to be established providing that a single opinion by an Ethics Committee is valid for the entire Member State. Where the trial is being conducted in more than one Member State, a single opinion is to be given for each Member State.<sup>14</sup>

## France

### Summary Points

- France is a single national government.
- Ethical review is conducted by a Consultative Committee for the Protection of Persons Participating in Biomedical Research (CCPPRB).
- Applicants may solicit only one opinion on a particular research project. This opinion is then valid for the whole of France.
- The CCPPRB has a time limit of 5 weeks to give an opinion on the validity of a research proposal.

## Governance

Ethical review of medical research in France is governed by the *Law Huriet-Sérusclat No 88-1138 on the Protection of Persons Participating in Biomedical Research*.

## The application process

Ethical review is conducted by a Consultative Committee for the Protection of Persons Participating in Biomedical Research (CCPPRB). The CCPPRB is a multidisciplinary, independent body. It is composed of twelve people, eight of which are medical and four of which are to represent society at large. In general, CCPPRBs are accommodated in hospitals and university clinics; in a few cases they are housed in the government regional authority for health and social affairs.<sup>15</sup> More than one committee may be established in a particular region, and approximately 48 CCPPRBs have presently been constituted.

An investigator is to submit the research proposal to a CCPPRB in the appropriate region. The investigator can only solicit one opinion on the proposal; this ruling is then valid for the whole of France. There is a time limit of five weeks to give an initial opinion on the validity of the research proposal. This ruling may be prefaced by

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<sup>13</sup> Article 6(6)

<sup>14</sup> Article 7

<sup>15</sup> Provision of Support for Producing a European Directory of Local Ethics Committees (LECs), 28

one request for additional information. Where this occurs, the committee has an additional four weeks after the questions have been answered in which to return their decision.

Following the issuing of a decision, the opinion is communicated to the French Agency for the Safety for the Health of Health Products (AFSSAPS) or to the Minister of Health. While AFSSAPS then has the power to modify the committee ruling, in practice this is rarely done. With implementation of the European Directive, the role of CCPPRBs appears to have been strengthened, allowing them to directly authorise a research proposal.

### **Multi-centre studies**

Only one opinion on the research project can be solicited from a CCPPRB and this opinion is valid for the whole of France. No formal local ethics review takes place; however, a number of hospitals have their own local ethics committee that informally review proposals.

## **The Netherlands**

### **Summary Points**

- The Netherlands is a single national government.
- Research involving human subjects is regulated under the *Medical Research Involving Human Subjects Act*. The Medical Research in Human Subjects Act and the Medicine Law have now been revised to accommodate the requirements of the EU Directive.
- Medical Ethics Review Committees (METCs) are accredited and established as independent administrative agencies, with their decisions subject to judicial review.
- Under the revised legislation, METCs are expected to reach a decision within 60 days of receipt of an application.
- In multi-site studies, a separation is made between the scientific and medical issues associated with the research proposal, and the local feasibility of the research.

### **Governance**

Research involving human subjects has been legally regulated since 1999, under the Medical Research Involving Human Subjects Act (the WMO). In 2002, the Central Committee on Research Involving Human Subjects (the CCMO) released a manual for the review of medical research involving human subjects, providing guidance for the operation of Medical Ethics Review Committees (METCs). Recently, the requirements of the EU Directive were transposed into the revision of the Medical Research in Human Subjects Act and the Medicine Law.

## The application process

All research involving human subjects must be assessed by an ethics committee. Two types of committees are involved in the assessment of research protocols involving humans, the Medical Ethics Review Committees (METCs), and the CCMO. The CCMO carries out the initial review for specific designated trials, being gene therapy, xenotransplantation, and non-therapeutic intervention where subjects are not capable of giving informed consent. In general, all other clinical trials will be reviewed by METCs.

METCs are accredited pursuant to the WMO. In order to fulfil the accreditation requirements, METCs must:

- include one or more physicians, a research methodologist, an ethical expert, a lawyer and a lay person. This minimal composition is currently being extended to include a pharmacist and a clinical pharmacologist;
- have an appropriate standing order which regulates the operation of the committee; and
- review at least 10 research protocols per year.

Currently, there are 34 accredited research ethics committees in the Netherlands.

Once accredited, an METC becomes an independent administrative agency. It is required to forward to the CCMO copies of all the decisions made. The CCMO may reverse these decisions on administrative appeal. Appeal against a CCMO decision can be made to the administrative law division of the appellant's High Court. At present less than 10 appeals from METC decisions are made per year.

A METC is to meet as often as is required to perform its duties properly, and at least once a month. Prior to implementation of the EU Directive, METCs were expected to reach a decision within eight weeks of the date that the review application is received. If this was not possible, the METC was required to inform the applicant within the said period how long it will need to reach a decision. In the revised WMO, the maximum term for the assessment is 60 days. For trials involving medicinal products for gene therapy, somatic cell therapy and all medicinal products containing genetically modified organisms, an extension of 30 days is permitted. A further extension of 90 days is possible in the event of consultation of an expert group. There is no time limit for research involving xenogenic cell therapy.

## Multi-centre studies

Multi-centre research is governed through the *Directive of the Central Committee on Research Involving Human Subjects concerning the procedure for the review of multicentre research and the external review of monocentre research* (the External Review Directive), which came into force on 1 May 2004.

The applicant obtains from each participating centre a local feasibility declaration, stating that the research satisfies all relevant local feasibility criteria, being:

- sufficient expertise, competence and experience of local researchers;
- suitable local facilities, given the requirements of the proposed research; and

- that the research is consistent with the institution's policies on research and patient care.

The applicant chooses a reviewing committee, being one whose field of operation covers all participating centres. The applicant submits to this committee the protocol and local feasibility declarations. The reviewing committee then makes a decision regarding the scientific and medical ethics issues associated with the research.

## United Kingdom

### Summary Points

- The United Kingdom is a single national government.
- The EU Directive has been incorporated into UK law.
- Ethics review decisions must be delivered within 60 days of receipt of a valid application.
- One decision is valid for the whole of the UK.
- There is a limit of one written request for clarification or further information to applicants.
- There is a separation of site-specific assessment and main ethics review.

## Governance

The EU Directive has been incorporated into UK law through the *Medicines for Human Use (Clinical Trials) Regulations*. The regulations came into effect on 1 May 2004. Under the *Medicines for Human Use (Clinical Trials) Act*, no person shall conduct a clinical trial unless an accredited ethics committee has given a favourable opinion and the clinical trial has been authorised by the licensing authority.<sup>16</sup>

## The application process

A single application is submitted by the chief investigator on the national research ethics committee application form. Generally, the applicant may book the application either into to the Central Allocation System (CAS), a telephone booking service, which allocates research applications to recognised RECs, or directly through to a particular research ethics committee (REC). All clinical trials of investigational medicinal products, and research involving sites in more than one NHS domain, are allocated through the CAS.

Three distinct types of RECs exist in the UK. Type 1 RECs, often linked to specific institutions, are only authorised to review phase 1 clinical trials in healthy volunteers. Type 2 RECs review clinical trials which will take place in a single NHS domain. Type 3 RECs are recognised for review of research taking place in more than one

<sup>16</sup> Medicines for Human Use (Clinical Trials) Act, 12(1) and (3)

NHS domain. Type 2 and type 3 RECs are regional, rather than institutional, and the CAS is used to book these applications.

RECs must issue their decision within 60 days of receipt of a valid application. In order to do this, RECS are required to meet on a monthly basis. To further enhance efficacy, applicants are encouraged to attend the REC meetings, or be available by telephone. The committee can only seek clarification of specific issues on one occasion; while the committee is waiting for a response from the applicant the 60 day clock stops.

Unfavourable opinions from ethics review can be appealed to the United Kingdom Ethics Committee Authority.

### **Multi-centre studies**

Multi-site studies are subject to one primary review and limited site-specific assessments.

In making a site-specific assessment, the main issue to be considered is the suitability of the site for the conduct of the research. This includes, but is not limited to:

- The suitability of the principal investigator;
- The adequacy of local facilities;
- Arrangements for notifying other health care staff; and
- Local arrangements for making legal representation available for the giving of informed consent.

The site-specific assessment is not considered to be a separate ethical review; rather, it forms a part of the single ethical review of the research. As such, the process of site-specific assessment is, as far as possible, to take place in parallel with the main review. While the local REC may draw wider concerns to the attention of the main REC, it should not raise formal objections except on site-specific grounds. The main REC can over-rule these objections if it is satisfied that they are not valid. A local REC has 25 days from receipt of application to notify the main REC of its decision.

Approval for each site will be given by the main REC as part of the single ethical approval for the study. A letter of ethical approval will not usually be issued until the main REC has received at least one notification of no objection from an assessor.

### **Singapore**

#### **Summary Points**

- System of government is a single national government.
- Pharmaceutical trials are regulated under the *Medicines Act* and the *Medicines (Clinical Trials) Regulations*.
- The ethics review system separates scientific from ethical review.

- Applicants have the onus of obtaining a scientific review prior to seeking an ethics review.
- Two-tiered system of ethics review, with initial review at an institutional level, and secondary submission to the national Health Sciences Authority for review by the Medical Clinical Research Committee.
- For multi-centre research, a ‘lead’ institutional review board (IRB) is designated to coordinate the initial ethics review.

## **Governance**

Pharmaceutical trials are regulated under the *Medicines Act* and the *Medicines (Clinical Trials) Regulations*. All proposals for pharmaceutical trials must undergo an independent ethics review process, and comply with the ‘*Singapore Guidelines for Good Clinical Practice*’. In November 2004, the Bioethics Advisory Committee published guidelines for ethics governance of research involving human subjects, ‘*Research involving human subjects: Guidelines for IRBs*’. This report has been accepted by the Life Sciences Ministerial Committee.

## **The application process**

Prior to seeking ethics review of a research proposal, the applicant is required to obtain an objective review of the scientific merits of the proposal. These findings are to be made available to the institutional review board(s) (IRB) that will be conducting the ethical review. It is the responsibility of the researchers to satisfy the IRB that an objective review of scientific merit has been carried out. The review of scientific merits may be carried out by such committees, bodies or agencies as the IRB may recognise as appropriate. IRBs may require a more extensive or rigorous review of the scientific merits where the scientific review has been carried out by, or for, the agency that funds the research.

The Singapore Government requires that IRBs are established as full-time permanent supervisory bodies in all institutions in which research is carried out. Where it is impractical to establish and maintain an IRB of its own, institutions should make clear arrangements with other institutions which maintain IRBs for research proposals to be considered by the IRB of larger institutions. Alternatively, several institutions may jointly appoint a shared IRB.

IRBs are responsible for:

- Ethics review and approval of research programs;
- Continuing review and supervision of research programs;
- Reporting to their respective institutions on unusual or unexpected events arising from the research;
- Maintaining dialogue with their constituent researchers about applicable standards; and
- Receiving feedback from research subjects.

If the IRB approves the research proposal, it is submitted to the licensing body for pharmaceutical trials, the Health Sciences Authority (HSA). In deciding on regulatory approval for a pharmaceutical trial, the HSA consults an expert advisory committee, the Medical Clinical Research Committee. Their responsibility is to ensure that the rights, safety and well-being of human subjects involved in a trial are protected. The Committee currently comprises five members, all of whom are clinical specialists.

### **Multi-centre studies**

In multi-centre research, a 'lead' IRB is designated from amongst the participating institutions. The choice of the lead IRB should be dictated by considerations such as the principal institution of affiliation of the principal investigator, the location where the greatest part of the research is carried out, the expertise of the constituted IRB, and where the largest number of subjects is located.

The lead IRB plays the main role in conducting the ethics review and ensuring that a proper scientific assessment has been carried out. Copies of its decisions are sent to the IRBs of other institutions involved, which may then choose to conduct an expedited review. When submitting their application, researchers are encouraged to distinguish between core elements of their research, and those elements that can be altered to comply with local IRB requirements.

### **New Zealand**

#### **Summary Points**

- System of government is single national government.
- Scientific and ethical reviews are separated by means of the SCOTT committee.
- Regional ethics committees have been established to consider research in distinct geographic areas.
- A single national ethics committee has been established specifically for review of multi-centre research proposals.

### **Governance**

The Health Research Council (HRC) Ethics Committee is responsible for accrediting institutional and regional ethics committees throughout New Zealand and maintaining the standards of ethical review. Regional ethics committees are established under the *New Zealand Public Health and Disability Act 2000*.

## **The application process**

All research proposals involving human participants are subject to ethical review. To commence the review process, applicants must complete the National Application Form for Ethical Approval of a Research Project.

From 1 December 2004, six regional ethics committees have been established to consider research carried out in the four geographical regions of New Zealand. A seventh, the Multi-region Ethics Committee, considers any research to be conducted in more than one Regional Ethics Committee region. Consequently, each application is only reviewed by one ethics committee.

Where a trial involves the administration of medicine to human participants, an applicant is required to obtain scientific/technical approval from the Standing Committee on Therapeutic Trials (SCOTT). The purpose of SCOTT is to:

- Determine whether the proposed clinical trial will provide enough information to demonstrate clinical efficacy and safety;
- Ensure that researchers have the requisite skills to conduct the clinical trial; and
- Recommend improvements to the design of the clinical trial.

It appears that the SCOTT assessment is done in parallel to the ethical review.

The HRC notes that applicants should allow at least two months for the ethical review process to be completed. The committees meet approximately once a month and meeting dates of the regional ethics committee are publicly available. Researchers may attend meetings of the committee either in person or by teleconference. Notification of the committee's decision will be given within 7-10 days of the meeting at which the research proposal is discussed.

The decision of the Director-General of Health to approve or decline an application for trial is based on both the recommendation received from SCOTT and that received from an accredited REC.

## **Multi-centre studies**

The Multi-regions Ethics Committee has been operating in New Zealand since 1 December 2004. The committee is responsible for the primary ethical review of multi-centre studies, including studies that:

- Have study localities in more than one ethics committee region;
- Are actively recruiting participants in more than one ethics committee region; and
- Use database, samples or other information gathered from more than one ethics committee region.

A locality assessment for each region in which the research is to be conducted is included as a part of the review of national and multi-centre studies. The secondary review only assesses specific 'locality issues', being the suitability of any local researcher and of any local research environment and facilities; and any specific issues relating to the local community. Assessment is usually done by the host

research organisation, such as district health boards and the Ministry of Health. Where there is no research host organisation, review is to be done by a health and disability ethics committee in each region in which the proposed study is to be conducted.

## Canada

### Summary Points

- System of government is a federation.
- Ethics review is done through Research Ethics Boards (REBs).
- There is no national system of oversight for REBs.
- Institutions receiving research funding from the three federal granting agencies must establish a REB, as do institutions conducting clinical trials of new drugs, medical devices or natural health products.
- REBs may choose to coordinate their review of multi-site research proposals.
- Applicants specify core and non-core elements of their research to facilitate coordination between REBs.

## Governance

There is no national system of oversight for research ethics boards (REBs). However, institutions receiving research funding from the three federal granting agencies – the Canadian Institutes of Health Research (CIHR), the Natural Sciences and Engineering Research Council (NSERC) and the Social Sciences and Humanities Research Council (SSHRC) – are required to adhere to the *Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans 1998* (TCPS). This specifies that institutions undertaking research on human subjects must establish a REB, and that all such research must be submitted to the board for review. Health Canada regulations governing the conduct of clinical trials of new drugs, medical devices or natural health products also require the approval of a REB. Health Canada may refuse applications, suspend the sale of drugs and cancel the conduct of those clinical trials in Canada which do not meet the generally accepted international principles of Good Clinical Practice.

At present, there is no requirement that Canadian REBs be accredited. The desirability of such an accreditation requirement is currently under consideration.

## The application process

Prior to initiating a clinical trial, the proposed trial protocol and informed consent procedures must be reviewed and approved by a REB. The REB should consist of at least five members, covering both ethical and scientific expertise. REBs are to meet regularly in order to discharge their responsibilities. No frequency of meetings is suggested in the documentation, nor has a time limit been set for the issuing of decisions.

## Multi-centre studies

Each local REB remains responsible for the ethical acceptability of research undertaken within its institution. In multi-site research, when several REBs consider the same proposal from the perspective of their respective institutions, they may reach different conclusions on one or more aspects of the proposed research. To facilitate coordination of ethics reviews, the researcher is encouraged to distinguish between core elements of the research and those elements that can be altered to comply with local requirements. REBs are encouraged to coordinate their review of multi-site projects, and to communicate any concerns they may have with other REBs reviewing the same project.

## United States

### Summary Points

- System of government is a federation.
- Ethics review is carried out by an estimated 4,000 – 6,000 institutional review boards (IRBs).
- There are differing ethics review requirements depending on the source of research funding.
- IRBs are permitted to use joint review or to rely on the review of another qualified IRB; however, legal responsibility stays with the institutions.
- No timeframes are established regarding the frequency with which the IRB should meet or the length of time that may elapse before issuing a decision.

## Governance

Not all clinical trials in the US require review by a research ethics committee; differing levels of protection apply depending on whether the research is funded or conducted by the federal government, state government, foundations or industry.

Most research that is funded or conducted by the federal government is covered by the Department of Health and Human Services regulations on the protection of human subjects [45 CFR Part 46], known as the 'Common Rule'. This applies to all research involving human participants that is 'conducted, supported or otherwise subject to regulation by a federal department or agency which takes appropriate administrative action to make this policy applicable to such research'. Federal funds administered by a Department or agency may not be administered for research involving human subjects unless the requirements of the policy have been satisfied. The Common Rule is currently being followed by 17 federal departments and agencies; the Food and Drug Administration (FDA) applies its own set of regulations, which are broadly similar to the Common Rule.

Each institution engaged in research that is covered by the Common Rule is required to provide written assurance that it will comply with the requirements set

out in the policy. Many domestic research institutions have a broad assurance, which covers all research carried out at the site and generally needs to be reviewed every five years. Other institutions must obtain separate assurances for each funded project.

### **Application process**

The application process for ethics review will differ depending on the institution. No timeframes appear to have been set in the regulations regarding the frequency with which the IRB should meet or the length of time which may elapse before issuance of a decision.

### **Multi-centre studies**

In the conduct of cooperative research projects under the Common Rule, each institution involved in the research is responsible for safeguarding the rights and welfare of human subjects and for complying with the regulations. However, with the approval of the Department or Agency head, an institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort. Similarly, the FDA regulations generally provide that each institution will review the research proposals independently. However, institutions involved in multi-institutional studies may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort.

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