

Ethical Intensive Care Research: Development of an Ethics Handbook

A. RISCHBIETH, D. BLYTHE, for the AUSTRALIAN AND NEW ZEALAND INTENSIVE CARE SOCIETY CLINICAL TRIALS GROUP (ANZICS CTG)

Department of Clinical Nursing, University of Adelaide, SOUTH AUSTRALIA

Department of Intensive Care, Fremantle Hospital, Fremantle, WESTERN AUSTRALIA

ABSTRACT

Conduct of research involving humans in the intensive care unit (ICU) setting is complex and challenging. The vulnerable nature of critically ill patients raises issues of patient safety, and informed consent is difficult. With an increasing global interest in human research ethics, broadened government mandates have targeted improvements in research participant protection and research governance. A parallel rise in health consumerism and advocacy for privacy and protection of personal health information requires a clear understanding of the research participant role and importance of risk disclosure. In addition, the potential for conflicts of interest in a climate of increasingly competitive research funding, requires caution and transparency in related financial and contractual arrangements.

The Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG) fosters collaborative ICU research activity. We have developed An Ethics Handbook for Researchers (EH) for the ANZICS CTG for intended use by researchers in Australian and New Zealand ICUs. The purpose of the EH is to act as a practical advisory guide/supplement; to add clarification regarding ethical issues specific to intensive care research, to assist in the expedition of ethics committee research submission and to summarise available useful resources.

This article introduces a précis of key issues from the EH including specific ethical difficulties pertaining to ICU research, a summary of the process by which ethics committee decisions in Australia and New Zealand are informed, and the use of ethical checklists to assist researchers. (Critical Care and Resuscitation 2005; 7: 310-321)

Key words: Ethics, intensive care research, ethics handbook, consent, ethics committee, human research, clinical research, critical care, research ethics

Intensive care medicine is based upon a combination of experience, theory and evidence, although the evidence base is often of poor quality or lacking altogether.¹ Nevertheless, important intensive care related research questions have been addressed more recently,²⁻⁶ despite the fact that conduct of this type of research is difficult.⁷⁻¹² Sampling, recruitment, and data management are challenging in this limited and vulnerable cohort,

often necessitating collaboration and use of multi-centre research design.¹³ Collection of data can be expensive and there are inevitable resource constraints.

Critically ill patients are essentially captive, vulnerable and fully dependent on the ICU team for all care and therapy. This vulnerability raises issues of patient safety, and informed consent is difficult.^{7,8,13-16} Most critically ill patients lack decisional capacity due

Correspondence to: Amanda Rischbieth, Department of Clinical Nursing, University of Adelaide, Adelaide, South Australia 5000 (e-mail: amanda.rischbieth@adelaide.edu.au)

to underlying disease and administered medications, and therefore require special protection.¹⁶⁻¹⁹ Intensivists, in their role as clinicians and/or investigators, must have a sound knowledge of ethical principles that govern clinical research. Any research in which they participate must demonstrate ethical integrity throughout the study design, implementation, monitoring and dissemination phases. With increasing global interest in human research ethics, broadened government mandates are directed at improved research participant protection and overall research governance.²⁰⁻²⁵

A rise in health consumerism, and advocacy for privacy and protection of personal health information, requires a clear understanding of the research participant role and risk disclosure.^{16,26-30} Furthermore, the potential for conflicts of interest in a climate of more competitive research funding, requires a need for caution and transparency in associated financial and/or contractual arrangements.^{8,14,31-34}

DEVELOPMENT OF AN ETHICS HANDBOOK FOR RESEARCHERS

The Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG) fosters intensive care research and, in particular, collaborative efforts, such as the SAFE study.² We have developed an *Ethics Handbook for Researchers* (EH) for the ANZICS CTG for intended use by researchers and clinicians in Australian and New Zealand ICUs.³⁵ Researchers are required to interpret, and comply with, a plethora of ethical guidelines and ethics committee proformas.^{21,22,27,28,36-40} The purpose of the EH is to act as a practical advisory guide/supplement: to add clarification regarding complex ethical issues specific to the conduct of intensive care research, to assist in the expedition of research to ethics committees, and to summarise available useful resources. It is intended to be a dynamic document to be revised as required. It summarises fundamental ethical principles, gives guidance on ethical integrity throughout the research process, human research ethics committee submission, expedited review, research in the unconscious person and critically ill, principles and types of consent, guardianship, risk declaration, retrospective ethical approval, shared assessment schemes, National Application Form (NAF) development, indemnity, privacy, when quality assurance requires ethical review, peer review, authorship, conflicts of interest, responsible research practices, data management, international declarations/conventions/guidelines/codes, and useful ethical checklists for researchers.³⁵

This article introduces a précis of these issues within the EH including specific ethical difficulties pertaining to research in the critically ill in the ICU, summarises

the process by which ethics committee decisions in Australia and New Zealand are informed, and includes examples of useful ethical checklists that may assist those involved in this type of research.

HUMAN RESEARCH IN AUSTRALIA AND NEW ZEALAND

The current position in Australia is that medical research is performed in accordance with guidelines issued by the National Health and Medical Research Council (NHMRC). The NHMRC has statutory backing and Human Research Ethics Committees (HRECs) are bound to consider research proposals in accordance with NHMRC and Australian Human Ethics Committee (AHEC) recommended processes and procedures. These recommendations are set out in the NHMRC *National Statement on Ethical Conduct in Research Involving Humans* (*National Statement*) NHMRC *Human Research Ethics Handbook*.^{21,29} AHEC is a principal committee of NHMRC, established to advise on ethical issues relating to health and developing guidelines for the conduct of medical research involving humans.

The *National Statement* is aimed primarily at researchers, is succinct and is intended as a summary of principles. The *Human Research Ethics Handbook* expands these principles, offers commentary and legal discussion, and is aimed at both HREC members and researchers. In New Zealand, the equivalent body is the Health Research Council of New Zealand (HRCNZ). The equivalent documents are the HRCNZ *Guidelines on Ethics in Health Research* and the HRCNZ *Operational Standard for Ethics Committees*.⁴⁰

RESEARCH IN THE CRITICALLY ILL

Critical illness carries a high mortality and considerable associated morbidity, underscoring the need for effective clinical research.^{14,41} Improvements in survival, quality of care both in the ICU and beyond, and organ dysfunction reduction are common clinical research themes. Important research is also needed to ascertain accurate outcome predictors and to inform end-of-life decision making.¹⁴

Research in the critically ill is challenging because critically ill patients are rarely able to consent, conflicts of interest can occur amongst investigators and protection of research participants from risk is difficult. The ethical difficulties are complex, with no single piece of encompassing legislation. It is the responsibility of researchers to be familiar with the relevant legislation and guidelines that apply to the community in which the research is to be conducted, including relevant government (Commonwealth and State/Territory) Acts. However, it is the lack of consensus, combined with complex arrangements in legal and

jurisdictional governance (in particular regarding consent, privacy, and guardianship), that presents additional challenges, particularly when multi-centre research is to be considered.^{13,42-45}

Education of researchers, clinicians and HREC members in ethical issues, processes, obligations and governance, is integral to the minimisation of ethical problems that can arise during design and conduct of research in the critically ill.^{9,16,21,29} Ethical 'checklists' are advocated as tools to assist throughout clinical trial design, implementation, monitoring and dissemination phases.^{14,35,46} In the EH, we commend the use of such checklists and give a number of useful examples.³⁵

General remarks: Principles of ethical conduct

The purpose of ethical principles and guidelines is twofold:

1. Protection of the rights and welfare of research participants.
2. Facilitation of research that is designed to contribute to knowledge and be of benefit to the researcher's community and/or to humankind.^{29,37}

The *Belmont Report* describes three basic ethical principles relevant to the ethical conduct of research involving humans, namely respect of persons, beneficence and justice.³⁷ The *National Statement* acknowledges these as a foundation and incorporates *integrity* of the researcher as an additional core principle on which the *Statement* rests.²¹ The New Zealand *Operational Standards* take a similar approach.⁴⁰

UNDERSTANDING HUMAN RESEARCH ETHICS COMMITTEES

Role and function of an HREC

Research proposals involving human participants must be approved by a properly constituted HREC, which is established by, and advises, an institution or organisation regarding ethical approval for research projects. A HREC must ensure that it is sufficiently informed on all aspects of submitted research proposals. Additional expertise may be sought either from individuals or from specific dedicated 'shared assessment scheme' groups as considered necessary. Minimum membership of a HREC is seven, men and women, with members appointed for their expertise and not in a representative capacity.²¹

HREC legal responsibilities

Individual HREC members have legal responsibilities in relation to protection of research participants, and can, in principle, be sued by an aggrieved researcher or injured research participant.^{19,47} An institution and its HREC should consult with, and be guided by, its professional legal advisors in relation to

insurance, indemnity and compensation issues. Provision of evidence that any external sponsor(s) have appropriate and sufficient insurance to meet the legal liability to research subjects for harm arising out of research is important for participating organisations, including clarification of all inclusions and exclusions.^{29,48}

HREC research proposal submission

Most HREC members hold honorary positions although fees may be payable to an HREC or institution for research proposal consideration. If clarification on ethical issues is needed *prior* to submission of the proposal, direct contact with the HREC chairperson by telephone or email may be useful. Presentation in person to HRECs is less common in Australia than New Zealand, but may be requested for complex proposals. HRECs may reject proposals because of poor preparation and/or inadequate information, rather than necessarily due to deliberate contravention of an ethical standard. This often leads to requests for further information or explanation, repeat submission(s), and frustrating delays. An ethical checklist for research submission is presented in Table 1.

Compliance, monitoring and complaints

It is the researcher's responsibility to report immediately to the HREC anything that might warrant additional ethical review. Such matters may include Adverse Events (AEs), Serious Adverse Events (SAEs), protocol changes of any nature, and/or the need for premature cessation of a trial for any reason. HRECs may differ in reporting requirements. Interim reports by the researcher to the HREC are mandatory and are usually intended to be a brief summary of progress. Final reports are often an abstract of the study. Additional legislative reporting and compliance responsibilities exist for researchers under the Therapeutic Goods Act 1989 (TGA) (e.g. for CTN and CTX trials) in Australia.⁴⁹ All HRECs are required to have an appropriate complaints handling process and designated contact person.²⁹

QUALITY ASSURANCE VERSUS RESEARCH

Quality Assurance (QA) is considered integral to healthcare. Most quality assurance activities are initiated by health care providers, individually or collectively, as part of a health service organisation. While specific consent for these activities may be obtained, it is often presumed that health service recipients expect, and at times require, that QA be undertaken automatically within the auspices of high quality health care provision. QA rarely poses any patient risk, and is usually not intended to lead to peer-reviewed journal publication because the results are usually valid only in the local environment. However,

Table 1. Ethical checklist: research proposal submission to a HREC

<i>Find the correct HREC(s)</i>	<ul style="list-style-type: none"> ▪ Individual HREC secretaries or the AHEC Secretariat -ahec.nhmrc@nhmrc.gov.au, can provide HREC contact details. ▪ If multi-centred approval is required, a 'shared' or 'common' protocol application proforma may be available, or there may be reciprocal agreements between hospitals/organisations. ▪ To co-ordinate the responses of various ethics committees to the same protocol, indicate to which institutional ethics committee(s) the protocol has been submitted.
<i>Submit on time</i>	<ul style="list-style-type: none"> ▪ HREC members usually require a minimum of two weeks to consider a protocol <u>prior</u> to consideration by the full committee. ▪ A <u>meeting timetable</u> (obtained from HREC secretary) is useful to optimise protocol submission timeliness.
<i>Submit in the correct format</i>	<ul style="list-style-type: none"> ▪ Research protocols should comply with the requirements/obligations of the relevant individual HREC(s), including format and presentation. ▪ Protocol template(s)/proforma(s) are available from the HREC secretary. ▪ A 'version no....' should be placed as a footer of the submitted protocol to facilitate tracking of any amended documents.
<i>Submit a team effort</i>	<ul style="list-style-type: none"> ▪ Early agreement should be established on all aspects of the research protocol, individual roles of contributors including matters of study design, authorship and publication, by all investigators, supervisors and collaborators.
<i>Submit with good science</i>	<ul style="list-style-type: none"> ▪ HRECs need to be satisfied that the research design can produce valid results <u>and</u> can protect the health and welfare of the participants. ▪ Statistical issues should be considered early in study design including power calculations. Articulation of contribution to social value and the scientific integrity of the research is important.
<i>Submit with careful attention to consent and participant information</i>	<ul style="list-style-type: none"> ▪ Some HRECs recommend and prefer their own 'consent' and 'participant information sheet' proformas. ▪ Participant information sheets should be written in plain English to a reading/comprehension level of 12 years. ▪ All information declared in the consent and patient information sheet(s) should correlate accurately with the content within the study proposal, in particular, detail of any and all perceived risks. ▪ Specific personal health information to be sourced should be stated. ▪ Participant recruitment should be managed carefully in the ICU, including consideration of an initial approach by a direct caregiver to elicit if the patient or surrogate is willing to be contacted.
<i>Submit comprehensive information</i>	<ul style="list-style-type: none"> ▪ Reduce likelihood of study rejection or approval delay, all issues such as indemnity, (i.e. who has it and proof of any such agreements, data use, protection and storage, study timelines, privacy, consent, safety considerations, and resource considerations (including a 'financial statement' with declarations of funding sources), should be included.
<i>Ask for help</i>	<ul style="list-style-type: none"> ▪ The NHMRC/AHEC 'Ad-hoc Advisory Service' provide advice on a range of research related ethical issues: ahec@ahec.nhmrc.gov.au ▪ Advice and experiences sought from fellow researchers is recommended. ▪ Inclusion a researcher with a 'track record' in the list of investigators can often be helpful, particularly if a funding/grant application is to be considered.
<i>What to do when a protocol gets rejected or further information is sought</i>	<ul style="list-style-type: none"> ▪ If a research proposal does not receive ethics approval, correspondence from the HREC should state the rationale, including references to relevant sections of the <i>National Statement</i> and/or other documents/processes where compliance has not been satisfied. ▪ An unconditional letter of approval from an HREC is required before a clinical trial commences. Where the HREC has approved a clinical trial subject to minor amendments it may authorise the chairperson to certify that those amendments have been completed and issue the letter of approval; with the chair reporting to the next full meeting. This is in the interest of preventing unnecessary delay.
<i>Notification of decisions</i>	<ul style="list-style-type: none"> ▪ It is reasonable that researchers be notified of the HREC's decision as soon as practicable following the meeting at which the research proposal has been reviewed. If the proposal is approved, written correspondence from the HREC should state all conditions of approval, if applicable.
<i>Expedited review</i>	<ul style="list-style-type: none"> ▪ AHEC recommends that all HRECs have an 'expedited review' process whereby a full committee review may not be required in certain circumstances, (used for consideration of some quality activity (qa) proposals, and for some observational or epidemiological studies / studies that involve minimal risk, burden, alteration of care or invasion of privacy).
<i>Retrospective ethics approval</i>	<ul style="list-style-type: none"> ▪ Consideration should be given to issues of intended publication as some peer reviewed journals have requested 'retrospective ethical approval' when they believed a study to be 'research' although it was submitted as 'audit/quality assurance' activity. This is problematic with no provision for this made in the <i>National Statement</i>. ▪ One solution may be to adopt the NHMRC/AHEC 9 questions demonstrating a low risk study in addition to seeking an expedited review.
<i>Clinical trial registries</i>	<ul style="list-style-type: none"> ▪ Early registration of a clinical trial should be completed before first participant is recruited.

they may identify issues that subsequently develop into a formal research project. It is clear that some QA activities may not merit ethical review, for instance epidemiological studies using de-identified data.^{36,50}

The National Statement states: "...it is the responsibility of each institution to develop criteria to classify which of its activities are reviewable by an HREC and which are not". However, AHEC recognised the difficulty posed to researchers and health-workers in distinguishing between 'audit/QA' and 'research'. They conceded that: "no Australian authority has been able to create definitions that clearly separate quality assurance from clinical research".³⁶

To assist researchers and HREC members as to when ethical review is warranted, the NHMRC sought broad consultation and published a guiding document:

*'When does quality assurance require independent ethical review?'*³⁶ In this guide, a process of asking 9 specific questions is recommended to inform decision making regarding whether ethical review is required. If all 9 questions are answered in the negative, no HREC consideration is required. If one or two are answered 'yes', then the proposal may only require expedited review. If yes is answered to a number of questions, a full review is usually warranted. The HRCNZ currently recommends the Canterbury Ethics Committee flow

chart to provide guidance for NZ researchers when determining if ethical review is required for audit. The flow chart is not dissimilar to the AHEC '9 questions' in that if the answer is 'No' to all, ethical review is not required in NZ.⁴⁰

ETHICAL APPROVAL FOR MULTICENTRE RESEARCH

Because of the inherent interpretative nature of the *National Statement*, it may not be uncommon to find disparate opinion between ethics committees that may result in approval by some and not by others.^{21,51-53} In recognition of these difficulties, and given the current edition was published in 1999, NHMRC/AHEC have sought broad consultation to review and revise the *National Statement* during 2005. An ethical checklist (from the EH) for additional considerations in multi-centre research ethics committee submission, is presented in Table 2.

SPECIFIC ETHICAL DIFFICULTIES IN ICU RESEARCH

Research involving unconscious persons

The issue of whether it is justified to include an unconscious patient in a research project without his or her consent is the most difficult issue facing ICU research

Table 2. Ethical checklist: multiple HREC submissions

<p><i>Multiple HREC submissions</i></p>	<ul style="list-style-type: none"> ▪ HRECs are essentially self-regulating (as long as they remain compliant with AHEC and the <i>National Statement</i>), and as such, researchers must comply with their various requirements. This can be problematic when application to a number of HRECs is required for the one study. ▪ NHMRC and AHEC believe it is the responsibility of individual HRECs to make approval decisions independently, or elect to 'accept' other HREC(s) approval, or to conduct an 'expedited review'. ▪ Shared assessment schemes and approvals are an emerging trend in an attempt to address some apparent anomalies and resource inefficiencies, within a collaborative structure. AHEC have knowledge of current scheme locations. ▪ A 'National Application Form' (NAF) is currently being developed (2005). The NAF will be supported within a web-enabled platform and will be modular in structure. Researchers will supply basic information about their project with the relevant modules subsequently made available for detailed completion. It is anticipated that the NHMRC will develop and include a specific ICU research module within the NAF development process. ▪ New Zealand has a National Application Form for all ethics committees: http://www.newhealth.gov.nz/ethicscommittees/application.htm Single region applications go to one of six regional committees and proposals involving more than one region are assessed by a national multi-region ethics committee: http://www.newhealth.gov.nz/ethicscommittees/committees/multi-region.htm HRECs in New Zealand may request a second opinion from the health research council ethics committee: http://www.hrc.gov.nz/assets/pdfs/policy/secondopinion.pdf Applicants may appeal decisions to the National Ethics Advisory Committee: http://www.newhealth.gov.nz/neac.htm
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chers and HRECs.^{8,14,29} Most national and international guidelines concur that such research is justified as long as stringent safeguards are in place.^{20,21,37,39}

The *National Statement* outlines categories of vulnerable persons that may be involved in research activity, and discusses the relevant ethical considerations that apply to these groups.²¹ Children are considered within this incompetent persons category. NHMRC/AHEC recommend careful consideration of these highly vulnerable groups as identified and defined within NS 6.1- 6.8. There has been confusion over which category is most appropriate for the '*unconscious ICU patient*'; and subsequent confusion therefore regarding which ethical considerations should prevail. NS 6.8, which refers to *one* of these vulnerable groups: '*research involving unconscious persons*', would appear the most appropriate clause for consideration of the ICU patient. However, a section of this clause (NS 6.8) may appear restrictive for prospective ICU research activity if applied literally (i.e. "...such persons should be excluded from all but minimally invasive observational research"). It is this phrase that has been the subject of different interpretation by HRECs.⁴⁸ This issue has been identified as one that is to be addressed in the *National Statement* (2005) revision process.

NHMRC/AHEC (through their 'HREC Bulletin' publications), have advised HRECs and researchers that although the word "*should*" was chosen here in NS 6.8, the intention was to 'caution' but not necessarily 'confine' all research involving this group. Indeed, they add a protective element in NS 6.9 to ensure consideration of: "*additional matters about which an HREC must be satisfied before it approve research involving any of the categories of participants in 6.1-6.8*".⁴⁸

They also comment that: "...Although the vulnerability of these people will render it difficult to design ethically sound research for their involvement, paragraph 6.9 contemplates that ethically acceptable research with such people can be designed, approved and conducted".⁴⁸

Importantly, it is NS 6.9 and 6.10 that provide a mechanism whereby an HREC can approve research proposals before receiving participant consent. "*In these types of situations, where conformity to the principle of consent is not possible, a research project may be approved by an HREC if the committee is satisfied that:*

- a) *inclusion in the research project is not contrary to the interests of the patient; and*
- b) *the research is intended to be therapeutic and the research intervention poses no more of a risk than*

that which is inherent in the patient's condition and alternative methods of treatment; and

- c) *the research is based on valid scientific hypotheses which support a reasonable possibility of benefit over standard care; and*
- d) *as soon as reasonably possible, the patient and/or the patient's relatives or legal representatives will be informed of the patient's inclusion in the research and of the option to withdraw from the research without any reduction in quality of care".* (NS 6.9)²¹

Therefore, it is the careful interpretation of NS 6.8, NS 6.9 and 6.10 that may assist ICU researchers and HRECs to inform their decisions, conduct ethically sound quality research within the ICU population, and remain 'compliant' with the *National Statement*.²¹

Paramount in these considerations is the careful weighing of potential risk and potential benefit. A competent individual may weigh these risks and benefits for himself, however analysis of risks and benefits by a surrogate on behalf of an incompetent individual poses a range of ethical difficulties, especially if the proposed research offers no direct benefit to that individual. To conduct ICU research, an understanding of the way in which an HREC weighs risk and benefit is crucial.

Risk / benefit analysis

The importance of an analysis of risk and benefit was recognised in early documents concerning biomedical research, including the Belmont Report which advises that: "...for a research subject who is legally incompetent....these groups should not be included in research unless the research is necessary to promote the health of the population represented...and this research cannot instead be performed on legally competent persons".³⁷

The Helsinki declaration considers that it is ethical to conduct research in the incompetent patient even if there is no anticipated direct benefit to the individual, as long as:

- the research is intended to promote the health of the population from which the patient is drawn
- the research cannot be performed on individuals competent to give informed consent
- the risks to the patient are considered to be minimal, or no more than that which is inherent in their condition and the alternative means of treatment.³⁹

Minimal risk

The concept of so-called 'minimal risk' has been used to justify research formats in which, although there is no direct benefit to the patient, there is no increased risk either. Minimal risk is that degree of risk implied

by participation in the research that is no more than that risk encountered by the patient in those aspects of the patient's everyday life, which relate to the research. In the case of a critically ill patient this degree of risk is the degree of risk posed by their disease process plus the risk of standard therapy. The minimal risk requirement is difficult to categorically define in a field such as intensive care, where the knowledge base underlying the disease process and therapeutic options is often limited. The New Zealand *Operational Standards* do not specifically invoke the minimal risk concept but require that the risks be "reasonable in relation to the anticipated benefits".⁴⁰

PAEDIATRIC RESEARCH: SPECIAL CONSIDERATIONS

Research in children presents scientific, ethical, and practical challenges. Children are considered a vulnerable group and require additional protection as research participants. The ethics of paediatric research are addressed separately in most guidelines and remain complex. Obtaining the assent of a child and the permission of a parent or guardian is not the same thing as obtaining informed consent from a competent adult. Thus, regulations require institutional ethics committees to carefully scrutinise the potential risks and benefits of all research involving children.^{21,54-56} The practical difficulties of research involving children include the small number of children with certain diseases, the need to study children of different ages, recruitment difficulties, the need to prepare appropriate medication formulations and the possibility that an approved medication, for example, may be used only by a small number of patients. As children grow, their body size and composition, physiology, and cognitive and motor function change, adding to the challenge of research design in this population.⁵⁴

When a research participant is a child, permission from the responsible relative replaces that of the subject in accordance with national and state legislation. Whenever the child is able to give consent, the child's consent must be obtained in addition to the consent of the child's legal guardian.³⁹ The Belmont Report notes that "*each class of subjects that one might consider as incompetent (e.g. infants and young children ..) should be considered on its own terms*".³⁷ Refer also to the *National Statement* Chapter 4²¹ and The Royal Australian College of Physicians, Division of Paediatricians, *Policy Statement: Ethics of Research in Children*, 1998.⁵⁷

CONSENT

General principles of consent

International guidelines recognise that some clinical

research will involve patients who are physically incapable of giving consent.^{20,23,39} Principle 26 of the Helsinki Declaration states: "*Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical or mental condition that prevents obtaining informed consent is a necessary characteristic of the research population*".³⁹

This remains a useful overall principle. In such cases, it is necessary to obtain consent from a surrogate or, with the approval of the local HREC, to proceed without consent. It is important for the researcher to recognise that there may be alternative strategies to obtaining surrogate consent or requesting a waiver. The HREC should ensure that these strategies have been considered before allowing the researcher to proceed in the absence of patient informed consent. For example, it may be possible to perform the research on a group of patients while they are still competent, or it may be possible to identify participants prospectively and obtain consent before the patients become incompetent. The process whereby consent is obtained follows naturally from the above considerations.

Governing requirements for consent

Three different governing requirements regarding consent require consideration in any human research activity:

1. Consent to medical treatment

Each Australian State, and New Zealand, has legislation to cover the situation of the adult incompetent to give his own consent for medical treatment. The legislation varies as to what situations are covered, but some common themes emerge. In an emergency, medical treatment may be provided without the consent of any person. If a person is assessed as not being competent, consent must be sought from someone who has lawful authority to consent on his or her behalf. If the courts have appointed a person to be a guardian for an incompetent individual, then the guardian can consent. However, even for formally appointed guardians, certain procedures may not be allowed and the consent of a guardianship authority is required.

If there is no guardianship order, then, strictly speaking, consent for medical treatment may only be given by the guardianship authority. Some States have legislated to allow this authority to be delegated to a "person responsible" or "statutory health authority" without prior formal appointment. This person would usually be a spouse, close relative or unpaid carer of the incompetent individual. As with formally appointed guardians, the powers of

a “person responsible” are limited by statute. If there is no person with legally granted authority to consent on behalf of an incompetent adult, medical treatment may be provided if a) it is in the patient’s best interest, and b) if the patients views (if known) or the views of those with an interest in the patients welfare, are taken into account. Refer also ‘Adult guardianship’.

2. Consent to research involving humans

Consent to research for unconscious individuals (incompetent adults) in intensive care is not covered in most legislation.^{58,59} Three Australian States have limited provision for such circumstances. Researchers should become familiar with the legislation that exists in their own jurisdiction, in addition to the ‘consent’ section of *The National Statement* and *HRCNZ Operating Standards*.^{21,40}

3. Consent to collection, use, and disclosure of health information

Consent to collection, use, disclosure of health information is predominantly governed by the Privacy Act 1988, NHMRC Guidelines in both the public and private health sectors, and personal privacy protection in health care information systems.^{22,27,28,30} Most Australian states have additional jurisdictional codes and are not uniform across health departments.

A new framework for consent in the critically ill

It is possible, within the above constraints, to develop a model for obtaining consent in the critically ill.^{2,60} This is outlined in the *Ethics Handbook* in more detail.³⁵ The key features are the useful distinction between research performed in emergency situations and non-emergency situations, and the consequent need for a waiver in the emergency situation; an appreciation of the limitations of “surrogate” consent in a legal sense; and an understanding of clinical equipoise. In addition, the *National Statement* and the *NZ Operating Standards* remain the current reference documents with which researchers must comply.^{21,40}

Emergency research

Some research must necessarily be performed on patients in emergency situations, as with all other categories of patient. In an emergency, the patient is too unwell to give consent. Surrogate consent will also be lacking in a true emergency (which, by definition is unexpected). In these circumstances research can only proceed with a waiver of consent. Critical to the notion of a waiver is the understanding that the waiver allows research to proceed insofar as the patient is enrolled and research procedures, interventions and data collection begun in the absence of consent. It does not obviate the

need to obtain consent at the first available opportunity, unless specific provision for a complete waiver is made by the HREC.

In the SAFE study, written informed consent was obtained from all competent patients.² In cases in which prior consent could not be obtained from the patient because of critical illness or the use of sedative or anesthetic drugs, consent was delayed, and a provision for delayed consent was applied. In such cases, the patient or his or her surrogate decision maker was informed of the study as soon as practicable and consent was sought to continue the study procedures and to access the participant's medical records for study-related data. The patients or their legal surrogates were informed of their right to request that the study procedures be discontinued and their right to refuse the study-related use of their medical records. In this study of over 7000 patients, provision for delayed consent was used for 95 percent of the recruited participants.^{2,60}

Non-emergency research

The more common situation will be that the need to enrol and randomise the patient does not necessarily arise in the context of an emergency. Nevertheless, patient consent may be impossible because of illness, unconsciousness or sedation. In this situation, surrogate consent must be obtained before research may ethically proceed. In general, the surrogate should decide whether or not to consent to the research based on their knowledge of the beliefs and values of the potential participant. Importantly, the surrogate has the opportunity to refuse consent if they believe this would be the wish of the patient.

Surrogate consent

The rules and definitions for terms such as ‘next of kin’ and ‘legal guardian’ in a research context may differ between States and Territories in Australia and in New Zealand. The specific legislation covering each region in which the study is being conducted should be checked and adhered to before commencing enrolment of patients in the study. Regulations also differ as to the choice of who is permitted to be a surrogate decision-maker. Court appointed surrogates have the advantage of a defined legal standing. A surrogate may be considered to be the closest relative, unpaid carer or other person with a close, continuing relationship with the patient who is contactable at the time of randomisation or such a person nominated by the patient. The precise definition in each region should be confirmed with the appropriate local body.

Withdrawal of consent

Where a patient or surrogate has provided consent to

participate in a study, this consent may be withdrawn at any time without reason. Should continuing participation be refused, the randomly allocated intervention/treatment will no longer be used, and the patient will receive whatever intervention/treatment is preferred by the treating clinician. The question of whether any data that has been collected up to this point can be used should be addressed at this time.

ADULT GUARDIANS

The Adult Guardian is an officer who is appointed to protect interests and rights of adults with impaired decision-making capacity, no matter the type or cause of impairment. The Adult Guardian is an independent statutory officer. There is separate legislation in each State and Territory in Australia to cover guardianship applications with subtle but important differences between States. The legislation in New Zealand is broadly similar to Australian legislation.

In all jurisdictions, the Adult Guardian may act as decision-maker for an adult with impaired decision-making capacity if: a) the Adult Guardian has been appointed by the Guardianship and Administration Tribunal as the person's guardian, or b) if the person concerned had previously signed an Enduring Power of Attorney appointing the Adult Guardian as their attorney for personal and health matters. An enduring power of guardianship may be exercised if and when the person making the appointment becomes mentally incapacitated, and can not be delegated to anyone else. The advantage of appointing an enduring guardian prior to developing a mental incapacity is that the person decides for him or herself who is to be the guardian and can say in advance how they want the guardian to make decisions on their behalf.

In the majority of cases, a person in need of intensive care treatment will not have a formally appointed guardian. The practice of most health care institutions is usually to consult a relative, an unpaid carer or other person with whom the patient has a close continuing relationship who is available, willing and appropriate to discuss consent for medical treatment.

In some jurisdictions an individual empowered to consent in such circumstances is then deemed the "statutory health attorney". Alternatively, the concept of a "person responsible" is used, but the notion is the same; a next-of-kin is utilised by the practitioner to make decisions when the need arises, without having been previously appointed in this capacity. In other jurisdictions there is no provision at all for the obtaining of consent from any person other than a legally appointed guardianship authority. The salient point remains, that even with a formally appointed guardian, such individuals are generally not empowered to give

consent for research. The legislation may be silent on the issue, or it may prohibit the guardian from giving consent. Whatever the circumstance, it is incumbent upon the researcher to be aware of the views of the relevant authorities in his own jurisdiction and to act in accordance with those authorities and to remain compliant with the *National Statement* or the *NZ Operating Standards*.^{21,40}

PRIVACY

Application of the Commonwealth Privacy Act 1988 to medical research

Section 14 of *The Privacy Act 1988 (Commonwealth)* sets out 11 Information Privacy Principles (IPPs) that govern the conduct of Commonwealth agencies in their collection, management and use of data containing personal information. The IPPs do not permit agencies to use or disclose, in identifiable form, records of personal information for research and statistical purposes, unless specifically authorised or required by another law, or the individual has consented to the use or disclosure. Additional jurisdictional privacy codes and guidelines also apply in different Australian states which add to the complexity.

Privacy in the Public Sector in Australia

To avoid breaches of the above Privacy legislation where access to health information may be required for research purposes, the NHMRC (in March 2000, with permission from the Privacy Commissioner) issued specific supporting guidelines for use by HRECs and researchers.²⁷ These *Guidelines Under Section 95 of the Privacy Act 1988 (s95 Guidelines)* were developed to provide a framework for the conduct of medical research where identifiable information held by any Commonwealth agency needs to be used without consent; i.e. "if the public interest in the promotion of the research is of a kind that outweighs 'to a substantial degree' the public interest in maintaining adherence to the IPPs". Without the existence of the s95 Guidelines, significant research could be in breach of the Privacy legislation. The s95 Guidelines also require the proposed medical research to have been approved by a properly constituted HREC.

Privacy in the Private Sector in Australia

Introduction of *The Privacy Amendment (Private Sector) Act 2000* established minimum privacy standards for the Australian private sector including all organisations that provide health services and hold health information. It allows sharing of information where necessary within strict safeguards. Following on, in December 2001, NHMRC issued *Guidelines approved under Section 95A of the Privacy Act 1988*

(s95A Guidelines) to provide a similar framework (to the s95) broadened to encompass the private sector.²⁹

Privacy considerations in New Zealand

The *New Zealand Privacy Act 1993* applies to the handling of all personal information collected or held by government agencies and most businesses. The legislation identifies 'personal information' as information about an identifiable living person, irrespective of whether it is on a computer or a paper file.²⁶

CONFLICTS OF INTEREST

Conflicts of interest, or 'competing interests' may be commercial, personal, political, academic or financial. They occur when individuals and or organisations have relationships with a person or persons which then influences their actions. If these relationships have the potential to influence research conduct or dissemination at any stage, they must be recognised and disclosed by researchers, authors, and reviewers.^{14,32,34,61-63} ANZICS CTG has developed an internal policy document on issues of potential or actual conflict of interest issues: http://www.anzics.com.au/ctg/files/conflict_doc.pdf

CLINICAL TRIAL REGISTRIES

The International Committee of Medical Journal Editors has reaffirmed its clinical trial registration policy and endorsed the World Health Organisation's minimal registration data set of 20 fields.³⁸ It asserts the following requirements for an acceptable clinical trial registry:

- it must be electronically searchable, with free access;
- it must be open to all registrants;
- the trial date must be validated; and
- it must be a not-for-profit concern

The Australian Government has funded and established The Australian Clinical Trial Registry (ACTR) at the NHMRC Trials Centre in Sydney which complies with these requirements.⁶⁴ In parallel, as more national trial registries emerge, the World Health Organisation is developing an approval process to assess trial register compliance.⁶⁵

CONCLUSION

Ethics and ethical principles extend to all aspects of human activity and govern interactions in the conduct of human research. Research in the critically ill population is complex and the associated ethical challenges require specific knowledge, consideration and education.

Education regarding ethical principles and the conduct of ethically sound clinical research in the intensive care setting is as paramount as it is in any clinical research environment. However, the vulnerable

nature of critically ill research participants in the ICU, requires additional caution and understanding. The use of ethical check-lists may assist researchers through the myriad of ethical requirements.

The authors of the *Ethics Handbook for Researchers* for ANZICS CTG hope to contribute to this understanding in Australian and New Zealand critical care; to guide improvement in ethical and scientific integrity of research design, conduct, monitoring and dissemination processes. It is incumbent on all researchers (and critical care clinicians involved in research) to be individually informed regarding ethical principles, processes and relevant guidelines and legislative acts in the conduct of human research in the intensive care setting.

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