

**GUIDELINES FOR RESEARCH
CONDUCTED WITHIN THE CHILD
AND ADOLESCENT HEALTH SERVICE**

For Submission to

**THE PRINCESS MARGARET HOSPITAL FOR
CHILDREN ETHICS COMMITTEE**

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1. THE PROCESS

This set of guidelines has been produced so that investigators will be aware of the diverse requirements that must be satisfied before scientific and ethical approval can be given for any research project. The mechanism for submitting applications has been clearly defined so that there will be minimum delay in the processing of applications.

All research applications submitted to PMH Ethics Committee for approval must be compliant with the National Health and Medical Research Council's (NHMRC) [National Statement on Ethical Conduct in Human Research \(2007\)](http://www.nhmrc.gov.au/publications/synopses/e72syn.htm)

These guidelines are based on the above mentioned National Statement and will be reviewed at regular intervals. We invite investigators to comment upon any aspect of this document so that its contents can continue to evolve and more effectively facilitate the performance of research within the campus of Child and Adolescent Health Service (CAHS).

Throughout this document the term 'patient' may refer to both "patients" and "parents, or guardians".

Further information can be obtained from:

The Ethics Committee Secretary
Tel. 9340-8221; email: pmhethics@health.wa.gov.au
Ethics Committee Intranet site at: <http://intranet.pmhkemh.wa.gov.au>

1.1 THE ETHICS COMMITTEE

1.1.1 It is the duty of the Ethics Committee to provide advice, adjudicate on submitted protocols, and monitor the ethical standards of research.

In this regard, the Ethics Committee is committed to compliance with all of the recommendations that have been constructed by the National Health and Medical Research Council (NHMRC).

1.1.2 The Ethics Committee is composed of men and women reflecting different interests and includes at least the following:

- A chairperson
- A lawyer
- A laywoman not associated with the hospital
- A layman not associated with the hospital
- A minister of religion
- at least one member with knowledge of, and current experience in, the areas of research that are regularly considered by the Committee
- at least one member with knowledge of, and current experience in, the professional care, counselling or treatment of people.

1.2.3 **SCIENTIFIC ADVISORY SUB-COMMITTEE (SASC)**

All research protocols are subject to scrutiny of their scientific validity. To streamline this procedure the following guidelines have been established:

1.2.4 **Medical record reviews** will be approved by the Executive Director of Medical Services, bearing in mind the value of the review and strain on personnel and resources. Applications from outside the campus may only be made through a staff member. For Hospital staff wishing to carry out a medical record review a form is available from the Executive Director of Medical Services (telephone: 9340 8245). The recommendation of the Executive Director of Medical Services will come before the Ethics Committee for final oversight and approval.

1.2.5 The Ethics Committee recognises the requirement for ethical oversight of **Quality Assurance activity**. Medical record reviews, audits and quality assurance projects conforming to clauses 5.1.18 to 5.1.23 of the National Statement, will be submitted to the relevant Hospital Quality Improvement Committee for consideration and approved by the Executive Director Medical Services. These activities are monitored by the Office of Quality, Safety and Performance and the Executive Director Medical Services. These activities are noted by the Ethics Committee but not reviewed or monitored by the Ethics Committee unless specifically requested to do so by the Executive Medical Director.

1.2.6 Research projects will be considered for scientific validity by the Scientific Advisory Sub-Committee (SASC). The SASC meets monthly, two weeks before the Ethics Committee meeting. If problems exist, or if the SASC has suggestions to improve the science, the researcher will be contacted with suggestions as to content. The researcher will be given the opportunity to remedy any problems. The application will then be placed before the Ethics Committee, together with the scientific advice, for approval. This process takes account of the requirement for Research Merit and Integrity (clause 1.1 to 1.3 of the National Statement).

1.2.7 No research project may proceed without prior consideration and approval of a written protocol by the Ethics Committee. This includes all forms of clinical investigation undertaken within the campus of the CAHS. All projects submitted must have a supervisor who is a current staff member of the CAHS. The supervisor is responsible for the scientific validity of the study and for ensuring ethical guidelines are adhered to. **Note: Students must obtain the approval of their Institution's Ethics Committee prior to submitting their project to this Ethics Committee**

1.2.8 The decision whether or not research work requires detailed ethical review can only be made by the Ethics Committee. When the distinction between research and other activities such as innovative medical practice, educational exercises, or quality assurance programs are in doubt the matter should be referred to the Ethics Committee. The Ethics Committee will seek advice regarding the scientific validity of all protocols submitted.

1.3 **RESPONSIBILITIES OF MEDICAL RESEARCHERS:**

1.3.1 The public has a right to expect that medical research has the potential to provide beneficial results, that entry into a study will not harm the participants, that investigators will regard all personal information as strictly confidential and that the dignity of patients/subjects should be preserved at all times. The Ethics Committee is required to take into account the competence of the researchers to provide for the well-being of the research subjects. Investigators should understand that the

ethical evaluation of research proposals is not an obstacle to be overcome, but an integral part of the research process.

- 1.3.2 In completing the cover sheets for an application a researcher must indicate that all departments that may be affected by a study (e.g. Pharmacy, Pathology, Biochemistry, Psychological Medicine, and Physiotherapy) have been made aware and approve of the study involving that department. If it is later shown that the researcher did not contact all affected departments and obtain agreement the Ethics Committee may withdraw approval for the study.

1.4 **Responsibilities of Signatories to an Application:**

- 1.4.1 All applications must include the signatures of both the Head of Department and the Directors of the Clinical Care Unit in which the study is based. These signatures indicate that the Department and Clinical Care Unit are both aware of the research and approve of the study taking place in their department/unit. Where appropriate (e.g. student or staff member is undertaking research as part of an educational qualification) a supervisor may also be required for a particular study. The supervisor must be a member of the CAHS staff. The signatories should be aware that they take on the following responsibilities when signing the Declaration page of a research study:

Head of Department

- Ensures the research is appropriate for that particular department;
- Ensures that patients of the department are not being asked to take part in too many studies;
- Ensures that adequate resources are available for the study to take place
- Ensures that the study does not over utilise Hospital resources
- Ensures that Hospital resources utilized are appropriately accounted, noted and available for audit by the relevant Executive Committee
- Ensures that the study does not interfere with routine patient care
- Ensures that the investigator has obtained approvals from all other departments that may be affected by the research.
- Ensures that all study personnel are appropriately trained and credentialed for their duties
- Ensure that all study personnel are compliant with the “Working with Children Checking and Criminal Record Screening WA Health Policy
- Ensures that all study personnel are compliant with the National Statement on Ethical Conduct in Human Research

Directors of Clinical Care Unit (or nominee)

- Ensures that the proposed research furthers and/or falls within the aims of the Clinical Care Unit and the CAHS;
- Ensures that both the researcher and the head of department have complied with the requirements for an application to the Ethics Committee;
- Ensures appropriate procedures are in place for the research to be completed should the researcher leave the CAHS.

Supervisor

- Takes responsibility for overseeing the research carried out for the study and is accountable if any complaints or adverse events arise during the study.

1.5 THE SUBMISSION OF APPLICATIONS:

1.5.1 All applications must be delivered to the Ethics Committee Secretary (located at PMH), preferably unstapled/unbound. When submitting a clinical trial sponsored by an outside commercial organisation 10 copies of both the protocol and investigator's brochure should be included. The issues that must be considered when constructing a protocol are detailed in these guidelines. A checklist of items is available on the hospital website (<http://pmh.health.wa.gov.au/development/resources/ethics.htm>) The following must be submitted with each application:

- a) A completed Checklist
- b) Completed Cover Sheets including lay summary and approvals from all departments affected by the research
- c) A protocol
- d) A subject/parent information sheet - to be retained by the subject/parent (and DNA information sheet if required)
- e) A standard consent form (and DNA consent form if required)
- f) A copy of any questionnaire or interview outline to be used
- g) A copy of the approval from the Ethics Committee of the parent institution where the research forms part of the requirement for a degree or diploma from an outside institution.
- h) A completed Declaration of Interest
- i) A detailed budget.

Particularly difficult issues should be discussed with the Chairperson of the Ethics Committee or the Chair of the Scientific Advisory Sub-Committee, and all matters of ethical concern should be addressed within the protocol.

1.5.2 Submission Fees:

Applications for projects which are sponsored by external agencies (e.g. pharmaceutical companies or other commercial bodies) will attract a submission fee, payable on submission. A fee will be charged for amendments to such projects. Applications by individual researchers for non-sponsored projects or for competitive grant applications will not attract a fee, except those that include a CTN where a fee may payable.

1.5.3 The use of Unregistered Drugs or Drugs outside their approved indications:

The submission of all studies that include the use of unregistered drugs must highlight the fact that the study includes use of an unregistered drug. A copy of the Clinical Trial Notification (CTN) or Clinical Trial Exemption (CTX) documentation and Clinical Investigators Drug Information must be submitted with the application and the necessary approvals must be obtained before the study commences. The information letter must highlight the fact that the drug being studied is not registered for use in Australia or is being used outside the registered indication or dose.

1.5.4 The investigator is required to notify the Ethics Committee of any serious adverse event (SAE) that occurs during the study. Most studies carried out under CTN or CTX will have a SAE reporting form. For Serious Adverse Events occurring at CAHS or other areas for which Ethics Committee has given approval to conduct the trial the investigator should notify the Ethics Committee within 72 hours of the event. Proforma Serious Adverse Event forms are available (<http://pmh.health.wa.gov.au/development/resources/ethics.htm>) .

1.6 POTENTIAL CONFLICT OF INTEREST:

1.6.1 The source of research funding must be declared to the Ethics Committee. This requirement is to protect the researcher from potential conflicts of interest e.g. some hospital staff may be in a position to influence the availability of drugs within the hospital from a particular pharmaceutical company. The awarding of large research grants by the company to those staff could be seen as an inducement to gain a commercial advantage. When submitting a research proposal the Chief Investigator will be required to include a signed “Declaration of Interest” that should include such items as to whether or not any member of the research team (including the Chief Investigator) involved in the particular project or any relative or any related entity of any member of the research team:-

(For studies funded by an external commercial organisation)

- has any pecuniary interest in the Company – either as a shareholder of Director;
- has undertaken any paid consultancy work for the Company;
- has received any sponsorship or fellowship from the Company;
- has received a research grant, travel grant or conference expenses from the Company; or
- will derive financial benefits if the product/drug is endorsed as a result of the research.

(Or for **all** other studies)

- has any pecuniary interest in the proposal; or
- has undertaken any paid consultancy work relating to the research proposal;
- has received any sponsorship or fellowship in respect of the proposal;
- has received a research grant, travel grant or conference expenses relating to the proposal;
- and will derive financial benefits if the product/drug is endorsed as a result of the research.

It is the Chief Investigator’s responsibility that a full disclosure is made to the Ethics Committee and that the declaration covers all members of the research team involved in the particular project. The form for such a declaration is contained in the cover sheets that must be included with the submissions to the Ethics Committee. If funding/monies are received after the Ethics Committee has approved the study such a disclosure should be immediately forwarded to the Ethics Committee.

Furthermore, all beneficial gifts from outside sources to hospital or Institute employees should be directed through the Chief Executive, Director of Clinical Care Unit, Head of Department or Institute Director, as appropriate.

1.7 The use of DNA or Genetic Information:

The Cover Sheet of all studies that include the collection, use and/or storage of DNA or other genetic information should indicate that the study involves the use of this material. A separate DNA information sheet and consent form should be used in addition to the standard study consent form.

1.8 The use of Ionising Radiation:

The Cover Sheet of all studies that include the use of radiation beyond that required for the normal clinical management of patients must indicate that the study has been discussed with an approved Radiation Safety Officer. CAHS Radiation Safety officer is Paul Gould telephone 9340 8648 email Paul.Gould@health.wa.gov.au

1.9 Compliance with Guidelines:

Failure to comply with the guidelines outlined in this document will result in a request to rewrite the application before it is considered by the Ethics Committee. It is better to engage in dialogue in the pre-submission phase of a study, rather than having to take corrective action after a protocol has been submitted for review.

1.10 Dates of Meetings:

The Ethics Committee meets monthly. Applications submitted by the due date (see Schedule) will be considered at the next meeting.

1.11 Grant Application Requests:

The Ethics Committee recognises that many proposals being submitted to outside bodies for the purposes of funding may require rapid review. Full approval, following the procedures outlined in this document, will be required before the project commences.

1.12 The Review Process:

Copies of the complete application are initially reviewed by the Scientific Advisory Sub-committee. If problems exist with the scientific contents, the researcher or supervisor will be contacted prior to the meeting of the Committee, with the aim of remedying problems where possible. This process should ensure the minimum delay in having projects approved, while maintaining the highest ethical standards.

The Investigator should respond point by point to the considerations of the Scientific Advisory Sub-committee and the Ethics Committee during the review process. The investigator should ensure that all revisions and amendments to the protocol are to be indicated to the SASC or the Ethics Committee for further consideration. The investigator should provide one tracked copy indicating any changes and one “final” copy for the Ethics Committee

Decisions by the SASC and Ethics Committee are arrived at by consensus. Committee members will abstain from this process if there is a perceived conflict of interest. Following the Recommendation of the Ethics Committee, Final approval for study is given by the Chief Executive.

1.13 All Amendments to approved projects and Changes to Protocol must be submitted for consideration and approval by the Ethics Committee.

If, during the study, any unforeseen consequences arise these must be immediately reported to the Ethics Committee.

1.14 All approved projects are subject to annual renewal via satisfactory progress reports:

A proforma annual report can be found on the website (<http://pmh.health.wa.gov.au/development/resources/ethics.htm>) together with the annual report regarding progress of the study, the chief investigator will be required, where relevant, to include a declaration of interest form. This declaration will follow the same format as the declaration completed when first submitting a study for approval.

The annual report and declaration must be completed and returned to the Ethics Committee Secretary for review by the Ethics Committee. The proforma report and declaration can be downloaded from the Hospital's website.

(<http://pmh.health.wa.gov.au/development/resources/ethics.htm>).

In the event that a study does not commence within 12 months of being approved by the Ethics Committee the study must be resubmitted to the Committee for approval. The resubmitted study must include updated cover sheets containing the signatures of the relevant heads of department, clinical care unit directors, supervisors and other departments affected by the research.

1.15 All Projects must provide a Final Report:

The Ethics Committee requires reports about studies that are published in the medical literature. But, perhaps more importantly, the Committee also requires reports on studies that do not result in a formal publication.

2. The NHMRC NATIONAL STATEMENT ON ETHICAL CONDUCT IN HUMAN RESEARCH 2007

The *National Statement on Ethical Conduct in Human Research 2007*

(<http://www.nhmrc.gov.au/publications/synopses/e72syn.htm>) contains Australia's primary guidelines for the ethical conduct of research involving human participants. Referred to as the "National Statement" within this document.

The *National Statement* has been co-issued by the NHMRC, the Australian Research Council and the Australian Vice-Chancellors' Committee.

All researchers must be aware of the requirements of the National Statement and comply with their responsibilities as outlined within the National Statement.

3. PRIVACY

For proposals where personal information of subjects is to be used researchers must ensure that the Information Privacy Principles (IPPs) (where information is obtained from Commonwealth agencies) or the National Privacy Principles (NPPs) (where information is collected, used or disclosed by organisations in the private sector) are observed. In instances where consent will be obtained from subjects prior to the personal information being sought compliance with both sets of Principles can be said to have been observed. However, if **consent is not being sought** a researcher must refer to the Principle(s) that may be breached and give reasons for believing that public interest in the research outweighs to a substantial degree the public interest in adhering to the Principles.

The NHMRC has issued *Guidelines under Section 95 of the Privacy Act 1988* which incorporates the IPPs and *Guidelines approved under Section 95A of the Privacy Act 1988* which includes the NPPs. Copies of these guidelines are available from the Ethics Committee Secretary or from the NHMRC web site. Copies of both the IPPs and NPPs are available from the Office of the Privacy Commissioner's web site www.privacy.gov.au/publications (respective titles are "Privacy:

Information Privacy Principles” and “National Privacy Principles”). In addition the IPPs are set out in Appendix 2 of the *National Statement on Ethical Conduct in Research Involving Humans*.

4. MISCONDUCT IN RESEARCH

4.1 Concern has been expressed within the Medical literature about misconduct in research.

According to The University of Western Australia, misconduct in research includes:

- a) The fabrication of data, claiming results where none have been obtained.
- b) The falsification of data, including changing records.
- c) Plagiarism, including the direct copying of textual material, the use of other people's data without acknowledgment, and the use of ideas from other people without adequate attribution.
- d) Misleading ascription of authorship, including the listing of authors without their permission and attributing work to others who have not in fact contributed to the research, and the lack of appropriate acknowledgment of work primarily produced by a research student/trainee or associate.
- e) Other practices that seriously deviate from those commonly accepted within the research community for proposing, conducting, or reporting research.
- f) Intimidation of a research worker, and/or bringing undue pressure to bear by one research worker upon another, to misrepresent results and/or authorship.
- g) Conducting spurious research on behalf of a sponsor organisation e.g., purely to gain tax offset benefits.

Conduct contrary to ethics guidelines.

4.2 The Chairperson of the Ethics Committee will accept, and regard as confidential, any concern about misconduct in research. If it is considered appropriate, the matter will be reported to other authorities and the Chief Executive.

4.3 COMPLAINTS PROCEDURE IN RELATION TO APPROVED RESEARCH PROJECTS

- (a) All complaints in relation to Research Projects approved by the Ethics Committee are to be forwarded immediately by the Ethics Office to the Executive Director Medical Services.
- (b) The Executive Director of Medical Services shall write to the complainant acknowledging the complaint and advising that further investigation is pending.
- (c) The Executive Director Medical Services shall inform the Secretary and Chairman of the SASC within three working days of receipt of a complaint to the office of the Executive Director Medical Services and provide copies of sufficient information to enable identification of the Research Project referred to in the complaint.
- (d) The Chairman of the SASC will meet at the earliest opportunity after receiving notice of a complaint with Executive Director of Medical Services.
 - (i) To discuss the complaint;
 - (ii) To determine if immediate sanctions or suspension of the Research Project is warranted

- (e) Upon receiving notice of the complaint the Secretary will inform the Chairman of Ethics Committee of the complaint and the Chairman of the SASC will confer with Chairman of the Ethics Committee about the complaint.
- (f) Chairman of the SASC or delegate will within 3 working days of receiving notification of the complaint contact the investigator and the supervisor of the Research Project :
 - (i) to notify the investigator and supervisor of the complaint,
 - (ii) to investigate the circumstances and confirm details surrounding the complaint;
 - (iii) to prepare a report for the Ethics Committee and the Executive Director of Medical Services
- (g) The complaint will be tabled at the next Ethics Committee meeting for notice and consideration of the full Ethics Committee.
- (h) Following receipt of a report from the Chairman of the SASC, the Chairman of the Ethics Committee will provide its considerations and recommendations regarding the Research Project and the complaint to Executive Director of Medical Services.
- (j) The Executive Director of Medical Services will correspond with the complainant.

5. TOBACCO INDUSTRY SUPPORT

In accordance with State Government policy : "Public authorities should seek the approval of the Minister responsible (or the Minister's delegate), for the administration of the public authority before considering entering into any sponsorship arrangements in the following areas: tobacco-related sponsorships . For further information :

<http://www.ssc.wa.gov.au/files/government/sponsorship.pdf>

6. THE CONSTRUCTION OF A PROTOCOL

The study protocol is a written agreement between the investigators, the subjects, the Ethics Committee, and the scientific community. No major changes should be made to an initial protocol unless cleared by the Ethics Committee. Although the structure of a research protocol is a matter of personal style, it should flow in a logical manner and serve as a clear guide for those who wish to know about the study. This is particularly important because all hospital staff involved in the clinical care of a patient have the right of free access to any relevant research protocol. Protocols should be widely disseminated and made available to others upon request.

6.1 **Background Information**

The purpose of this section of a protocol is to provide a comprehensive review of the literature so that the current study can be viewed in perspective. It should be written for those who are not familiar with this area of knowledge. It must present a logical and coherent account of the subject. It must not consist of a series of staccato sentences without any discursive content. Anyone who reads this section of the protocol should be quite clear about the problem that is being addressed. In other words, it must provide the scientific justification for performing the study and comment upon the potential benefits that might result from the study.

6.2 The results of any pilot studies should be included in this section.

Besides providing useful information about the worth of the proposed study, it will also serve to convince others that you are capable of performing this type of research.

6.3 **Objectives**

6.3.1 Each study should be directed towards answering a primary question:

It is crucial that this primary question, as well as any subsidiary questions, is carefully selected and clearly defined. After all, the design of a study depends upon the exact question that is being addressed by the investigators.

It is not enough merely to provide a general objective for a study. There must be a clearly stated specific objective that tests a predetermined hypothesis. Many experienced investigators spend a great deal of time trying to define a clear and explicit statement of the main aim for a study. They argue that once this has been decided upon, the remainder of the protocol becomes a series of mechanistic steps that merely furnish a logical and reliable technique for collecting the relevant information. This step also helps to ensure that the investigators do not embark upon a study that is logistically difficult, or perhaps impossible, to complete. Inexperienced investigators frequently make the mistake of designing a protocol that is unnecessarily complex.

6.3.2 Secondary objectives usually relate to useful information about related issues that will be collected in the study. Protocols that list several aims about the same general topic are open to suspicion. The lack of clearly defined aims results in studies that are an excuse for gathering data. This may be a useful technique for hypothesis generation, but must be avoided when testing hypotheses. Hence, the extent that reliable conclusions can be drawn from a study will relate to the structure of the study. A study may be unethical purely because of over-analysis.

6.3.3 **Pilot Studies:**

The Ethics Committee understands that there may be a need for preliminary or pilot studies before embarking upon a definitive clinical study. Where possible such an application should demonstrate knowledge of the relevant literature and, where appropriate, be based upon prior laboratory and animal experiments. Although it is accepted that the conclusions that can be drawn from such studies are limited, these studies should be designed so that they can at least contribute to subsequent meta-analysis (L'Abbe KA et al. Meta-analysis in clinical research. *Annals of Internal Medicine* 1987; 107:224-33). Pilot studies are frequently required to establish the variability of the outcome measure, or to validate a questionnaire.

6.3.4 **Quality Assurance:**

The Ethics Committee recognises the requirement for ethical oversight of Quality Assurance activity. Medical record reviews, audits and quality assurance projects conforming to clauses 5.1.18 to 5.1.23 of the National Statement, will be submitted to the relevant Hospital Quality Improvement Committee for consideration and approved by the Executive Director Medical Services. These activities are monitored by the Office of Quality, Safety and Performance and the Executive Director Medical Services. These activities are noted by the Ethics Committee but not reviewed or monitored by the Ethics Committee unless specifically requested to do so by the Executive Medical Director.

7. **STUDY POPULATION**

7.1 **Eligibility Criteria:**

These must be stated using unambiguous language. It is not enough to state, for example, that "patients with rheumatoid arthritis will be included in the study":

There must be a clear and, whenever possible, objective list of factors that define the criteria for inclusion in the study. It must be appreciated that these criteria will influence the extent that the results of the study may apply to clinical practice and the speed of recruitment of patients into the study.

7.2 **Exclusion Criteria:**

Any subject to whom an intervention is known to be harmful should not, except in unusual circumstances, be admitted into a study e.g., a study of beta-blocking drugs would usually exclude patients with a history of asthma. Where pregnancy is a matter of concern, the steps that will be taken to exclude pregnant patients from study, and possibly prevent the onset of pregnancy whilst the study is in progress, must be documented in detail. In particular studies, the usual practice suggested by the Committee is to ensure that, in studies where pregnancy may be of concern and where it is appropriate, females participate only during the first 10 days of their menstrual cycle. This issue should be considered, where appropriate in studies involving adolescent females.

7.3 **Withdrawal Criteria:**

Patients must always be able to withdraw consent without fear of their withdrawal affecting their normal care. In addition, subjects may develop conditions during a study that would have excluded them from entry into the trial. Such patients must be withdrawn from study. These possibilities must be allowed for when determining the methods that will be used to analyse the results of the study.

7.4 **Sample Size**

The number of subjects to be studied, and the justification for selecting this number, must be declared in the protocol. Studies should have sufficient statistical power to detect differences that are considered to be of clinical interest. It is unethical to choose a sample size based purely upon a set length of time, the amount of resources that are available, or some arbitrary number. It is unethical to include too few subjects to enable a valid conclusion to be reached; or to include more subjects than needed. A pilot study may be needed to determine the number of subjects required.

7.5 **Recruitment Projections:**

Some investigators tend to exaggerate their ability to attract subjects into a study. If this is combined with poor organisational assistance, it may be impossible to complete the study. Ethical

approval can only be granted if the investigators can demonstrate a high likelihood of being able to complete the study. The protocol should clearly indicate the basis for claims about the accrual rate of subjects into the study. If necessary, pilot studies should be performed in order to establish an accurate basis for the estimation of the accrual rate. In addition, it may be wise to prospectively define mechanisms that will allow for the effective prolongation of the study if unforeseen circumstances adversely influence the accrual rate.

7.6 It is unethical to continue to Study Subjects once a reliable answer has been obtained to the Study Aim.

For studies evaluating interventions that have serious side effects, an alternative study design, such as sequential trial design, should be considered. For such studies or for those in which accurate sample size estimation cannot be made before commencement, researchers are advised to pay particular attention to study design and to consider the possibility of incorporating an interim analysis. In such circumstances, researchers are urged to seek statistical advice. All protocols for clinical trials must declare the mechanisms for the trial close-out and lay down criteria for the early closure of studies i.e., formal stopping rules.

7.7 Entry Mechanisms

The protocol must contain an unambiguous explanation of the method that will be used to recruit subjects into the study.

It is necessary to consider the procedures to be used in selecting subjects, the techniques to be used to invite subjects to participate, and the place of the subject's doctor in the research relationship. However subjects are approached, it must always be made clear to them that they are completely free to refuse to participate in the study.

The following procedures are to be followed when recruiting patients for research projects:

Patients Currently In Hospital

If the investigator is the responsible consultant:

- the request to the patient/parent to participate in the study can be made directly. However, the consultant must take into account the dependent nature of the patient in such cases and he/she must ensure that the moral and legal obligations he/she has to the patient are observed.

If the investigator is **not** the responsible consultant

- the investigator must ensure the responsible consultant is aware of the study before the patient is approached to take part in the study. This can be done by informing (in writing) the relevant Clinical Directorate, the Head of the relevant department and relevant consultants of the study and of the characteristics of the subjects required.
- It should be noted that consultants do not 'own' patients and that patients and/or their parents have the right to decide whether or not they participate in a particular research project. The consultant cannot make this decision on behalf of the patient.
- Once the responsible consultant is made aware of the study, the investigator may:

directly ask the patient/parent if they wish to participate in the project,

or

the consultant may give the information regarding the study to the patient/parent who can contact the investigator if they wish to participate or agree to be phoned by the investigator (or agent) after discharge.

Outpatients

The same procedure as that outlined above should be followed when investigators wish to recruit outpatients for a study.

Where the investigator is **not** the responsible consultant and it is not practicable for the investigator to have direct contact with the potential subject at an outpatient appointment, a proforma letter (modified for the particular study) signed by the responsible consultant can be used as the initial contact point for recruitment purposes. Alternatively, a proforma letter (modified for the particular study) signed by the Director of the relevant Clinical Care Unit could be used. To ascertain suitable patients for such recruitment, names and addresses only may be obtained from Medical Records or other sources. At no time should the medical record of a patient be accessed without the prior consent of the patient.

A copy of the proforma letter is available on the hospital website (<http://pmh.health.wa.gov.au/development/resources/ethics.htm>).

Patients **Not** Currently Attending the Hospital

If the investigator was the responsible consultant:

- contact can be made directly to ask if these patients would be willing to participate in the study.

If an investigator was **not** the responsible consultant:

- and wishes to contact past patients of the Hospital to recruit them for a study, a letter from the Director of the relevant Clinical Care Unit (and signed by him/her) is the only manner in which initial contact with such patients should be made. To ascertain suitable patients for such recruitment, names and addresses only may be obtained from Medical Records or other sources. At no time should the medical record of a patient be accessed without the prior consent of the patient.

A proforma letter (to be modified for the particular study) is available on the hospital website (<http://pmh.health.wa.gov.au/development/resources/ethics.htm>).

Information relevant to the clinical care or well-being of a patient may be obtained during the course of a study. Under these circumstances the researcher has an overriding ethical duty to act in the interests of the subject, even if this might prejudice the value of the research.

7.8 Indigenous Peoples:

Special considerations apply to research involving indigenous peoples and, if relevant, investigators should seek a copy of the NHMRC document: “Guidelines on Ethical Matters in Aboriginal and Torres Strait Islanders Research”. Researchers should also be aware that research involving indigenous people should also be submitted to the Western Australian Aboriginal Health Information and Ethics Committee (contact executive officer on 9222 4469) for approval.

Further Information about this committee and necessary forms can be obtained from <http://www.aboriginal.health.wa.gov.au/ethics/index.cfm>

7.9 Recruitment of Students or Employees:

It should be noted that within the NHMRC National Statement on Ethical Conduct in Research Involving Humans indicates that:

No student or member of hospital or laboratory staff under the direct line management of the investigator may be the subject of his or her experiment.

This statement does not apply to training exercises that students may be required to perform, or to investigators participating in their own studies. However, it is a requirement that such exercises are approved by the Ethics Committee.

7.10 Volunteers may be paid for inconvenience, travel costs and their time, but such payment should not be so large as to be an inducement to participate in a research project:

Payment should preferably be in the form of reimbursement of expenses. Occasionally, a payment of Honorarium may be appropriate. The extent of any honoraria must be stated in the study protocol.

7.11 Advertising for Research Subjects:

It is accepted that verbal advertising would only enable an investigator to communicate within their circle of acquaintances e.g., staff and medical students. Because the use of such a captive population for research is undesirable, there is a legitimate need to advertise for research subjects. The advertisement must contain brief details of the project and details of who to contact. Any such advertising material to be used in conducting a study must be approved by the Ethics Committee prior to its use.

7.12 A Record of Volunteers:

It is important that volunteers should be screened by the investigators for suitability before being accepted into a study. These steps must be discussed in the protocol.

It is the duty of the chief investigator to maintain a record of all volunteers who have participated in a study as study subjects for a period of at least 5 years after the completion of the research project.

It is obvious that such records become crucial when evaluating a retrospective complaint about a research group. Each department should maintain a Register of Study Subjects, to ensure that

individual children are not being “overused”. This register should be available for scrutiny on request.

7.13 **Medical Records:**

In some studies, the investigator may wish to obtain the names and addresses of potential subjects from Medical Records, in advance of any contact with the patients, in order to prepare letters to be used for recruitment purposes. While a list of names and addresses may be obtained from Medical Records after the Ethics Committee has approved the study, the investigator should **not** access the full medical record of a patient prior to that patient consenting to participate in the study and giving consent for his/her medical records to be reviewed. In planning such a study, investigators must:

- (a) Demonstrate that due confidentiality will be observed regarding the confidentiality of Medical Records in line with WA Health Policy and relevant Privacy Legislation
- (b) Make administrative arrangements with the Medical Records Department. A form for requesting records is available from the Office of the Executive Medical Director. When submitting the completed form to Medical Records a copy of the letter of approval for the study from the Executive Medical Director should be included. The extent that hospital facilities can be used for research purposes is limited and must therefore be open to negotiation.
- c) Studies that consist of a review of medical records with no patient contact will usually be approved by the Executive Director of Medical Services and come before the Ethics Committee for notification.

7.14 **Qualification or Waiver of Consent**

The investigator is required to address all points detailed in the relevant sections of the National Statement regarding Conditions for Qualification or Waiver of Consent for the consideration of the Ethics Committee where Ethics Committee approval for Qualification of Conditions of Consent is requested for a research study.

8. STUDY DESIGN

8.1 Scientific Integrity:

The Ethics Committee is concerned with the research merit and integrity of any proposed research project as per The NHMRC National Statement on Ethical Conduct in Research Involving Humans (2007).

8.1 Biostatistics:

Researchers are advised to seek expert advice prior to planning a research study. Protocols that fail to achieve a satisfactory standard of sophistication will be referred back to the investigators for remedial action prior to submission for ethical approval.

8.2 A Flow Chart:

Most readers find it easier to understand the outline of a study if the basic steps are outlined in a simple flow chart. This serves as a 'road map' for the study and it ensures that readers are not lost within a maze of detail once they start reading the text.

8.3 Allocation of Patients into a Study Group:

It is sound scientific practice to compare a new therapy with a control group. Randomisation is the preferred way of assigning subjects to control and intervention groups because it ensures that there is not a biased assignment of patients. Explicit details about the randomisation procedure must be carefully documented in all relevant protocols. It is particularly important to ensure that any breaches of the randomisation are documented. The details of these monitoring techniques must be included in the protocol.

8.4 Baseline Data:

It is essential that baseline data are measured in all clinical studies. Baseline data refer to the status of patients before the commencement of any intervention i.e., they describe the type of subjects being evaluated in the study. It is impossible to interpret the results of any clinical study unless there is a comprehensive account of the types of patients who have entered into the study. This is particularly important when studies evaluate risk or prognostic factors. Randomisation does not guarantee that the groups under study are equivalent because it can lead to chance fluctuations between groups. It is always easier to accept the results of a statistical analysis if the groups are similar with respect to factors that are known to influence the main endpoints of the study.

8.5 Follow-Up Schedule

8.5.1 The need:

It is necessary to provide a detailed follow-up schedule so that the logistics of the study can be clearly evaluated by anyone reading the protocol. The schedules should include the timing of all investigations, a roster for the clinical assessments, and the period of review for the subjects in the study. It is important that each study has realistic objectives.

8.5.2 Home Visits:

If it is essential for a researcher to visit the home of a subject, the researcher must have:

- (a) Already obtained ethical approval to perform the home visit, and
- (b) Obtained prior permission from the subject to perform a home visit including making arrangements about the specific time of the visit.

In addition, investigators must be clearly identified with an official badge, stating their name and their institution of employment, and the investigator must be able to produce identification papers.

8.5.3 Loss to Follow-Up:

It is vital that investigators consider the possibility that patients may be lost to follow-up. In studies that involve the long-term evaluation of subjects, there may be a need to define techniques for maintaining contact e.g., the mailing of regular reports on the progress of the study and periodic conversations using a telephone.

Loss to follow-up can also be minimised by providing detailed explanations at the time of recruitment of subjects into the study. If permission is obtained, the details of several relatives or

acquaintances can serve as a contact point. However, investigators must always respect the right of any subject to withdraw from a research project at any time without prejudice.

9. THE INTERVENTION

9.1 Description of the Intervention:

The specific ingredients and timing of all interventions must be completely specified using clear-cut language. If other agents or techniques are being used, there must be sufficient documentation to confirm that the intervention is an established component of routine clinical care. The validity of using new techniques should have been established in the section of the protocol devoted to background information.

9.2 Adverse Events:

There must be a full disclosure of the adverse events that could result from the intervention. In addition, investigators must describe the steps that will be taken to prevent and manage any adverse events that occur during the course of the study.

9.3 The Intervention Schedule:

When the protocol involves complex or prolonged interventions, it is advisable to outline the schedule of events in a table or figure.

9.4 The Control Group:

It is crucial that patients in control groups receive what is considered to be the best treatment currently available. In some instances this may be either observation alone or the administration of a placebo. This requires careful consideration when comparing new drugs to placebo.

9.5 Questionnaires:

Although the use of questionnaires may appear to be fairly innocuous, they can create a number of problems relating to invasion of privacy, collection of sensitive information, incursion into another clinical domain, and the misinterpretation of data. In particular, inadequate response rates create a situation in which there are selection pressures that may distort the truth. For these reasons, a copy of the questionnaire must be submitted with the protocol.

If the questionnaire is not part of a formal research project, or part of a routine administrative inquiry by a formally constituted body within the hospital, then the questionnaire must be submitted to the Ethics Committee for approval prior to distribution. It is evident that great care must be taken when designing forms and questionnaires.

9.6 Ionising Radiation:

If a study involves subjecting patients to ionising radiation which is not a part of their normal clinical management, it is essential that all of the relevant details are discussed with a Radiation Safety Officer. There are officers on the Radiation Safety Committee for each campus.(see 1.8 for CAHS Radiation Safety Officer). Radiation Safety Officers on the campus are overseen by the Head of the Department of Medical Physics, Royal Perth Hospital. Additional documentation will be required by Radiation Safety Committee.

9.7 Genetic Material:

Those investigators wishing to evaluate aspects of human gene therapy and genetics should consult the National Health and Medical Research Council's publications entitled " Guidelines for Genetic Registers and Associated Genetic Material (1999)

In addition, investigators must include both a specific DNA information sheet and consent form to be used in the conduct of any study in which DNA / genetic material is collected, used or stored. A proforma for these is available from the hospital website (<http://pmh.health.wa.gov.au/development/resources/ethics.htm>) and it should be modified to reflect the particular study for which it is to be used.

10. CLINICAL TRIALS

10.1 The Rules:

A clinical trial can involve testing a drug, a surgical or other therapeutic or preventive procedure, or a therapeutic, preventive or diagnostic device or service. The investigator must comply with: "The Australian Code for Responsible Conduct in Research, NHMRC 2007" and "Good Clinical Practice (CPMP/ICH/135/95)"

The Ethics Committee recommends that researchers proposing to perform a study which involves the evaluation of a drug should ensure that:

- (a) A pharmacologist or clinical pharmacologist has been involved in the preparation of the protocol,
- (b) For trials involving new drugs, the protocol includes a full investigational profile of the drug or drugs to be used,
- (c) The protocol contains concise information on dosage, formulation, frequency of administration, and methods of assessing safety as detailed in "Good Clinical Practice (CPMP/ICH/135/95), Clinical Trial Protocols .

10.2 Evaluation Of Drugs Usually Proceeds In Four Stages:

- (a) Phase I Studies investigate the safety and dosage scale of a drug (either patients or healthy subjects are involved).
- (b) Phase 2 Studies consist of small scale investigations into the effectiveness and safety of a drug.
- (c) Phase 3 Studies compare the drug with either the current standard therapy or a placebo - this is the conventional 'clinical trial'. In general, when there is no known treatment for a disease, placebo control trials are ethical. However, comparison trials are usually required when the current therapy is known to be superior to a placebo. Where a placebo is to be used, investigators should ensure that the control group has access to a recognised "rescue" treatment.
- (d) Phase 4 Studies monitor the long-term effects of a drug after it has been released for routine clinical use.

10.3 Drugs not approved for marketing in Australia are subject to full Pharmacological review before the study can be approved:

The Commonwealth Department of Health and Aged Care provide two mechanisms:

- (a) The Clinical Trial Exemption (CTX) Scheme: Studies sponsored by drug companies under this scheme require a special set of core documents, and
- (b) The Clinical Trial Notification (CTN) Scheme: This allows for the investigation of agents under less stringent Commonwealth control than in the CTX Scheme. Studies sponsored by drug companies under this scheme only require approval by the Ethics Committee. The appropriate documentation must be supplied to the Ethics Committee.

10.4 The costs imposed by Studies must be financed by the Investigators:

As in any other area of research, it is necessary for investigators to obtain sufficient funding to enable a study to be completed according to the details outlined in the protocol. Although allowance may be made for routine costs that would have accrued in the absence of a study, it is clearly unacceptable for investigators to attempt to finance drug studies at the expense of the hospital's Drug Budget.

10.5 **Study Endpoints**

Study endpoints are outcomes that are measured in order to answer the study objectives e.g., a study of chemotherapeutic agents might be interested in quality of life, objective response rates, and the survival time. Alternative terms are 'response variables' and 'outcome events'.

10.6 **The use of Human Tissues:**

Many studies involve the use of human tissues, and in this regard blood and DNA are tissues. In Western Australia the relevant legislation is the Human Tissue and Transplant Act 1982 and the Human Tissue and Transplant Amendment Act 1987 and the National Statement 2007, section 3.4. In essence, the use of any tissue for research must be sanctioned by the Ethics Committee. Of special note:

- (a) Multiple blood samples: Care must be taken so that a minimum volume of blood is removed.
- (b) For blood samples taken from children the following conditions apply:
 - only one attempt at venepuncture is to be made per sample;
 - the sample is to be taken by a certified paediatric phlebotomist;
 - for children 12 months of age and younger, a maximum of 5mls is to be taken per sample.
 - for children aged 2 years the maximum volume per sample is 8mls.
- (c) Samples for research and development: Informed Consent is required.
- (d) All tissues to be used only for the stated approved purpose. Researchers must reapply for ethical approval for any other use of tissues.

10.7 **Selection of Endpoints:**

It is best if a single endpoint can be used to evaluate the main aim of the study.

- (a) The probability of a chance positive result increases when the analysis of results includes multiple endpoints.
- (b) If the results are inconsistent it is necessary to explain why some endpoints provided conflicting information.

One way of overcoming the problem of multiple endpoints is to combine endpoints into an index. However, it is necessary to demonstrate that the index has validity. This process is often more demanding than the original project.

10.8 **Substitute Endpoints:**

The optimum endpoints in clinical studies are usually clinical events. The problem is that the evaluation of many clinical events is difficult because of their poor reliability or the infrequent nature of the event. Investigators may use a substitute endpoint under these circumstances e.g., a measure of deep vein thrombosis rather than the more relevant onset of a clinically detectable pulmonary embolus. It is evident that the use of substitute endpoints diminishes the range of conclusions that can be drawn from the results of a study.

10.9 **Blinding Strategies:**

Such techniques diminish the problems of bias during data collection and assessment:

- (a) Single blind studies: The subject is aware of the therapy, but the assessor of outcome events does not know which intervention has been performed i.e., what group the subject is in.
- (b) Double blind studies: Both the subject and the assessor are unaware of the intervention that has been performed, e.g. placebo controlled drug study.

10.10 **Compliance:**

Although the extent of compliance with regimens will relate to the nature of the intervention, high rates of compliance are most easily obtained by educating the research subjects. Each protocol must document the steps that will be taken to promote and measure compliance without placing excessive demands upon the research subjects.

10.11 **Quality Control:**

It is axiomatic that during all stages of a study sufficient effort must be spent to ensure that all key data are of high quality. Potential problems include:

- (a) Missing or incomplete data: The opportunity to collect good quality information is usually transient, and investigators must avoid being confronted by missing data for the first time once the study has been completed.
- (b) Failure to collect information using constant criteria: This may apply to information such as the definition of a clinical event, measurements performed on poorly calibrated equipment,

searching for a common event using different investigation modalities, and poorly controlled laboratory tests.

- (c) Variability in the observed characteristics reduces the opportunity to detect real changes: The variability may be due to the process under investigation (e.g., diurnal variation) or may relate to the beholder (e.g., inter- and intra-observer variation).

Regardless of the source of the variability, there are some common themes i.e., vagueness in definition, inadequate methodology, lack of training of personnel, and carelessness. As a general principle all studies should contain information about the quality control of data. This is a tedious process so attention must be focused on the key data that influence the conclusions of the study.

11. DATA MANAGEMENT

11.1 Categories of Data:

The NHMRC Statement sets out the following categories of data:

- a) Identified - data that allow the identification of a specific individual.
- b) Potentially identifiable (coded, re-identifiable) - data may have identifiers removed and replaced by a code. In such cases it is possible to use the code to re-identify the person to whom the data relate so that the process of de-identification is reversible.
- c) De-identified (not identifiable, anonymous) - the process of de-identification can be irreversible if the identifiers have been removed permanently or if the data have never been identified.

If the researcher or the Ethics Committee require potentially identifiable data that has been coded to be used only as de-identified data for a particular study, the code may be kept by the Ethics Committee. In such cases the researcher must undertake not to keep a copy of the code. Approval for these studies will not be finalised until such time as the code for the data has been submitted to the Committee.

11.2 Data Collection:

No study is better than the quality of its data. It is the responsibility of the Chief Investigator to ensure that appropriate work books and data sheets contain accurate information. Original work books must be kept in a condition that would enable inspection by an independent body in the event that an investigation was considered necessary. Ideally, work books should be bound with consecutively numbered pages, to ensure pages can not be added or removed. Special care must be taken to avoid typographical errors when transferring information from a sheet of paper onto a file within a computer.

11.3 Medical Records:

Access to medical records or other records for research is restricted to properly qualified researchers and research associates responsible to them following documented approval from the relevant CAHS authority and the Executive Medical Director.

Therefore:

- (a) All research access to medical records must be based upon the consent of the participant, the clinician and the team concerned with the care of the patient,
- (b) Where past patients are being contacted by investigators through access to medical records the initial contact must be through a letter signed by the Director of the relevant Clinical Care Unit. This letter must be based on the proforma recruitment letter available from the hospital website (<http://pmh.health.wa.gov.au/development/resources/ethics.htm>),
- (c) Information about each individual is to be treated with the same confidence by the researcher as the clinician,
- (d) Unless specific consent is obtained, research must be published in a form that does not allow the public identification of any individual, and
- (e) Specific consent from the patient is necessary when that course of action adds physical, psychological, or sociological risk to individuals (Code of Federal Regulations, Title 45, paragraph 46:101. Department of Health, Education and Welfare 1983).
- (f) Requests for waiver or qualifying conditions for informed consent should take account of the principles outlined in the National Statement on Ethical Conduct in Human Research except where approved by the Executive Medical Director for Quality Assurance Activity

11.4 Security of Data:

Data must always be held in a secure place, and access to identifying information must be restricted to those who need to have it for the purpose of the study. Once the basic information has been acquired, any information that directly identifies an individual should be held in a physically separate place from the research information. For example, **hospital record numbers should not be recorded on data sheets**, especially where the data sheets are to be made available to others, including pharmaceutical companies. The Ethics Committee may keep the code for potentially identifiable data in some instances. The Committee recognises that pharmaceutical companies and drug regulatory authorities need to be able to verify the existence of patients, to ensure they in fact meet the study entry criteria. It is appropriate to keep a list of subject medical record numbers and study numbers. This list should be stored apart from data sheets and can be made available for inspection, if required. **This list must not be given to the pharmaceutical company.**

11.5 Retention of Data:

At first sight it would be reasonable to suggest that research records should be destroyed when their original purposes have been fulfilled, and this might allay people's fears about future misuse. However, such a policy would make it impossible to answer important questions that might be raised in the future about the scientific or ethical validity of the original research. Hence,

Under the NHMRC guidelines investigators are required to keep the original research documents, including questionnaires, tapes, etc. for a period of at least five years after the completion of a research project. In the case of clinical trials for pediatric subjects all records and data should be retained for at least 25 years.

Electronically archived data should take account of State Record Keeping Standard for State Organizations see <http://www.sro.wa.gov.au/src/documents/src-standard8.pdf> for participants of Human Research who are patients of CAHS.

Whenever possible, original data should be retained in the department or research unit in which they were generated. This information must be recorded in a durable and appropriately referenced form.

12. STATISTICAL ANALYSIS

12.1 Numeracy:

The NHMRC National Statement on Ethical Conduct in Research Involving Humans indicates that:

Institutional Ethics Committees should be assured of the statistical validity of the design of a proposed trial.

It is therefore crucial that investigators who are unfamiliar with the use of statistics seek help when designing a study. Each protocol must contain detailed information about how the investigators intend to analyse the data that will accrue from the study.

13. ETHICAL ISSUES

13.1 Documentation:

Each protocol must contain a section that discusses the specific ethical issues related to the study.

13.2 Confidentiality:

This is a central theme for many of the comments that have been made in these guidelines. The Australian Law Reform Commission has pointed out that a person should be able to exert an appropriate measure of control on the extent that information about themselves is available to others in the community. The Ethics Committee has to weigh the rights of individuals against the need to help society at large by performing medical research.

The *NHMRC Guidelines under Section 95 of the Privacy Act 1988* and *Guidelines approved under Section 95A of the Privacy Act 1998* set out points that should be addressed within the protocol where personal information is involved and consent is not being obtained, although many of these points should still be addressed where consent is being obtained from subjects. These points are as follows:

(a) the aims of the research;

(b) the credentials and technical competence of the researcher;

(c) the data needed and how it will be analysed;

(d) the source of the data;

- (e) *the study period;*
- (f) *the target population;*
- (g) *The reasons why identified or potentially identifiable information is needed, if de-identified information is not to be used, and the reasons why it is not proposed to seek consent to the use of the personal/health information;*
- (h) *the specific uses to which the personal information collected or used during the study will be applied;*
- (i) *the proposed method of publication of results of the research;*
- (j) *the estimated time of retention of the personal information;*
- (k) *the identity of the custodian(s) of the personal information collected or used during the research;*
- (l) *security standards to be applied to the personal information (should be retained in a form that is at least as secure as it was in the sources from which the information was obtained);*
- (m) *a list of personnel with access to the personal information;*
- (k) *the level of protection that will be applied to protect the personal information. These should include:*
 - (i) *terms of any disclosure agreement between the agency/organisation that holds the personal/health information and the researcher to govern limits on the use and disclosure of the personal/health information; and*
 - (ii) *proposed methods of disposal of the personal/health information on the completion of the research (in accordance with the relevant legislation); and*
 - (iii) *standards that will be applied to protect privacy of personal/health information where it is made available to others if that is proposed.*

14. **MULTICENTRE STUDIES**

Many studies require the participation of multiple centres to allow recruitment of sufficient subjects in a reasonable time frame. Many studies of new drug treatments fall into this category. Each participating investigator must obtain ethical clearance from the local Ethics Committee. Specific local factors may render a multicentre study protocol unsuitable for a particular centre.

The maintenance of high ethical standards has a hard practical implication. Where research is sponsored by a pharmaceutical company, it is in the company's interests to have its multicentre trials conducted at the highest level of scientific and ethical practice. This is the only means by which its products can become marketable in countries like the United States of America and Canada. It is clear that the conduct of multicentre trials will in future be subject to much greater levels of scrutiny, monitoring, and evaluation than has been the case in the past. There will be greater emphasis on trials which involve outpatients. Many of these studies will involve detailed cost-benefit analyses.

When submitting multicentre studies for approval, the formal protocol may need to be supplemented by additional notes in order to meet the requirements outlined in these guidelines. This particularly applies to the Patient Information Sheet and Consent form.

14.2 **Peer Review:**

Investigators have an obligation to justify their work to peer review from the time of its conception until its final publication.

14.3 **Reporting Requirements:**

Regardless of the source of the project or the source of funding, the Ethics Committee requires the scientific validity and research merit of the project be assessed by the Scientific Advisory Sub-Committee.

The Ethics Committee has an obligation to maintain a register of all research projects and to keep the progress of research projects under surveillance in order to be satisfied that they continue to conform to approved ethical standards. The Ethics Committee will only continue to give approval for a project upon receipt of a satisfactory progress report each year. If the study does not commence within the first twelve months of the approval period the study must be resubmitted to the Committee for approval. Investigators are required to provide an annual progress report. A copy of the proforma report can be emailed to investigators and the completed report lodged electronically if the investigator so wishes.

All reports must be typed to ensure legibility.

If a request for an annual progress report is not replied to within 60 days, then ethical approval for that project may be withdrawn.

In addition, there is a requirement to provide a final report on completion or cessation of the study.

The investigator is obliged to report to the Ethics Committee any serious adverse event that occurs during, or as a result of, the study. Such events should be reported within 72 hours to the Ethics Committee and not held over until an annual or final report is due. Proforma of CAHS Adverse Event Reporting Forms available from the Ethics Office and Website.

The investigator should take account of the NHMRC Australian Health Ethics Committee Position Statement regarding Monitoring and Reporting of Safety for Clinical Trials involving therapeutic products, May 2009.

14.4 **Financial Matters:**

It is the responsibility of the Chief Investigator to ensure that patients are not charged for investigations and other activities that are performed for research purposes. Privately insured patients must not receive accounts for treatment received in respect to studies beyond that associated with routine clinical care.

It is essential that investigators obtain sufficient funding to enable a study to be completed according to the details outlined in the protocol. Research studies cannot be performed at the expense of routine patient care.

All applications must include a detailed budget for the proposed study which should contain the extent and source of funds and resources to be used. It is the responsibility of the head of department to approve this budget as part of the agreement for the department's involvement in the study.

It is also essential that the investigator include a completed Declaration of Interest form with an application. This is applicable to **all** studies, not only those funded by external commercial organisations. The purpose of this form is to ensure that all research is and most importantly, is seen to be, carried out in a rigorous and transparent fashion.

14.5 **Responsibility:**

The Ethics Committee assumes that the personnel listed in the protocol will be responsible for the conduct of the study. In particular, the Chief Investigator must accept overall responsibility for the conduct of the study. Where the Chief Investigator is from an Institution not located on CAHS campus, the "on site" Supervisor assumes overall responsibility for the study. Students may be required to provide credentials for the consideration of the Ethics Committee to confirm their competency to undertake the role of Chief Investigator of a protocol

A staff member must be associated with every project because:

- (a) Junior staff move to other hospitals and it is untenable to have a project in progress, or under retrospective review, without a responsible person on the staff of these hospitals, and
- (b) CAHS has an obligation to ensure that students and junior staff members are provided with adequate supervision when performing research studies. It is illogical to suppose that an imperfect study can be ethically acceptable when it is performed by someone who lacks knowledge about acceptable scientific standards in medical research. In addition, the educational content of a poorly supervised piece of research is open to question.

The relevant Head of Department and Clinical Care Unit Directors (or nominee) have responsibilities in relation to studies they approve and sign for as detailed within this document.

15. **REFERENCES**

15.1 **The Requirement:**

Each protocol must contain appropriate references to the works of others, and these must be presented using a conventional format.

15.2 **Availability**

References must be readily available to members of the Ethics Committee from the investigator. Copies should be available from the applicant on request by the Ethics or SASC Committee.