



A guide to good research practice

4th Edition, February 2011



CONFIDENTIAL

School of Public Health
and Preventive Medicine

MONASH UNIVERSITY

**FACULTY OF MEDICINE, NURSING
AND HEALTH SCIENCES**

**School of Public Health and Preventive Medicine
Department of Epidemiology and Preventive Medicine**

A Guide to Good Research Practice

4th Edition

February 2011

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Also available on the department web site: <http://www.med.monash.edu.au/sphpm/>

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Abbreviations

HREC	Human Research Ethics Committee
PI	Principal Investigator
PICF	Participant Information and Consent Form
RGC	Research Governance Committee
RGO	Research Governance Officer
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SPHPM	School of Public Health and Preventive Medicine

1. Introduction

Clinical and Public Health research must be conducted in accordance with a large number of laws, regulations and conventions. These are designed to protect the participants, the researchers and the institutions where research is conducted.

Well conducted research flourishes best in a culture which emphasises respect for research subjects and a focus on accuracy and honesty.

At the Monash School of Public Health and Preventive Medicine we are fortunate to have a number of our senior staff involved in ethics and research governance, as well as in research. Over several years we have developed activities designed to ensure that our research is conducted at the highest standard and that our working culture emphasises all of the attributes needed in support of this goal.

As well as producing this Guide, we have focused on careful induction of new staff and ongoing education and quality assurance activities, directed by our Research Governance Officer and an active research governance committee.

I would like to record my appreciation of the many people who have participated in the development of this guide and also in the development of the research governance framework of the School. In particular I would like to thank Stephanie Poustie, Giuliana Fuscaldo and Megan Brooks, all of whom have provided outstanding support in their research governance roles and Andrew Forbes & Marina Skiba in their roles as Chair of our Research Governance Committee. I commend this work to all new staff of our School.

John McNeil PhD FRACP
Head of School



2. Promoting High Quality Research

1. Purpose

The purpose of this document is to ensure that medical research conducted within our School meets the highest scientific and ethical standards.

- It outlines a set of standards that must be adhered to by all those involved in any research capacity.
- If you identify any significant departure from these guidelines this must be brought to the attention of your supervisor and/or the Research Governance Officer.
- Diligent supervision and monitoring of research projects by appropriately trained and experienced individuals is a core expectation within the School.
- Particular care must be taken to ensure full compliance with consent and privacy requirements. The highest level of confidentiality must be maintained with all research data at all times.
- Research misconduct in any form is totally unacceptable. This behaviour would have implications, not only for the individual researcher, but for the School and the University.
- The position of Research Governance Officer has been established to oversee the school's research and assist investigators in all aspects of good clinical research practice. The Research Governance Officer has been authorised to conduct audits of all School research projects.
- The guidelines outlined in this booklet are available for quick reference. It is highly recommended that investigators enrol in programs and courses on ethics and good clinical research practice.

2. Risk Management

Although research misconduct has generally resulted from aberrant behaviour by individuals, the senior staff of the School have a responsibility for establishing a culture and environment that reduces the likelihood of such an event.

Within SPHPM we have certain vulnerabilities to research misadventure that puts us at risk. These include:

- A large number of research projects with responsibility dispersed amongst many senior investigators.
- A heavy reliance on relatively junior staff and PhD students to supervise research assistants and to analyse research results.
- A high level of investigator initiated research that is not monitored by external bodies such as pharmaceutical companies.

- Some data collected off-site by research staff working away from direct supervision.

Because of these concerns the Department has established a Risk Management Plan that attempts to foresee our major areas of risk

Throughout this document we have noted areas of risk and our strategies for addressing them.

3. Good Research Practice: Fundamentals

The following principles have been adapted from the National Health & Medical Research Council “Guidelines for good clinical practice in clinical trials”¹.

- Clinical studies should be conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and the ICH/Good Clinical Practice Guidelines.
- A study should only be initiated and continued if the perceived benefits for the individual participant or society justify the risks and inconvenience.
- The rights, safety and wellbeing of the participants are a most important consideration and should outweigh other considerations
- Clinical studies should be scientifically sound and clearly described in the study protocol.
- Studies should be conducted in compliance with a protocol that has been authorised by an appropriate HREC (Human Research Ethics Committee).
- Individuals conducting the study should have an appropriate level of education, training and experience to perform their tasks.
- Freely given informed consent should be obtained from every participant prior to study participation.
- All study data should be recorded, handled and stored in a way that allows their accurate reporting, interpretation and verification.
- The confidentiality of participant records should be protected, respecting the privacy and confidentiality rules of the applicable regulatory authority.
- Systems with procedures that ensure the quality of every aspect of the study should be implemented.



4. Research Ethics: Fundamentals

It is important that researchers understand the approach taken by ethics committees to various types of project. This is described in appendix 1. A brief description of the responsibility of researchers in dealing with ethics committees is provided below.

(a) Ethics Committee Approval

Ethics committees have been established in all institutions receiving funds from the National Health & Medical Research Council for medical research. Their purpose is to look after the rights and safety of research participants.. It has become established practice to seek ethics committee approval for any project that involves contact with individuals or utilising their data.

All research undertaken must comply with the authorising ethics committee requirements. In particular:

- Projects must not begin until ethics committee approval is obtained in writing.
- The authorised study protocol must be followed in all cases.
- Ethics committee approval must be sought for protocol amendments, even if they are relatively minor.
- Projects must not run longer than the approved completion date, unless an extension has been obtained in writing.

Ethics committees require all study participants to be provided with an approved “participant information and consent form” (PICF) and to sign their name to signify their preparedness to participate in the project. These forms must be carefully filed and be made available for scrutiny by auditors operating on behalf of the ethics committee or the study sponsors.

Any serious adverse events considered reasonably likely to have resulted from study participation, must be notified urgently the appropriate ethics committee.

The work of ethics committees is guided by:

- National Statement on Ethical Conduct in Human Research. <http://www.nhmrc.gov.au/publications/synopses/e72syn.htm>,
- ICH/GCP Guidelines, an international ethical and scientific quality standard. <http://www.tga.gov.au/docs/html/ich13595.htm>.

Research institutions also have their own specific requirements that need to be observed. For example:

Monash University: Monash University has a central Human Research Ethics Committee - the Monash University Human Research Ethics Committee (MUHREC). The MUHREC web address is <http://www.monash.edu.au/researchoffice/human/>.

All Monash University staff and students must obtain approval from MUHREC even if they are conducting their research at another institution (e.g. a public hospital) and have received ethics approval from that institution i.e. you must have MUHREC approval as well. Monash has a memorandum of understanding with a number of institutions to make this process as easy as possible (for details see the website under "multicentre research").

The Alfred Hospital: Application forms and guidance on submitting an application can be downloaded from <http://www.alfredresearch.org>.

Southern Health: Application forms and guidance on submitting an application can be downloaded from http://www.southernhealth.org.au/page/Research/Human_research_ethics/.

(b) Special restrictions

Ethics committee approval is commonly provided with specific caveats. When multiple ethics committees are involved, it will be necessary to liaise with each of the relevant committees to ensure that final agreed protocol meets the requirements of each committee.

(c) Documentation

An approval letter containing caveats should be copied to all study staff. All study staff must be made aware of site specific requirements.

(d) Duration of approvals

Ethics committee approvals are typically time-limited (for a two or three year period) but this is contingent on satisfactory progress reports submitted on an annually. If progress reports are not received the HREC may revoke their approval for the study.

5 ETHICS COMMITTEE REVIEW OF PROJECTS

The general focus of ethics committee deliberation is to protect the 'rights and welfare' of human subjects. This goes beyond simply protecting them from egregious behaviour or undue risk. In general, it looks to ensure that research subjects are treated in accordance with three basic principles referred to in the 1978 Belmont Report (US). These are:

1. Respect for the individual ie. individuals should have total control and authority over everything that happens to them

2. **Beneficence:** refers to the obligation of carers and researchers to maximise benefits and minimise harm
3. **Justice:** a more general concept that includes the undesirability of certain disadvantaged groups taking all the risks of research while other groups benefit.

In practice these principles are operationalised as follows:

Scientific validity: Ethics committees now take the view that it is unethical to approve scientifically flawed research because individuals should not be expected to undergo the risks, inconvenience and expense of research that is unlikely to provide a scientifically valuable result. As a result studies with substantial design errors or a major susceptibility to bias are unlikely to be approved until these deficiencies are remedied. EC's are increasing scrutinising sample-size calculations since underpowered studies are unlikely to provide scientifically useful results.

Experience has also made most large ethics committees aware of the adage that 'the devil is in the detail'. This is the reason for insisting on the provision of detailed protocols with every application.

Scientific value: It is also unethical to expect sacrifices from volunteers that are out of keeping with value of the potential findings.

Credentials: The EC requires that the curriculum vitae of all investigators on all submitted studies to be held on file. The research credentials and previous experience of investigators are matched against the nature of the study and a judgement formed about whether the individuals involved are appropriately trained to be undertaking the proposed research. Commonly a research team may be asked to add a more experienced investigator, or someone experienced in a particular specialty of medicine. NHMRC guidelines require a clinical pharmacologist to be involved in very early phase drug studies.

Increasing concern is being felt about the low level of training afforded to staff at the front end of clinical research e.g. research fellows, research nurses and research assistants.

Risks (including treatment forgone): A fundamental requirement for an ethics committee is to ensure that the foreseeable risks of the study have been identified and presented in an explicit fashion to the participants in the plain language form (see below). The most significant risks to health arise during early phase drug studies (when relatively little may be known about a drug's safety profile) and with invasive studies. In general EC's are guided by the following principles.

1. Studies involving healthy volunteers, children and those where there is no likely benefit, should pose risks that are little greater than those of everyday life.
2. Studies involving patients treated with new or experimental techniques should not involve known risks substantially greater than the best alternative treatment, (unless there is a substantial possibility of significant benefit) and the individual understands and freely accepts the risks involved.

It is unlikely that any EC would approve a research project with a high level of physical risk (regardless of an individual's willingness to accept those risks, and regardless of the community benefit involved) unless there was a correspondingly high likelihood of benefit for the individual participant.

One particularly common form of risk is that arising from withdrawal of regular treatment (e.g. from anti-hypertensive or anti-asthmatic medication). Under such circumstances, EC's will require strict limits on the severity of patients involved, the duration of the period without therapy. Careful and frequent clinical monitoring and instructions to patients about procedures in case of emergency will also be mandated

Safety monitoring: In many research studies the risks are not fully established at the time the research commences. If substantial numbers of subjects are involved in such studies, EC's commonly require a safety committee or safety monitor to be appointed. This committee or individual will regularly review the un-blinded study data and alert the investigators, and EC's, about safety concerns.

Proper safety monitoring during the course of clinical research projects is also required. For example, regular FBE's or liver enzymes may need to be monitored and in such circumstances it is imperative that arrangements are in place for the study monitor to review such results immediately and bring abnormalities to the attention of the investigators and to the individual's attending doctors.

Inconvenience etc: Many studies involve considerable numbers or trips to hospital, time away from work, which must be explicitly described in the plain language statement.

Informed consent: Participants in clinical research must be fully informed about the nature of any research project that they participate in and be free to choose whether or not to take part. Basic ethical principles dictate that:

1. subjects have an unambiguous right to decline participation or to withdraw their consent at any time without an obligation to provide a reason.
2. there is a full disclosure of any known risks that might influence their decision about whether or not to participate.
3. subjects involved are provided with the most explicit and accurate account of personal inconvenience and expenses likely to be encountered.

The Plain Language Information Sheet is the key document in the consent process (see section 4.4). Its purpose is to provide prospective participants with a simple and easily understood account of the rationale for the research and a detailed description of all foreseeable risks and benefits. Ethics committees are required to review these documents and to endorse their contents as providing a fair and balanced account of risks and benefits. In fact, much EC time is spent adjusting the language of plain language forms so that they can be understood by an average person. A check list of contents is shown in section 1.7

Early cessation: A study that continues well beyond the time that convincing evidence of benefit has been demonstrated, is denying many participants access to a superior therapy. Procedures are therefore regularly put in place with very large trials to stop a trial early in the event that a significant benefit (or risk) becomes evident before the scheduled end of the study.

Adverse events: All serious adverse events occurring in patients participating in clinical research projects must be reported to the EC and any sponsor within 24 hours. For this purpose 'serious' refers to any event that is fatal, life threatening, results in hospitalisation, prolongs hospitalisation, leaves a permanent disability or takes the form of a birth defect. These events should be reported unless one is very certain that the experimental drug or procedure is not the cause.

SPECIAL ISSUES

CTN/CTX studies: In the early 1990's, the Commonwealth Government introduced new procedures designed to speed up the approval process for clinical trials of new drugs. Essentially, companies could choose whether to introduce new agents to clinical research under a CTN scheme or a CTX scheme. If the CTX route was chosen the company would submit the available data on their drug to the Commonwealth Department of Health and Aged Care (DHAC) where, for a substantial fee, an evaluation of its safety and suitability for use in clinical trials would be carried out.

Companies wishing to avoid the delays inherent in this process could alternatively introduce their drug through the CTN scheme, under which they are merely required to notify DHAC of their intention to undertake studies and the relevant ethics committees then assume responsibility for evaluating the drug. In practice most ethics committees will only approve CTN drugs if they have been evaluated through a CTX-type process in one of the three countries with similar drug evaluation standards to Australia (USA, UK, Sweden).

Consent in Special Circumstances

In some studies, special procedures are required with informed consent. These may include studies on:

- human genetics;
- vulnerable patients (eg. mentally handicapped);
- minors; and
- subjects unable to provide consent (eg. unconscious, demented).

In these circumstances, advice must be obtained from the relevant Ethics Committee/s during development of the consent documentation. It is strongly recommended that researchers who may be recruiting from these special groups be familiar with the Guardianship Act (October 2010 amendment)⁶.

Emergency care research & research on unconscious patients: In situations where an individual may be unconscious or in no position to provide informed consent, an ethics committee in Victoria is authorised to allow important research to go ahead on the basis of consent from a „responsible person“, normally the next of kin (with a carefully defined hierarchy).

Ethics committees will not approve such research unless it is clearly not to the disadvantage of the research participant and it could not be undertaken with consenting participants.

In some rare instances an ethics committee is authorised to allow highly important research to take place without specific consent of either a participant or a “person responsible” using an approach referred to as „procedural authorisation“. HREC approval under this arrangement is typically restricted to low-risk research. After an individual has been entered into a study using procedural authorisation it is necessary to complete and fax a section 42T certificate to the Guardianship Board as soon as is practically possible.

Detailed discussions should be held in advance with the Ethics Committee Secretariat if either approach is contemplated.

Children: when children are involved, there must be no risks greater than those of everyday living and permission must be obtained from both parents and participants.

When samples are to be taken and stored for genetic studies, references must be made to specific Ethics Committee requirements. Typically these require the PICF to make it clear that certain genetic findings may signify an increased risk of illness, and if this becomes known to the participant it may be necessary to disclose this fact when applying for personal insurance cover.

Long term disabled: consent for involvement in clinical research must be obtained under special consent arrangements (person responsible consent). The Ethics committee secretariat will provide details of what is required.

Genetic research: collection of blood or other biological samples for genetic testing is a rapidly developing area of research with the potential to improve the diagnosis and treatment of many common diseases. It also raises a number of particular ethical issues which have lead the NHMRC to develop a specific policy on this type of research. The policy incorporates the following principles.

1. Gene banks should be established within an academic research environment under the control of experienced and highly reputable researchers
2. The researchers involved must be aware of the potential ethical issues associated with access to data from the bank and have adequate resources and strategies in place to deal appropriately with them.
3. Committees typically, in the first instance, approve the establishment of the gene bank and the specific project linked to the application. Future research involving different markers will require further separate applications before approval will be given.
6. Individuals providing samples for a gene bank should be aware that they must disclose upon request any adverse information about their risk of future illness which is provided to them as a result of genetic testing to life insurance and superannuation

companies. Possession of this information may increase their premiums or may have them denied cover (or employment) altogether.

7. Individuals should also be aware of the possibility that information held by the gene bank may be discoverable by a court of law.
9. The researcher in charge of the gene bank should also have a protocol to determine what information should be provided unsolicited to individuals as a result of findings generated by the research. Generally the Ethics Committee should be informed of such actions.

Innovative therapy: increasingly the introduction of new and innovative therapy is being handled in a fashion similar to a research project. Applications involve a justification and literature review, a protocol and a Plain Language Statement. Commonly new procedures are referred to an ethics committee and an innovations committee.

Research in Private Doctors Rooms: Ethics committees are often asked to review projects conducted in private settings. There has been some reluctance to do this because some committees feel insufficiently familiar with the governance of research in such settings to be able to provide endorsement. Sometimes there may also be unease about the financial arrangements involved. With the progressive decline in hospital outpatients it is likely that more and more research will move to such settings. Details can be obtained from the Ethics Committee secretariat

Audit: NHMRC requires that as a 'minimum' ethics committees monitor research conducted in their institutions by requiring a structured annual report. Some EC's supplement this by an audit program looking at such matters as consent forms, data storage, randomisation processes, bias control and source data verification.

(a) Breaching Ethics Committee requirements

(i) Examples of serious breaches

- Entry to a study of patients whose personal characteristics do not meet those of the approved entry criteria. (This may also breach the contract with the study sponsor)
- Failure to inform a participant of the risks of participation in a research project
- Alterations to a protocol without ethics committee approval
- Failure to respect the privacy of an individual's private information.

Vignette: A researcher was conducting a trial comparing two standard treatments for heart failure. He decided to commence with a pilot study without obtaining ethics committee approval or consent from the participants.

The Ethics Committee required the researcher to attend a meeting where he was reprimanded. It was made clear that this was an unapproved pilot study that had not received approval.

Vignette: A researcher decided that since his research involved only a blood collection it would reasonable to enrol participants without obtaining their consent. A member of the hospital staff notified their concern to the Ethics Committee and an audit was conducted. The researcher was reprimanded and the Committee required that the study could continue only if that researcher was not involved.



3. Institutional Requirements

1. Conflicts of Interest

The School requires that all investigators pay careful attention to compliance with institutional policies regarding conflict of interest. Every significant conflict of interest must be declared both to the Ethics Committee and Journal.

Ethics committees generally require a detailed account of the budget of a study and an explicit description of any personal benefits that an investigator will receive as a result of undertaking the research project. There is often a requirement for such matters to be mentioned in the PICF

The HREC will scrutinise the financial statement to determine whether the funding is sufficient to allow the study to proceed. In some instances, major issues will need to be considered by the senior administrators of an institution.

Most journals also require a detailed statement of conflicts of interest to accompany published manuscripts. Undeclared conflicts that are subsequently identified may require statements of contrition that are highly detrimental to a researcher, his/her colleagues and their institution.

Compensation of study participants for incidental expenses is appropriate, as is small payments to compensate for inconvenience etc. Unlike in the US, Australian ethics committees have been generally unwilling to allow more substantial payments in case they provide an inducement to participation against better judgement.

The Monash University conflict of interest policy is provided at

<http://www.adm.monash.edu.au/workplace-policy/conduct-compliance/conflict-interest.html>.

2. Intellectual property

Students and staff are encouraged to identify new innovations or inventions that may arise from their work. Monash University has a policy to enable students and researchers to share in any commercial rewards that arise from such developments.

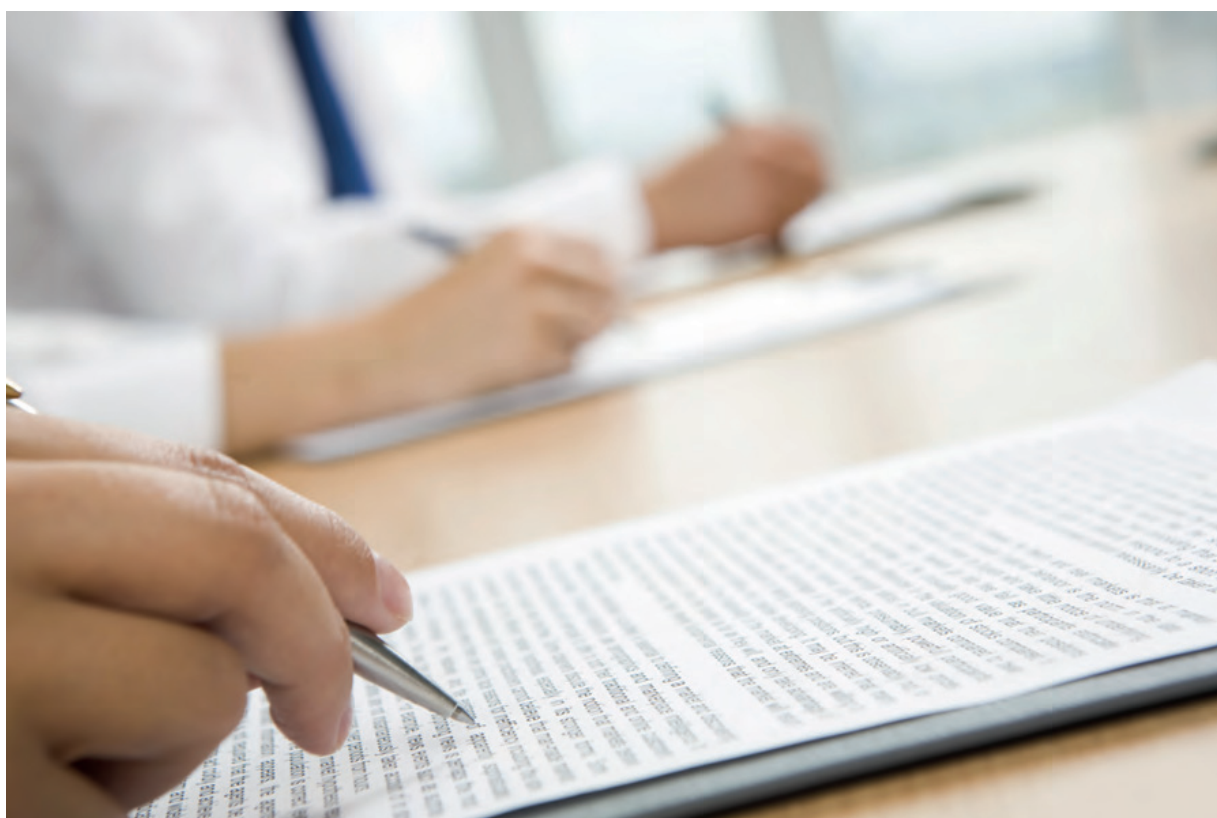
Care is taken to protect the interests of doctoral students who, unlike staff, are not bound to share intellectual property that they develop through their sole efforts,

In the vast majority of cases however, staff and students are involved in collaborative research that involves contributions from multiple people and resources established well before they joined the School. This is particularly the case with collaborative or grant-funded research projects. Participation of a student in such projects may only be approved if the student agrees to „sign over“ his/her IP rights to Monash University. This arrangement is not designed to negate the rights of doctoral students, but to avoid the complexities that might arise if a student asserted „ownership“ over a portion of a research activity making it impossible to complete the total project.

3. Research agreements between institutions

Clinical and Public Health increasingly involves a multi-institution collaboration where different aspects of a project are undertaken by different organisations. To avoid disputes it is essential that multi-institution agreements be accompanied by a document that specifies exactly what each institution (and employee of the institution) will be responsible for and what funds will flow as a result of these activities.

Agreements should also specify the composition of any committees involved in supervising the research activity and the approach to be taken in relation to authorship and financial reporting.



4. Essential Research Documentation

1. The Protocol

The study Protocol is a document that describes the rationale, objective(s), design, methodology, and organisation of a study. The protocol provides the basis for Ethics Committee approval and up to date copies should be made available to every member of the study team. NO research activities, even relatively minor ones such as a pilot study, should be undertaken except in accordance with a protocol that has been approved by an Ethics Committee.

See Appendix B for details on what the Protocol should contain.

Protocol changes: Once a project has been approved by an ethics committee, any change (eg changing the questionnaire to collect new information), should be immediately notified in writing to the ethics committee(s) where approval has been obtained. All protocol changes should be clearly identified on an updated version of the protocol and procedure manual. Changes to a protocol may also necessitate changes to the PICF.

2. Procedure Manual

All large studies require a detailed Procedure Manual which incorporates and expands upon the study Protocol. The purpose of the Procedure Manual is to provide a detailed account of all study procedures. It is the day-to-day reference document for all staff involved in any large research project. It should provide enough information to allow a new staff member to take any role in the study at any time. Copies of the Procedure Manual must be provided to all research staff involved in a study (including updates or amendments agreed to at study meetings).

See Appendix C for details on what the Procedure Manual should contain.

3. Consent Documentation

Informed consent must be sought from all participants involved in medical research. The „consent process“ typically involves a detailed discussion with each participant that includes the reason that the study is being undertaken, together with an explicit description of any risks or inconveniences involved. The person involved in discussions with the participant must be „manifestly capable“ of describing the risks and benefits of the study. This means that the person involved in consent discussions must be either an investigator or a research officer who has become fully acquainted with all aspects of the study. The consent process must never be delegated to junior members of a study team unless the project is of relatively low-risk.

On occasions an ethics committee may vary the normal requirements for consent. For example in very low risk settings a committee may approve opt-out consent, or even a waiver of consent. However such circumstances are only approved in situations where the ethics committee determines that consent is impractical, undesirable (eg by the likelihood of distressing participants) or would impair the scientific validity of the study.

4. The Participant Information and Consent Form

The Participant Information and Consent Form (PICF) is an essential accompaniment of the consent process and is given to all study participants at the time when their participation in research is first discussed with them. It must be made available in the language of study participants.

This document should be written in simple text that a younger teenager could understand. It should describe the reason the study is being conducted, the demands to be made of the participant and any risks that may occur as a result of their participation. It should also describe arrangements to ensure privacy of the information collected..

The PICF must be updated if significant new information becomes available during the course of the study. The update should be approved by the Ethics Committee, and only the most recent approved version should be provided to potential volunteers.

Section 4.8.10 of the ICH/GCP Guidelines³ and section 2.2.6 of the National Statement² provides an outline of the information that should be included within a PICF. Many institutions also require that specific wording is included in a PICF covering local requirements (e.g. privacy legislation)

Typically the information to be included in a Participant Information and Consent Form includes:

1. An invitation to participate.
2. The fact that the study is a research project.
3. The nature and purpose of the project.
4. A description of any randomisation procedures and the use, if any, of placebos.
5. A description of any medical procedures to be undertaken
6. A description of any drugs or isotopes to be used.
7. The availability of alternative treatments.
8. An explicit account of what is involved in participating including changes in lifestyle required , the expected number and timing of follow-up visits, and any monetary costs likely to be borne by the participant
9. The anticipated duration of the study.
10. The approximate number of patients treated similarly to date.
(when the research involves a new drug or device)
11. The possible benefits to the subject and others, stressing when appropriate that these benefits are not assured.
12. Foreseeable risks, side-effects and discomforts.

13. That requirement that the subject must advise the researchers of any other research in which they are participating or drugs they are taking.
14. Any requirement that current treatment being taken by a participant may need to be suspended.
15. Steps to be taken in case of therapeutic failure or adverse events.
16. Insurance and other procedures for compensation in case of injury due to the study.
17. The fact that participation in the research project is entirely voluntary and that the subject is free to withdraw at any time without any negative effects on his/her relationship with the researcher or influence on subsequent treatment.
18. The circumstances under which the subjects participation may be terminated.
19. The fact that the subjects" records may be inspected for the purposes of source data audit by individuals from inside or outside the hospital.
20. That precautions that will be taken to protect the confidentiality of the subjects medical information
21. The names and telephone numbers of the person to contact for further information about the study and the person to contact in case of emergency.
22. A statement about the funding of the study and any payments to study personnel.

Ethics Committees increasingly require that patients be given time to properly consider these Plain Language Information Sheets (and discuss them with friends or relatives) before deciding whether to participate, particularly in long-term or invasive studies. . Participants must also be given an opportunity to ask questions and should only be asked to provide consent when the researcher is confident that the participant understands what is required of them and is consenting willingly.

“Immediate consent” is increasingly restricted to low risk studies or those where immediate treatment is required. When there is urgency in commencing an intervention (as with research in acute stroke or myocardial infarction) patients are often distressed and not receptive to detailed explanations of a research project. In such cases an abbreviated discussion may be acceptable if this approach has been approved by the ethics committee. However in such circumstances it is also important to seek the assent of relatives before any experimental interventions are commenced.

(a) Documenting Informed Consent

The original, signed PICF must be kept in the Study Document file (see section 1.7) and a copy should be provided to the participant. Where appropriate, another copy should be placed in the participants' medical record.

(b) Witness

When required by the ethics committee a witness who is independent of the study should be asked to witness the participant's signature. In doing so the witness is signifying with the identity of the participant and the fact that he/she is not signing under duress.

The witness does not have to be familiar with the study and does not have to explain any part of the study to the subject. Furthermore, if the investigators consider that obtaining a witness's signature is neither practical nor possible, they should discuss the matter with the secretary of the appropriate ethics committee and request an exemption.

The person who signs as investigator may be a delegate of the investigator (but should generally not be the participant's treating physician unless the project is relatively low risk).

(c) Access to Participant Information and Consent forms

Signed Participant Information and Consent forms from every participant must be available for examination in case of an audit. They should be stored with study documentation after the completion of a study.

5. Advertising for participants

Advertising for participants to take part in studies must be undertaken with care and must receive HREC approval. This includes newspaper advertisement, radio advertisements as well as flyers.

Advertising should be targeted to the appropriate audience. Local newspapers may have advantages over state wide newspapers particularly for studies with multiple visits. It is important that any public advertising avoids wording that might imply endorsement of other institutions (such as hospitals)

6. The Study Document File

A Study Document File should be kept by the study coordinator/investigator as a central depository of all significant documents and correspondence involving the study.

5. Secure Maintenance of Study Records

1. Proper Document Management

- All paper work relating to a study must be maintained in a neat and orderly fashion. Clinical research requires meticulous record keeping. Study documentation may be audited at any time, even some years after it has been completed.
- All study documentation must be kept for at least 7 years after the completion of studies not involving drugs and a minimum of 15 years for drug trials although some institutions require indefinite archiving
- It is recommended that the following documents be kept in the study document file:
 - * Ethics Committee applications, including all correspondence and reports
 - * Protocol and amendments
 - * Participant Information and Consent Form (all approved versions)
 - * Subject Identification List
 - * Case Report Forms and/or questionnaires
 - * Study brochures
 - * Data dictionary
 - * Correspondence with granting agencies
 - * Contracts or agreements
 - * Minutes of study meetings
 - * Computer database specifications including data entry and verification procedures
 - * A record of any changes to data on computer files after data collection
 - * Drug dispensing records
 - * Randomisation schedule
 - * Adverse events reported
 - * Progress reporting forms
 - * Quality control and/or monitoring reports
 - * Study reports & publications

2. Maintaining Security of Study Record

Study participants are often asked to provide information of a personal and private nature. Sometimes research involves extraction and collection of personal data from hospital records or records held by other bodies. Confidentiality refers to the strict avoidance of disclosure of this information to anyone other than authorised individuals.

(a) Privacy Principles and guidelines

State and Federal legislation is in place to ensure privacy standards for the handling of health information. In December 2001, the Commonwealth *Privacy Act* (1988)⁹ was extended to cover all Australian private sector organisations. The Victorian *Health Records Act* (2001)⁸ applies to both private and public sectors that handle health information and took effect in July 2002. Together, these Acts impose a series of Privacy Principles that regulate the collection, use, disclosure and handling of personal information, including health information (see appendix C).

Exemption from specific requirements of the Privacy Act may be allowed for a medical research study. Ethics committees have the authority to grant such exemptions provided certain criteria are met. These include:

- The research is of major public health significance.
- The research is being carried out by bona fide researchers with appropriate experience.
- The data will be kept secure and adequate privacy protection is in place.
- The data is not of a highly sensitive nature.
- Consent to access the information is obtained from each individual unless compelling reasons exist (typically the requirement for consent would result in invalid results or cause distress).

If access to medical information is granted it is the responsibility of the research team to ensure the participant's privacy is adequately safeguarded. The following requirements apply:

- Information collected must be used only for the study for which approval has been given.
- Personal identifying information must be removed from all data collection forms and computer files. Typically, if identifying information is recorded in a data collection form it should be located on page 1 which is removed and stored separately from the rest of the form. Codes linking participant information to their data must be kept separately in a locked safe or filing cabinet. Access to data on computer should be under password control.
- Access to data should be available only to a limited number of individuals, directly responsible to the investigator(s), and each should sign a privacy declaration every year.

- The principal investigator or head of the appropriate unit should take responsibility for the destruction of records containing personal information (after the required archival period, as described above).
- No data capable of association with a particular participant should be published.
- **Research data containing identifying information must never be kept on USB sticks lap-top computers or home computers.**

Vignette: A researcher was undertaking some data-analyses in an airport lounge. Their data was held on a USB stick which contained names, addresses and laboratory test data (including HIV test results). In the haste to leave the investigator left the unprotected memory stick in the publicly accessible computer. This was found by the next computer user and given to a journalist colleague

(b) Medical Record Access

In general clinical records can only be accessed by employee of the hospital and with the permission of the ethics committee of the institution. University staff conducting research in a hospital typically require an honorary position in the hospital to be allowed to access clinical records. External individuals (such as pharmaceutical company monitors) who require access to medical records will need to obtain written approval from the institution (usually via the Ethics Committee and the Medical Director's Department). A statement that such access is likely should be included within the PICF provided at the commencement of the study.

(c) Risks Associated with Serious Breach of Confidentiality

- A serious breach of confidentiality could cause serious embarrassment to a research participant. This might result in legal action and significantly lessen the likelihood of future participants providing confidential information.
- The likelihood of an ethics committee approving future projects requiring collection of personal data would be jeopardised

To minimise this risk the following requirements have been introduced

- Staff signs privacy declarations annually.
- New staff attends an Ethics/Good Research Practice course soon after their commencement.
- Requirements for privacy and data-security are emphasised to new staff by unit head and the Research Governance Officer (RGO).
- Data storage for all studies is reviewed periodically by the RGO

Vignette: A research study was undertaken involving volunteers suffering from severe depression. They were recruited by advertising in the general community. The volunteers underwent nerve velocity testing, undertaken by a research assistant. One of the volunteers was the daughter of a neighbour of the research assistants mother. The researcher told her mother about the volunteers illness ... who in turn mentioned the fact to the mother of the study participant, commenting "I did not know your daughter was depressed". A complaint was made to the hospital administration and the researchers were reprimanded.



6. Collecting and Recording Research Data

1. Principle

Most clinical and epidemiological research projects require a systematic gathering of information on data collection forms. In practice, these forms may be either paper based or electronic, the latter allowing direct entry of data into a database. All data collected for the study should be recorded directly, promptly, accurately and legibly. Also, the individuals responsible for the integrating of the data, computerised and hard copy, should be identified.

Important points to remember for all data collection are:

- **Good form design:** Badly designed data collection forms will seriously impair the quality of any research project. All questions must be clear and simple. Whenever possible it is advisable to create new forms by adapting others that have proven successful in other studies.
- **Standard questionnaires and coding:** Whenever possible, standard questions should be used. Examples are the SF36 for quality of life estimation, and the standard smoking questions adopted by the National Heart Foundation. Other standard codes that should be used include:

For disease coding: ICD-10⁷.

For occupation coding: ASCO (Australian Standard Classification of Occupations) is available from the ABS.

For industry coding: ANZSIC (Australian & New Zealand Standard Industrial Classification) is available from the ABS.

For Respiratory Symptoms: there is a standard questionnaire established by the UK Medical Research Council (see Prof Michael Abramson).

For country and language codes: standard ABS codes are also available.

- **Identifiers:** All pages of a data-collection form should be prominently labelled with a unique numerical identifier that allows linkage to the name, address etc, if needed.
- **Questionnaire elements:** Whenever new questions are developed for a questionnaire or data collection instrument, it is essential that:
 - * the options are comprehensive, i.e. they cover all possible responses; and
 - * the options are mutually exclusive, i.e. only one option can be chosen for any specific situation (unless it is designed as a multi value field).
- **Special instructions:** Special instructions should be provided in small print on the data collection form (e.g. How to interpret or code specific responses). These instructions require great thought and considerable pilot testing prior to the introduction of the completed form.
- **Pilot testing:** Pilot testing is required for all data collection instruments. The nature and results of the piloting should be recorded in the study coordinator's log.
- **Easy coding of forms:** Whenever possible forms should be self-coding, i.e. those completing them should enter the data directly into coding boxes in the form. Decimal points should be clearly marked and each box must be large enough to allow legible recording. Particular care should be paid to having separate codes for „missing“, „not known“ and „refused to answer“ data; 99, 88, and 77 are often used for these, provided that they are not within the range of valid responses.
- **Training of data collectors:** Study coordinators must carefully explain every question and every response to new staff involved in data collection. When the form is to be completed at interview, the study coordinator must personally supervise the first interviews until he/she is confident that the information is being collected correctly.
- **Written comments:** Interviewers must also be encouraged to record comments with the data whenever a new or unusual situation is encountered. These should be brought to the coordinators attention at the regular study meetings.
- **Erasure of data:** Data collectors must be instructed not to erase any entry on a data collection form. If a mistake has been made, a line should be placed through the original entry so that it remains visible. The corrected value should be written in an adjacent space and a comment provided as to why the correction was made. Study coordinators are required to check every data collection form for completeness, as soon as possible after it has been completed and in no case more than one week after the interview. They must initial every form to indicate that it is ready for data entry.
- **Documentation:** Detailed quality control procedures must be used to verify and promote the quality and integrity of the data

2. What can go wrong

- A research assistant or student responsible for interviewing patients in isolation e.g. in their homes, may falsify data rather than meeting the rigors required by the protocol.
- A researcher may falsify subject characteristics so that they meet eligibility criteria for a study.
- Research personnel may falsify data to make the results more likely to fit his/her preconceived idea as to what results should show.

These risks are more likely when:

- Research personnel collect data from external sources without close supervision.
- Research personnel employed on a study are new to research and have not been appropriately trained and briefed.
- Research personnel collect data without likelihood of their data being audited
- Senior staff are overcommitted and do not have sufficient time to discharge their supervisory responsibilities.

These events could lead to the serious consequences including

- Results of the study become unreportable and unpublishable. If already published, article may require a formal withdrawal with risk of severe reputational damage to both the researchers and their institution.
- A study may have to be repeated with the cost borne by the department. This may delay the results becoming available and lead to breach of contract (and liability to damages) especially if data is critical for the development of a drug or device.
- If grant funding is involved the fact must be reported to the funding body with possibility of severe criticism of the level of supervision. A requirement to review previous data collected by the researcher may lead to high cost and interference with other work..



Vignette: A new research assistant was engaged in a project involving telephone counselling after traumatic stress. The assistant strongly believed in the value of the study and the certainty (in her mind) of a positive result. When the actual result of a test she undertook was unfavourable she recorded different data to make it appear that the result was positive in each patient. This was picked up during a routine quality control check, when it was found that her results were different to the results of the other research assistants employed.

Falsification of data in this way can have the most serious results for everyone involved and would be grounds for instant dismissal. The research assistant might well find it impossible to gain employment in a health or research occupation.

3. Approach in other industries

The pharmaceutical industry pays particular attention to this risk because such an event could delay the program of development of a new agent resulting in large financial losses. Regulators also require rigorous data validation because of previous occurrences of fraudulent data collection.

As a result of these concerns many pharmaceutical studies are accompanied by rigorous data validation procedures. Monitors employed by the pharmaceutical company periodically visit participating centres and carry out source data verification. This involves the matching of trial data with information from patients' medical records, original pathology reports etc.

Pharmaceutical companies also require units undertaking early phase drug studies to have a series of SOP's (standard operating procedures) that specify the procedures to be undertaken in deriving and recording all data elements

4. Barriers to occurrence

- Most institutions now attempt to establish a strong culture that emphasises care and accuracy in data-collection. This will involve:
 - * Ensuring that new staff are adequately trained in research methods/ethics.
 - * Requiring all research protocols to have adequate quality control procedures that would be likely to detect falsified data.
 - * Chief investigators must have regular study meetings with their research team in which quality control measures are reviewed.
 - * SOP's are required for most key data collection procedures including quality control procedures.

5. Database Management

Guidelines regarding School requirements for data management are regularly updated. The IT manager or his/her staff will provide assistance with storage and transfer of data and the Director of the Data Centre will provide assistance in the establishment of databases.

All data files (electronic or hard copy) and study documents must be stored securely at all times. This should involve the use of password protection for electronic data and locked cabinets for hard copy. In particular, any document that could identify a study participant should not be left exposed or unattended on a desk or bench.

It is acknowledged that, for practical reasons, some staff may take data from the premises. However researchers and/or students must never allow identified information to leave the department

Identified research data should never be sent via email or faxes.

If it is necessary to send sensitive data to any external party, researchers should first discuss the transmission options with the RGO to establish how it should be sent/received. It may also be helpful to discuss transmission options with local ICT support staff.

USB sticks must never contain or transfer sensitive or identified information.

Secure file transfer services, such as AARNET's CloudStor, are available but would need to be used by both the sender and receiver. CloudStor is Australian based and endorsed by Monash University TSG. For additional information regarding data security go to www.its.monash.edu.au.

(a) Software packages: The principal software packages used for databases in the School are Microsoft Excel and Microsoft Access. Access is well supported, easy to learn, has good security and data checking features and is highly recommended for most studies. Monash University runs several short courses on database management with Access and, in view of the fundamental importance of Access to our work; all staff should have familiarity with this package. SAS and Visual Basic may also be used but there is limited support from our computer staff for these programs. Epi-Info is occasionally useful for small studies involving fewer than 100 subjects and fewer than 50 fields.

(b) Database documentation: Each database should be accompanied by a folder containing the following information:

- copies of the questionnaires and/or other data collection instruments;
- database information including an explanation of the various files, languages & data formats used, the directory structure and the key programs used to manipulate the data;
- the data dictionary which lists all variables, variable names, coding rules etc. (see example below);
- coding manuals eg. listings of all occupation codes, drug codes etc; and
- the database log used by the study coordinator and database manager to record the nature of, and reasons for, all modifications, data cleaning etc.

(c) Example of a Data Dictionary

Table Name	Participant Details			
Comments	List of visit dates for each participant and their capsules Record count + 409			
Field	Description	Validation	Type	
Study Number	Number that uniquely identified participants	Primary Key	Number	
Mstat	Marital status of participant	1 = single 2 = married 3 = divorced	Number	
Chol	Laboratory tested cholesterol result	>0 and <20mmol/L	Number	

(d) Data Log: It is the responsibility of the study coordinator to ensure that this log is maintained. In particular, he/she should ensure that the log shows the identity of individuals entering data onto the main database or correcting data, any changes made to questionnaires or data entry screens, any auditing or checking undertaken and any difficulties experienced. Coding changes introduced and variables subtracted or added must also be documented. When significant changes are made, notification should be circulated to all investigators and added as an appendix to the Procedure Manual.

(e) Storage of data: All paper-based data must be correctly stored and a procedure to ensure the security of data must be developed. The exact procedures to be followed may depend on the sensitivity of the data set and on specific caveats imposed by the ethics committee. A storage site must be designated and security procedures established (e.g. responsibility for locking cabinets, location of keys, provision of passwords to key individuals and nomination of individuals with differing levels of access).

- (f) **Privacy of computer files:** Similarly data files kept on computer should be separated from files containing identifying information and the data linked only by a numeric key. Access to all computer files should be under password control and a copy of the password made available to the Principal Investigator.
- (g) **Commercial data entry:** Data entry from paper forms is often achieved by sending batches to an external company. Written records outlining privacy assurance procedures of any external company should be obtained and stored. To avoid wasting considerable funds, it is essential that all forms are carefully checked in advance for completeness and legibility and that the nature of the task required is explained in great detail. The data enterers should not need to interpret responses, ie. they should never have to do more than simply enter the numbers provided. Double entry, whereby two independent people enter the same forms and any differences are reconciled, is a usual requirement.
- (h) **Direct data entry:** Data may be entered directly onto computer based data entry screens, entered via Teleform or entered using marked sense cards which are read directly into a data base. These are more difficult to check and require special procedures for checking, mainly through the use of range and consistency checks (see below).
- (i) **Range and consistency checks:** Following data entry, and before finalisation of a data set, it is necessary to run a series of data verification procedures. These include *range checks* (to identify values that are likely to be outside a valid range), and *consistency checks* (e.g. checking that non-smokers do not have entries under „numbers of cigarettes smoked per day“). After these are complete, a sample of the paper records should be checked against the final data file and errors rectified until it is virtually certain that no errors exist in the key variables, and the error rate is less than (perhaps) one percent in less critical fields. During this process it is critical to have changes made on a single copy of the database to avoid confusion in identifying the ultimate version. It is also critical that version control procedures are employed to document the current version of the database.

(j) Back up:

Clinical and public health research commonly involves the use of large computer data-bases which are continuously being updated as new data is added and older data is checked and edited. A highly organised and systematic process is needed to ensure that changes are being made to the appropriate (ie the latest) copy of the data bases and that the most current copy of the database is backed-up regularly and kept in a secure location.

At every stage during the creation of the data base it is necessary to employ a systematic backup procedure. This should be carefully described in the Procedure Manual and strictly observed. Documentation of files can be established with names in the format: <Database/StudyName>_Bkp_Noeg. VECAT_Bkp_3.

A record of who performed the backup, and at what date and time, should be kept on paper or in a text file with the backups (or both). The IT manager will describe the best way to back up each data-set . Regular backup on to zip discs held *outside* the department is highly recommended. This precaution guards against the unlikely events of fire or theft.

(k) Risks associated with loss of data due to inadequate back-up procedures

What can go wrong:

- A database is destroyed in a computer „crash“ or via accidental erasure. A research assistant may accidentally erase the current version of the data-base.

How can this happen?:

- The risk is greatest when databases are established and maintained by researchers without the close support of an experienced programmer or database manager.
- The risk is greater in large datasets where databases are constantly being updated, especially if more than one person is involved in data-entry or if different people are involved in data entry and data editing.
- A high risk exists in the data checking/editing stage where it is often easy to loose track of which is the most current version of the database.
- Data may also be lost due to theft, malicious destruction or fire. If all copies of a database are kept in the one location or on the same computer.

Consequences:

- The likely consequences may range from irreversible loss of essential data to a highly expensive and time consuming process in reconstructing a data-base. If not recognised or remedied this could lead to the publication of inaccurate data.

Prevention:

- Development of detailed “SOP”s” related to data management which are incorporated into the study documentation.
- Handling of all large data-sets within the data-centre.
- Review of data management procedures by the research auditor.

(l) Final “locked” dataset

When final corrections have been made and the database is finalised, it should be burnt onto specially labelled and numbered copies of CD-ROMs and distributed to senior investigators. The CDs should include a file containing any randomisation key. No analysis of the data should be conducted until the final database is created.

(m) Statistical analysis of data

All research data should be analysed by a statistician. No original results should be published without the senior researcher being able to certify that either (a) a statistician has undertaken the analysis or (b) that the analysis of the data has been checked by a statistician or (c) a statistician has reported to the senior investigator that the head of biostatistics has sufficient confidence in the researcher undertaking the analysis to warrant that the requirements for checking are not necessary. All PhD students should have key results checked by a statistician.

Analysis of large data sets by computer requires high levels of expertise gained only from experience under adequate supervision. Mistakes are easy to make and may be difficult to detect because intuitive „feel” for data is less than with small paper-based data-sets. Modern computer packages allow sophisticated analytical procedures to be undertaken by inexperienced people with little understanding of what they are doing. Serious errors are more likely if analysis of large data-sets is unsupervised and conducted by relatively junior researchers

Serious error made in analysis of a data set may lead to retraction of a published article or report. Under worst circumstances this could alter outcomes of research that had already been acted upon at considerable cost and lead to substantial legal liability. This could have serious implications for the scientific career of a researcher and his/her colleagues and/or threaten the financial viability of the department.

To prevent this from happening it is school policy that all „final” data-analyses should be checked by a statistician.

7. Study Management

1. The Principal Investigator

A single individual, the Principal Investigator, must be specified as having ultimate responsibility for the conduct of the study. He/she has responsibility for the design, conduct, analyses and reporting of the study and should:

- ensure that all investigators are aware of their responsibilities and that they conduct the study in accordance with the study protocol;
- ensure that appropriate systems are in place to guarantee appropriate quality control of every aspect of the study;
- ensure that all persons involved in implementing the protocol are adequately informed about the protocol, the nature of the intervention and their study-related duties;
- ensure that clear lines of communications are present between all study investigators;
- ensure that the case report forms (CRFs) are adequately designed to capture the required data
- manage the resources for the study in a way that ensures that the study finishes within the available budget; and
- ensure that the results are analysed, written up, reported and disseminated appropriately.

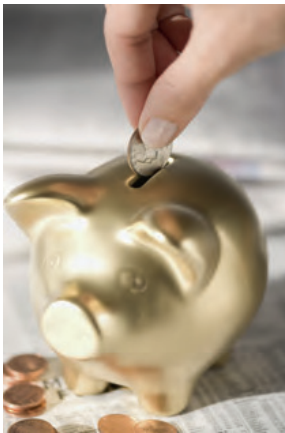
Other key individuals fulfilling different roles in a study may include:

- (a) **Study Co-Investigator:** each co-investigator has the responsibility for the conduct of the study within his/her participating centre and/or area of expertise.
- (b) **Study Coordinator/Manager/Executive officer:** often a senior research fellow, who may be responsible for the day to day management of the study or some aspect of the study.
- (c) **School Research Manager:** Is an official appointee of the School who must be provided regularly with copies of relevant study documentation including
 - the grant application
 - the protocol;
 - the ethics committee approval& correspondence
 - letter of agreements/contracts between the Institution and the

- annual reports to granting bodies & ethics committees
- Details of where the study has been archived, if applicable

2. Finances and human resources

- financial management of each study will be the responsibility of the Principal Investigator. He/she must keep accurate and timely records of all expenditure and inform the head of School and School manager of any concerns or irregularities.
- job descriptions based on a generic proforma will be provided for all staff associated with the project listing their responsibilities. These should be signed by the principal investigator and the staff member.



3. Study meetings

(a) **Regular meetings:** the Principal Investigator and Study Manager must arrange for regular meetings of the study staff. In early stages, such meetings should be at least fortnightly and at later stages at least every two months. Formal minutes should be kept and circulated to all involved parties.

(b) **Study management committee** (for larger studies only)

this committee should meet at specified intervals to review progress of the study.

decisions concerning changes to protocols, case report forms or modus operandi must be ratified and recorded at meetings of this group.

minutes of these meetings should be made and circulated as soon as possible after the meeting and stored in the Study Document File (see above).

Each member of the supervisory committee should be provided with the protocol, the PICF approved by the Ethics Committee, the case report forms including any questionnaires and procedure manual and the minutes of the study committee.

The principal investigator will ensure that copies of all protocol amendments and minutes of all meetings are circulated to each committee member for inclusion in his/her folder.

(c) Interviewer safety

If interviews are undertaken in a participant's home, interviewers should notify the Department office of the time and location of all interviews. For personal safety, calls should be made to the office after interviews are completed and the interviewer has left the home. Interviewers undertaking interviews after hours should always take a mobile phone and organise a call-in procedure. A compressed air horn should also be carried. Wherever doubts occur about the advisability of interviews, a second individual should accompany the interviewer.

(d) Diaries

Diaries must be kept by all study personnel. These should detail their contact (or attempted contact) with study participants, the hours of such contact and a record of any matters arising.

(e) Randomisation

Randomisation or blinding codes must be kept by an individual totally separate from the study and *must not* be available to the study team. It must be emphasised to all staff that *under no circumstances* must a randomisation or blinding code be broken until the final cleaned data set has been produced. Any emergency un-blinding must be developed and have the approval of the ethics committee.

(f) Staff management

It is the responsibility of the study investigator(s) and the study coordinator, to provide appropriate training for staff and to monitor the work performance of all those involved in data collection, management and analyses. This supervision should include specific instructions concerning privacy, data handling, quality control, security during interviews etc., and adherence to these guidelines must be monitored. All staff must sign a document acknowledging their willingness to abide by privacy guidelines before commencing work. All staff involved in the conduct of the study should maintain a daily log book in which they record details of their day to day activities, including such matters as patient interviews, attempts at contacting participants, travel for study purposes etc.

(g) If things go wrong

If there is evidence of poor study practice, the study team should know how to deal with the problem in a positive way. Solving the problem *at an early stage* is the best way to reduce damage to study participants and researchers. Informal confidential advice from senior colleagues may be helpful in deciding what action to take. There may be times when it is not possible for the study team to deal with a problem alone. In these cases, they should share the problem with colleagues who are in a position to act. However, if there is a pattern of poor practice which could place participants at risk, this would be the time to refer the problem to a more senior level.

(h) Follow up of abnormal pathology result

Many studies involve the measurement of physiological variables (such as blood pressure) and the undertaking of various pathology tests (such as full blood examinations or liver function tests). When large numbers of individuals are tested there is a strong possibility of finding abnormalities of clinical significance that may not be known to the individual or his/her medical practitioner. In some instances recognition of the abnormality may allow effective treatment to be introduced.

Each study must have a procedure to review the results of physical examinations and pathology tests and have an efficient procedure to pass on important clinical information. If failure to pass on crucial clinical information meant that a potentially curable illness was not detected it could lead to legal action for negligence. These procedures must be documented in the protocol and procedure manual and adherence monitored by the RGO.

(i) Emergency Procedures

Some clinical research projects, particularly those conducted on patients with conditions such as asthma or hypertension may require special attention to monitoring and the availability of emergency care. For example clinical trials of new drugs may require withdrawal of usual therapy with clinical monitoring to ensure the detection of deterioration. The risk of medical complications resulting from such actions may be significant. If emergency care was not immediately available and, as a result a study participant died or developed serious complications repercussions would follow for both the investigator and the department.

This risk is most likely to be encountered in drug trials and in physiological studies. The risk is greater when studies are supervised by inexperienced staff and when senior clinical investigators are unavailable or uncontactable.

Management of this risk is handled by the development of SOP's that cover as many emergency scenarios as possible. At a minimum they should make each participant know who to contact in case of emergency. The RGO will monitor the adequacy and functioning of these procedures.

8. Quality Assurance

1. Quality Control (QC)

Quality control procedures should be conducted by the Principal Investigator or his/her nominee and will usually involve:

- verification of the availability of signed consent forms;
- verification that the protocol is being followed;
- verification of appropriately secure data handling;
- source data verification (eg checking study database against original pathology records)
- review of completeness of Case Report Forms
- duplicate interviewing of a percentage of participants as a reliability check;
- verification of an appropriate audit trail accompanying data changes;
- verification of appropriate computer back up; and
- if a study involves administration of medication, all “returns” should be kept in storage in the bottles which were provided to participants. These can be later used to verify the medication provided.
- Verification that serious adverse reactions have been reported
- Verification that emergency procedures are in place and are operational

2. Audit

An audit is a systematic and independent examination of study-related activities and documents to determine whether these activities were conducted according to the protocol, applicable standard operating procedures, good clinical practice and the applicable ethical & regulatory requirements.

The School of Public Health and Preventive Medicine has a Research Governance Officer whose role, in part, it is to conduct audits of the projects being undertaken within the School. In addition to randomly selecting projects for auditing the Research Governance Office will audit other projects on request of the Head of School or the Research Governance Committee.

Audits may also be undertaken after a request from an individual researcher. These requests are often helpful for inexperienced researchers and/or those working in isolation.

The School has also developed a brief self audit tool. This is available from the Research Governance Officer or on line at <http://sphpm.med.monash.edu.au/Main/SelfAudit>. This tool has also been adopted by

some local HRECs and is required to be completed for each study as part of the annual ethics progress report.

The brief self-audits are sent to each research coordinator and are to be completed by that person. Encouragement is given to identify any areas where compliance with GRP requirements is less than ideal. The completed form must then be given to the principal investigator to make comments, then sign and return to the RGO and/or ethics office

Individual researchers are also encouraged to make use of this tool as a way of checking that their study procedures are in line with the School guidelines.

During a formal audit, particular attention will be paid to the completion of PICFs. The audit will also ensure that the signed PICFs and other documentation are stored securely.

While the study co-ordinator is responsible for the day to day conduct of a research project the ultimate responsibility lies with the principal investigator. Investigators are therefore reminded to oversee the conduct of their studies and to ensure all activities are undertaken appropriately. Study staff are reminded to keep their supervisors informed at all times.

- **Study closure**

On completion of the study, procedures must be put in place to:

- * notify participants and their doctors of the results, if applicable;
- * provide reports to the Ethics Committee(s) and funding bodies;
- * arrange storage of study documentation
- * label storage boxes clearly with the title of the study, the principal investigator, the completion date and the date on which records can be destroyed; and
- * provide information about where documentation is stored to the school's research manager.

Vignette: A PhD student finished her project, analysed the data and wrote their thesis. She then started looking for employment and found a new position, but her employment was contingent on successfully gaining the PhD. In the process of moving institutions she disposed of anything she did not need, including her research documentation. Unfortunately, the examiners did have questions and asked for further analyses. With so much of the research documentation destroyed the student was faced with the need to repeat much of her project.

(a) Communication with a participant's doctors

When enrolling a patient into a clinical research project it is essential to

- (i) Communicate with their treating physicians to ensure there is no reason why the participant may not be suitable. .
- (ii) With the patients' permission, keep their GP & other treating physicians informed regarding their involvement in the clinical trial.

(b) Payments to Research Volunteers

Provision of appropriate compensation to research participants for expenses incurred is essential. These payments should be disclosed to the Ethics Committee(s). Other payments are sometimes approved provided that it is judged that such payments are not an inducement for a person to participate against their better judgement.

(c) Using drugs and other therapeutic agents during a trial

When clinical trials of therapeutic agents are undertaken, preparation of medication for patients must ALWAYS be done in consultation with a Pharmacy Department. Bulk medication should always be stored in the Pharmacy Department, rather than in the School unless the storage arrangements have been deemed suitable by Pharmacy.

(d) Insurance Cover

Insurance provided by Monash University covers damage to study participants resulting from professional negligence in the design of the research protocol. It will also provide cover for non-medical research staff involved in clinical activities outside public hospitals.

Insurance cover against actions for medical negligence by a patient from a public hospital is the responsibility of the Victorian Managed Insurance Agency. It is critical that all medical practitioners participating in clinical research involving such patients have an appointment (or adjunct appointment) at a public hospital to qualify for this cover.

When the study is being conducted in a general practice setting the University will not provide insurance for negligible acts on the part of participating general practitioners. Those doctors would be required to have cover for their research participation included within the policy provided by their medical defence organisation or purchase their own additional insurance. Alternatively the investigators may seek specific insurance to cover a particular research activity.

Externally sponsored studies are usually provided with an indemnity by the sponsor assuming liability for injury to participants in a clinical research project that they have initiated. Such arrangements agree to compensate injured participants on a no fault basis in accordance with Medicines Australia's guidelines for compensation¹². However such indemnity may become void if the injury is sustained as a result of a protocol violation. However, if the study is investigator- initiated the employing

institution takes on the role of sponsor and therefore the responsibility for providing insurance cover.

In some instances injury to a research participant may result from the harmful effect of a product under investigation resulting from a defect in its manufacture¹². This is usually the responsibility of the sponsor or manufacturer of the investigational project and is covered by a product liability agreement.

It must be emphasised that insurance cover may not be valid unless:

- a human research ethics committee, constituted in accordance with National Health and Medical Research Council guidelines, must have reviewed and approved the clinical trial in question;
- the clinical trial is conducted in accordance with the terms of any human research ethics committee approval, and
- the practitioner's involvement in the clinical trial must come within the category of practice for which the practitioner is insured.¹³

(e) The Study Report

Completed studies must be summarised in a final report that accurately and completely presents the study objectives, methods, results and the principal investigator's interpretation of the findings.

Funding agencies and/or sponsors must be informed of the study results in a manner that complies with applicable regulatory requirements. There is an ethical obligation to disseminate findings of public importance. Scientific peers shall be informed of study results by publication in the scientific literature or presentation at scientific conferences, workshops or symposia. Potential conflicts of interest should be disclosed. Authorship of publications should be determined in accordance with the School authorship guidelines (available from the Department folder of the V: drive). Ideally, authorship should be discussed prior to the commencement of the study.

Appendix A: ETHICAL REVIEW OF RESEARCH PROJECTS

The term „ethics“ refers to the principles of good, desirable and/or acceptable conduct that should govern interactions in all spheres of human activity. Ethical guidelines related to medical research have been developed primarily to establish standards for the protection of the welfare and the rights of participants in research projects. They also provide assistance to researchers by providing guidance in how to conduct research in an ethically responsible manner.

Ethical review of research is a relatively recent phenomenon. The Judgement of the Nuremberg Military Tribunal on War Crimes contained a series of principles describing acceptable medical research practice. They were developed further by the World Medical Association in its 1964 publication 'The Declaration of Helsinki'. Subsequently many countries have adopted these principles into their own guidelines, modifying them when necessary to accommodate new problems such as genetic testing.

In Australia, the NHMRC has released its own publication entitled ' National Statement on the Ethical Conduct in Human Research". This was released in 2007 and can be downloaded from the NHMRC web site (http://www.nhmrc.gov.au/guidelines/ethics/human_research/index.htm). Australian ethics committees use this document to guide their decisions about the ethical acceptability of most clinical research projects. The document has been supplemented by several other documents that give more detailed instructions about such matters as privacy, and 'Good Research Practice".

The NHMRC guidelines require that every institution in receipt of NHMRC funding must have an appropriately constituted ethics committee. As a result virtually all hospitals and universities and many research institutes have established ethics committees.

In some case specific legislation has been introduced covering areas such as confidentiality of medical information. Naturally ethics committees will never (knowingly) approve a project that is in breach of the law or would place its home institution at legal risk. In the event that legal and ethical requirements both apply, the legal requirements will normally apply.

ETHICS COMMITTEE SUBMISSIONS

Membership of Ethics Committees: To comply with NHMRC guidelines, ethics committees (EC's) must have a minimum of eight members including a chair, layman, laywoman, two health researcher, clinical carers, minister of religion and a lawyer. Most committees require more members to cope with the workload but retain a balance between non-researchers who can reflect community standards and researchers who can understand the clinical details.

Application process: HRECs or their institutions may have simplified review processes for some low risk projects involving e.g. a review of patient records, simple questionnaires or studies on discarded tissues can be notified to the ethics via a simplified „low-risk“ application process. In most cases however, a full application is needed. Many HRECs now only accept the National Ethics Application Form (NEAF) which is normally accompanied by a Victorian Specific Module and an institution/site specific assessment form. The Common Application Form (designed by the Victorian Department of Health) is another standard form that is accepted by some Victorian Hospitals..

There is an increasing move towards streamlined ethics review, both at a State and a Commonwealth level. Under these arrangements projects are submitted to a single hospital for ethics review. When this step has been successfully completed, the application passes to individual research institutions for a governance review. The governance review looks principally at the willingness of each individual institution to be involved. It considers aspects such as the interest of staff, their workloads, the adequacy of the financial and insurance arrangements, conflicts of interest (if any) and whether staff are sufficiently trained.

Fees: Virtually all ethics committees now charge commercial entities for processing their applications. Many charge a reduced fee (or no fee) for grant funded projects and amendments.

Modus operandi: An increasing challenge for ethics committees is the increasing workload and the possibility of letting something 'slip through' because insufficient time has been spent on the review process. One common approach to addressing this problem has been to stratify projects into different levels of risk. Lowest risk projects may be sent to a small number (perhaps one or two) of members who provide comments which are reviewed if necessary at the main monthly committee meeting. The low risk group included most questionnaire studies, student projects, quality assurance projects and studies requiring only clinical record reviews.

The remaining studies are typically reviewed by a search committee which is often a subcommittee of the main ethics committee. This committee typically consist of several experienced researchers. Its role is to flag problems and attempt to resolve them prior to the main EC meeting. Occasional projects which raise special ethical issues may be flagged for interview. Typically CTN & “first in man” trials, studies with devices or invasive procedures, and studies involving the collection of sensitive patient data may be interviewed (along with those flagged for attention by subcommittee members).

Documentation: The first step in the review process is typically a review of the documentation provided to ensure it is complete. The majority of problems occur with:

1. Failure to provide a non-technical description of the project. This frustrates lay members.
2. Failure to provide a budget with sufficient explicit detail.
3. Failure to provide resource utilisation forms signed by the clinical services to be used.
4. Failure to include essential CTN documentation, particularly that related to CTX approval in the US, UK or Sweden
5. Failure to include questionnaires.
6. Failure to provide details of 'after hours emergency contact'.

Appendix B: PROTOCOL OUTLINE

- **Title Page**

This page should include the following:

- title of the research project
- names of the investigators
- version number of the protocol
- date of completion of the protocol

The title page should also include the *signature of the Principal Investigator*.

- **Background**

An explanation of why the study is being conducted and the specific question being addressed. This section will comprise:

- a Literature Review describing previous relevant literature summarised in a fashion which explains the rationale for the research.
- the Study Hypothesis or Study Objectives and
- the Study Aims and Purpose

- **Study Design**

A description of the design of the proposed study including (when appropriate) methods of treatment allocation and/or choices of controls.

- **Justification of Sample Size**

A description of sample size calculations demonstrating that the study will have adequate statistical power or statistical precision.

- **Inclusion and Exclusion criteria**

Inclusion and exclusion criteria for participants.

- **Subject Recruitment**

This should include the source of study subjects, how participants will be recruited (advertisements in newspapers, notices around the institution etc), the anticipated approach to subjects, procedures for establishing eligibility and confirming entry criteria, procedures for handling consent, and a description of any special measurements to be made (eg. invasive and non-invasive measurements, questionnaires).

- **Interventions**

The exact nature of the study intervention(s) and details relating to their preparation, stability, safety and, if necessary, a rationale for the choice of dose(s).

- **Randomisation**

This is the process of assigning study participants to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

Details should include how randomisation will be conducted, what allocation concealment will be used, who will be blinded, where the randomisation code will be stored, and the circumstances when unblinding is permitted.

- ***Study Endpoints (Outcome measures)***

Outline the primary and secondary variables to be measured to meet the study objectives.

- ***Bias and Confounding control***

Predictable sources of bias, variability and confounders should be addressed, as well as measures taken to minimise them. Details of how blinding will be conducted and maintained and who is blinded should be included. All study staff must be informed that unblinding must never be permitted except according to the Protocol. The decision to unblind a participant or the whole study should only be made by the Principal Investigator, unless a contingency plan has been established for emergencies.

- ***Data Management***

Include a description of how data will be handled, how privacy concerns will be addressed and how storage and back up of data will be undertaken.

- ***Quality Assurance and Control procedures***

Outline the quality assurance and control procedures to be employed to ensure integrity and validity of the data.

- ***Data Analysis***

A specification of any „a priori“ subgroup analyses and the statistical methods to be used for data analysis should be included. For some studies, interim analysis of data for safety monitoring and/or early study cessation will be required. Details of such analyses should be provided.

- ***Study Time Lines***

This should indicate the anticipated time line for each of the major stages of the study. Particular attention should be paid to participant recruitment.

- ***Signature of the Principal Investigator***

In all cases, the principal investigator should sign and date the final study protocol and any amendments to the protocol.

Appendix C: PROCEDURE MANUAL OUTLINE

- ***Final Protocol***

The study Protocol as approved by the Ethics Committee(s) (see above).

- ***Data Collection Documents***

A copy of the approved Plain Language Statement, Consent and all data collection forms.

- ***Study staff***

A description of all members of the study team including their roles, responsibilities and reporting arrangements. Members of various study committees, together with their contact details should also be provided. Also, an appropriate schedule of training for staff involved in the project should be included. The need to maintain strict confidentiality in relation to any personal information concerning participants should be stressed.

- ***Funding details***

Sources of funding for the study as well as the expectation of funding bodies (eg. timing of allocation of funds, deadlines for progress reports.)

- ***Study flow charts***

A separate chart should be developed describing, in detail, the critical pathway for handling study participants and the sequence to be used in handling questionnaires, coding, data entry, data verification, cleaning and storage of hard copies and back-up of data files.

- ***Clinical measurements of the study endpoints***

Detailed procedures to be followed for clinical measurement of the study endpoints eg. blood pressure. Details of quality control of such measurements, maintenance of equipment, and methods of recording of results, calibration of equipment and the labelling and storage of biological specimens.

- ***Compliance measures***

Details, when appropriate, of compliance tests (including plasma measurements) and who will perform them.

- ***Adverse events and contingencies***

The nature of any adverse events that might occur together with the approach that should be taken to manage them. Contingency plans for these events should be documented. Such events must be reported to all necessary agencies. These will vary from study to study but might include the ethics committee that originally authorised the study, other study personnel, the study sponsor, and the TGA. In general, notification of serious adverse events should occur within 24 hours, should be in writing and signed by the principal investigator. Researchers should refer to the appropriate ethics committee for clarification of local requirements.

- ***Clinical abnormalities***

Follow up of abnormal laboratory investigations, or other issues that require further action (including liaison with the participant's medical practitioner).

- ***Specific procedures***

To enable the study to cope with sick leave, holidays, occasional duties (eg equipment maintenance, cleaning, office supplies and tidying). Emergency contact details should be documented.

- ***Data Management***

The procedure manual will also provide detailed information about data management as outlined in section 1.10.

Appendix D: References / Useful Resources

1. Medical Research Council “Guidelines for Good Clinical Practice in Clinical Trials 1998.” <http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002416>
2. National Statement on Ethical Conduct in Human Research. <http://www.nhmrc.gov.au/publications/synopses/e72syn.htm>,
3. ICH/GCP Guidelines, an international ethical and scientific quality standard. <http://www.tga.gov.au/docs/html/ich13595.htm>
4. Alfred Hospital Research & Ethics Unit (Alfred Hospital Ethics Committee). <http://www.alfredresearch.org/>; tel79 3848 (9076 3848 for external calls)
5. Monash University Human Research Ethics Committee (MUHREC). <http://www.monash.edu.au/researchoffice/human/>
6. Guardianship and Administration Act 1986 (Act No.40/1999) 2006 amendment. http://www.austlii.edu.au/au/legis/vic/consol_act/gaaa1986304/
7. ICD10: available from the World Health Organisation website. <http://www.who.int/classifications/icd/en/>
8. Application of the Privacy Laws to Medical Records in Victoria. Your obligation under the Victorian Health Records Act 2001 and the Commonwealth Privacy Act 1988.” Australian Medical Association (Victoria) publication. Melbourne 2002
9. Commonwealth Privacy Act. http://www.nhmrc.gov.au/files_nhmrc/file/publications/synopses/e26.pdf
10. Health Services Commissioner, Privacy Legislation. <http://www.health.vic.gov.au/hsc/legislation.htm>
11. Southern Health. http://www.southernhealth.org.au/page/Research/Human_research_ethics/
12. http://hwlebsworth.ensoconsultancy.com.au/health_sept09/insurance-and-indemnity-for-human-research.html
13. http://203.202.1.186/___data/page/416/Insurance_and_Indemnity.Commercial_for_w eb3.pdf

