MONASH
UNIVERSITY

FACULTY OF MEDICINE, NURSING AND HEALTH SCIENCES

A GUIDE TO GOOD RESEARCH PRACTICE

DEPARTMENT OF EPIDEMIOLOGY & PREVENTIVE MEDICINE

CENTRAL & EASTERN SCHOOL

MONASH UNIVERSITY

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Contents

1.1 Introduction

- The purpose of this document is to ensure that medical research is conducted to the highest scientific and ethical standards.
- It should be studied in detail by those involved in research as it outlines a set of standards that should be adhered to.
- It is the responsibility of all research staff to ensure that the work they are involved in adheres to these guidelines. Significant departure from these guidelines should be brought to the attention of your supervisor.
- It is important to emphasise that all research must be supervised by appropriately trained and experienced individuals. Appropriate collaborators should be sought when the research involves procedures outside the experience and expertise of study staff.
- Particular importance should be attributed to research privacy including the need for research personnel to sign a privacy agreement and the maintenance of confidentiality in all circumstances.
- Research fraud, in any form, degree or circumstance, is totally unacceptable. Clearly, this has implications, not only for the individual researcher, but will impact adversely upon the scientific community and the department.
- The position of Clinical Research Governance Coordinator has been established to oversee the department's research and assist investigators in all aspects of good clinical research practice. This initiative, in conjunction with the Good Clinical Practice Guidelines/Research Risk Management Plan (below) and the Department's series of clinical research short courses, forms the basis of research quality assurance within the Department.
- The guidelines outlined in this booklet are available for quick reference. It is highly recommended that investigators enrol in programs and courses on good clinical research practice.

1.2 Principles of Good Clinical Research Practice

The following principles have been adapted largely from the:
ICH/GCP Guidelines, an international ethical and scientific quality standard available at
http://www.health.gov.au/tga/docs/html/ich13595.htm
Medical Research Council "Guidelines for good clinical practice in clinical trials" available at
http://www.mrc.ac.uk/pdf-ctg.pdf

- Clinical studies should be conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.
- 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 the most important consideration and should prevail.
- 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 ethics committee.
- Individuals conducting the study should have an appropriate level of education, training and experience to perform his/her tasks.

➤Freely 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 its 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.

1.3 Research Ethics

All research should be conducted strictly according to the

- ***National Statement on Ethical Conduct in Research Involving Humans*** available at
  www.health.gov.au/nhmrc/publications/pdf/e35.pdf

It is recommended that you access this website and search for the new handbook. (Alternatively, call AusInfo on Freecall 13 24 47)

- ***ICH/GCP Guidelines***, an international ethical and scientific quality standard are available at
  www.health.gov.au/tga/docs/html/ich13595.htm

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

Monash University

Monash University requires researchers to obtain a clearance for any research in which humans are involved. The University has a central human Ethics Committee - the Standing Committee on Ethics in Research Involving Humans (SCERH). Ethics approval must be granted before research can proceed. SCERH is constituted under the guidelines of the National Health & Medical Research Council (NHMRC) and considers proposals to ensure that they conform to the National Statement on Ethical Conduct in Research Involving Humans.
The SCERH web address is http://www.monash.edu.au/resgrant/human-ethics/

The Alfred Hospital

Alfred Hospital Ethics Committee Application forms and a guide can be downloaded from
http://www.alfredresearch.org
Alternatively, contact Ms Rowan Frew, Secretary of the Ethics Committee
79 3848 (internal calls) or 9276 3848 (external calls).

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
- Protocol amendments must be authorised by the relevant committee(s)
- Projects must not run longer than the authorised period, unless permission to do so has been obtained in writing.

1.4 The Protocol

The study Protocol is a document that describes the objective(s), design, methodology, statistical considerations and organisation of a study. The protocol also usually gives the background and rationale for the study. While in smaller studies it may provide the full study documentation, in most larger studies the Protocol is incorporated into a substantially more detailed study Procedure Manual. These documents should provide a clear description of why the study is being undertaken, the methods to be employed and how the results will be analysed.

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.

The Protocol should contain the following information:

• ***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 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.

• ***Inclusion and exclusion criteria***

Selection 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, where the randomisation code will be stored, and the circumstances when unblinding is permitted.

• ***Study endpoints (outcome measures)***

The primary and secondary variables expected to be affected by the study intervention or risk factor.

• ***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 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***

Including 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***

To be employed to ensure integrity 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.

1.5 The Procedure Manual

All large or prolonged studies require a detailed Procedure Manual. This should be prepared prior to the onset of the study and will generally incorporate and expand upon the study Protocol. The purpose of the Procedure Manual is to provide a detailed account of all study procedures and will be the day-to-day reference document for all staff involved. It should provide enough information to allow a new staff member to take over the study at any time. Both the data manager and statistician should be involved in production of the Procedure Manual.

Copies of the Procedure Manual must be provided to all research staff involved in a study, together with updates or amendments agreed to at study meetings. Specific documents also need to be provided to the Department's Business Manager (see section 1.14)

1.5 The Procedure Manual continued

The Procedure Manual should contain the following information:

• ***Final Ppotocol***

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

• ***Data collection documents***

A copy of the approved patient information and consent forms, case report forms and all data collection and data extraction 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 or serious 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 adverse or serious events should occur within 24 hours, should be in writing and signed by the principal investigator. Researchers should resort 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.

1.6 The Participant Information and Consent Form

The Participant Information and Consent Form is now becoming a commonly accepted term for documents previously known as the Patient Information Sheet, Participant Information Sheet and Plain Language Statement. Some institutions continue to use alternate names. Whatever its name, the form should describe the reason the study is being conducted, the demands to be made of the participant and arrangements to ensure privacy of the information collected. It should also be written in a fashion that can be easily understood.

Languages

The Participant Information and Consent Form must be made available in the language of the participant.

Maintaining Department records

In general, the Consent Form is incorporated into the Participant Information Form. Each participant must sign a copy before entry into the study. One signed, the original copy must be kept in the Department and another provided to the participant. Where applicable, another copy should be placed in the clinical history.

Information required

The information contained in a Participant Information and Consent Form should:

- be on the official hospital or university letterhead (various hospitals may require their own insignia as well);
- inform the participant that the study is a research procedure and invite him/her to participate;
- explain the nature and purpose of the research, including the randomisation procedures, the use of placebos if any, and the uncertainties of the study;
- explain all procedures that involve the participant, including the use of drugs or radioisotopes;
- explain the availability of alternative treatments;
- explain what is required of the participant, for example a change in lifestyle, the expected number and timing of follow-up visits and any additional costs to the participant;
- explain the duration of the study;
- advise of the approximate number of participants treated to date (when appropriate);
- explain the possible benefits, both to the participant and to others, stressing that these benefits are by no means assured;
- advise of any foreseeable risks, side effects and discomforts;
- ask the participant to advise of any other studies in which he/she is participating;
- ask the participant for information about any medications being used;
- advise of the measures that will be taken in the event of therapeutic failure or an adverse event;
- advise of insurance and other procedures for compensation in case of injury due to the study;
- advise that the participant's records may be inspected for the purposes of source data audit by authorised persons within the institution (eg Ethics Committees) or outside the institution (eg sponsors or regulatory bodies);
- advise of the precautions which will be taken to ensure the confidentiality of the participant;
- advise that consideration will be given to any relevant new findings that may become available during participation in the study;
- advise the names and telephone numbers of appropriate persons to contact if necessary, or for further information about the study.

Time to consider

Potential participants should be given sufficient time to consider the information and to decide whether or not to participate. The investigator (or a suitable delegate) should personally inform the participant and make a conscientious effort to ensure that he/she understands, preferably in the presence of a witness. The Consent Form should acknowledge receipt of the Participant Information Form.

Consent form completion

Three signatures are required on all consent forms - participant, witness and researcher (investigator). These signatures should be obtained at all times. All signatures must be dated on the same day. In general, someone who is independent of the study should witness the participant's signature. The role of the witness role is simply to witness the signature of the subject. As such, 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. Most ethics committees do require a witness's signature although they may vary on this requirement. Furthermore, if the investigators consider that obtaining a witness's signature is neither practical nor possible, they should check with the appropriate ethics committee to discuss an exemption. This exemption should be sought and received in writing.

The person who signs as investigator/researcher may be a delegate of the investigator. This person, when obtaining consent, must have had suitable expertise and adequate training in order to obtain fully informed consent. It is the responsibility of the PI to ensure that all delegates meet this standard.

Special circumstances

In some studies, the procedures required to obtain informed consent differ. These may include studies on:

- Human genetics
- Vulnerable patients (eg. intellectually disabled)
- Minors
- Subjects unable to provide consent (eg. unconscious, demented)

In these circumstances, advice must be sought from the relevant Ethics Committee/s during development of the consent documentation. These special groups have attracted considerable attention recently. In particular, changes have been made to the Guardianship Act that affect the way some potential subjects can be consented for research projects. It is strongly recommended that researchers who may be recruiting from these special groups be familiar with the revised legislation.
This can be accessed at: http://www.dms.dpc.vic.gov.au/12d/G/ACT01488

1.7 The study document file

The primary objective of good data handling and record keeping is to ensure that data collected on participants are accurate and unbiased with respect to the study treatment allocation. The procedures and documentation used to ensure that the data contained in the final report agree with original observations should be made explicit.

Coordinator responsibilities for documentation

A Study Document File should be kept by the study coordinator/investigator as a central record of all important issues involving the study.

Proper document management

- It is important to keep all paper work for a study in an orderly fashion and to have a paper trail that can be followed throughout the study.
- Keep in mind that your study may be audited at any time, even years after it has been completed. Audits will refer to the paper trail, hence the importance of keeping organised files.
- Records must be kept for a number of years following the completion of a study (at least 7 years for studies not involving drugs and 15 years for drug trials).

Documentation for inclusion

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 Form (all approved versions)
- Signed Consent Forms (sealed in a labelled envelope)
- Subject Identification List (sealed in a labelled envelope)
- Completed Case Report Forms and/or questionnaires
- Study brochure (if applicable)
- Data dictionary
- Correspondence (general)
- Contracts or agreements (if applicable)
- Minutes of study meetings (these must be circulated to all study team members)
- Computer database specifications
- A record of any changes to data on computer files after data collection.
- Coding anomalies
- Drug dispensing records
- Randomisation schedule
- Adverse events
- Progress reporting forms and consistency checks
- Study Reports

1.8 Data Confidentiality

Confidentiality is the prevention of disclosure, to other than authorised individuals, of a participant's identity.

Privacy imperative

Study participants are often asked to provide information of a personal and private nature. Sometimes research also involves extraction and collection of data from hospital records or records held by other bodies. It is a legal and ethical imperative to protect the privacy of this information.

Privacy Principles

New legislation has recently been introduced, at State and Federal levels, to ensure minimum privacy standards for the handling of health information. In December 2001, the Commonwealth *Privacy Act* (1988) was extended to cover all Australian private sector organisations. The Victorian *Health Records Act* (2001) 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

1.8 Data Confidentiality continued

Principles that regulate the collection, use, disclosure and handling of health information. The following principles of the Acts are particularly pertinent to research:

- Information should only be collected where necessary and with consent of the individual.
- Only use or disclose information for the primary purpose for which it was collected, or for a directly related secondary related purpose.
- Information should be kept accurate, complete and up to date.
- Information should only be destroyed or deleted in accordance with the Acts' guidelines.
- Information that is retained should be protected against misuse, loss, unauthorised access and modification.
- Individuals have a right to request access to their information and correct it if it is inaccurate.

It is recommended that all researchers familiarise themselves with the new privacy legislation. Summaries published by the Health Services Commissioner are available on line at http://www.health.vic.gov.au/hsc/act.htm

Any study requiring access to data held in a Commonwealth institution is covered by Section 95 of the Commonwealth Privacy Act (1988) - http://www.health.gov.au/nhmrc/publicat/pdf/e26.pdf
This section allows the NHMRC (with the approval of the Privacy Commissioner) to issue guidelines for the protection of privacy in the conduct of medical research. Although technically these guidelines apply only when access is required to personally identifiable records held by a Commonwealth Agency, they are commonly used by Ethics Committees to guide their decisions on all privacy issues.

Privacy guidelines

To satisfy privacy guidelines and to ensure the participant's privacy is adequately safeguarded:

- Information collected must be used only for the study for which approval has been given.
- Security procedures should be applied to maintain confidentiality. Consent forms must be separated from the case reports forms. Security also involves the removal of personal identifying information from data collection forms (case report forms, questionnaires etc) and computer files. Typically the name, address etc of the participant will be located on page 1 of the data collection forms that are removed and stored separately from the rest of the form. Codes linking participants to data must be kept in a locked cabinet and 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 should have signed a privacy declaration.
- 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 will be published.

Medical record access

Access to the medical records of patients of any hospital requires written approval from the Senior Medical Officer in the unit involved. Approval is not provided for access to individuals outside the hospital without the **additional** written approval of the Medical Superintendent. These documents should be filed in the Study Document File.

Consent for examination of private records

In keeping with the above principles, NHMRC guidelines point out that consent of participants should generally be obtained for the use of their medical records in medical research. However the Ethics Committee is able to approve the granting of access to records without consent if:

- the procedures required to obtain consent are likely to cause unnecessary anxiety, or prejudice the scientific value of the research.
- the research is in the public interest.

Such a determination may only be made if an Ethics Committee determines that the benefit of the research outweighs to a substantial degree society's interest in the protection of the individual's privacy.

1.9 Data collection

Most clinical and epidemiological research projects require a systematic gathering of information on data collection forms. In practise, these forms may be either paper based or electronic, the latter allowing direct entry of data into a database. Direct data entry poses a number of special challenges that must be addressed. 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: There is a copy of ICD-9 in the library which can be borrowed for short term use. ICD-10 is available from the National Centre for Classification in Health http://www.cchs.usyd.edu.au/ncch/

***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 A/Prof Michael Abramson).

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

- ***Separate personal identifiers***

When personal identifying information is collected it should be collected on a separate page which is removable so that it can be detached and stored separately to the main body of the questionnaire. All pages of the questionnaire 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, ie. they cover all possible responses
- the options are mutually exclusive, ie. only one option can be chosen for any specific situation.

• ***Special instructions***

Special instructions should be provided in small print on the data collection form (eg. 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, ie. those completing them should enter the data directly into coding boxes on the right hand side of the form. Coding boxes must be designed in conjunction with the person responsible for developing the database and each box should be labelled with the name of the relevant field in the database. 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 both are confident that the information is being collected correctly. Records of such interviews should be recorded in the study coordinator's log.

• ***Written comments***

Interviewers must also be encouraged to write comments on the data collection sheet whenever a new or unusual situation is encountered. These should be brought to the coordinator's attention at the next regular meeting.

• ***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 detailed 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***

All procedures used to verify and promote the quality and integrity of the data must be outlined in writing. An historical file of these procedures should be maintained, including all revisions and the dates of each revision. Any changes in data entries should be documented.

1.10 Database management

Information concerning Departmental requirements for data management are contained in the document 'DMAP' (Data Management Assistance Protocol) available in the Department of Epidemiology and Preventive Medicine (DEPM) library. Information available from this document should be supplemented with the assistance of an experienced database manager.

Software packages

The principal software packages used for databases in DEPM are Microsoft Excel and Microsoft Access. This package is well supported within DEPM, is 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.

Database documentation

Each database should be accompanied by a folder containing the following:

- copies of the questionnaires and/or other data collection instruments
- database information including an explanation of the various files, languages and 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.
- the database log used by the study coordinator and database manager to record the nature of, and reasons for, all modifications, data cleaning etc.

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 identifies participants	Primary Key	Number
Name	Participant name	Must include a name	String / text
Mstat	Marital status of participant	1 = single 2 = married 3 = divorced	Number
Chol	Laboratory tested cholesterol result	>0 and <20 mmol/L	Number

Data Log

It is the responsibility of the study coordinator to ensure that this document is maintained and used properly. 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.

Storage of data

All paper-based data must be correctly stored and a protocol to ensure the confidentiality 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. The personal identifying information on the front sheet of the data collection forms must be detached and stored separately from the remainder of the form in a locked filing cabinet. A storage site must be designated and security procedures established (eg responsibility for locking cabinets, location of keys, provision of passwords to key individuals, and nomination of individuals with differing levels of access). You are reminded that consent forms should be separated from case report forms.

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.

Commercial data entry

Data entry from paper forms is often achieved by sending batches to an external company. 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, should be specified.

Direct data entry

Data may also be entered directly onto computer based data entry screens 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).

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* (eg 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.

Back up

At every stage during the creation of the database it is necessary to employ a systematic backup procedure. This should be carefully described in the Procedure Manual and strictly adhered to. Documentation of files can be established with names in the format:

<Database/StudyName>_Bkp_No eg. 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). If your department has a computer network, you should speak to your IT manager to find out the best way of backing up your data. Regular backup on to zip discs held *outside* the department is highly recommended. This precaution guards against the unlikely events of fire or theft.

Final "locked" data

When final corrections have been made and the database is finalised, it should be burnt onto specially labelled and numbered copies of CD-rom disks 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.

Statistical analysis of data

Serious error made in analysis of a data set may lead to retraction of a published article or report or legal liability and could impact significantly upon the career of a researcher and the financial viability of the department.

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 statistician has undertaken the analysis or
- that the analysis of the data has been checked by a statistician or
- 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.

1.11 Study Management

Meticulous study management is required for:

- training, monitoring and supervision of new staff and continuing professional development,
- regular checks on data recording and notebooks,
- occasional checks on the day to day conduct of experiments

The Principal Investigator

A single individual, the Principal Investigator, should 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 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 are designed to capture the required data at all study sites and that the information is appropriate to the aims of the study,
- manage the resources for the study in a way that maximises the chances of the study finishing within the available funding and
- ensure that the results are analysed written up, reported and disseminated appropriately.

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.

Study Coordinator

This is another specified individual, typically a research fellow, who will be responsible for the day to day management of the study.

Finances

Financial management of each study will be the responsibility of the Principal Investigator. He/she must keep accurate and timely records of all expenditure. Furthermore, funding for all studies should be administered through the departmental finance officer. This officer should hold copies of all documentation relating to study funding and personnel employment.

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.

Study Supervisory Committee

- 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).
- 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.
- Each member of the supervisory committee should be provided with the Protocol, the Plain Language form approved by the Ethics Committee, the questionnaire and Procedure Manual and the minutes of the study committee.
- The Principal Investigator will ensure that copies of all Protocol and questionnaire amendments and minutes of all meetings are circulated to each committee member for inclusion in his/her folder.
- Ethics committees will be notified of all Protocol and questionnaire changes immediately and approval sought before implementation.

Security

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 copy and locked cabinets or similar storage receptacles and office locks 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 take confidential or identifiable data home. Researchers should realise that this poses a potential security/privacy breach. If temporary storage of such material is necessary, the Department recommends that staff have secure measures in place at home. These should include a lockable room and cabinet similar to those in the Department, a password protected computer and means to de-identify computer files.

Interviewer safety

When undertaking interviews 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.

Recruitment reviews

Each meeting conducted prior to the completion of recruitment will consider a report on recruitment achieved versus the recruitment target. At all meetings, particular note will be taken of progress versus anticipated time-lines, preferably presented in a graphic format.

Budgetary monitoring

The budgetary position of the study is the responsibility of the Principal Investigator and must be monitored at least monthly with the assistance of the departmental Business Manager.

Diaries

Diaries need to be kept by 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.

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 unblinding must have the approval of the Principal Investigator.

Staff management

It is the responsibility of the study investigator(s) and the study coordinator, to provide appropriate training for staff and to monitor and advise upon the work 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 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.

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.

Termination

The decision to terminate a study prematurely should be taken with great caution, should be based on good scientific and ethical reasons, and should be documented in writing. In rare instances, administrative reasons may require study termination; such decisions must be made independent of study results. Investigators and sponsors should specify and agree in advance about the circumstances under which the study could be terminated early. Included should be a mechanism for resolution of any disagreement.

Quality Assurance (QA)

This incorporates all those actions that are established to ensure that the study is performed and the data are generated, documented, and reported in compliance with these guidelines of good clinical research practice and the applicable regulatory requirements.

Quality Control (QC)

These are the operational techniques and activities undertaken within the quality assurance system to verify that the requirements of the study-related activities have been fulfilled. Quality control procedures must be developed and documented for all studies. This is the joint responsibility of the Principal Investigator and the Study Coordinator.

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 validation check;
- verification of an appropriate audit trail accompanying data changes;
- verification of appropriate computer back up;
- 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.

Monitoring

This is the act of overseeing the progress of a clinical study, and of ensuring that it is conducted and recorded in accordance with the protocol, standard operating procedures, good clinical practice and the applicable regulatory requirements.

Audit

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

1.13 Study closure

Some ethics committees require study documentation to be kept on site for a variable period prior to archiving. The requirements of the responsible ethics committee must be fully complied with upon study closure.

On completion of data collection and during all analyses of the data, 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 in a systematic fashion for at least 7 years after the last publication of study results (at least 15 years for drug trials). It should be noted that the time required for storage of study documentation is currently under review and will vary from study to study. Advice should be sought from the relevant Ethics Committee.
- 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;
- provide information about where documentation is stored (kept in the Study Document File and provided to the Department's Business Manager).

All data management and statistical analysis programs, and packages used in the analysis should be documented.

Storage of Study Documentation

The following is a list of documentation that should be stored for each study and archived at the completion of the study:

- Ethics Committee applications, including all correspondence and reports
- Protocol and amendments
- Participant Information Form (all approved versions)
- Signed Consent Forms (sealed in a labelled envelope)
- Subject Identification List (sealed in a labelled envelope)
- Completed Case Report Forms and/or questionnaires
- Study brochure (if applicable)
- Data dictionary
- Correspondence (general)
- Contracts or agreements (if applicable)
- Minutes of study meetings (these must be circulated to all study team members)
- Computer database specifications
- A record of any changes to data on computer files after data collection.
- Coding anomalies
- Drug dispensing records
- Randomisation schedule
- Adverse events
- Progress reporting forms and consistency checks
- Study Reports

1.14 Specific requirements for Good Research Practice

Ethics Committee Approval

No project that involves human subjects or their personal information should be commenced until Ethics Committee approval has been *confirmed in writing*.

1.14 Specific requirements for Good Research Practice continued

Protocol changes

Once a project has been approved, any change in protocol or procedures (eg changing the questionnaire to collect new information), should be immediately notified by letter to the Ethics Committee(s) where approval has been obtained. If you are uncertain about whether a change requires ethics approval, seek the opinion of the Ethics Committee secretary and keep documentation of that query. All protocol changes should be clearly identified on an updated version of the protocol and procedure manual. This may also create changes to the participant information form creating a new version and date.

Adverse Events

All serious adverse events occurring to participants in a clinical study must be reported regardless of whether it is considered related to the study or not. This includes the following:

- the death, for any reason, of a study participant
- the hospitalisation of a volunteer or the prolongation of a patient's hospitalisation
- any illness leading to permanent disability
- any abnormality in a child born to a female participant.

For any serious adverse event, the principal investigator must notify the Ethics Committee(s) and the study sponsor immediately. The study sponsor will then notify all other sites and investigators conducting trials with the same medication and will contact the various regulatory bodies (eg. TGA, FDA). If the trial is not sponsored, the investigator must assume this notification responsibility.

The protocol/procedures manual should provide specific details of the procedure to be adopted in reporting adverse events, including a specification of the individual responsible for reporting and managing these problems. However, the Principal Investigator has ultimate responsibility.

Special restrictions imposed

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 documentation has been provided to each committee.

Documentation

An approval letter containing caveats must be copied to all study staff and wherever possible, the protocol immediately modified to reflect the required changes. The modified protocol must be given a new version number (with a date) and circulated to all study staff. For multicentre trials where it is not possible to modify the protocol, all study staff must be made aware of site specific caveats.

Business Manager requirements

Copies of the following documents must be kept with the business manager:

- The Protocol
- Ethics Committee approval
- The grant application eg NHMRC
- Letter of agreements/contracts between the Department/Principal Investigator/grant bodies/sponsor
- Research Grants and Ethics Branch Fund Code request form
- Grant body / Ethics Committee annual reports
- Details of where the study has been archived, if applicable.

Duration of approvals

Ethics Committee approvals may be provided for a defined time (eg, at the Alfred Hospital for 2 years). Care must be taken to request extensions when appropriate. This usually requires only a letter or completion of a form (often available at Ethics Committee web sites).

Progress reports

Ethics Committees always require periodic progress reports of studies they have approved. Copies of these reports must be kept in the Study Document File.

Participant Information forms

Ethics Committees require that participants be given a Participant Information form as well as a consent form. These forms must be identified by a version number and date and updated if significant new information becomes available, the update approved by the Ethics Committee, the most recent version only should be provided to potential volunteers.

Storage of consent forms

Signed consent forms from every participant must be stored securely and be available for examination in case of an audit. They must be stored kept separately from the case report forms.

Advertising for participants

Advertising for participants to take part in studies must be undertaken with great caution. Use of public advertisements in recruitment must be approved by the Head of the Unit and by the Ethics Committee. Additional approval (eg at a more senior university level) may be required in some circumstances.

Special circumstances

When individuals with long term mental disability (eg those with dementia, psychiatric conditions or brain injury) are involved in research, permission must be sought from the Guardianship Board on an individual basis for each participant. Details of the Guardianship and Administration Act 1986 are available at: http://www.dms.dpc.vic.gov.au/sb/2002_Act/A01109.html. 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.

Payments

Payments to participants in research studies are sometimes made to cover costs incurred by the participants. Review carefully to ensure they do not contribute to an individual participating against better judgement. Appropriate compensation for expenses however is essential. Proposals for payments should be disclosed to the Ethics Committee(s) in all circumstances.

Medical problems identified

During the course of a typical study, it is not unusual to identify a medical condition or adverse event that should be reported (with the patient's consent) to the patient's treating doctor(s). It is essential that the procedure

manual describe in detail who is responsible for such notification and how this will be handled. Any such activity should be recorded in the study coordinator's log. Such notification must be provided verbally and in writing, and appropriate copies kept in the Study Document File. In general, when reporting various outcomes (eg. adverse events, blood results) to the patients' treating doctors, you require written consent from the patient. Some ethics committees have special form for this process.

Therapeutic agents

When clinical trials of therapeutic agents are undertaken, preparation of medication for patients must ALWAYS be done by a Pharmacy Department. Bulk medication must always be stored in the Pharmacy Department, never in the Study Department.

1.15 The study report

Completed studies shall 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.

The final report shall include, at a minimum:

- Descriptive title
- The names, titles, degrees, addresses and affiliations of the principal investigators and all co-investigators
- Names and addresses of sponsors
- Dates on which the study was initiated and completed
- An abstract
- Introduction with background, purpose and specific aims of the study
- A description of the research methods including:
  -the selection of the study subjects and controls
  -the data collection methods used
  -the transformations, calculations or operations of the data, and
  -statistical methods used in the analysis.
- Description of circumstances that may have affected data quality or integrity
- A summary and analysis of the data
- A statement of the conclusions drawn from the analysis of the data
- A discussion of implications of study results including prior research in support of and in contrast to present findings, possible biases and limitations
- References

Government agencies and sponsors shall 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.

2.1 Introduction

Experience elsewhere has demonstrated that a serious misadventure in research activity could have repercussions resulting in disrepute to the entire research program and possibly compromise research activities elsewhere on the campus.

Although such episodes have generally resulted from aberrant behaviour by individuals, responsibility for establishing a culture and environment that reduces the likelihood of such an event rests with management of a research department or institution.

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

- A large number of research projects with responsibility dispersed amongst several senior investigators. There is no single individual or committee with oversight responsibility for standards across our research program
- A heavy reliance on relatively junior staff and PhD students to supervise research assistants and research nurses 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 assistants working apart from direct supervision.

Because of these concerns the Department has established a Risk Management Plan with the following components:

- Development of Good Research Practice Guidelines that are distributed to all staff and set a standard for research activities conducted within the department
- Development of an annual Good Research Practice Course which must be attended by all new staff involved in research activities
- Appointment of a part-time research auditor responsible for a rolling review of all research projects to ensure compliance with the Good Research Guidelines
- Establishment of a research Risk Management plan that attempts to foresee our major areas of risk and ensure that barriers are in place to reduce the likelihood of occurrence.

2.2 Purpose of the Research Risk Management Plan

The purpose of the Research Risk Management plan is to attempt to identify the most significant risks that we face in the conduct of our research program. The program also brings a focus on the approaches taken by department management and staff to reduce the likelihood of these risks eventuating. The document will be constantly updated as new risks are identified and new strategies are devised to counter them.

2.3 Fraud in collection of data

Description of risk

- Research personnel responsible for interviewing patients in their homes invents data rather than meeting the rigors required by the protocol
- Research personnel 'adjusts' subject characteristics to make them meet eligibility criteria for a study
- Research personnel alters data to make the results more likely to fit his/her preconceived idea as to what results should show.

Likely circumstances

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

Likelihood of occurrence

Moderate risk in appropriate circumstances.

Likely consequences

- Negation of study data resulting in results being unreportable and unpublishable. If already published, article may require withdrawal with risk of severe embarrassment to researchers and department.
- Study may have to be repeated at cost to the department, delay in results becoming available may lead to breach of contract and liability to damages, especially if study is critical for the development of a drug or device.
- If NHMRC funding is involved, the fact would need to be reported to NHMRC with likelihood of severe criticism of level of supervision. Requirement to review previous data collected by the researcher may lead to high cost possibility of further adverse findings
- Ethics committees would have to be notified

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 or by contract monitoring companies 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 laboratories 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.

Barriers to occurrence within DEPM

DEPM must establish a strong culture that emphasises care and accuracy in data-collection.
This will involve -

- Ensuring that all new staff are adequately trained in research methods/ethics. Those without strong research background should be required to attend our courses in epidemiology and research methods.
- Requiring all new research staff to attend the good research practice short course.
- Requiring all research protocols with outside data collection to have adequate quality control procedures that would be likely to detect falsified data. All chief investigators should be required to have regular study meetings with their research team in which data-collection forms are reviewed and procedures involved in the collection and handling of data are reviewed and quality control measures are reviewed.
- Requiring that all new staff adequately briefed in the need for accuracy in data collection by the study directors and the research auditor.
- Ensuring that SOP's are in place for most key data collection procedures including quality control procedures.

2.4 Serious Errors in Analysis of Data

Description of risk

- Serious error made in analysis of a data set leading to the need to retract a published article or correct a 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.
- Researcher may fraudulently alter results to fit preconceived hypothesis or to increase the publishability of the results. After discovery this could mandate review of previously published work, require retractions and raise spectre of legal action as above. Colleagues involved in current and previous research could have their reputations tarnished.

Likely circumstances

- 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 that with small paper-based data-sets. Serious errors are more likely if analysis of large data-sets is unsupervised and conducted by relatively junior researchers
- Much epidemiological data requires sophisticated statistical analysis. Computer packages allow these procedures to be undertaken with relative ease by inexperienced people but this results in a high risk of inappropriate application.
- Fraud in data analysis is unlikely with large data sets because their size makes them resistant to manipulation. However an inadequate research culture and poor supervision would make it possible.

Likelihood of occurrence

- Moderate risk in appropriate circumstances, especially when full responsibility for data analysis is delegated to a relatively junior researcher or research student.

Likely consequences

- Negation of study data resulting in results being unreportable and unpublishable. If already published article may require withdrawal with risk of severe embarrassment to researchers and department.

Approach in other industries

- It is increasingly common in the pharmaceutical industry for all data to be independently analysed by two statisticians.

Barriers to occurrence with DEPM

- 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.

2.5 Loss of data due to inadequate back-up procedures

Description of risk

- 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.
- It is often a very prolonged and expensive process to reconstruct a database that is destroyed in a computer 'crash' or in the unlikely event of a fire or theft. For this reason systematic processes are needed with frequent checks that the procedures are being adhered to.

Likely circumstances

- 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.

- A substantial risk of data loss due to theft, malicious destruction or fire may occur if all copies of a database are kept in the one location or on the same computer.

Likelihood of occurrence

This is a highly probable occurrence unless highly specific precautions are taken.

Likely 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

Barriers to occurrence

Because of the high likelihood of this problem arising it is necessary to have highly detailed procedures in place to lessen the risk.

These include:

- development of detailed “SOP’s” related to data management which are incorporated into the good research practice guidelines;
- provision of training in data-management procedures via short course and postgraduate programs;
- review of data-management procedures as an essential component of reviews conducted by the research auditor.

There is a general recognition that this problem will not be adequately addressed until the department has the resources to develop a data-management unit that can provide advice and support for all parts of the department.

2.6 Serious breach of protocol or ethics committee requirements

Description of risk

- All research involving humans must be endorsed by an appropriate ethics committee. Ethics approvals are specific to the particular protocol (including plain language information leaflets and data-collection sheets. Entry of patients to a study whose personal characteristics do not meet those of the approved entry and exclusion criteria is a breach of the condition of ethics approval. It may also lead to a breach of contract with a study sponsor. If an individual who was ineligible for entry to a study experiences an adverse event they may have grounds for legal action that would not be covered by the institutions insurers.

- Ethics committees pay particular attention to circumstances of consent. They require all study participants to be provided with an approved ‘plain language’ information sheet and sign an approval form that signifies 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. Should an individual claim that they had not been adequately informed of the risks and benefits of participation this documentation provides an important line of defence for investigators. Entry of patients to a study without consent is an egregious error which could lead to severe sanctions and highly adverse publicity.

- Serious adverse events affecting any study participant, and considered reasonably likely to have resulted from study participation, must be notified urgently to study sponsors and the appropriate ethics committee. Failure to do this may lead to sanctions by either of these agencies.

Likely circumstances

- The areas of greatest risk are studies involving significant risk to participants such as drug trials and invasive studies.
- The risk is higher in investigator initiated research where there is no program of independent monitoring by a study sponsor.
- The risk is also likely to be higher in units with research programs where senior staff are too busy to provide adequate supervision of their research programs.
- Failure to meet ethics committee requirements is usually a result of a lack of knowledge of an ethics committee's role in the regulation and monitoring of an institutions research program.
- Thus it is more likely amongst those who have not undertaken formal research training.

Likelihood of occurrence

High risk

Likely consequences

If significant alterations are made without ethics committee approval the research may effectively be progressing without ethics approval. Under such circumstances the investigators may lose the protection of their institution and their insurers. They may lose the confidence of their local ethics committee and the management of their institution. Adverse events affecting an individual admitted to a research project without permission could lead to serious adverse publicity and serious legal liability as well as a loss of insurance cover

Barriers to occurrence

- Insistence on adequate training of all research staff (including participation in good research practice course)
- Research auditor has specific instructions to monitor compliance with ethics committee requirements and will check that:
  - consent forms are available for all studies
  - approved plain language sheet is provided to participants
  - all serious adverse events have been reported
  - all participants in studies meet approved entry and exclusion criteria.

2.7 Serious breach of confidentiality

Description of risk

- Clinical and public health researchers commonly collect information of considerable sensitivity which is divulged only because of guarantees of confidentiality provided by the researchers. In other instances ethics committees may approve the use of health-related data without the consent of individuals when the public benefit is considered to substantially outweigh the concerns regarding privacy.
- Ethics committees approve the collection of personal health-related data for research purposes only if they are assured that the data will be maintained under strict conditions that protect the confidentiality of the subject participants.

- Privacy requirements to be observed by researchers have recently become more explicit with the adoption of new legislation that must be observed by all those involved in the collection of personal data. Breaches of these requirements may result in criminal penalties.

- Components of the procedures required for privacy protection include:
  - restriction of access to personal data to a small number of individuals with a need for access
  - training of researchers at all levels in the issues related to data confidentiality
  - provision of secure storage of confidential data which includes restricted access to areas where such data is stored, separation of identifying data from the other data elements, secure password access to data in computers and development of a specific protocol for destruction of identifying data when no further need exists to retain this information.
  - requirement of all staff involved in data collection or processing to sign a confidentiality declaration at yearly intervals

Likely circumstances

- Breaches of privacy are most likely in cases where there has been little attempt to create a culture of confidentiality and reinforce it.
- Privacy breaches are also more likely where new researchers who have not been adequately educated about the rationale for confidential data handling are given responsibilities in this area.
- A specific instance of risk is where a research staff member handles data from an individual known to the researcher and is tempted to mention this outside the department

Likelihood of occurrence

Moderate risk

Likely consequences

- A serious breach of confidentiality could result in serious adverse publicity that could significantly lessen the likelihood of future participants providing confidential information.
- It would probably reduce the likelihood of gaining ethics approval for future projects requiring collection of personal data.
- It might lead to legal action from the individuals whose privacy had been breached

Barriers to occurrence

- Requirement for all DEPM staff to sign privacy declarations annually.
- Requirement for all new DEPM staff to attend good research practice course.
- Requirement for privacy to be emphasised to new staff by unit head and research auditor.
- Data storage for all studies to be reviewed periodically by research auditor.
- Obligation on senior management to create a culture of confidentiality.

2.8 Failure to identify and follow-up abnormal pathology results

Description of risk

Many DEPM 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.

Likely circumstances

The primary risk setting is where screening tests are being done on large numbers of individuals either as part of eligibility screening for a research study or as part of an epidemiological study.

Likelihood of occurrence

High unless anticipated and a highly organised approach is developed to assess and handle abnormal results.

Likely consequences

Failure include efficient procedures to pass on important clinical information. may mean that a potentially curable illness is not detected. This could lead to legal action for negligence.

Barriers to occurrence

All studies involving physiological measurement or laboratory testing must include specific procedures to review all abnormal results. These procedures must be documented in the protocol and procedure manual and adherence monitored by the research auditor.

2.9 Failure of emergency procedures leading to death or injury

Description of risk

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 sufficiently high as to mandate the availability of urgent medical assessment and/or emergency care. If such emergency care was not immediately available and, as a result a study participant died or developed serious complications serious repercussions would follow for both the investigator and the department.

Likely circumstances

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.

Likelihood of occurrence

Low to moderate

Likely consequences
Injury to participant, legal action against researcher, adverse publicity

Barriers to occurrence
- Detailed SOP's
- Research auditor review of procedures

2.10 Attack on a Research Nurse or Research Assistant

Description of risk
Several epidemiological studies involve visits to participants homes to conduct interviews or to collect samples. Often these visits are conducted by research nurses after hours. Under these circumstances there is a risk to the safety of the research staff.

Likely circumstances
After hours visits by lone research nurse

Likelihood of occurrence
Moderate

Likely consequences
Injury to staff member with the senior DEPM management accountable for lack of appropriate preventive action.

Barriers to occurrence
- Research staff will contact participants by phone in advance of visit to assess acceptability of visit
- If any concerns visits will be undertaken with companion and during daylight hours.
- The department will provide all research staff undertaking such visits with mobile phones and personal alerts. They will call a designated individual before and after the visit.
- Adherence to this protocol will checked by the research auditor

Updates & Useful Resources

Updates

This document is subject to regular updating. This version was last updated on 11/3/03. The latest version is available on the department web site at http://www.med.monash.edu.au/epidemiology

Useful Resources

Medical Research Council "Guidelines for Good Clinical Practice in Clinical Trials 1998."
www.mrc.ac.uk/pdf-ctg.pdf

National Statement on Ethical Conduct in Research Involving Humans
www.health.gov.au/nhmrc/publications/pdf/e35.pdf

ICH/GCP Guidelines, an international ethical and scientific quality standard
www.health.gov.au/tga/docs/html/ich13595.htm

Alfred Hospital Research & Ethics Unit (Ethics Committee)
http://www.alfredresearch.org/
telephone: -79 3848 (9276 3949 for external calls)

Monash University Standing Committee on Ethics in Research Involving Humans (SCERH)
www.monash.edu.au/resgrant/human-ethics/

Guardianship and Administration Act 1986 (Act No.40/1999)
www.dms.dpc.vic.gov.au/12d/G/ACT01488/

National Centre for Classification in Health
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INDEX