

The Alfred Medical Research and Education Precinct Guidelines to Good Clinical Research Practice

These guidelines are based on the Monash University Department of Epidemiology and Preventive Medicine Guidelines to Good Clinical Research Practice, 2nd edition, 2003.

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1. Introduction

- The purpose of these guidelines is to ensure that medical research undertaken within the Alfred Medical Research and Education Precinct (AMREP) is conducted to the highest scientific and ethical standards.
- 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 or department head.
- 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, department and the institution.
- A Research Governance Officer has been appointed to oversee clinical research performed within AMREP and to assist investigators in all aspects of good clinical research practice. This initiative, in conjunction with these Guidelines on Good Clinical Research Practice, the Risk Management Plan for Research and the short courses in clinical research offered by the Monash University Department of Epidemiology and Preventive Medicine form the basis of research quality assurance within AMREP.
- These guidelines are provided for quick reference. It is highly recommended that investigators enrol in programs and courses on good clinical research practice.

2. Principles of Good Clinical Research Practice

The following principles have been adapted largely from the:

ICH 'Good Clinical Practice Guideline E6(R1)' available at

<http://www.ich.org/LOB/media/MEDIA482.pdf>

UK Medical Research Council 'Guidelines for Good Clinical Practice in Clinical Trials (1998)' available at

<http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002416>

- 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 considerations, 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 approved by The Alfred Human Research Ethics Committee.
- Individuals conducting research studies should have an appropriate level of education, training and experience to perform their 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.

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- 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.

3. Research Ethics

- All research should be conducted strictly according to: the National Statement on Ethical Conduct in Human Research (2007) (<http://www.nhmrc.gov.au/publications/synopses/e72syn.htm>) and the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (<http://www.ich.org/LOB/media/MEDIA482.pdf>)
- Researchers within AMREP must comply with the requirements of The Alfred Human Research Ethics Committee. Ethics approval must be granted before research can proceed. Details of the ethics approval process are available at <http://www.alfredresearch.org/ethics.htm>.

3.1 The Alfred Human Research Ethics Committee (Ethics Committee)

Application forms and guidelines can be downloaded from The Alfred Research and Ethics Unit website at <http://www.alfredresearch.org/ethics.htm>

Further details may be obtained from Ms Rowan Frew, Ethics Manager and Secretary of the Ethics Committee (telephone: 9076 3848; e-mail: r.frew@alfred.org.au) or Dr Angela Henjak, Ethics Officer (telephone: 9076 8825; e-mail: a.henjak@alfred.org.au).

All research undertaken must comply with Ethics Committee requirements. In particular,

- Projects must not commence until approval has been obtained in writing
- The authorised study protocol must be followed in all cases
- If resources (eg. pathology services) are required from within The Alfred hospital, complete a Resource Centre Declaration Form (available from <http://www.alfredresearch.org/ethics/applicat.htm>) and obtain the signature of the resource centre manager
- All protocol amendments must be approved by the Ethics Committee
- Projects must not run longer than the authorised approval period, unless permission for an extension to the approval period has been obtained in writing.
- Adverse events must be reported to the Ethics Committee (see <http://www.alfredresearch.org/ethics/adverse.htm>)

3.2 Projects involving Alfred patients and staff with Monash/Alfred appointments

Researchers who have joint Alfred/Monash appointments need to apply to both The Alfred Human Research Ethics Committee and the Monash University Standing Committee on Ethics in Research Involving Humans (SCERH) for approval to conduct their research when Alfred patients, staff or resources are involved. These researchers should make contact with both committees beforehand to determine the procedures involved.

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, not even relatively minor ones such as pilot studies, should be undertaken except in accordance with a Protocol that has been approved by the 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 also 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**

(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**

(A description of the 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.

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.

The Procedure Manual (or Investigator Site File) should contain the following information:

- **Final Protocol**

(The study Protocol as approved by the Ethics Committee (see Section 4))

- **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**

The details of all members of the study team, including their roles, responsibilities and reporting arrangements, should be provided. Members of various study committees, together with their contact details, should also be provided. 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 etc.))

- **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 should be included.

- **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 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 seek clarification of local requirements from the Ethics Committee (see <http://www.alfredresearch.org/ethics/adverse.htm>).

- **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 10.

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.

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

- **Maintaining records**

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

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- **Information required**

- The Participant Information and Consent Form should be prepared in accordance with the requirements of the Ethics Committee (a 'Clinical Studies' template and a 'Non-Clinical Studies' template are available at <http://www.alfredresearch.org/ethics/applicat.htm>).

- **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 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 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 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 experience and adequate training in order to obtain fully informed consent. It is the responsibility of the Principal Investigator 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 Ethics Committee 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 are familiar with the revised legislation

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.

7.1 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.

7.2 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 stored indefinitely following completion of a study. Full details of Ethics Committee requirements are available at <http://www.alfredresearch.org/ethics/archiving.htm>.

7.3 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)
- Screening failure log
- 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
- Study archive record
- Form FDA 1572 (if applicable)

8. Data Confidentiality

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

8.1 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.

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

8.2 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 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 the consent of the individual.
- Information should be used or disclosed only 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.

Any study requiring access to data held in a Commonwealth institution is covered by Section 95 of the Commonwealth Privacy Act (1988). 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 (see <http://www.alfredresearch.org/ethics/privacy.htm>).

8.3 Privacy guidelines

To satisfy privacy guidelines and to ensure that the participants' 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 Report 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 who 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.

8.4 Access to medical records

Access to the medical records of patients of The Alfred requires evidence of ethics approval. Forms are provided on the Alfred Ethics website, (see <http://www.alfredresearch.org/ethics/patient.htm>). If individuals outside The Alfred hospital wish to access information in medical records they will need to approach the Secretary of the Ethics Committee in the first instance.

8.5 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.

9. Data Collection

Most clinical 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. 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 integration of the data, both 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 form 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-9 is available in the library and may be borrowed for short term use. It is available from the National Centre for Classification in Health.
- **For occupation coding:** ASCO (Australian Standard Classification of Occupations) is available from the Australian Bureau of Statistics (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.
- **For country and language codes:** Standard ABS codes are also available.

- **Separate personal identifiers**

Personal identifying information should be collected on a separate, removable page so that it can be detached and stored separately from 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, i.e. they cover all possible responses
- the options are mutually exclusive, i.e. 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, i.e. 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 attention 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.

10. Database Management

10.1 Software packages

The principal software used for databases within AMREP are Microsoft Excel and Microsoft Access. This software is well supported in all of the AMREP institutions, is easy to learn, has good security and data checking features and is highly recommended for most studies. Staff should undertake training courses in Excel and Access, where appropriate.

10.2 Database documentation

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

- copies of the questionnaires and/or other data collection instruments

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- 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 mmol/L	Laboratory tested cholesterol result	>0 and <20	Number

10.3 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 into 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.

10.4 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 dataset 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.

10.4 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.

10.5 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. Those undertaking data input should not need to interpret responses, i.e. 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.

10.6 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 database. These are more difficult to check, and require special procedures for checking, mainly through the use of range and consistency checks (see below).

10.7 Range and consistency checks

Following data entry, and before finalisation of a dataset, 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.

10.8 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). You should speak to your IT manager to find out the best way of backing up your data on the appropriate computer network. Regular backup on to zip discs held outside the department is highly recommended. This precaution guards against the unlikely events of fire or theft.

10.9 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 CDs and distributed to senior investigators. Each CD should include a file containing any randomisation key.

10.10 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 Principal Investigator 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 Principal Investigator that the head of biostatistics (or equivalent) has sufficient confidence in the researcher undertaking the analysis to warrant that the requirements for checking are not necessary. All key research data should be analysed by two independent persons, with a statistician involved.
- All students undertaking a postgraduate degree should have key results checked by a statistician.

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.

11.1 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 Co-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 communication exist between all study investigators;
- organise a study initiation meeting where all parties involved in study attend (eg. Pharmacy, Pathology etc).
- 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;
- ensure that the results are analysed, written up, reported and disseminated appropriately.

11.2 Study co-investigators

Each co-investigator has the responsibility for the conduct of the study within his/her participating centre and/or area of expertise.

11.3 Study coordinator

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

11.4 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.. The budgetary position of the study must be monitored at least monthly. It is the responsibility of the Principal Investigator to ensure that sufficient funds are available to cover all costs associated with conducting and completing the research study.

11.5 Regular meetings

The Principal Investigator and Study Coordinator 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 parties involved.

11.6 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 (for non commercial studies).
- Minutes of meetings should be written and circulated as soon as possible after the meeting and stored in the Study Document File (see section 7).
- Job descriptions based on a generic proforma are to 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 Study 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 meetings.
- 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.
- The Ethics Committee will be notified of all Protocol and questionnaire changes immediately, and approval sought before implementation (see <http://www.alfredresearch.org/ethics/amend.htm>).

11.7 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 not acceptable for staff to 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, it is recommended that staff have secure measures in place at home. These should include a lockable room and cabinet similar to those in the work place, a password protected computer and means to de-identify computer files.

11.8 Interviewer safety

When undertaking interviews in a participant's home, interviewers should notify their department / institution of the time and location of all interviews. For personal safety, calls should be made to the department 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 personal alarm should also be carried. Wherever doubts occur about the advisability of interviews, a second individual should accompany the interviewer.

11.9 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 graphical format.

11.10 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.

11.11 Randomisation

Randomisation or blinding codes must be kept by an individual who is 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 dataset has been produced. Any emergency unblinding must have the approval of the Principal Investigator.

11.12 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. All e-mails, faxes and correspondence will be kept in the Study Document File.

11.13 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.

11.13 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.

11.14 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 on Good Clinical Research Practice and the applicable regulatory requirements.

11.15 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 used later to verify the medication provided.

11.16 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 research practice and the applicable regulatory requirements.

11.17 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 research practice and the applicable regulatory requirements.

12. 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 and funding bodies
- consult the Secretary of the Ethics Committee regarding interim storage of documents until permanent archiving is required
- once permanent storage of documents is required, contact the Secretary of the Ethics Committee for labels etc.
- consult The Alfred’s archiving policy at <http://www.alfredresearch.org/ethics/archiving.htm>

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

12.1 Storage of study documentation

The following is a list of documentation that should be stored for each study and archived indefinitely 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
- 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, abstracts and publications
- Clinical research folders

13. Specific requirements for Good Research Practice

13.1 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.

13.2 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 (see <http://www.alfredresearch.org/ethics/amend.htm>).

If you are uncertain about whether a change requires ethics approval, seek the opinion of the Secretary of the Ethics Committee 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 necessitate changes to the Participant Information Form, creating the need for a new version and date.

13.3 Adverse events

All serious adverse events occurring to participants in a clinical study must be reported regardless of whether these are considered to be 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 and the study sponsor immediately (see <http://www.alfredresearch.org/ethics/adverse.htm>). 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 responsibility for this notification.

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 events. However, the Principal Investigator has ultimate responsibility.

13.4 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.

13.5 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.

13.6 Duration of approvals

Approvals granted by The Alfred Human Research Ethics Committee are for two years. Extensions may be sought prior to the approval expiry date (see <http://www.alfredresearch.org/ethics/extension.htm>).

13.7 Progress reports

The Ethics Committee requires annual progress reports of studies it has approved. A final report is also required. Copies of these reports must be kept in the Study Document File (see <http://www.alfredresearch.org/ethics/extension.htm>).

13.8 Participant Information Forms

The Ethics Committee requires 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 updated version should be approved by the Ethics Committee and the most recent version only should be provided to potential volunteers.

13.9 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 separately from the Case Report Forms.

13.10 Advertising for participants

Advertising for participants to take part in studies must be undertaken with great caution. Use of public advertisements for recruitment must be approved by the Head of Department and by the Ethics Committee. Additional approval may be required in some circumstances.

13.11 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. 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.

13.12 Payments

Payments to participants in research studies are sometimes made to cover costs incurred by the participants. Review carefully to ensure that 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 in all circumstances.

13.13 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 for the Procedure Manual to 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 a patient's treating doctor(s), written consent from the patient is required. Some ethics committees have a special form for this process.

13.14 Therapeutic agents

When clinical trials of therapeutic agents are undertaken, it is expected that storage and preparation of medication for patients will be done by a Pharmacy Department. There may be exceptions but these must be agreed upon by the Ethics Committee, Pharmacy, study sponsor and study investigator. To request The Alfred Pharmacy Department to dispense medication, see <http://www.alfredresearch.org/ethics/pharmacy.htm>

13.15 Complaints

Complaints by patients about the conduct of an approved research project may be directed to the Patient Representative or the Secretary of the Ethics Committee. It is important to quote either the project number or project title when registering a complaint or enquiry. The Alfred Ethics Committee policy on the management of incidents / complaints related to research activities is available at <http://www.alfredresearch.org/ethics/complain.htm>.

14. 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 (see <http://www.alfredresearch.org/ethics/monitor.htm>)

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.

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