I.

RESEARCH ETHICS BASICS.

1. Introduction

Many human rights abuses have occurred in the name of research in the twentieth century. Some examples are the experiments conducted by the Nazis in the concentration camps during World War II, the Tuskegee and Guatemalan Syphilis experiments, Radiation experiments conducted on soldiers in the USA, Willowbrook and many others. The World Medical Association published the Declaration of Helsinki in 1964 in response to these abuses. This document has been updated several times, (the most recent in 2008) and is regarded internationally as the fundamental statement of the ethical principles of research. Every researcher should have read and be familiar with its contents. The Declaration of Helsinki can be found at www.wma.net/e/policy/b3.html

In 1976 The National Commission for the Protection of Human Subjects was signed into Law in the USA. The purpose of the Commission was to investigate the exploitation of Human Research Subjects. On April 18, 1979 the Belmont Report was published which identified 3 principles for ethical research:-

Respect for Persons - by recognizing autonomy and upholding rules of informed consent, respecting privacy and confidentiality.
Beneficence - the obligation to protect from harm and to do good
Justice - ensure that the benefits and burdens of research are fairly distributed i.e. that vulnerable developing world populations are not targeted for high risk research from which they may never benefit.

The Belmont Report can be found at http://ohsr.od.nih.gov/guidelines/belmont.html

The following local and international guidelines should also be consulted and complied with:

2. What Research must be submitted to a Research Ethics Committee for approval?

The National Health Act No 61.2003 (NHA) requires that all “health research” is reviewed and approved by an ethics committee. (See Section 73 Health Research Ethics Committees) The definition of health research in the NHA is very broad:

‘health research’ includes any research which contributes to knowledge of-
(a) the biological, clinical, psychological or social processes in human beings;
(b) improved methods for the provision of health services;
(c) human pathology;
(d) the causes of disease;
(e) the effects of the environment on the human body;
(f) the development or new application of pharmaceuticals, medicines and related substances; and
(g) the development of new applications of health technology;

All health research involving humans (alive or dead), human biological specimens or animals should be submitted to a Research Ethics Committee for registration and approval. In addition laboratory based studies that do not involve human biological specimens, but include the use of anything that could reaasonbly be considered biohazardous, or studies involving radiation, also require ethics approval. If a researcher is unsure if a project requires ethics approval or not, it is advisable to contact the HREC office and seek advice.
Researchers conducting research that is for degree purposes should ensure that they also comply with requirements for ethics review and approval, as determined by the Postgraduate Committee for Education.

Currently there are two equivalent Health Research Ethics Committees (HREC1 and HREC2). These committees each review the full range of health related human research that is conducted under the auspices of Stellenbosch University. Researchers apply for ethics review and approval using one standardized HREC form. An electronic form will be phased in, in 2011. The HREC office administrative staff will allocate each project that is submitted to either HREC1 or HREC2, depending on the next available open meeting agenda. The HREC that approves the project will take responsibility for the ongoing monitoring and annual re-approval of the project.

“Research” is defined as “a systematic investigation, including research development testing and evaluation, designed to develop or contribute to generalisable knowledge. Any such investigation raises ethical issues. The issues themselves may be small, but because studies may involve subordination of at least the immediate interest of the individual participant to the objective of the advancement of knowledge, the studies must be submitted to ethical review.” (MRC Guidelines on Ethics for Medical Research: General Principles. 2.1.2)

“Human Subject Research”
A Human Subject means a living individual about whom an investigator (whether professional or student), conducting research, obtains:
1. Data through intervention or interaction with the individual or
2. Identifiable private information.

Intervention includes both physical procedures by which data is gathered and manipulation of the subject or his/her environment for research purposes. Interaction includes communication or interpersonal contact.

Private Information includes information that has been obtained for a specific purpose, but that the individual can reasonably expect will not be made public, (eg a medical record, X-Rays etc). Private Information is identifiable information or is information that can be linked to a specific individual for up to 20 years after his/her death. (Promotion of Access to Information Act. No.2. 2000)

The key words here are systematic investigation that will contribute to generalisable knowledge, i.e. all data collection that is for a presentation, a degree or a publication should get formal ethical clearance.

NB! It is essential to submit the research protocol and obtain the necessary ethical approval BEFORE a start is made on the research, not “after the fact”!

3. Retrospective Clinical Audits

Please note that all retrospective clinical audits that fall under the above definition of research must be submitted for ethics approval before the research starts.

A common prevailing misconception is that it is not necessary to get consent or ethics approval for all forms of retrospective research using clinical records, often referred to as an ‘audits’. This is a false misconception and does not comply with international ethical research practice and regulations AND with the National Health Act 61. 2003. However it may not be necessary to get individual patient consent to use non-identifiable private information in research. (This means that the research information is collected anonymously or using a study code only and that no identifying information, such as a hospital number and name, is recorded. (See below)

A researcher can request the ethics committee to grant a waiver of informed consent under the following conditions:

Without an informed consent waiver it will be impossible to do the research because of the difficulty in tracing individuals. The research to be done will produce valuable information that is likely to improve patient care in the future or will benefit the community.
The information will be collected in such a way as to protect patient confidentiality. This means that the data capture sheet or database will only contain a study code. Identifying information linked to the study code will be kept separately e.g. in a separate file or password protected database. Access to this information will be restricted to senior members of the research team.

NB! Section 7 Epidemiology Pages 35-37 in *Ethics for Health Research: Principles, Processes and Practice* addresses these issues in detail and with clarity. URL ref on page 11 allows an accessible file that can be printed as a paper copy.

II.
WRITING A RESEARCH PROTOCOL FOR ETHICS COMMITTEE SUBMISSION.

1. What are ethics committee members looking for when reviewing research protocols?

The following checklist is a useful indication of the ethical fundamentals that will be considered by the Health Research Ethics Committee (1 or 2), when reviewing research protocols. It should be kept in mind and frequently referred to, when planning writing up and submitting research projects.

BENCHMARKS OF ETHICAL RESEARCH - A 7-POINT CHECK LIST
(Ezekiel J Emmanuel et al. What makes research in developing countries ethical? The benchmarks of ethical research. *Journal of Infectious Disease* 2004:189 (1 March) 930-937)

1. Collaborative partnerships
   Have the necessary partnerships between communities, makers of health policy, health care providers etc been developed? Has permission been obtained from external stakeholders, if required?

2. Social and scientific value
   Is the research question relevant?
   Has the research been done previously?

3. Scientific validity
   Ethics committees have a clear mandate to only approve research that is scientifically valid.
   Is the design and methodology of the study sound and appropriate with respect to the research questions and study objectives?
   Has the statistical analysis plan been adequately considered and discussed?
   Is the sample size adequate?
   NB! Research that is scientifically flawed is not ethical, because it is a waste of time and resources, and may produce misleading results.

4. Fair Selection of study population
   Has the study population been fairly chosen?
   Have any groups been excluded that could benefit from the research because of non-scientific reasons, such as non-English or Afrikaans speakers?
   Is the study population vulnerable in any way?

5. Favourable risk-benefit ratio
   Have the risk and benefit been assessed as accurately as possible?
   Is the risk/benefit ratio favourable?
   Are risks minimized?
   Are benefits maximized?

6. Independent review
   Will the research be submitted for independent ethical review?

7. Informed Consent
   Has the community been involved in any way in the informed consent process?
   Has sufficient information been disclosed in a culturally and linguistically sensitive manner?
8. Respect for Participants and Study Communities
Do the participants know they can withdraw from the study at any time?
Have issues of confidentiality and privacy been adequately addressed in the information and consent document as well as in the protocol.

2. A Stepwise Approach to Writing a Research Protocol for Ethics Committee Submission

Step 1.
Topic, title and key personnel

Once the area of interest has been identified, it is necessary to identify person(s) who will act as supervisor(s) or mentor(s), co-investigators or sub-investigators, as well as other people who may be able to be of assistance or play a valuable role in the research endeavor for example, a statistician. Together, the research team should draw up a preliminary research plan and develop the title of the study. It is important that the title is as concise and specific as possible. (See also Step 3).

All the key people involved in the study must be identified and their respective roles clarified. e.g. Co-Investigators, Sub-investigators, study coordinator (if applicable) etc. A short 2 page CVs of all key study personal must be submitted or filed with the HREC administrative office. It is however not necessary to submit CVs of collaborators not involved in the day-to-day study activities. HREC reserves the right to request these documents.

Step 2.
Literature review.

Before proceeding further, the next crucial step is to do a thorough literature review around the proposed topic. The following are some of the broad questions that must be answered in the literature review.

- What other similar research projects or studies have been undertaken in this field? What were the results?
- How will the proposed study contribute to this field of knowledge?
- What makes this proposed research project different to ones that have preceded it?
- What is the scientific and clinical relevance of the proposed research?
- Is the research proposal of particular relevance to the community in which the researcher is working, or to the broader South African community?

As a final step in this preliminary process, ensure that a consistent and recognized reference system is developed. The most commonly used reference system in medical journals is the Vancouver System. By consulting a journal such as the SAMJ, it is useful to see exactly how this system is structured.

Step 3.
Define the problem and develop a research question or hypothesis.

Some of the research projects submitted to the HREC give one the impression that the researcher does not appear to have a clear idea of what he/she wants to find out or prove. This is particularly true of studies that involve retrospective reviews of clinical records.

It is thus important to define the research question or hypothesis as clearly and as specifically as possible. If the initial idea is vague, then the result may be similarly “vague”, lacking in substance and useful implication, and/or difficult to interpret in a meaningful way. The following are examples of vague, as opposed to specific research questions. (From Katzenellenbogen, Joubert, 1997 OUP. Epidemiology: A manual for South Africa. Pg 58)

Example 1.
To study the problem of measles in SA

OR

1 This policy is likely to change in 2011. Researchers who submit protocols regularly to the HREC or who are involved with more than one study will have the opportunity to file a CV with the HREC administration office. This CV will be valid for a period of 3 years.

Example 2.
To investigate alcohol consumption as a contributor to adult death, OR
To determine the proportion of adult deaths that are due to alcohol related conditions.

Example 3.
To study the health profile of children in Mitchell’s Plain, OR
To study the nutritional status of children under 5 years old, in Mitchell’s Plain.

Step 4.
Consult a statistician and develop a written statistical analysis plan.

This is a most important and valuable step that many new researchers leave out, or address only at the end of their research. By consulting a statistician at this early point of hypothesis development you will get valuable input into methodological issues such as experimental design, study population, sample size, questionnaire techniques, etc. The Centre for Statistical Consultation offers consultations to researchers, at the Tygerberg Campus. Contact them at 021 938 9181 on Mondays and Wednesdays or email Prof Kidd at mkidd@sun.ac.za.

It is important that you include at least one paragraph, usually after your methodology, on how you plan to analyse your results from a statistical perspective. This compels you to think ahead and consider whether or not the data you plan to capture will actually address your research questions. The HREC regards this aspect as an essential component of any research project and the committee may elect to return the protocol to the researcher without approval, if this element is missing or inadequate. (See step 8)

Step 5.
Aims and Objectives and Rationale
These components are similar to the research question, but should be formulated in more detail; preferably in point form. Each objective should ‘stand alone’, but also be connected to the others in some way. It may be appropriate to list “Primary Objectives” and “Secondary objectives”. The objectives will ultimately determine the planning and methodological design of the study. For example, if your study involves a questionnaire, it is important to structure your questionnaire to ensure that each of your objectives can be met.

Step 6.
Definition of Terms (Optional)
It may be appropriate to include a list of definitions before describing the methodology. This will depend on the particular research project and field and may not always be necessary. This can also be included under the methodology heading.

If many abbreviations will be used, then it is also advisable to include a list of abbreviations, or a Glossary.

Step 7.
Methodology
The methodology is a step-by-step detailed description of what is going to be done in order to obtain data that will be analyzable and permit conclusions to be reached, or research questions answered. Ensure that the chosen methodology will adequately address each of the listed objectives.

The following are some of the points should be included in the methodology:
A description of the study design eg: This is a retrospective descriptive study; a prospective analytical case controlled study; a randomized controlled clinical trial, etc.
Study population. Define the study population or study base as precisely as possible.
Sample size and sampling methods. These should be explained and justified.
Inclusion criteria. Characteristics of participants that will make them eligible for inclusion and why.
Exclusion criteria. Characteristics of participants that will make them ineligible for inclusion and why.
A detailed and precise description of all study procedures, including the informed consent process, if applicable.

Pilot study description, if applicable.

Step 8.
Data management and statistical analysis.
(See step 4 above) Describe briefly how data will be recorded and processed. Also describe what statistical methods will be used.

Step 9.
Time plan and study logistics
Study Flow Chart (optional, but often very helpful to include a graphical description of the study on one page)
A time chart for all steps of the process could be included here, from writing the protocol, to preparing an article for submission for publication.
It may also be useful to describe the responsibilities of different members of the research team, if applicable.

Step 10.
Ethical aspects
Discuss all ethical issues that are considered relevant to the study and describe how these will be addressed. In particular indicate how participant privacy and confidentiality will be protected.
If a Waiver of Informed Consent is being applied for, then a clear motivation should be provided at this point.
The Informed Consent form must contain a statement to the effect that “this research study has been approved by a Health Research Ethics Committee at the University of Stellenbosch and will be done according to internationally accepted ethical standards and guidelines”.

Step 11.
Resources
Describe the resources that are available and also address resource limitations, if any.
Declare the source of funding for the project.
Outline a realistic budget. (See an example of a budget on page 18).

Step 12.
Strengths and Limitations
Many research projects do have unavoidable limitations due to factors that are partly, but not entirely, beyond control due to, budgetary, logistical or time constraints that affect the methodology, sample selection, etc. It is helpful for both researcher and the reviewer if the limitations have been clearly outlined and that any steps that could be taken to decrease the impact of the problems that have been identified, have been taken.

Step 13.
Reporting of Results.
Describe how the results will be reported or published and how they could be translated into action. Be sure to include a description of how feedback will be given to all relevant stakeholders, including participants and the community, if appropriate or feasible. Unpublished or unreported research can be considered a waste of time and effort and, as such, unethical.

Step 14.
References
These may also be included directly after the literature review if deemed appropriate.

Step 15.
Appendices
All additional documentation that will be used in the research study must be included in the protocol as a list of Appendices. Some examples are:-
III.
SUBMITTING A NEW RESEARCH PROTOCOL FOR ETHICS REVIEW AND APPROVAL

HREC 1 and 2 each meet once a month to review new and ongoing research. HREC 1 meets on the 1st Wednesday of the month and HREC2 meets on the 3rd Wednesday of the month. The dates for each meeting are circulated to all departments at the beginning of each academic year, and may be obtained from 021 938 9207. The dates are also posted on the HREC website. The agenda usually closes 2/3 weeks prior to the meeting date. Projects will be allocated to the next available meeting, as they are received. Two paper copies of all documentation must be submitted.

An expedited (Fast Track) review process is available for minimal risk protocols, particularly for degree purposes. However, the demand for this service currently far exceeds the available administrative and review capacity. Researchers other than students wishing to have their protocols “fast tracked” should provide some form of written motivation and, in addition to the hard copies, the protocol MUST be submitted on a CD as well. Please refer to the HREC Standard Operating Procedures on the web site for further information. Interventional studies are always reviewed by the full committee.

The application should include the following:

1. An application form
Application forms and all other documentation are available electronically, either from the Division for Research Development and Support website or from 021 938 9207. Make sure that the application form is completed accurately and in typescript. In particular PLEASE make sure that the supervisor and Head of Department sign the form.

2. The Checklist
This could be regarded as a nuisance, but it does help to be sure that everything has been considered and included. Complete either the General or Clinical Trial Checklist, whichever is applicable.

3. A Protocol Synopsis or Summary
Very Important! No application will be accepted without a protocol synopsis which must be a maximum of 2 typed pages, NOT more.

Not all committee members will get to see the entire protocol. Most committee members will only see the protocol synopsis and participant information leaflet and consent form. (ICF) Thus it is very important that a succinct protocol synopsis is submitted that clearly outlines the research rationale, objectives and methods.

The protocol synopsis should contain:
- Title
- A short introduction, motivation and literature overview (1 paragraph only)
- Research question or hypothesis
- Aims and Objectives
- A concise summary of the methodology

4. Study Protocol (See Section II)

2 The HREC administration office will be implementing and phasing in an electronic research ethics information system (InfoEd) in 2011/2012). It is anticipated that an E-application form will also be introduced during this time period. Initially researchers will need to complete the form online and then print it out to attach to their hardcopy application. In-time the ethics application process will be entirely web based.
5. A Participant Information and Consent form (ICF)
Wherever possible, researchers are encouraged to use the available templates and adapt one or more to the needs of the study. Templates are available for general use, research involving children, research involving colleagues or students, and for DNA studies. Sections that are not relevant to the research project can be ignored and deleted. Sometimes it may be more appropriate to provide information to participants in the form of a letter.

The ICF can be submitted in either English or Afrikaans. Once the requested changes (if any) have been made, then the HREC expects the researcher to submit translations in English/Afrikaans and Xhosa with a translation certificate or letter of authenticity, stating that the documents are an accurate translation of the original approved ICF.

NB! If it has been decided that Xhosa/Afrikaans/English consent documents are not necessary for the particular study, then the applicant is required to specifically justify this in the protocol under Ethical Considerations.

6. A Short CV of the Principal and Sub Investigators

This should not comprise more than 2 pages.

7. An Investigator and Supervisor Declaration

Investigators involved in the study must each sign an “investigator declaration” and declare any conflict of interest. If the study is for degree purposes a supervisor declaration should be signed by the study supervisor. Please read the form and complete it properly - don’t just sign it.

8. A budget (if not included in the protocol) and financial contract if applicable i.e. external funding.

IV. Submitting a new Clinical Trial for ethics review and approval.

The process is essentially the same as that described in Section III. As of the 1st April 2009 both HREC1 and HREC 2 review and approve clinical trials, including industry sponsored drug trials. The standard HREC application form should be submitted together with the CLINICAL TRIAL CHECKLIST, which is different from the checklist used for all other research projects. Additional documents are required for industry sponsored drug trials and may also be applicable to grant funded multi-site studies as well. Please see list below:

1. Covering letter (optional)
2. HREC application form
3. Clinical Trial checklist
4. Protocol synopsis/flow chart
5. A description of the study site, including the available infrastructure and the roles and responsibilities of study staff.
6. Clinical trial protocol
7. Site specific patient information leaflet and consent form
8. MCC approval or proof of application if applicable
9. Clinical trial financial agreement, with a clear indication of where funds are to be deposited, and budget. if applicable
10. Detailed budget
11. Proof of insurance if applicable
12. Letter of legal indemnity, extended to Stellenbosch University and Tygerberg / Stikland Hospital, if applicable
13. Material for distribution to patients, including diary cards, QOL questionnaires etc
14. Recruitment material and advertisements if to be used.
15. CV’s of investigators (List names)
16. Investigator declarations
17. Proof of GCP training
18. SA approved package insert(s) of registered comparators
19. Investigator’s brochure if applicable
20. Payment instruction form if applicable
V USEFUL INFORMATION.

1. Documents
All documents listed below are available on the updated Division for Research Development and Support Website (www.sun.ac.za/rds - application package) or from the Ethics Admin Office. (Tel 021 938 9207)

Standard operating procedure
Guidelines for new researchers
Application forms
Checklists
Investigator declaration
Supervisor Declaration
Informed consent templates for general use, studies involving children or where legal guardians must sign consent, DNA studies.
Adverse event report forms
Study progress report
Amendment application form and guideline

2. Example of a Budget
See page 16, OR contact 021 938 9156, for assistance with a budget spreadsheet.

3. Useful References and URLs

Codes and Guidelines

Books
Abramson. Survey methods in community medicine. 1999. TYG W 84,5 ABR

Other
US Dept Health and Human Services, Office for Human Research Protections. (OHRP) http://www.hhs.gov/ohrp/
## Budget

<table>
<thead>
<tr>
<th>Category</th>
<th>Period</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Personnel Compensation</strong></td>
<td></td>
</tr>
<tr>
<td>Principal investigator</td>
<td>R -</td>
</tr>
<tr>
<td>Project coordinator</td>
<td>R -</td>
</tr>
<tr>
<td>Research nurse</td>
<td>R -</td>
</tr>
<tr>
<td>Data typist</td>
<td>R -</td>
</tr>
<tr>
<td>Data typist</td>
<td>R -</td>
</tr>
<tr>
<td><strong>Participant Compensation</strong></td>
<td>R -</td>
</tr>
<tr>
<td><strong>Consulting services</strong></td>
<td></td>
</tr>
<tr>
<td>Training services</td>
<td>R -</td>
</tr>
<tr>
<td>Database programmer</td>
<td>R -</td>
</tr>
<tr>
<td>Statistical services</td>
<td>R -</td>
</tr>
<tr>
<td><strong>Travel</strong></td>
<td></td>
</tr>
<tr>
<td>Airfare</td>
<td>R -</td>
</tr>
<tr>
<td>Accommodation</td>
<td>R -</td>
</tr>
<tr>
<td>Meals &amp; incidentals</td>
<td>R -</td>
</tr>
<tr>
<td>Travel to clinics</td>
<td>R -</td>
</tr>
<tr>
<td><strong>Equipment &amp; furniture</strong></td>
<td></td>
</tr>
<tr>
<td>Computer &amp; printer</td>
<td>R -</td>
</tr>
<tr>
<td>Cell phone</td>
<td>R -</td>
</tr>
<tr>
<td>Office furniture</td>
<td>R -</td>
</tr>
<tr>
<td><strong>Other Direct Costs</strong></td>
<td></td>
</tr>
<tr>
<td>Item</td>
<td>R</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>---</td>
</tr>
<tr>
<td>Telephone, cell phone &amp; fax</td>
<td>R</td>
</tr>
<tr>
<td>Internet &amp; email</td>
<td>R</td>
</tr>
<tr>
<td>Office supplies</td>
<td>R</td>
</tr>
<tr>
<td>Courier &amp; postage</td>
<td>R</td>
</tr>
<tr>
<td>Printing &amp; copying</td>
<td>R</td>
</tr>
<tr>
<td>Ethics committee fee</td>
<td>R</td>
</tr>
<tr>
<td>Staff training</td>
<td>R</td>
</tr>
<tr>
<td><strong>Total direct costs</strong></td>
<td>R</td>
</tr>
<tr>
<td><strong>Indirect costs (12%)</strong></td>
<td>R</td>
</tr>
<tr>
<td><strong>Total Expenditures</strong></td>
<td>R</td>
</tr>
</tbody>
</table>