

SPECIAL PROGRAMME OF RESEARCH, DEVELOPMENT AND RESEARCH TRAINING IN HUMAN REPRODUCTION

GUIDELINES FOR GENDER CONSIDERATIONS

Definitions

Gender refers to the socially constructed characteristics of men and women, whereas *sex* refers to the biological differences between males and females. People are born male or female, but in every society men and women are assigned different roles, and these roles determine the power they have in their daily lives. Gender-sensitive research looks at the lives of men and women in a holistic way, and asks: how does the technology, intervention or behaviour “fit” in women’s or men’s lives? More specifically, what constraints need to be addressed for women or men to use the technology, seek the intervention, or change to health-promoting behaviour? For instance, it takes into account questions as to whether the woman or man has control of the necessary time, knowledge, and financial resources to use the technology or service, or change behaviour, and whether all women or men have the right to use the technology or service.

Gender considerations

In line with the UN system’s mandate to integrate a gender-perspective into its work, the Department of Reproductive Health and Research is committed to ensuring that no intervention or research contributes to gender inequality or aggravates existing gender inequality. Ideally, research and resulting interventions should contribute to the promotion of gender equality whenever possible.

The measures that will be taken to ensure that the proposed research is *gender-sensitive* should be addressed by answering the following four questions.

1. The topic of the research: Does the research address a demonstrated public health need and a need expressed by women and/or men? Women and men have different reproductive health needs which are both biologically determined and affected by gender roles. Reproductive ill-health affects women more than men, yet women are less likely to be in a position to have their voices heard concerning their own priorities in health needs. Building on the rationale for the study provided in section 3.1.1, section 4B should provide evidence that the proposed research addresses a demonstrated public health need, and whether, and if so how, the proposed research responds to women’s (or as appropriate men’s) expressed or felt needs in reproductive health.

(There are a number of ways that “felt needs” can be identified. Involving women’s or men’s health advocates in institutional priority-setting (a prior phase) and in designing the study can be especially helpful in making sure the research is relevant and sensitive to people’s experiences.)

2. The topic of the research: Reducing gender inequities in health and health care. The principle of gender equity means that the proposed technology or intervention should reduce disparities in health between men and women, and not exacerbate them. The principle of equity means those with the greatest need have the greatest claim on resources.

The proposal should describe how the proposed research will affect gender equity, and at least demonstrate that it will not increase inequities or inequalities between women and men. It should also discuss potential constraints affecting the use of adoption of the technology, intervention or behaviour.

3. *The process of research: Disseminating results and sharing knowledge.* In reproductive health research, where the subjects may often be women, particular plans may need to be developed for ensuring the results of the research reach those subjects and the wide community of women and men (see also Part 2, number 11). The proposal should present plans for sharing the information produced.

4. *The process of research: Composition of the research team.* Does the nature or topic of the research make it important that the researchers are women rather than men, or vice versa? Please explain. What is the sex composition of the research team and what are their duties and responsibilities in the proposed research.

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**GUIDELINES FOR RESEARCH ON
REPRODUCTIVE HEALTH INVOLVING ADOLESCENTS**

Definitions

Adolescents are individuals who are between childhood and adulthood, in the process of reaching sexual maturity. WHO defines the adolescent age range as the second decade of life, 10-19 years. However, it must be recognized that adolescence is a combination of physical, psychological and social changes which are culturally based. This is an important issue when consent and the involvement of parents (and guardians) is considered since the degree of autonomy of decision making is considerably varied across cultures and stages of adolescence.

Statement of the Problem

The justification for conducting research on reproductive health in adolescents is the same as that for any biomedical or behavioural research: only by carrying out well-designed studies can adequate information be gained that will enable delivery of appropriate preventive and therapeutic services to this population group. Therefore, research on reproductive health involving adolescents should be undertaken in order to enhance scientific knowledge specific to these individuals. The omission of such research can perpetuate inadequate understanding of the particular reproductive health needs of adolescents and result in failure to deliver adequate services to this group.

Legal and Ethical Issues

There are no clear ethical justifications for excluding from research adolescent subjects below the age of legal majority. If there are reproductive health problems that are restricted to, or occur also in, adolescents which cannot be solved with existing knowledge, there is an ethical duty of beneficence and justice to conduct appropriate research to address these problems.

Parents (or guardians) have legal and ethical responsibilities to provide dependent adolescents with preventive and therapeutic health care. Sound research equips parents to discharge such legal and ethical responsibilities. Parents have the best interest of their children at heart, and therefore should have no reason to deny dependent adolescents participation in sound research that could improve preventive and therapeutic care.

In general, the law does not grant parents veto power over decisions of mature (that is, competent) adolescents who decide to participate in research on their reproductive health. In such cases where adolescents are or are about to be sexually active, investigators commit no legal offence in undertaking research that promises a favourable benefit-risk ratio. However, where the law specifically denies decision-making authority to mature or competent adolescents below a given age, that provision must be respected.

Guidelines

1. Before undertaking research involving adolescents, investigators must ensure:
 - (a) that the information to be gained could not scientifically be obtained from adult subjects;
 - (b) that a goal of the research is to obtain knowledge relevant to the health needs of adolescents;
 - (c) that the risk presented by interventions having no direct benefit to the individual subject is low and commensurate with the importance of the knowledge to be gained; and
 - (d) that the interventions intended to provide direct benefit are at least as advantageous to the individual subject as any available alternative.

Among adolescents, younger subjects should not be enrolled when older adolescents are scientifically suitable for recruitment as research subjects. When the specific objective of the research is to gain information about young adolescents, for example, about pregnancy or lactation in 12-year-olds, then research involving this age group is ethically justified.

2. Unless specific legal provisions exist, consent to participate in research should be given by the adolescent alone. Capacity to consent is related to the nature and complexity of the research. If adolescents are mature enough to understand the purpose of the proposed study and the involvement requested, then they are mature enough to consent.

Rationale: Since the requirements for obtaining informed consent include the provision that subjects be capable of understanding the purpose, procedures, risks, benefits, and alternatives of the research, the participation of adolescents who satisfy this condition is ethically justified.

3. The ethical principle of confidentiality must be adhered to in research involving adolescents.
4. Even when consent to the participation of adolescents is granted by parents or by both adolescents and their parents, confidentiality must be maintained.

Rationale: Research on reproductive health, including contraception and abortion, involves sensitive issues about which adolescents have an interest in, and a right to, confidentiality being maintained. For example, some adolescents may be at risk of physical or psychological harm if others learn that they are sexually active. Moreover, without ensuring confidentiality, some important research could not be carried out since adolescents may refuse to participate if they are told that information they reveal might be disclosed to others.

5. Institutions participating in research involving adolescents must be sensitive to the needs of adolescents and should have the appropriate staff and facilities to care for this population group.
6. In circumstances where researchers believe they are obligated to report adolescent behaviour to any authorities, the adolescent subject must be made aware of the possibility of such reporting prior to their involvement in the research.

SPECIAL PROGRAMME OF RESEARCH, DEVELOPMENT AND RESEARCH TRAINING IN HUMAN REPRODUCTION

GUIDELINES ON REPRODUCTIVE HEALTH RESEARCH AND PARTNERS' AGREEMENT

Definitions

The term *partner* is used in these Guidelines rather than the term *spouse*, since the latter term does not accurately describe all situations in which these Guidelines may apply. Who is regarded as a partner will be determined by the laws, customs and practices of each community in which the research is being proposed.

The term *agreement* is used in these Guidelines rather than *consent* in order to distinguish between consent, which can be given only by the subjects who will be taking part in the research themselves, and agreement that can be given by a partner.

Basic Principles

It has become common in many settings to refer to partners' (or spouses') consent, but this is not appropriate. Only subjects can consent to their participation in research. Where subjects are not competent to consent, others may be permitted by law to authorize their recruitment into studies. Such authorization, even when legally required, does not constitute consent in ethical terms. Reproductive health research should not be undertaken on subjects who are not competent to consent to it unless there are no competent subjects who are scientifically eligible for study. For instance, studies on contraceptive compliance in mentally impaired women may be undertaken with the authorization of the legal guardian.

Ideally, partners will discuss research participation and reach agreement. However, one partner's agreement should not be made a condition of the other's recruitment to a study, unless the research will so immediately affect the partner as to make him or her comparable to a subject of the research.

A requirement of partner agreement or authorization for an individual to participate in research violates the autonomy of research subjects and their right to confidentiality. Therefore, as a matter of ethical principle, a requirement of partner agreement or authorization should not be permitted in studies supported by the Special Programme of Research, Development and Research Training in Human Reproduction.

Ethical principles embody an ideal to strive for, and a standard against which to measure current practices. However, because of existing cultural, religious, political or legal constraints, it is sometimes impossible to achieve the ethical ideal and exceptions to this general principle may have to be accepted, as indicated below.

Exceptions

- (a) **Social/Cultural Factors:** In rare circumstances, it may be necessary for researchers to conform to local custom and request partner agreement. An example would be the impossibility of recruiting any research subjects for a study in a particular country without partner agreement and the subsequent impossibility of gaining approval in that country for a new contraceptive drug or device. If failure to conduct the research would result in an

inability of people in that country to receive the benefits of the drug or device, this consequence might be judged as sufficiently negative for the common good of the public to outweigh the usual prohibition against partner agreement for the individual subject.

- (b) **Legal Requirements:** There may be a legal requirement to request partner agreement in some countries. However, researchers should take appropriate steps to find out if partner agreement or authorization is actually embodied in law and is not just an institutional requirement or merely customary. It is sometimes believed that a practice is mandated or prohibited by law when, in fact, it is a matter of customary institutional practice rather than law. Researchers can help to strive for ethical ideals of respect for the autonomy of the individual as a research subject by rejecting customary practices and challenging institutional requirements for partner agreement or authorization that violate the individual's autonomy.
- (c) **Partner Notification:** If there is any physical risk to the partner of the research subject, such as infertility or infection, and/or pregnancy in the case of the female partner, notification of the partner is justified. Depending on the circumstances of the research, notification may even be required.

In those situations in which partner notification is held to be justified, researchers should make this clear to potential subjects at the interview stage, prior to recruitment into the study. Any research subjects who consider that partner notification is unacceptable, should be informed that they are not eligible for recruitment to the study. The research subject's consent to partner notification must be obtained before any such notification is undertaken.

Guidelines

1. A requirement of partner agreement or authorization for an individual to participate in research violates the autonomy of research subjects and their right to confidentiality. Therefore, as a matter of ethical principle, provisions for obtaining partner agreement or authorization should not be permitted in studies supported by the Special Programme of Research, Development and Research Training in Human Reproduction. The consent form to be signed by the research subject should **not**, therefore, include an additional line for the signature of the partner.
2. The requirement of agreement by a research subject's partner can be justified in rare and unusual circumstances in studies supported by the Special Programme of Research, Development and Research Training in Human Reproduction. In cases where the signature of the partner is to be requested, investigators must supply a full and complete justification for this procedure and include this justification under "ethical considerations" in their application. In cases where it is thought absolutely necessary to obtain partner agreement, prior agreement of the research subject must be obtained to approach the partner.
3. Partner notification of a research subject's participation in a study is permitted in the following situations.
 - 3.1 Studies of male sterilization procedures and male contraception in which it is not known if the risk of pregnancy to the partner is greater than that of alternative established procedures.

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- 3.2 Studies in which both members of a couple are subjects and in which recruitment of the second partner depends on identification by the first. In this case, each partner should be made aware of the other's participation in the research.
 - 3.3 Studies in which a risk of infection to the partner of the research subject results from the research procedures themselves or from the conditions required for carrying out the research.

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GUIDELINES FOR DATA MANAGEMENT AND STATISTICAL PROCEDURES

INTRODUCTION

These guidelines have been prepared to assist in the provision of the information to be included in sections 3.3.9 *Data management*, 3.3.10 *Data analysis*, and 3.3.11 *Number of subjects and statistical power* of the project proposal application. They describe what will be required in the proposal in terms of: (i) a data management plan; (ii) a statistical analysis plan; and (iii) sample size calculation.

1. Data management plan

Outline how forms, labels, and flow of information will be prepared. Describe how data will be transcribed from forms to computer. Double entry of data is advised to minimise key-punch errors. An algorithm should be developed to detect out-of-range, discrepancies and other errors. Original source documentation should be kept to allow auditing, especially in the case of corrections to the data collection forms or to computer databases.

2. Statistical analysis plan

The main aim of the description of the statistical analyses is to convince the reviewer that the researcher has the ability to undertake appropriate analyses which answer the research objectives. Initially, it is important to define the primary outcome of interest and how that relates to the objectives. Indicate independent and dependent variables. Outline how these important variables will be analysed. Variables may be classified as nominal, ordinal, or interval. These three types of classifications are sometimes overlapped.

Univariate analyses are statistical methods used to analyse a set of measurement that contains one dependent variable and no independent variable. For nominal scale variables, describe them as a proportion or rate and give a confidence interval. For an ordinal scale variable, describe using median and inter-quartile range. For an interval scale variable, use mean, standard deviation, or median and inter-quartile range, where appropriate.

Bivariate analyses are concerned with one dependent variable and one independent variable. Describe the parametric or non-parametric statistical methods/tests to be used, also the desired significance level or confidence interval. Justify the use of a non-parametric method, if applicable. If a data transformation is needed, outline how data will be transformed and analysed. If the analysis involves paired or repeated measurement data, describe the appropriate methods. If necessary, provide details to check assumptions required for certain types of data, e.g., proportional hazards, normality, etc.

Multivariate analyses are used in situations where there is one dependent variable and two or more independent variables. Describe whether multivariate analysis will be used for prediction or for controlling extraneous variables in a hypothesis test. If regression methods will be used, describe how the parsimonious model will be selected. If appropriate, describe how the final model will be interpreted.

3. Sample size calculation

Please give the rationale for the proposed sample size. In particular it is important to know what is the outcome that is being estimated. It is desirable that investigators indicate the desired type I and II errors (or statistical power) wanted. Alternatively, investigators should provide information on the precision associated with the proposed sample size by giving the desired confidence interval. For a study comparing two groups or more, the baseline estimate(s) of the outcome event(s) in the control or the comparison group should be provided, together with the expected magnitude of the outcome in the experiment or study group. Also, it should be stated if the hypothesis will be tested on the basis of a one-sided or two-sided test, and the use of the test justified.

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**GUIDELINES FOR THE ESTABLISHMENT
OF SCIENTIFIC AND ETHICAL REVIEW BODIES**

INTRODUCTION

These guidelines have been prepared in response to requests for guidance in setting up institutional scientific and ethical review committees. The guidelines are based on the International Ethical Guidelines for Biomedical Research Involving Human Subjects, the International Guidelines for Ethical Review of Epidemiological Studies, and the International Guiding Principles for Biomedical Research Involving Animals, issued by the Council of International Organizations of Medical Sciences (CIOMS), and have drawn heavily on the experience, collective and individual, of members of the Scientific and Ethical Review Group (SERG) of the Special Programme and incorporates ethical principles proposed by the United States National Commission for the Protection of Human Subjects (see Annex).

Although the guidelines refer to the operations of institutional review committees, such committees need to operate within the framework of national policies. Should such policy require that project review is carried out also by a national committee, the principles of review remain the same for both institutional and national bodies.

Each institution has unique features. These guidelines cannot encompass the many variations of institutional structure or function, of culture, or of political environment. However, every institution should apply the principles of scientific and ethical review, even though these may not adhere strictly to the procedures suggested in this document.

Most institutions will need more than one review committee: one for scientific review, another for ethical review, and perhaps a third for review of research involving laboratory animals. Each institution must decide how best to meet its needs in this regard.

RELATIONSHIP BETWEEN ETHICAL AND SCIENTIFIC REVIEW

Ethical review is directly linked to scientific review.

A proposal for biomedical, social and behavioural research involving human subjects that is scientifically unsound cannot be ethical. Scientific review should precede ethical review but both review committees are responsible for ensuring that the research is scientifically sound.

PROPOSALS THAT REQUIRE ETHICAL REVIEW

All proposals for research that involve human subjects, or laboratory animals, must be submitted to independent, prospective ethical review.

This principle is inviolable and applies irrespective of the source of the proposal.

Proposals for research that includes the use of laboratory animals should not be thought of as less important than proposals for research on human subjects. For such projects, review

committees are responsible for ensuring that investigators follow the *International Guiding Principles for Biomedical Research Involving Animals*, CIOMS, 1985.

MEMBERSHIP OF REVIEW COMMITTEES

The membership should be sufficiently diverse to ensure that all projects can be reviewed adequately.

The membership of a scientific review committee should include a sufficiently wide diversity of expertise to cover all aspects of the design and assessment of the proposed research including, if possible, statistics, epidemiology, social sciences and health service research.

Members of an ethical review committee should be drawn from as wide a community as possible to include scientists, ethicists and members of the lay public. Both sexes should be included in the membership as well as persons who would be able to speak for a range of cultural and ethical values. The ability to judge the ethical acceptability of various aspects of a research proposal requires a thorough understanding of a community's customs and traditions. The ethical review committee must have, as either members or consultants, persons with such understanding, so that the committee may evaluate proposed means of obtaining informed consent and otherwise respecting the rights of the prospective subjects. Such persons should be able, for example, to identify appropriate members of the community to serve as intermediaries between investigators and subjects, to decide whether material benefits or inducements may be regarded as appropriate in the light of a community's gift-exchange traditions, and to provide safeguards for data and personal information that subjects consider to be private or sensitive.

The membership should change periodically.

Regularly changing the membership of review committees provides an opportunity for a variety of individuals to participate in the work of the review committee and prevents the formation of an elite group. However, membership should be of sufficient duration to allow members to become experienced in the review process. The replacement of members should be staggered, perhaps with two or three members being rotated off the committee at the end of each year. This encourages the development of a collective memory in the review committee, facilitating project monitoring and avoiding repetitive discussions of the same issues.

Avoidance of conflict of interest.

The independence of investigators and avoidance of conflict of interest are to be maintained by excluding any member with a direct interest in a proposal from participating in its assessment. To facilitate free and uninhibited review, such members should not be present during the proposal's review.

FUNCTIONS OF REVIEW COMMITTEES

For all research proposals involving human subjects, the Committee will provide technical and ethical assessment, particularly with respect to the:

- need for carrying out the study in the human.

- acceptability of the research design and study instruments, including the recruitment procedure, the number of subjects, the criteria for subject selection and exclusion, and the criteria for subject or study discontinuation.
- adequacy of toxicological and pharmacological data, for the types and intended dosages of the of drugs (devices) to be used, intended dosages, and the planned duration of treatment.
- training and experience of the clinical investigators.
- adequacy of the clinical research facilities at the study location.
- risks and benefits to the participants.
- the manner in which informed consent is obtained, the clarity and comprehensibility of the documentation given to each subject, and assurance that the subject has the right to withdraw from the study at any time without prejudice to his/her further medical treatment.
- the certificate of consent including a summarized version of all of the relevant information provided in the information given to the subject under the main headings of: *Purpose of the research; Risks and discomforts; Benefits; Compensation; Alternatives to participation; Additional items.*
- the certificate of consent ending with a paragraph indicating that the subject is fully informed and freely consents to participate in the study.
- assurance that the budget for the project does not include any undue inducement for subject participation, apart from legitimate compensation for travel and lost earnings.
- adequacy of the provisions to protect the confidentiality of data, as for example by omitting information which might lead to the identification of individual subjects, by limiting access to the data, or other appropriate means.
- assurance that the Principal Investigator has signed a statement, forming part of the proposal, that the research will conducted in conformity with the Declaration of Helsinki (*Recommendations guiding physicians in biomedical research involving human subjects*, adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975, the 35th World Medical Assembly, Venice, Italy, October 1983 and the 41st World Medical Assembly, Hong Kong, September 1989).
- assurance that the research will have a direct or potential benefit, in the present or future, for the population of the country in which the research is to be conducted.

MEETINGS

The review committee should meet at regular, scheduled times.

Meetings should be held at advertised dates and times so that investigators know well in advance when to submit proposals for review. The holding of regular meetings encourages the review committee, in addition to its primary function of reviewing proposals, to take part also in

other activities; such as the preparation of local guidelines for research proposals, the review of training programmes in which ethical issues arise, and the convening of broader meetings both within the institution and the community to discuss specific research or ethical issues.

The review committee should keep an agreed, written record of decisions made at each meeting.

The advantages of such a record are obvious; it constitutes objective evidence of review decisions which may be consulted should there be queries from any source in the future.

RULES AND PROCEDURES

The review committee should establish and widely disseminate its rules and procedures.

The review committee should establish working rules regarding, for instance, eligibility for membership, a quorum of members, frequency of meetings, decision-making procedures, and review of decisions.

The working rules of the review committee, should be distributed to investigators and made available also to nurses who may be involved in the recruitment and follow-up of subjects, and, secretaries who may have responsibility for the security of confidential information. A summary of the review committee's composition, functions and responsibilities could be prepared for wider dissemination.

The review committee should encourage the preparation of proposals in a standard format.

All investigators, or prospective investigators, should be able to obtain guidance from the review committee on the preparation of proposals for review. It is suggested that each review committee should design its own standardized format for research proposals. This would draw the investigator's attention to aspects that might otherwise be omitted, and would facilitate the work of the review committee. (For a suggested list of items to be included in a research proposal see pages 42-43 of the *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, CIOMS, 1993).

A principal investigator should have the right to attend the review committee meeting when his or her proposal is being reviewed.

At the level of local review, principal investigators should be encouraged to attend for the review of their proposals but should absent themselves from confidential discussions and from the final assessment of the proposal by the review committee. The costs of attendance should be borne by the investigators. Where review is carried out by a national committee it may be impractical, because of distances and cost, for the principal investigator to attend.

For every research project there should be at least one primary reviewer from among the review committee's membership.

The work of the review committee is considerably assisted if one or more of its members are designated to present the proposal, along with their respective reviews, to the review

committee. The designated reviewers should be selected, by the review committee secretariat or chairperson, for their expertise in the scientific area to which the proposal refers.

The review committee should have the authority to request project review from outside scientists, and to include such scientists in meetings when required.

There will be occasions when a research proposal is submitted for review that is in a field in which there is no expertise within the review committee membership. In such instances the power to seek assistance from outside the review committee is essential if the proposal is to receive a thorough and objective review.

Members of review committees should observe the highest ethical standards.

Members should be scrupulous in the observance of ethical standards in their own work and must also strictly observe the confidential nature of the review process. In particular, they should protect the confidentiality of review-committee documents and discussions. Also, they should not compel investigators to submit to unnecessary repetition of review. Review committees should help prospective investigators, not hinder or harass them.

There should be several categories of recommendation.

The decision of the review committee should be conveyed to the investigator. If the committee considers that the proposal needs revision or cannot be approved, complete and clear reasons for this decision must be provided to the investigator.

The Scientific and Ethical Review Group (SERG) of the WHO Special Programme uses the following five levels of recommendation:

- (i) *approval* - indicating that the proposal is approved as submitted;
- (ii) *approval after clarifications* - indicating that the proposal is approved if the clarification(s) requested are provided to the satisfaction of the WHO Secretariat;
- (iii) *approval after amendment(s)* - indicating that the proposal is approved subject to the incorporation of the specified amendment(s);
- (iv) *deferment* - indicating that the proposal is not approved as submitted but it can be re-assessed after revision to address the specified reason(s) for deferment;
- (v) *disapproval* - indicating that the proposal is not approved for the reasons specified.

These categories have proved valuable to SERG and investigators alike over many years. New review committees are recommended to employ the same, or a similar, system.

The review committee should report publicly on its work.

To foster increased dialogue and understanding between the scientific community and the general public, review committees should consider issuing annual reports of their work. The report would not contain confidential information nor indicate the outcome of individual project reviews but it would provide an overview of the review committee's work, such as: the number of proposals reviewed; the number approved; the number deferred; the number rejected, with the reasons for rejection. An annual report also would provide an excellent opportunity to highlight other activities of the review committee.

INFORMATION

The ethical review committee should have available, particularly for its own members, investigators and all who wish to consult them, copies of internationally accepted or recognized guidelines on the ethics of biomedical research.

Examples of such documents are given below.

1. *The Declaration of Helsinki. Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects.* (The original 1964 Declaration has been amended on several occasions, most recently by the 48th General Assembly, Somerset West, Republic of South Africa, October 1996.)
2. *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, CIOMS, 1993. (See particularly the section on Review Procedures: Guidelines 14 & 15).
3. *International Guidelines for Ethical Review of Epidemiological Studies*, CIOMS, 1991. (See particularly the section on Ethical Review Procedures, pp. 19-24).
4. *International Guiding Principles for Biomedical Research Involving Animals*, CIOMS, 1985.

The following publications are also of relevance.

1. *Ethics and Research on Human Subjects, International Guidelines.* Proceedings of a CIOMS Conference, 1993. (Containing also number 2 above).
2. *Ethics and Epidemiology, International Guidelines.* Proceedings of a CIOMS Conference, 1991. (Containing also number 3 above).
3. *WHO Guidelines on Good Clinical Practice (GCP) for Trials on Pharmaceutical Products*, WHO (in preparation).

Of importance also are national guidelines or documents describing relevant national legislation.

MONITORING

The obligations of the review committee do not end with project review.

The review committee should be perceived as being responsible, within the institution, for maintaining ethical, and scientific, standards throughout a research project. An annual enquiry about any changes in the project that might raise ethical issues is useful. Monitoring of scientific and ethical standards is a sensitive issue and each review committee must devise its own monitoring mechanisms, while always maintaining respect for the investigator.

Monitoring is not a substitute for creating awareness of ethical concerns.

One of the principal objectives of review committees should be to encourage a demand for rigorous scientific and ethical standards of research, from both scientists and the public. This may be achieved by including training in ethics in undergraduate and postgraduate courses and by discussions with community groups, and presentations to the public through the mass media. Provision of information on the review committee's work, by whatever means, should be reassuring to the public and may even aid in the recruitment of subjects to some studies.

Responsibility of the review committee in the event of breach of scientific and ethical standards by the investigator or sponsor

Inevitably, investigators or sponsors will sometimes breach scientific or ethical standards, either deliberately or, more commonly, through oversight. The review committee must then take action. The first response should be to establish clearly the facts, the second should be to seek ways of helping the investigator re-establish acceptable standards. If the investigator cannot or is unwilling to re-establish acceptable standards and this problem cannot be resolved by discussion between the investigator and the review committee, it is the responsibility of the committee to notify the granting body accordingly.

It is essential that scientists see the review committee as being helpful rather than punitive, responsive rather than authoritarian.

Completion of the project

The review committee should also oversee publication of the data resulting from the study to ensure that confidentiality is maintained.

ANNEX

ETHICAL PRINCIPLES FOR PRACTICE AND RESEARCH

Respect for persons: The duty to respect the self-determination and choices of autonomous persons, as well as to protect persons with diminished autonomy (e.g. young children, persons with mental retardation, and those with mental impairments). Respect for persons includes fundamental respect for the other; it should be the basis of any interaction between professional and client.

Beneficence: The obligation to secure the well-being of persons by acting positively on their behalf and, moreover, to maximize the benefits that can be attained.

Nonmaleficence: The obligation to minimize harm to persons and, wherever possible, to remove the causes of harm altogether.

Proportionality: The duty, when taking actions involving the risks of harm, to so balance risks and benefits that actions have the greatest chance to result in the least harm and the most benefit to persons directly involved.

Justice: The obligation to distribute benefits and burdens fairly, to treat equals equally, and to give reasons for differential treatment based on widely accepted criteria for just ways to distribute benefits and burdens.

7. SPECIAL PROGRAMME OF RESEARCH, DEVELOPMENT AND RESEARCH TRAINING IN HUMAN REPRODUCTION

GUIDELINE FOR OBTAINING INFORMED CONSENT FOR THE PROCUREMENT AND USE OF HUMAN TISSUES, CELLS AND FLUIDS IN RESEARCH

INTRODUCTION

Clinical research frequently involves, and in many cases depends on, the use of human tissues, cells and fluids, including sperm, eggs, blood, urine and saliva. The donors of such specimens are, as a rule, volunteers who participate in the research of their own free will and have given prior informed consent in accordance with established local, national or other regulations and practices. The nature and extent of the information provided to such volunteers, and on which their consent is subsequently based, is becoming increasingly important and complex in the light of recent medical and technical developments. In particular, recent advances in the fields of diagnostics and genomics have highlighted the need for donors to be given the opportunity to indicate whether or not they want the samples they are donating for a particular research purpose to be stored for use in future research and, if so, whether they want to place any limitations on the storage time or restrictions on the use to which their samples can be put in such future research.

This Guideline has been drawn up to assist researchers in dealing with the ethical issues relating to how clinical research materials are obtained, used and eventually disposed of, and the corresponding informed consent requirements. While this guideline is intended for the future collection of samples, many of the ethical considerations in this guideline are relevant also to previously collected human biological materials stored in repositories.

***N.B.** As with any guideline, this document is intended to set out general guiding principles on the understanding that these need to be interpreted and implemented in the context of local laws and customs. Such laws and customs may differ considerably from one location to another and especially in the context of the subject matter of this particular guideline. For example, major cultural differences exist with regard to, and therefore in obtaining samples from, deceased people and the placenta.*

FACTORS GOVERNING OBTAINING SAMPLES FOR RESEARCH

When samples are to be obtained for research in the context of a planned diagnostic, prophylactic or therapeutic procedure, the patient/subject should be told that refusal to consent to provide specimens for research will not prejudice their medical or surgical care.

If the use of some of the sample for research may diminish the quality of the laboratory examination to be carried out for diagnostic purposes and this might affect

subsequent treatment, this should be fully explained to the subject. (For example: research using small pieces of a prostate gland that has been removed during a prostate operation for supposed benign disease, may reduce the chance of diagnosis of an early prostate cancer because the pathologist has been deprived of some of the tissue to examine).

INFORMATION TO BE PROVIDED IN SEEKING CONSENT TO OBTAIN RESEARCH SAMPLES

As well as the usual project-specific information that will be provided to any research subject as part of the standard informed consent process (see Part 1, 4.1 of this document), the following additional information also needs to be provided in order that the potential research subject can make a fully-informed decision about whether or not to agree to her/his samples being taken and used in the proposed research:

- the nature and amount of the samples to be taken;
- the procedures that will be followed to obtain the samples for research and whether these are routine, modified routine, novel or experimental procedures;
- the risks and discomforts associated with obtaining the samples for research and whether any increased risk is presented if the procedure for obtaining the samples is a modified routine, novel or an experimental procedure;
- the nature, extent and duration of any treatment to be provided in the event of complications or injury resulting from the procedure to obtain the research sample, and who will pay for this treatment;
- the use to which the samples will be put in the research;
- where the samples and any clinical information will be kept and details of any relevant security arrangements;
- who will have access to the samples;
- how long the research samples will be kept;
- the arrangements for disposal of the samples at the end of the research project.

Furthermore, the following supplementary information should also be given, where relevant.

- Whether the results of the research will be relayed back to the research subject and in what form (pooled and/or individualized). The foreseeable consequences to the research subjects of having this information need to be explained and they should be allowed to choose not to know.

- If there are potential adverse consequences of disclosure of the results of the research, information should be given about arrangements for counselling
- Whether the research could reveal non-paternity or non-maternity.
- Whether the research may identify past or current infectious disease.
- Whether the research will generate genetic or molecular information that may predict characteristics or future disease patterns in the research subject or his or her family.
- Whether, if confidentiality is not respected and the results of the research become known, employment prospects and health insurability of the research subject may be effected.
- If the research involves gametes or tissue containing gametes (e.g. testicular or ovarian tissue), whether these gametes will be used to achieve fertilisation and produce embryos. **(If so, refer to separate guidelines on embryo and germ line research – in preparation).**
- Whether the research may lead to profit. If there is a possibility of commercial value then research subjects should be told whether or not they would receive any money or other intellectual property benefit that may result from commercial applications of the research.
- Who is funding the research. For example, whether a public institution or a private corporation, or a collaboration between the two.
- Whether the sponsor of the research is paying the researcher for each subject recruited to the study and/or for each sample obtained and, if so, the amount of such payments that will be received by the researchers.

All of the above information and the procedures to be used for obtaining consent for the collection of human materials should be included in the corresponding research protocols submitted for scientific and ethical review.

DIFFERENT TYPES OF CONSENT FOR THE USE OF SAMPLES IN RESEARCH

There is a potentially great public health benefit from research using samples from banks of human material. When obtaining consent for the collection of samples for use in a specific research project, researchers should request consent for use of the samples also in future studies. However, individuals must be free to consent for the use of their samples in the immediate specified research only, or for the use of these samples in the immediate specified research and also in future research, either of a specified or unspecified nature, as indicated below.

Fully restricted consent

In this case, the donor restricts the use of the samples to the immediate research only and does not consent to its use in any future research.

Partially restricted consent

In this case, the research subject consents to the use of the samples in the immediate research and in future research of a specified type(s) and up to a specified time in the future.

Unrestricted consent

In this case, the research subject consents to the use of the samples in the immediate research and in future research of any kind and at any time in the future.

In all of the above three situations, the consent document should specify the arrangements for final disposal of the samples, indicating when, how and by whom this will be carried out.

ANONYMITY AND CONFIDENTIALITY OF RESEARCH SUBJECTS

The identifying link between the research subject and the sample or research result may be kept or removed. Because all samples are originally linked to personal clinical information, researchers should ensure appropriate measures are in place to provide appropriate protection of medical confidentiality and privacy.

All research subjects should be given information about whether the research results can be linked to them and about the measures taken to ensure protection of medical confidentiality.

Samples may be unidentified, coded (sometimes termed linked or identifiable) or identified.

Unidentified

The identity is removed so that nobody knows from whom the sample came, and there is no possibility of tracing the donor. Removal of identity may be at the time of sample collection (samples collected in this way are known as anonymous samples) or a researcher may remove the identity or unlink the code from samples after conclusion of the research for which they were obtained (samples handled in this way are known as anonymised samples). Research subjects providing samples under these conditions should be informed that, as it will not be possible to identify their samples, it will not be possible to provide them with any personal results from the study.

Coded

The sample is labelled with a code known only to certain researchers, rather than with personal identifying information. Coding of samples may be done by the person collecting the samples, which are then given to the researcher; or the researcher may

arrange with a third party to code samples. It is not possible for the researcher using the sample to link the biological information from the sample with the person from whom the samples was obtained without breaking the code. Research subjects should be given information about who has access to the code and the circumstances in which the code will be broken.

Identified

The sample is labelled with the name of the donor or other personal identifying information. Any researcher using these samples would be able to link the biological information from the sample directly to the individual from whom the sample was obtained. Research subjects should be given information about who will have access to the samples and how personal information will be made secure against invasions of privacy and breaches of medical confidentiality.

SPECIAL CONSENT SITUATIONS

Samples from minors

Samples may be obtained from minors before they are of an age to give consent if similar samples serving the same purpose in the proposed research cannot be obtained from adults. Parents may reasonably give consent on behalf of a minor child where the sample is being collected for research that may prove to have therapeutic benefit to the minor or to other children suffering from the same medical conditions.

The parents should be given full information about how the sample will be obtained and any risks to the child. Most parents will wish to know about all risks, including remote risks, and the “reasonable person” standard should apply when giving information, namely: *“What any reasonable parent would wish to know”*.

Even where consent is not legally required from the child, researchers should obtain the child’s **assent**.

Where samples have been obtained from minors and are kept in store and where identity is retained (whether coded or not), arrangements should be made to obtain consent from the minor later, when he/she has reached adulthood, for continued storage or any proposed further research. The research protocol and consent document should specify the action to be taken in later years should it not be possible to contact the person from whom the sample was obtained.

The situation may arise where testicular or ovarian tissue is obtained from a minor e.g. before cancer chemotherapy. Gametes obtained from a minor should not be used for research without consent of the minor when he or she has reached adulthood.

Samples from mentally incompetent people

The same requirements and safeguards should be used in connection with obtaining samples from mentally incompetent individuals as are proposed in connection with minors (see preceding section). In essence, samples should only be taken from mentally incompetent people if similar samples cannot be obtained from competent research subjects. If practical, assent should be obtained from the incompetent research subject.

Samples of foetal tissue

The "reasonable person" standard cannot be presumed to apply in connection with the use of embryonic or fetal tissue for research purposes because not all reasonable people agree about the ethical status of the embryo and fetus. Therefore, a woman's explicit consent is required for the use in research of such tissue following a spontaneous or induced termination of pregnancy.

In the case of induced termination of pregnancy, it is ethically preferable to have separate consent forms for the termination and for the use of the resulting materials in research, to ensure that the woman understands the distinction between the abortion and the research and makes a free choice regarding each procedure. Researchers may use a generic consent form for embryonic and for fetal tissue research; it is not necessary to provide details of the research protocol on the consent form, unless it is the intention to use the tissue for homologous or heterologous transplantation.

Monetary payment or other inducement for donating embryonic or fetal tissue for research is expressly prohibited.

The placenta and other extra-embryonic tissues and fluids are generally regarded as non-fetal materials, and the "reasonable person" standard would apply to the use of these materials in research if they were obtained following normal term delivery. However, the same provisions would apply to their use in research, as would apply to fetal samples, if these materials are obtained as a result of induced termination of pregnancy.

Samples from deceased people

In the context of reproductive research, samples should normally be obtained from living adults who are able to give informed consent. Researchers should only consider using tissue from dead people when it is not possible to obtain such samples from a living donor. In these circumstances, consent should be obtained from the relatives after they have been given all relevant information that would normally be given to a living research donor.

Information should be given to the next of kin about how the sample will be obtained and whether this will mutilate the body. If a post mortem is in any case being performed then there may be no additional mutilation but in other cases information about the position, nature and extent of any incision should be given to the next of kin.

PROVISIONAL CONSENT

There are situations when it may be appropriate to obtain provisional consent at the time the tissue is taken but then to keep the research sample for some weeks or months and then to reconfirm the consent later at a time when it is intended to use the sample. This may be appropriate for samples taken during labour or for foetal tissue or samples taken from deceased people. The intention of provisional consent is to allow time for the research subject (or relatives) to reach a final decision on consenting to the use of the samples after the stress of the operation (or the immediate grief) has passed.

PREVIOUSLY OBTAINED SAMPLES

In the case of samples obtained previously without any future use provisions, researchers should try to obtain informed consent from the original donors or their proxies for the use of these materials in research studies for which they were not originally obtained. Where this is not practicable, and the research is expected to produce important public health benefits, the researcher should request the research ethics committee to waive the informed consent requirement and, at the same time, to advise on the action to be taken in contacting the donors of the samples, or their proxies, depending on the nature of the research, the significance of the results and the consequences of disclosure or non-disclosure of this information.

Appendix A

SUMMARY OF INFORMATION ABOUT RESEARCH SAMPLES THAT SHOULD BE GIVEN TO RESEARCH SUBJECTS

What the sample is and how the sample will be obtained

Degree of invasiveness.

In case of invasive procedures, any additional risks.

Arrangements for treating complications that may arise during or after invasive procedure to collect specimens.

Consequences of any variation in normal histopathological examination caused by specimen collection.

In the case of vaginal examination or other intimate examination, how privacy will be protected.

What consent is being asked

Consent for the specific research project only (fully restricted).

Partially restricted consent.

Unrestricted consent to use sample for any type or research.

Whether identity will be retained or not

Unidentified (anonymous or anonymised).

Coded (linked or identifiable).

Identified.

How will confidentiality be ensured

How confidentiality and privacy of personal information will be protected.

Where samples and any clinical information will be kept.

Who will have access to the samples and the research results.

Whether the results of the research will be relayed back to the research subject.

For how long samples will be kept.

The final disposition of the samples and information.

In addition it may be appropriate to give information about

Arrangements for disposal of the samples at the end of the research project.

If the proposed studies will involve genetic research.

The possibility of revealing non-paternity.

Detection of infectious disease.

Whether the results may affect insurability.

Whether the research involves “fertilisation”.

Whether the research involves alteration to germ lines or embryos.

That the research subject will not receive any money from commercial applications of the research.

Who is funding the research.
Whether the researcher will receive per subject payments.
What treatment will be provided in the case of research-related injury in obtaining the sample, and whether monetary compensation will be available for any such injuries.

Appendix B

EXAMPLE CONSENT DOCUMENT FOR AN INVASIVE PROCEDURE SOLELY TO OBTAIN MATERIAL FOR RESEARCH

Normally, it is not necessary to obtain separate consent to obtain research samples as this consent will be given when the research subject is recruited and consents to join the research study. However if the research involves an operative procedure which, if being carried out for therapeutic purposes, would require an operation consent form, then this example operation consent document could be used.

Description of the procedure to be used and the sample to be obtained.

Statement that the procedure is to be done solely to obtain the research sample and that there is no therapeutic benefit to the research subject.

Description of any risks (even remote risks) of the procedure.

Notification that appropriate care will be provided if any adverse events arise during the procedure or a result of carrying out the procedure to obtain the sample.

I give permission for the procedure of

To obtain a sample of

For research

Signed

I have explained the risks of the invasive procedure. I have explained that this procedure is of no therapeutic benefit but is being done solely in order to collect the research sample.

Signed

Appendix C

EXAMPLE CONSENT DOCUMENT FOR VARYING A ROUTINE INVASIVE PROCEDURE TO OBTAIN MATERIAL FOR RESEARCH

Where a variation in a normal surgical technique is to be performed in order to obtain the research specimen, and where the specimen would not normally be removed as part of the therapy, then the following supplementary consent should be obtained in addition to the standard operation consent form.

Description of how the surgical technique will vary from the normal planned surgical procedure.

Description of the sample to be obtained.

Description of any additional risks (even remote risks) that are extra to the normal risks of the planned surgical procedure.

Description of care to be provided in event of a side effect.

I give permission for a sample of
to be collected for research purposes during the operation of.....

Signed

I have explained the variation in the normal surgical procedure required to collect the research sample. I have reviewed the additional risks of the variation in the normal procedure, over and above the normal risks of the planned surgery and the care to be provided if side effects occur. I have informed this patient that giving or withholding consent for obtaining the research sample will make no difference to the planned therapeutic surgery and subsequent follow up care and treatment.

Signed

Doctor/ surgeon who will undertake the surgical procedure.

Appendix D

CONSENT FOR USE OF HUMAN BLOOD, BODY FLUIDS

OR TISSUE GIVEN FOR RESEARCH

I consent to use of my specimen of(e.g. blood, urine, etc.) for the following research project.

Name of project

If any of my specimen is left over after this research project has been completed:

1. I wish this left over specimen to be destroyed immediately ★ ☐

OR

2. I give permission for the left over specimen to be kept for future research on condition it is **not** used for the following types of research:
.....
.....

and

is destroyed after the following period of time

and

my identity has been removed from the specimen ★ ☐

or

my identity is kept with the specimen. ★ ☐

OR

3. I give permission for the left over specimen to be kept for future research that is:

related to the medical condition that is the subject of this study ★ ☐

or

related to the following health conditions ★ ☐

4. I give permission for the left over specimen to be kept for future research of any type and at any time on the understanding that:

my identity has been removed from the specimen ★ ☐

or

my identity is kept with the specimen. ★ ☐

Name

SignatureDate.....

★The research subject should initial the boxes of their choice.