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Preparing a Research Project Proposal

Guidelines and Forms

(Fourth Edition)

WORLD HEALTH ORGANIZATION
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Contents

Introduction

This booklet consists of three parts.

Part 1: Provides general guidance for preparing a research project proposal to be submitted to the Special Programme for consideration for support. ***Please be sure to read this part carefully before starting to fill in the forms in Part 3.***

Part 2: Comprises a number of documents containing background information that will be helpful to you in preparing the research project proposal. They include extracts and summaries of internationally-recognized conventions to which the proposed study must conform, as well as guidelines developed by the Special Programme relating to the different types of research involving human subjects and to the process of research project proposal review at the level of the institution.

Part 3: Includes all the forms that need to be completed for submitting the project proposal.

Part 1. General guidance

All proposals submitted for possible support by the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (the Special Programme), must be submitted on the forms in Section 3 of this booklet and must include the following information, in the order indicated and on the forms indicated in parentheses:

1. Particulars of the project and investigator(s) (Form 1)
2. Project summary (Form 2)
3. Description of the project (Form 3)
4. Ethical considerations and gender issues (Forms 4a and 4b)
5. Budget (Form 5)
6. Other support for the proposed research (Form 6)
7. Other research activities of the principal investigator(s) (Form 7)
8. Curricula vitae of the principal investigator(s) and co-investigator(s) (Form 8)
9. Requisitions through WHO (Form 9)

The above list should be used as a check-list prior to sending all the forms to WHO. Note that Form 9 (Requisitions through WHO) needs to be completed and attached only if equipment and supplies for the project are to be ordered through WHO.

1. PARTICULARS OF THE PROJECT AND INVESTIGATOR(S) (FORM 1)

Complete all three pages of Form 1 and have page 3 signed by the appropriate persons. Please list all members of the research team, indicating their function and whether male or female.

With regard to "Approval of ethics committees" (item 9 in Form 1), in addition to answering the questions, the following documents should also be attached:

For research on human subjects and/or human biological materials:

- Evidence of approval of the local (institutional) ethics committee. This should be accompanied by a list of the current members of the committee, their affiliations and their responsibilities on the committee.

- A copy of the consent form that the study subjects will be asked to sign (plus an English language translation of the original, if this is not in English)

- Evidence of approval of the national ethics committee, if required. This should be accompanied by a list of the current members of the committee, their affiliations and their responsibilities on the committee.

For research on experimental animals:

- Evidence of approval of the local (institutional) or national ethics committee, if required. This should be accompanied by a list of the current members of the committee, their affiliations and their responsibilities on the committee.

NOTE

Without the above documents Form 1 will be regarded as incomplete.

Under item 11 in the Form, you are permitted to sign as both principal investigator and head of the institution, if applicable. However, you may **not** sign also on behalf of the administrative authority that will be responsible for the administration of the funds (see Part 2, Number 11, General conditions concerning WHO support for research or other technical services).

2. PROJECT SUMMARY (FORM 2)

The project summary should be typed in single spacing and should normally not exceed the space provided in Form 2. It should contain the most important aspects of the project, which may be extracted from the description of the project (see section 3 below). It is recommended that the project summary be written last, i.e., after the remainder of the project proposal has been written up. The project summary must include the following:

- *Justification for the project*. State why the project is important and, if applicable, how it relates to national reproductive health or family planning policies and/or to the objectives of the Special Programme.

- *Proposed research*. Outline briefly the information requested under sections 3.1 through 3.3, including the hypothesis(es) to be tested.

- *New features*. Indicate the most relevant differences, either in methodology or outcomes, between the proposed investigation(s) and studies already published.

- *Techniques and skills*. List the techniques and skills required for the investigation.

- *Problems anticipated*. Identify any scientific, ethical, or management problems that you expect may arise during the course of the project.

3. DESCRIPTION OF THE PROJECT (FORM 3)

Start the description of the project in the space provided in Form 3 and then continue on additional sheets as necessary. The description should include sufficient detail to enable reviewers to assess the proposal. Describe fully all methods and procedures and give details of any substantive differences from published methods. The text should be typed in single spacing, with double spacing between paragraphs and headings. List references at the end of the section.

Biomedical research protocols involving human subjects or the use of human biological materials should follow the format shown below. Sections that do not apply should be marked as "N/A" (not applicable).

For research projects involving humans in areas of science other than biomedicine (e.g., epidemiology, social and behavioural sciences) and for those not involving human subjects or materials, the format shown may have to be modified depending on the type of study. But even in those cases deviation from the format provided should be the minimum possible. As in the case of biomedical research protocols, sections that do not apply should be marked as "N/A" (not applicable).

3.1 Rationale and objectives of the study

3.1.1 *Rationale*

Describe the rationale of the study within the context of present knowledge and, if relevant, within the activities and objectives of the specified research area of the Special Programme. If applicable, justify the proposed study in terms of its demographic, social, or (reproductive) health impact, and of its policy, service, or programme relevance.

Explain clearly the hypothesis(es) being tested and the end points that will be used in the study to examine this (these) hypothesis(es). If the study involves human subjects, fully justify their inclusion. If the proposal is a renewal application, provide a detailed progress report.

3.1.2 *Objectives*

List the main and subsidiary objectives of the study.

3.2 Previous similar studies

Describe briefly the most relevant studies published, drawing upon systematic reviews where these exist. If a systematic review does not exist, a thorough review of relevant literature should be presented.

3.3 Design and methodology

3.3.1 *General outline*

Provide a brief outline of the most important features of the study, such as the nature of the study, number and main characteristics of subjects involved, number and frequency of follow-up visits, and investigations that will be undertaken. Justify the choice of the study design in relation to the objectives of the project.

3.3.2 *Criteria for the selection of subjects*

Describe the population that will constitute the source of subjects for the study sample and justify its selection in relation to the objectives of the study Specify the characteristics required for participation in the study (inclusion criteria) and those that exclude a potential subject from participating (exclusion criteria). If applicable, discuss the selection of comparison groups and matching criteria, and/or describe the sampling procedures, including the type of sample (e.g., quota, simple random, stratified random, and cluster). If a population-based sample is planned, discuss how the potential respondents will be approached.

When the proposed research requires the use of hospital or other records, provide evidence that you have the permission of the concerned authorities to use the records. If existing data are to be used for secondary analyses, provide evidence that the data will be available, and that there are no restrictions on the dissemination of the eventual findings of the study.

3.3.3 *Subject recruitment and allocation*

Indicate where, how and by whom the subjects will be recruited. Copies of any written materials and transcripts of any verbal messages advertising the study should be attached to the proposal.

If applicable, describe the type(s) and method(s) of allocation of subjects to index and comparison groups. State when this allocation will take place.

3.3.4 *Description of the drugs and devices to be studied*

For drugs and devices that are commercially available, give the proprietary names, chemical composition, amount of drug present per dose, and the names and address of the manufacturers.

For drugs or devices being used for the first time in humans, or drugs and devices that are still at an early stage of clinical study, or drugs that are generally available but are to be administered by different routes or in different dosages, give the chemical composition of the drug, the source, and the amount per dose. Summarize the relevant pre-clinical investigations in animals and describe the main pharmacological actions of the compounds. If available, give results of studies already conducted in humans. Also, provide the same information for any new vehicles to be used for the administration of the drugs.

3.3.5 *Admission procedure*

Describe where, when, how and by whom recruitment to the study will be carried out. Describe the proposed procedures for admitting subjects to the study, including the timing of admission and/or allocation to study groups. Describe the data to be collected at admission and, if available, attach a copy of the admission form as an annex to the proposal.

3.3.6 *Follow-up procedure*

Describe the frequency and timing of follow-up of subjects, the investigations to be conducted and the data to be collected at each follow-up visit. If available, attached copies of the forms to be used. Describe the procedures to be used in tracing subjects who do not comply with the follow-up schedule.

3.3.7 *Criteria for discontinuation*

Specify the conditions that would lead to a subject being discontinued from the study or to the termination of the study, in whole or in part.

3.3.8 *Laboratory and other investigations*

List the laboratory and other diagnostic and investigative procedures that will be carried out as part of the study. Important procedures — i.e., those that are essential for the achievement of the objectives of the study and methods not previously published — should be described in detail. For other procedures reference to appropriate published work would be sufficient.

3.3.9 *Data management*

State what procedures will be used for data management, including data coding, monitoring, and verification. Also describe the administrative and computer procedures to be used, the type of staff available and whether any training will be needed to facilitate data management.

3.3.10 *Data analysis*

Provide information on available computer facilities.

Outline the statistical methods that will be used for the analysis of the data, including a description of how the information collected will be used to test the stated hypothesis(es) and how any missing data (e.g., items not applicable in a questionnaire, follow up losses, and subjects withdrawing from the study) will be dealt with. If relevant, the major subgroup analyses and/or comparisons between the study groups that are anticipated should be specified.

For projects requiring special statistical techniques (life table analysis, multivariate analysis, logistic regression, etc.), describe how these will be used. If complex tabulations are planned, provide dummy tables.

For projects involving qualitative approaches (focus-group discussions, in-depth interviews, observational techniques, etc.), specify in sufficient detail how they will be analysed.

3.3.11 *Number of subjects and statistical power*

Describe and justify the assumptions underlying the estimates of prevalence and incidence rates for the main study objectives, the differences that the study is expected to detect and the power required to demonstrate such differences. The method of computation to be used in estimating the number of subjects to be recruited in each treatment group or at each centre, or for calculating the number of controls per case should also be described or referenced. Adequate allowance must be made for the estimated number of subjects expected to drop out before the study is completed and/or those that may have to be excluded from analysis.

Explain the variability to be expected in the findings, and state what differences will provide significant results. Give the probability that such differences will be detected, at a stated level of statistical significance, by the planned experimental and statistical methods with the given numbers of subjects.

3.3.12 *Duration of project*

Provide information on how much time would be needed for recruiting subjects for the study, collecting samples/specimens, follow-up of subjects, laboratory tests, data analysis, and for report writing.

It is recommended that this information be presented in the form of a detailed timetable with months across on the top and activities listed along the left margin. Activities in the case of social science projects, for example, include, pre-tests, questionnaire development, training of staff or interviewers, data collection, data coding, data entry, analysis, and report writing. For each of the activities mark a cross against the month(s) in which they will occur.

3.4 Project management

For collaborative projects involving several departments and/or institutions, indicate who will have overall responsibility for the project, which other departments (or institutions) will be involved and what their respective responsibilities will be, and the manner in which the work will be coordinated and monitored.

3.5 Links with other projects

Indicate if the proposed project is linked in anyway to other projects in progress within the relevant research area of the Special Programme, to other research areas of the Special Programme, or to non-WHO supported projects, if such relationships exist.

3.6 Main problems anticipated

Describe the main obstacles and difficulties which you expect might interfere with the successful completion of the project within the time and costs proposed. Discuss how these problems will be confronted. For studies involving a risk of unplanned pregnancy, indicate what advice and choice of management will be offered to the subjects.

3.7 Expected outcomes of the study

Indicate how the study will contribute to advancement of knowledge, how the results will be utilized, and by what means they will be disseminated (e.g., thesis, scientific publication, workshop). Section 2, number 11 presents the policies of the Special Programme concerning publication of research results.

If applicable, describe how the results are expected to affect health care policies and practices in areas such as reproductive health, family planning, or population.

3.8 References

List the references, alphabetically by first author, that have been quoted in the proposal. Provide complete bibliographical details for each reference: i.e., for *journal articles*, full name(s), year of publication, full title, name of journal, volume number, and page numbers; for *books*, name(s) of authors(s), year of publication, full title, place of publication, and publisher; and for *chapters in books*, name(s) of author(s), year of publication, full title of the chapter, full title of the book, name(s) of editor(s), place of publication, publisher, and page numbers.

4. ETHICAL CONSIDERATIONS AND GENDER ISSUES (FORMS 4a and 4b)

Ethical considerations

In Form 4a describe the measures that will be taken to ensure that the proposed research is carried out in accordance with existing ethical guidelines, viz. **"Recommendations guiding physicians in biomedical research involving human subjects"** (Declaration of Helsinki, see Part 2, number 1), **"International ethical guidelines for biomedical research involving human subjects"** (Council for International Organizations of Medical Sciences, see Part 2, number 2) and **"International guiding principles for biomedical research involving animals"** (Council for International Organizations of Medical Sciences, see Part 2, number 3).

For studies in humans (or involving human biological materials) evidence must be provided that the proposed research has been approved by the local, institutional or equivalent ethics committee and/or the national ethics committee.

For animal studies approval is required from the animal welfare committee of the institute or its equivalent. If no such committee exists, a statement signed by the principal investigator(s) that the research will be carried out in accordance with the guidelines presented in Part 2, number 3 should be provided.

4.1 Informed decision-making and confidentiality

A form must be provided with the proposal to indicate that the research subject has decided to take part in the study of her/his own free will. Once approved by WHO, this consent form becomes part of the project protocol. It should be written in the prospective subjects' mother tongue, and when this is not English, an English language translation should be provided as well. For multicentre studies, a common consent form will be taken as a minimum requirement, to which additions may be made as dictated by local circumstances. In such cases, the common consent form should be written in the mother tongue of the writer and translated into English and other languages as required. Institutes participating in multicentre trials must inform WHO whether they will use the common consent form and, if the common consent form will not be used, the institutes should provide a copy of the translated and/or amended version that will be used.

The consent form has two parts: (*a*) a **statement** describing the study and the nature of the subject's involvement in it; and (*b*) a **certificate of consent** attesting to the subject's consent. Both parts should be written in sufficiently large letters and in simple language so that the subject can easily read and understand the contents. As far as possible, medical terminology should be avoided in writing up the consent form.

The statement is given or read to each prospective subject. Any questions the subject may have are then answered and, if consent is given, the certificate is signed by the subject or, if consent was verbal, by the staff member who provided the information and ensured that it was understood. By signing, the staff member confirms that consent was given freely. A signed certificate must be obtained in this way for each subject admitted to the study, and a copy must be offered to the subject.

In writing up the **statement** take note of the following points:

- Indicate that this is a research study to distinguish it from routine care.

- Explain why the study is being done and why the subject has been asked to participate.

- Describe, in sequence, what will happen in the course of the study, giving enough detail for the subject to gain a clear idea of what to expect.

- Explain whether or not the study procedures offer any benefits to the subject or to others.

- Explain the nature, likelihood and treatment of anticipated discomfort or adverse effects, including psychological and social risks, if any. Where relevant, include a comparison with risks posed by standard treatments or drugs, and an indication of whether the drug or procedure under investigation bears risks equal to, greater than, or less than the standard. If the risks are unknown or a comparative risk cannot be given it should be so stated.

- State that all records are confidential. If absolute confidentiality cannot be guaranteed, explain why this is so. Also state which persons other than the researchers may have access to the records and/or to whom information may be disclosed.

- State that the subject has the right to withdraw from the study at any time without in any way affecting his/her current or future care.

The **certificate of consent** should begin with a brief summary of the main items from the above statement. Each item should be stated in a separate paragraph, in the following order:

- *Purpose* of the research.

- *Procedures* that will be followed, including the total time involved for the subject.

- *Risks and discomforts,* including psychological and social risks, if any.

- *Benefits* of the research, separated into "benefits to you" (the subject) and "benefits to others".

- *Compensation*, if any, provided to research subjects. Specify whether or not compensation for participating in the research will be provided, and if so, how much. When no compensation is offered, the consent form should include a statement to the effect that no compensation of any sort will be provided for participating in the research.

- *Alternatives to participation*. When the study involves the administration of investigational drugs or use of new therapeutic procedures, the consent form should include a separate paragraph stating that the subject has been given the option of choosing the **established** standard treatment.

- *Additional items*. For prospective clinical studies on methods of fertility regulation, the consent form should indicate what advice and choice of management will be offered to the subjects in case of unplanned pregnancy.

- *Contact information*. Full information must be provided to enable the prospective subject to contact study personnel, at any time, to obtain further information about the study and for the enrolled subject to seek information about, and if necessary treatment for, any adverse events that may occur during the study or during the immediate post-study period. The means of contacting the study personnel must be appropriate to the study population.

The certificate of consent should end with a paragraph such as the following:

'I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a subject in this study and understand that I have the right to withdraw from the study at any time without in any way affecting my further medical care.'

The document should be signed by the subject or, when the subject is illiterate, by the staff member who provides the information, and who ascertains that it was understood and confirms that consent was given freely.

Whenever feasible, the recruitment of illiterate subjects should take place in the presence of a literate witness. Whenever possible, the witness should be selected by the subject and he/she should not be connected with the research team. The witness should also sign the certificate of consent, confirming that the subject has been properly informed and voluntarily consents to participating in the study.

If biological specimens are to be taken during the course of the study, the subject must be told how any left over specimens will be disposed of when the study has been completed. If the investigators would like to store such left over specimens for use in future research, supplementary voluntary and informed consent must be sought and obtained for such storage and use and any time, use and anonymity restrictions the subjects may wish to impose must be respected and adhered to (see Part 2, number 7).

4.2 Risk-benefit assessment

Provide ethical justification for the proposed research in terms of its risks and benefits.

The risks to subjects should be minimized by using the safest procedures consistent with sound research design. Risks to subjects should be reasonable in relation to the anticipated benefits for themselves and/or others and to the importance of the knowledge to be gained.

Risks include not only the prospect of physical harm or discomfort, but also psychological and social risks. An example of psychological risk is anxiety or embarrassment felt by subjects being interviewed about, for example, their sexual behaviour or other intimate matters. An example of a social risk is breach of confidentiality that could lead to harm to a subject's interests (job loss, standing in the community, etc.).

4.3 Additional ethical concerns

Whenever the proposed research involves additional, "unusual" ethical issues, a description should be given of these issues and of the measures proposed to safeguard the interests of the subjects in accordance with the guiding principles of the declaration of Helsinki. Examples of such special ethical concerns would be situations where absolute confidentiality cannot be guaranteed, studies involving special groups of subjects (for example, minors, prostitutes, and prisoners or other institutionalized persons), and projects involving the use of human biological materials that are subject to local or national regulations or laws (for example, human eggs fertilized *in vitro* or *in vivo* and the products thereof) - see also Part 2, number 7.

Every attempt should be made to maintain absolute confidentiality and the measures taken to ensure confidentiality should be specified. If absolute confidentiality cannot be guaranteed, subjects should be told who might have access to the records of the study. In cases where both members of a couple are study participants, each partner should be informed of the extent to which confidentiality will be maintained. In cultures in which husbands may exercise control over their wives, women must be advised in advance of becoming a participant in the study whether information they disclose might be revealed to their spouses.

In all cases, researchers should seek to ensure that records of the research subjects are kept in locked files, and that people not connected with the research do not have access to them.

In accordance with Part 2, number 1, the use of vulnerable subjects as research participants should be avoided and must be justified if it is proposed. Vulnerable subjects include those in prisons, minors, mentally handicapped or emotionally disturbed persons. However, if a study promises considerable benefit that would not otherwise be available to a minor or other subject incapable of providing informed consent, those subjects may be recruited and consent may be granted by a parent or guardian, in accordance with applicable law. Whenever a minor child is in fact able to give a consent, his or her consent must be obtained in addition to the consent of the minor's legal guardian. The use of prisoners or other institutionalized persons as research subjects, or of those likely to be incarcerated, should be avoided because such individuals are in a socially vulnerable position.

Selection of subjects should comply with principles of justice. At the level of the individual, justice in selecting subjects requires that researchers exhibit fairness: potentially beneficial research should be offered to all subjects, and risky research must not be confined to persons judged to be "undesirable" by either the researchers themselves or by the society. Social justice requires that neither the benefits or the burdens of research fall disproportionately on a single social, economic, racial, or ethnic group.

Recruitment of subjects should take place without the use of force, fraud, duress, or undue influence. Undue influence can occur when an offer is made of an excessive or inappropriate reward for participation in a study, or in order to obtain compliance. Only under very rare circumstances which must be justified in full can it be permitted not to give full information to the subjects about the purpose of the study. This may be the case in, for example, epidemiological studies to avoid recall and other biases.

Gender issues

In Form 4b evidence should be provided that the gender relevance and gender implications of the proposed research have been considered and that the outcome of the research will not contribute to gender inequality. In particular, the four questions listed in Part 2, number 4, should be specifically addressed and the corresponding information provided.

5. BUDGET (FORM 5)

Research is supported by the Special Programme on a collaborative basis. The contribution of the institution is a recognized, though not always specified, component of the budget of any project.

The Special Programme can meet only the costs specifically incurred by the institution for conducting the project. The support offered by the Special Programme is only for the purpose of research conducted under the project and generally does not exceed three years. The Special Programme cannot provide, as part of its **project** support, institution strengthening funds whether for equipment, supplies or training beyond the need of the specific project. For such support, institutions in developing countries can apply separately to the Special Programme's component of National Reproductive Health Research.

The budget must be itemized and must be fully justified. Budget items include personnel costs, operating expenses, subject costs, major equipment, animals, travel, and other specified expenditure. Budget items must not include "miscellaneous" or "contingency" items or an overhead payment to the institution.

5.1 Personnel costs

Payments to staff of the institution on a regular salary may be included in the budget only for "overtime" spent on the project. Normally, the compensation for this overtime will be related to the actual amount of time spent on the project and to the local salary scale. As an exception, particularly in developing countries, it may be related to the "potential" income that could have been gained by using this time in private practice. Full reimbursement to the institution for personnel time spent on the project is only allowed for personnel not employed on a regular salary. In general, payments provided to personnel should not be interpreted, and should not be considered, as an incentive to conduct research. Funds requested for personnel costs should reflect actual labour costs. As an expression of spirit of collaboration in WHO-supported projects, principal investigators on a regular salary will not normally request a salary component for themselves.

5.2 Supplies

For supplies, budget justification must relate chemicals, glassware and other supplies to the number of procedures expected to be performed in the project. Equipment maintenance costs can be paid only for the time the equipment is used for the purpose of the project. For equipment and supplies to be purchased by WHO, complete Form 9 "Requisitions through WHO". Detailed instructions for completing this form are given on pages 14 – 16.

5.3 Subject costs

Subject costs must be reasonably related to time lost and/or actual transportation expenses. Costs for investigations and/or laboratory procedures may be included in the budget proposal if they are not a part of the routine medical care for the subjects and are performed only for the sake of the project. The costs shall not exceed the local fees normally charged for such tests.

5.4 Major equipment

No single piece of equipment costing more than US$10 000 will normally be supplied as part of project support.

5.5 Animals

If animals are to be purchased and maintained, full justification must be provided for the costs in terms of number of animals needed for the project and the length of time they need to be kept.

5.6 Travel of project personnel

Justifiable travel expenses of personnel involved in the study may be included in the budget. No vehicles can normally be provided as part of project support, unless fully justified.

5.7 Other costs

If the conduct of the project will necessitate additional support such as investigators' meetings, training workshops and external consultant inputs, this should be costed and an estimate provided under this budget item. Data analysis costs, costs of printing or photocopying forms, mail, telephone and telefax charges, etc., should also be specified under this item.

5.8 Budget summary

For each year of the duration of the project fill in the subtotals arrived at under each of the preceding budget items, and then add up each column to arrive at the grand total.

5.9 Budget justification

Provide justification for the amounts stated under each budget item. It is important to relate the total budget to the number of subjects to be included in the study. The cost per subject arrived at in the proposal will be compared with costs per subject in the same or other comparable projects carried out in different centres.

NOTE

In addition to the funds which WHO would have retained under the normal procedures for purchase of supplies on their behalf, institutions in countries with scarcity of hard currencies may request to keep some (or all) of the funds awarded for local expenses (including salaries) in a trust fund in Geneva to buy equipment and supplies. This reallocation of funds cannot exceed US$30 000 for each Technical Services Agreement. Such funds can be used only for equipment and supplies related to research in human reproduction. Orders for supplies and equipment against such funds—as is the case with all funds in trust—must be received in WHO by 31 December of the year following the end of the Agreement period; otherwise the funds will be lost.

6. OTHER SUPPORT FOR THE PROPOSED RESEARCH (FORM 6)

Answer the two questions in Form 6.

1. Indicate whether you are currently receiving any funds or assistance in any other form from another source for the project you are submitting to the Special Programme for support. In case you are receiving or are going to receive support from another organization, give the organization's full name and address, and provide details of the nature, amount and duration of such support.

2. If you have sent, or are planning to send, the proposal you are submitting to the Special Programme to another organization(s) for funding assistance, provide the name(s) of the organization(s), and by when you expect to hear their final decision.

7. OTHER RESEARCH ACTIVITIES OF THE PRINCIPAL INVESTIGATOR(S) (FORM 7)

List in Form 7 all your current research activities, indicating the titles of the projects, their source(s) of support, their duration, and the percentage of your working time spent on each of them.

8. CURRICULA VITAE OF THE PRINCIPAL INVESTIGATOR(S) AND CO-INVESTIGATOR(S) (FORM 8)

Curricula vitae are required for all the scientists who will take part in the project. This booklet contains only one copy of Form 8. Please make as many photocopies of the form as needed. If it is not convenient to make photocopies, provide all the information requested in Form 8 on another sheet of paper.

9. REQUISITIONS THROUGH WHO (FORM 9)

Consignee

Give full name of person for whom the goods are destined; also give the full name and complete address of the institute.

Address

Give complete address to where the goods should be sent, if different from above.

Date

Give the date when the order is sent to WHO.

Project No.

If known, give the number of the research project for which the supplies are being purchased. This number is particularly essential in the case of institutes that are recipients of several project grants.

Allotment No.

Leave blank. For WHO use only.

Special shipping instructions

Indicate whether the goods need to be shipped in any special way: by air parcel post, air freight, or surface mail (for heavy, bulky, inflammable and dangerous chemicals); via the country WHO Representative's Office or UNDP Office; etc. You may also indicate how the packages should be marked for customs clearance (e.g., 'Donation from WHO for Research Purposes'), and the city or port of entry into the country.

HRP reference

Leave blank. For WHO use only.

Priority No.

Group the required items by supplier (see **IMPORTANT NOTICE** at the end of these instructions). Then give each item a number (beginning always with No. 1) to indicate the order of priority. Should the money kept in the trust fund prove to be insufficient to order all the requested items, then WHO will provide items according to the priority accorded by the institution.

Complete description of the item

See **IMPORTANT NOTICE** at the end of these instructions.

If equipment and spare parts are required, for each item indicate the make and model number.

When major equipment is requested, it is strongly recommended that essential spare parts be included in the request.

For electrical equipment, state voltage and cycles.

For glassware and plasticware, state size, dimensions or volume required.

For chemicals and reagents, indicate the grade required, e.g., reagent grade or chemically pure.

For radiolabelled compounds, indicate the specific activity, number of curies requested and approximate date(s) you wish to receive the compounds. For radioactive compounds and assay kits with a limited 'shelf-life', a despatch schedule should be specified.

Catalogue No.

Provide the catalogue reference number of the items requested.

Quantity

Indicate the quantity by item. For example: 1 x 500 gm; 3 x 1 litre; 1 case of 500 tubes or 2 cases of 6 x 100 ml.

Unit price

Indicate price per unit, for example, US$12 per litre, CHF 20 per 10 gm.

Total price

Total price for the items requested. State currency used: US$, Euros, CHF, etc.

Supplier and date of catalogue used

If a lot of material is to be supplied, names and addresses of the suppliers may be listed and attached as an annex to the Form. The list must include the date and number (if any) of the catalogue used. Name also possible alternative suppliers. It is recommended that investigators request supplies from a minimum number of suppliers so as to reduce shipping costs. WHO cannot undertake to provide any catalogues. Institutes should write to suppliers directly to obtain up-to-date catalogues and to be included in their mailing lists.

IMPORTANT NOTICE

1. ***In order to avoid the need for retyping of the order list in WHO, Geneva, please group together items from the same supplier.***

2. ***Charges for packing, freight, and insurance (PFI) amount to approximately 15% of the total cost of an order; this expense should be included in the budget.***

Part 2. Supplementary information

1. DECLARATION OF HELSINKI

RECOMMENDATIONS GUIDING PHYSICIANS IN BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975, the 35th WMA General Assembly, Venice, Italy, October 1983, the 41st WMA General Assembly, Hong Kong, September 1989, the 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996, and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000. Note of Clarification on Paragraph 29 added by WMA General Assembly, Washington, 2002.

INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects**.** Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to

the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient’s information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents

obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists. *(See footnote*)*

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

FOOTNOTE:

Note of Clarification on Paragraph 29 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the

absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or

- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

Note: Information about the practical application of the principles set out in the above Declaration of Helsinki can be found in the *International Ethical Guidelines for Biomedical Research involving Human Subjects* (Council for International Organizations of Medical Sciences, Geneva, 2002).

2. COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES

INTERNATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (2002)

BASIC PRINCIPLES

N.B. The 2002 edition of these CIOMS guidelines consists of a total of 21 guidelines, each with accompanying commentary. Only the guidelines are provided here. The reader is encouraged to review the complete CIOMS document in order to better understand the background and rationale for the guidelines and to gain an appreciation of the different opinions expressed by the consultants. In some cases, consensus was not reached on some of the guidelines and this is reflected and explained in the commentary.

Guideline 1: Ethical justification and scientific validity of biomedical research involving human beings

The ethical justification of biomedical research involving human subjects is the prospect of discovering new ways of benefiting people's health. Such research can be ethically justifiable only if it is carried out in ways that respect and protect, and are fair to, the subjects of that research and are morally acceptable within the communities in which the research is carried out. Moreover, because scientifically invalid research is unethical in that it exposes research subjects to risks without possible benefit, investigators and sponsors must ensure that proposed studies involving human subjects conform to generally accepted scientific principles and are based on adequate knowledge of the pertinent scientific literature.

Guideline 2: Ethical review committees

All proposals to conduct research involving human subjects must be submitted for review of their scientific merit and ethical acceptability to one or more scientific review and ethical review committees. The review committees must be independent of the research team, and any direct financial or other material benefit they may derive from the research should not be contingent on the outcome of their review. The investigator must obtain their approval or clearance before undertaking the research. The ethical review committee should conduct further reviews as necessary in the course of the research, including monitoring of the progress of the study.

Guideline 3: Ethical review of externally sponsored research

An external sponsoring organization and individual investigators should submit the research protocol for ethical and scientific review in the country of the sponsoring organization, and the ethical standards applied should be no less stringent than they would be for research carried out in that country. The health authorities of the host country, as well as a national or local ethical review committee, should ensure that the proposed research is responsive to the health needs and priorities of the host country and meets the requisite ethical standards.

Guideline 4: Individual informed consent

For all biomedical research involving humans the investigator must obtain the voluntary informed consent of the prospective subject or, in the case of an individual who is not capable of giving informed consent, the permission of a legally authorized representative in accordance with applicable law. Waiver of informed consent is to be regarded as uncommon and exceptional, and must in all cases be approved by an ethical review committee.

Guideline 5: Obtaining informed consent: Essential information for prospective research subjects

Before requesting an individual's consent to participate in research, the investigator must provide the following information, in language or another form of communication that the individual can understand:

1. that the individual is invited to participate in research, the reasons for considering the individual suitable for the research, and that participation is voluntary;

2. that the individual is free to refuse to participate and will be free to withdraw from the research at any time without penalty or loss of benefits to which he or she would otherwise be entitled;

3. the purpose of the research, the procedures to be carried out by the investigator and the subject, and an explanation of how the research differs from routine medical care;

4. for controlled trials, an explanation of features of the research design (e.g., randomization, double-blinding), and that the subject will not be told of the assigned treatment until the study has been completed and the blind has been broken;

5. the expected duration of the individual's participation (including number and duration of visits to the research centre and the total time involved) and the possibility of early termination of the trial or of the individual’s participation in it;

6. whether money or other forms of material goods will be provided in return for the individual's participation and, if so, the kind and amount;

7. that, after the completion of the study, subjects will be informed of the findings of the research in general, and individual subjects will be informed of any finding that relates to their particular health status;

8. that subjects have the right of access to their data on demand, even if these data lack immediate clinical utility (unless the ethical review committee has approved temporary or permanent non-disclosure of data, in which case the subject should be informed of, and given, the reasons for such non-disclosure);

9. any foreseeable risks, pain or discomfort, or inconvenience to the individual (or others) associated with participation in the research, including risks to the health or well-being of a subject’s spouse or partner;

10. the direct benefits, if any, expected to result to subjects from participating in the research

11. the expected benefits of the research to the community or to society at large, or contributions to scientific knowledge;

12. whether, when and how any products or interventions proven by the research to be safe and effective will be made available to subjects after they have completed their participation in the research, and whether they will be expected to pay for them;

13. any currently available alternative interventions or courses of treatment;

14. the provisions that will be made to ensure respect for the privacy of subjects and for the confidentiality of records in which subjects are identified;

15. the limits, legal or other, to the investigators' ability to safeguard confidentiality, and the possible consequences of breaches of confidentiality;

16. policy with regard to the use of results of genetic tests and familial genetic information, and the precautions in place to prevent disclosure of the results of a subject's genetic tests to immediate family relatives or to others (e.g., insurance companies or employers) without the consent of the subject;

17. the sponsors of the research, the institutional affiliation of the investigators, and the nature and sources of funding for the research;

18. the possible research uses, direct or secondary, of the subject`s medical records and of biological specimens taken in the course of clinical care (See also Guidelines 4 and 18 Commentaries);

19. whether it is planned that biological specimens collected in the research will be destroyed at its conclusion, and, if not, details about their storage (where, how, for how long, and final disposition) and possible future use, and that subjects have the right to decide about such future use, to refuse storage, and to have the material destroyed (See Guideline 4 Commentary);

20. whether commercial products may be developed from biological specimens, and whether the participant will receive monetary or other benefits from the development of such products;

21. whether the investigator is serving only as an investigator or as both investigator and the subject`s physician;

22. the extent of the investigator's responsibility to provide medical services to the participant;

23. that treatment will be provided free of charge for specified types of research-related injury or for complications associated with the research, the nature and duration of such care, the name of the organization or individual that will provide the treatment, and whether there is any uncertainty regarding funding of such treatment.

24. in what way, and by what organization, the subject or the subject`s family or dependants will be compensated for disability or death resulting from such injury (or, when

indicated, that there are no plans to provide such compensation);

25. whether or not, in the country in which the prospective subject is invited to participate in research, the right to compensation is legally guaranteed;

26. that an ethical review committee has approved or cleared the research protocol.

Guideline 6: Obtaining informed consent: Obligations of sponsors and investigators

Sponsors and investigators have a duty to:

- refrain from unjustified deception, undue influence, or intimidation;
- seek consent only after ascertaining that the prospective subject has adequate understanding of the relevant facts and of the consequences of participation and has had sufficient opportunity to consider whether to participate;
- as a general rule, obtain from each prospective subject a signed form as evidence of informed consent – investigators should justify any exceptions to this general rule and obtain the approval of the ethical review committee (See Guideline 4 Commentary, *Documentation of consent*);
- renew the informed consent of each subject if there are significant changes in the conditions or procedures of the research or if new information becomes available that could affect the willingness of subjects to continue to participate; and,
- renew the informed consent of each subject in long-term studies at pre-determined intervals, even if there are no changes in the design or objectives of the research.

Guideline 7: Inducement to participate

Subjects may be reimbursed for lost earnings, travel costs and other expenses incurred in taking part in a study; they may also receive free medical services. Subjects, particularly those who receive no direct benefit from research, may also be paid or otherwise compensated for inconvenience and time spent. The payments should not be so large, however, or the medical services so extensive as to induce prospective subjects to consent to participate in the research against their better judgment ("undue inducement"). All payments, reimbursements and medical services provided to research subjects must have been approved by an ethical review committee.

Guideline 8: Benefits and risks of study participation

For all biomedical research involving human subjects, the investigator must ensure that potential benefits and risks are reasonably balanced and risks are minimized.

- Interventions or procedures that hold out the prospect of direct diagnostic, therapeutic or preventive benefit for the individual subject must be justified by the expectation that they will be at least as advantageous to the individual subject, in the light of foreseeable risks and benefits, as any available alternative. Risks of such 'beneficial'

interventions or procedures must be justified in relation to expected benefits to the individual subject.

- Risks of interventions that do not hold out the prospect of direct diagnostic, therapeutic or preventive benefit for the individual must be justified in relation to the expected benefits to society (generalizable knowledge). The risks presented by such interventions must be reasonable in relation to the importance of the knowledge to be gained.

Guideline 9*: *Special limitations on risk when research involves individuals who are not capable of giving informed consent

When there is ethical and scientific justification to conduct research with individuals incapable of giving informed consent, the risk from research interventions that do not hold out the prospect of direct benefit for the individual subject should be no more likely and not greater than the risk attached to routine medical or psychological examination of such persons. Slight or minor increases above such risk may be permitted when there is an overriding scientific or medical rationale for such increases and when an ethical review committee has approved them.

Guideline 10: Research in populations and communities with limited resources

Before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that:

- the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out; and

- any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.

Guideline 11: Choice of control in clinical trials

As a general rule, research subjects in the control group of a trial of a diagnostic, therapeutic, or preventive intervention should receive an established effective intervention. In some circumstances it may be ethically acceptable to use an alternative comparator, such as placebo or "no treatment".
Placebo may be used:

- when there is no established effective intervention;

- when withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms;

- when use of an established effective intervention as comparator would not yield scientifically reliable results and use of placebo would not add any risk of serious or irreversible harm to the subjects.

Guideline 12: Equitable distribution of burdens and benefits in the selection of groups of subjects in research

Groups or communities to be invited to be subjects of research should be selected in such a way that the burdens and benefits of the research will be equitably distributed. The exclusion of groups or communities that might benefit from study participation must be justified.

Guideline 13: Research involving vulnerable persons

Special justification is required for inviting vulnerable individuals to serve as research subjects and, if they are selected, the means of protecting their rights and welfare must be strictly applied.

Guideline 14: Research involving children

Before undertaking research involving children, the investigator must ensure that:

- the research might not equally well be carried out with adults;
- the purpose of the research is to obtain knowledge relevant to the health needs of children;
- a parent or legal representative of each child has given permission;
- the agreement (assent) of each child has been obtained to the extent of the child`s capabilities; and,
- a child`s refusal to participate or continue in the research will be respected.

Guideline 15: Research involving individuals who by reason of mental or behavioural disorders are not capable of giving adequately informed consent

Before undertaking research involving individuals who by reason of mental or behavioural disorders are not capable of giving adequately informed consent, the investigator must ensure that:

- such persons will not be subjects of research that might equally well be carried out on persons whose capacity to give adequately informed consent is not impaired;
- the purpose of the research is to obtain knowledge relevant to the particular health needs of persons with mental or behavioural disorders;
- the consent of each subject has been obtained to the extent of that person's capabilities, and a prospective subject's refusal to participate in research is always respected, unless, in exceptional circumstances, there is no reasonable medical alternative and local law permits overriding the objection; and,
- in cases where prospective subjects lack capacity to consent, permission is obtained from a responsible family member or a legally authorized representative in accordance with applicable law.

Guideline 16: Women as research subjects

Investigators, sponsors or ethical review committees should not exclude women of reproductive age from biomedical research. The potential for becoming pregnant during a study should not, in itself, be used as a reason for precluding or limiting participation. However, a thorough discussion of risks to the pregnant woman and to her fetus is a prerequisite for the woman's ability to make a rational decision to enrol in a clinical study. In this discussion, if participation in the research might be hazardous to a fetus or a woman if she becomes pregnant, the sponsors/ investigators should guarantee the prospective subject a pregnancy test and access to effective contraceptive methods before the research commences. Where such access is not possible, for legal or religious reasons, investigators should not recruit for such possibly hazardous research women who might become pregnant.

Guideline 17: Pregnant women as research participants

Pregnant women should be presumed to be eligible for participation in biomedical research. Investigators and ethical review committees should ensure that prospective subjects who are pregnant are adequately informed about the risks and benefits to themselves, their pregnancies, the fetus and their subsequent offspring, and to their fertility.
Research in this population should be performed only if it is relevant
to the particular health needs of a pregnant woman or her fetus, or to the health needs of pregnant women in general, and, when appropriate, if it is supported by reliable evidence from animal experiments, particularly as to risks of teratogenicity and mutagenicity .

Guideline 18: Safeguarding confidentiality

The investigator must establish secure safeguards of the confidentiality of subjects' research data. Subjects should be told the limits, legal or other, to the investigators' ability to safeguard confidentiality and the possible consequences of breaches of confidentiality.

Guideline 19: Right of injured subjects to treatment and compensation

Investigators should ensure that research subjects who suffer injury as a result of their participation are entitled to free medical treatment for such injury and to such financial or other assistance as would compensate them equitably for any resultant impairment, disability or handicap. In the case of death as a result of their participation, their dependants are entitled to compensation. Subjects must not be asked to waive the right to compensation.

Guideline 20: Strengthening capacity for ethical and scientific review and biomedical research

Many countries lack the capacity to assess or ensure the scientific quality or ethical acceptability of biomedical research proposed or carried out in their jurisdictions. In externally sponsored collaborative research, sponsors and investigators have an ethical obligation to ensure that biomedical research projects for which they are responsible in such countries contribute effectively to national or local capacity to design and conduct biomedical research, and to provide scientific and ethical review and monitoring of such research.
Capacity-building may include, but is not limited to, the following activities:

- establishing and strengthening independent and competent ethical review processes/ committees

- strengthening research capacity
- developing technologies appropriate to health-care and biomedical research

- training of research and health-care staff

- educating the community from which research subjects will be drawn.

Guideline 21: Ethical obligation of external sponsors to provide health-care services

External sponsors are ethically obliged to ensure the availability of:

- health-care services that are essential to the safe conduct of the research;

- treatment for subjects who suffer injury as a consequence of research interventions; and,

- services that are a necessary part of the commitment of a sponsor to make a beneficial intervention or product developed as a result of the research reasonably available to the population or community concerned.

3. COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES

INTERNATIONAL GUIDING PRINCIPLES FOR BIOMEDICAL RESEARCH INVOLVING ANIMALS (1985)

BASIC PRINCIPLES

I The advancement of biological knowledge and the development of improved means for the protection of the health and well-being both of man and of animals require recourse to experimentation on intact live animals of a wide variety of species.

II Methods such as mathematical models, computer simulation and in vitro biological systems should be used wherever appropriate.

III Animal experiments should be undertaken only after due consideration of their relevance for human or animal health and the advancement of biological knowledge.

IV The animals selected for an experiment should be of an appropriate species and quality, and the minimum number required to obtain scientifically valid results.

V Investigators and other personnel should never fail to treat animals as sentient, and should regard their proper care and use and the avoidance or minimization of discomfort, distress, or pain as ethical imperatives.

VI Investigators should assume that procedures that would cause pain in human beings cause pain in other vertebrate species, although more needs to be known about the perception of pain in animals.

VII Procedures with animals that may cause more than momentary or minimal pain or distress should be performed with appropriate sedation, analgesia, or anaesthesia in accordance with accepted veterinary practice. Surgical or other painful procedures should not be performed on unanaesthetized animals paralysed by chemical agents.

VIII Where waivers are required in relation to the provisions of article VII the decisions should not rest solely with the investigators directly concerned but should be made, with due regard to the provisions of articles IV, V, and VI, by a suitably constituted review body. Such waivers should not be made solely for the purposes of teaching or demonstration.

IX At the end of, or, when appropriate, during an experiment, animals that would otherwise suffer severe chronic pain, distress, discomfort, or disablement that cannot be relieved should be painlessly killed.

X The best possible living conditions should be maintained for animals kept for biomedical purposes. Normally the care of animals should be under the supervision of veterinarians having experience in laboratory animal science. In any case, veterinary care should be available as required.

XI It is the responsibility of the director of an institute or department using animals to ensure that investigators and personnel have appropriate qualifications or experience for conducting procedures on animals. Adequate opportunities shall be provided for in-service training, including the proper and humane concern for the animals under their care.

4. 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 10). 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.

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

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.

6. 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.

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.

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

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

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 …….

Signature ……Date…….

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

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

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.

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

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 Appendix 1 of the *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, CIOMS, 2002).

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 52nd General Assembly, Edinburgh, Scotland, October 2000.)

2. *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, CIOMS, 2002.

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, 1995.

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.

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

POLICIES ON DISSEMINATION OF RESEARCH RESULTS

1. General principles

1.1 A central tenet of all research, and an integral component of the activities of the Special Programme, is sharing the knowledge produced with all those concerned about the research, beginning with the study participants and extending to other ordinary women and men. This requires innovative approaches to disseminating the research findings, which are beyond scholarly meetings and publications.

1.2 All research projects initiated or supported by the Special Programme should include information on how the results will be disseminated to all appropriate audiences. These audiences must include the participants in the research, as well as the local community, the general public and the scientific community.

1.3 The Special Programme encourages the publication of results of research as soon as possible. However, the Special Programme recognizes the need to protect intellectual property and hence accepts that occasionally it may be necessary to delay publication of results where an invention is involved.

1.4 Writing up the results of research for publication in scientific journals is a necessary component of the research exercise. As part of its efforts towards strengthening capabilities for research in developing countries, the Special Programme encourages and supports developing country scientists to complete the research exercise by writing up their data and getting them published.

1.5 With a view to ensuring proper and timely dissemination of research results, where appropriate, the Special Programme will consider providing financial or other support for publication, within the overall support of the research proposal.

2. General policy

2.1 For research supported by the Special Programme, the manuscript of research articles must be reviewed and cleared by the Special Programme before publication. The Special Programme will take the necessary action to ensure that this review does not cause any undue delay in publication. The objective of the review, apart from providing constructive comments, is to ensure that the publication does not contradict WHO principles and policies and does not jeopardize patent applications or other intellectual property.

2.2 Support by the Special Programme should always be appropriately acknowledged in the publication.

2.3 The Special Programme should be provided with at least two copies of any publication resulting from research supported by it.

2.4 The Special Programme reserves the right to analyse further, in the light of new information, any data it has accumulated from previous studies supported by it. All publications resulting from such analyses will always include a reference to the original studies.

3. Multicentre studies

3.1 A collaborating institution may not publish its results or communicate them to scientific meetings or to the public before the completion of the multicentre study, except with the prior written approval from the Special Programme.

3.2 After publication of the results of a multicentre study, collaborating institutions may carry out further analysis of their own data and publish their individual results, with appropriate reference to the multicentre study.

3.3 The coordinator(s) of the study will have the responsibility of preparing the first draft of the manuscript. The manuscript should be reviewed and approved by all investigators before publication.

4. Authorship

4.1 The Special Programme encourages an authorship policy, conforming with the guidelines adopted by the International Committee of Medical Journal Editors (See Annex). Authorship should be limited to those who have participated sufficiently in the work to take public responsibility for the content.

4.2 For research carried out in a single institution, the order of authors will be determined by the institution.

4.3 For research conducted in more than one institution in the same country, and unless otherwise agreed by the investigators, the first author will be the coordinator of the study, and other authors will be listed in alphabetical order of their institution's city/town.

4.4 For multicentre research conducted in institutions in different countries, the author may appear as the World Health Organization. The names of the participants in the study will be given in a footnote, in alphabetical order of their institution's city/town. The name of the coordinator of the study will appear with the designation of coordinator in brackets. Other participants with specific inputs may also be designated with their inputs.

5. Research Group Committees

5.1 The Research Group Committees have the responsibility to ensure that the results of the research are adequately disseminated.

5.2 The Research Group Committees should review results of research before publication and should review and provide scientific and technical comments on manuscripts.

6. Staff and consultants of the Special Programme

6.1 The staff of the Special Programme are encouraged to publish and to present to scientific meetings reviews of the state of the art referring to and highlighting the published studies of the Special Programme.

6.2 The staff and consultants of the Special Programme can use only published data from studies supported by the Special Programme for their articles and presentations. Unpublished data may be released only with the agreement of the Director of the Special Programme.

6.3 The staff and consultants of the Special Programme may appear as co-authors in publications resulting from research conducted by the Special Programme, if they qualify under the guidelines developed by the International Committee of Medical Journal Editors (See Annex).

6.4 Generally, the names of the staff and consultants of the Special Programme will appear last in publications resulting from research conducted by the Special Programme. An exception to the rule is made when they have played a more participatory role in the research, as determined by the coordinator of the study.

6.5 According to WHO rules, all publications with a regular or temporary WHO staff member's name as one of the authors must be cleared by the Assistant Director-General through the Director of the Special Programme and the Chief, Office of Publications.

7. Press releases and contacts with the press

7.1 Centres participating in multicentre research initiated and funded by the Special Programme may not issue press releases independently. The Special Programme reserves the right to issue press releases in the case of such studies. The aim of this is to prevent conflicting statements being given to the press from a single study. The Special Programme will send advance copies of the press release to the centres involved, who are expected to respect any embargo on it. The centres are encouraged to issue press releases, based on the WHO press release, in the local language and context as necessary. These press releases should not be issued before the WHO press release is published. The researchers involved in the study are also encouraged to give interviews to the press as local experts.

7.2 In the case of single-country projects, the principal investigators are encouraged to disseminate information about their research to the press via press releases or press conferences, or both. However, any statement given to the press should have been cleared with the Special Programme. The purpose of this is to ensure that the text does not carry any statements that contradict WHO principles and that due credit is given to the support provided by the Special Programme.

ANNEX

The guidelines on authorship and acknowledgements for scientific papers quoted below were developed by the International Committee of Medical Journal Editors and published in *The Lancet* on 14 September 1985:

Authorship

Each author should have participated sufficiently in the work to take public responsibility for the content. This participation must include:

(a) conception or design, or analysis and interpretation of data, or both;

(b) drafting the article or revising it for critically important intellectual content; and

(c) final approval of the version to be published.

Participation solely in the collection of data does not justify authorship.

All elements of an article (a, b, and c above) critical to its main conclusions must be attributable to at least one author.

Acknowledgements

At an appropriate place in the article (title-page, footnote or appendix to the text; see journal's requirements) one or more statements should specify:

(a) contributions that need acknowledging but do not justify authorship;

(b) acknowledgements of technical help;

(c) acknowledgements of financial and material support.

Persons who have contributed intellectually to the paper but whose contribution does not justify authorship may be named and their contribution described, for example, "advice", "critical review of study proposal", "data collection", "participation in clinical trial". Such persons must have given their permission to be named.

Technical help should be acknowledged in a separate paragraph from the contributions above.

Financial or material support from any source must be specified.

11. GENERAL CONDITIONS CONCERNING WHO SUPPORT FOR RESEARCH OR OTHER TECHNICAL SERVICES

The following are the standard general conditions of the Technical Services Agreement form used by WHO to fund accepted projects. It should be noted, however, that these general conditions (in particular, general condition 6) may require modification for specific projects in order to fit particular circumstances.

1. Institution and Principal Investigator

1.1 The Institution and the Principal Investigator (or Responsible Technical Officer), who must be an employee of the Institution, shall be jointly responsible for all the technical and administrative aspects of the work referred to in this Agreement.

1.2 The Institution is required to notify WHO immediately of knowledge that the Principal Investigator will cease or ceases to be an employee of the Institution or is no longer continuing the responsibilities covered by this Agreement. Under such circumstances WHO has the right to:

a. cancel this Agreement; or
b. agree to continue the project under a new Principal Investigator proposed by the Institution and approved by WHO.

2. Financial arrangements

2.1 Payments shall be made into the bank account(s) of the Institution as specified in this Agreement and in accordance with the schedule of payments contained therein. If, after the submission of the final financial report referred to in paragraph 4.3 below, there remains an unused balance of funds with the Institution, this balance shall be due to WHO. In the event of this Agreement being cancelled under any circumstances, the Institution shall refund to WHO the balance of uncommitted funds. The funds provided under this Agreement shall be expended only in accordance with its terms.

2.2 The funds transferred to the Institution under this Agreement may not be used to meet any form of emoluments, travel costs or any other reimbursements of expenditure to a staff member of WHO.

2.3 Unless otherwise provided in this Agreement the funds may not be used to cover:

a. normal administrative and overhead expenses of the Institution;
b. cost of maintenance, repair, running or insurance of existing equipment and machinery belonging to the Institution;
c. cost of construction of new buildings or alterations and modifications of existing buildings and premises;
d. salary support of the Principal Investigator.

3. Equipment and supplies

3.1 Unless otherwise agreed, and subject to subparagraph 3.2 below, any equipment acquired under this Agreement shall become the property of the Institution. The Institution and the Principal Investigator shall be jointly responsible for the proper safeguard, maintenance and care of all equipment acquired under this Agreement.

3.2 Notwithstanding subparagraph 3.1 above, the Institution shall transfer ownership of any equipment acquired under this Agreement to WHO, if so requested by WHO, upon termination or expiry of this Agreement. In such cases the Institution shall despatch the equipment to any destination chosen by WHO, the cost of which will be borne by WHO.

4. Reports

The Institution shall submit technical and financial reports to WHO on the work as required, or at least annually, in accordance with the following provisions:

4.1 Technical reports shall be prepared by the Principal Investigator and forwarded through and countersigned by the authorized official of the Institution or his authorized representative. Each annual report shall summarize the results of the project and give in sufficient detail all its positive and negative findings so that the value of the work can be assessed.

4.2 Financial reports shall be forwarded after being jointly certified by the Institution's chief financial officer and the Principal Investigator, using form WHO 782. The reports must show the use of the funds provided by WHO compared with the original budget expenditure pattern agreed between the Institution and WHO.

4.3 All financial reporting is subject to audit by WHO's auditors, including examination of supporting documentation and relevant accounting entries in the Institution's books. In order to facilitate such financial reporting and audit, the Institution shall keep accurate and systematic accounts and records in respect of the project. The final financial report must be submitted within 90 days after the expiry of this Agreement.

5. Relationship and responsibility of parties

The relationship of the Institution to WHO shall be that of an independent contractor. The employees of the Institution are not entitled to describe themselves as staff members of WHO. The Institution shall be solely responsible for the manner in which work on the project is carried out and accordingly shall assume full liability for any damage arising from research or other technical services under this Agreement. No liability shall attach to WHO, its advisers, agents or employees.

6. Use of results, exploitation of rights, and publication

6.1 The results of the project funded under this Agreement may be freely used or disclosed by either party provided that, without the consent of the other party, no use may be made for commercial purposes and confidentiality shall be maintained with respect to results that may be eligible for protection by proprietary rights. The Institution shall provide WHO with the results, in the form of relevant know-how and other information, and to the extent feasible, tangible products.

6.2 The industrial or commercial exploitation of any intellectual property rights, including the ownership of know-how, arising from the project shall be designed to achieve, in so far as circumstances permit, the following objectives in the following order of priority:

a. the general availability of the products of creative activity;
b. the availability of those products to the public health sector on preferential terms, particularly in developing countries;
c. the grant to each party of additional benefits, including royalties, account being taken of the relative value of each party's financial, intellectual and other contribution to the research.

6.3 The rights referred to in para. 6.2 shall belong to the Institution, or to the Principal Investigator if the Institution and WHO so agree. To the extent that the former do not intend to exercise them, the rights shall be promptly transferred to WHO, if it so requests. Each party shall provide the other with its full cooperation to permit the effective exercise of the rights. The party in which the corresponding rights are vested may file applications for industrial property protection, promptly furnishing copies of the applications and other patent documents to the other party. All rights other than the right to file applications shall be exercised in accordance with an agreement which shall be negotiated in good faith between the Institution and WHO.

6.4 In any publication by the Institution or the Principal Investigator relating to the results of the project, the responsibility for the direction of the work shall not be ascribed to WHO. Unless WHO advises otherwise, all publications shall include a notice indicating that the underlying investigation received financial support from WHO. Two off-prints or copies shall be sent to WHO unless another number is stipulated. WHO funds may not be used for publication costs unless specifically authorized.

7. Research involving human subjects

7.1 Ethical aspects

It is the responsibility of the Institution and the Principal Investigator to safeguard the rights and welfare of human subjects involved in research supported in whole or in part by funds from WHO, in accordance with the appropriate national code of ethics or legislation, if any, and in the absence thereof, the Helsinki Declaration and any subsequent amendments. Such funds may be used only to support investigations where (*a*) the rights and welfare of the subjects involved in the research are adequately protected, (*b*) freely given informed consent has been obtained, (*c*) the balance between risk and potential benefits involved has been assessed and deemed acceptable by a panel of independent experts appointed by the Institution, and (*d*) any special national requirements have been met.

7.2 Regulatory requirements

It is the responsibility of the Institution and the Principal Investigator to comply with the relevant national regulations pertaining to research involving human subjects.

7.3 Protection of subjects

Without prejudice to obligations under applicable laws, the Institution shall make appropriate arrangements to eliminate or mitigate the consequences to subjects or their families in the case of death, injury or illness resulting from the conduct of research referred to in paragraph 7.1. Such arrangements shall, to the extent feasible, include medical treatment and financial relief. The Institution and Principal Investigator undertake to protect the confidentiality of the information relating to the possible identification of subjects involved in the research involving human subjects conducted under the auspices of this Agreement.

8. Research involving the use of laboratory animals

The Institution undertakes that living vertebrate animals, required for use as laboratory animals for the research to be carried out under this Agreement, shall be handled in accordance with generally accepted principles for the humane treatment of such animals and the avoidance of unnecessary suffering.

9. Research safety

It is the responsibility of the Institution to establish and implement policies and practices to assure and provide for the safety of its employees, the public, and the environment during the conduct of the supported research. If the supported research involves the use of dangerous biological agents, the Institution shall establish and implement an appropriate safety plan.

10. Publicity

The Institution and the Principal Investigator shall not refer to the relationship of WHO to the project, or to products or processes connected with the project, in any statement or material of a publicity or promotional nature issued for commercial purposes, or with a view to financial benefit.

11. Choice of law and settlement of dispute

The Agreement shall be construed in accordance with the law of Switzerland. Any dispute relating to the interpretation or execution of this Agreement shall, unless amicably settled, be subject to conciliation. In the event of failure of the latter, the dispute shall be settled by arbitration. The arbitration shall be conducted in accordance with the modalities to be agreed upon by the parties, or in the absence of an agreement, with the Rules of Arbitration of the International Chamber of Commerce. The parties shall accept the arbitral award as final.