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TWENTY-FIRST MEETING OF THE
PAHO ADVISORY COMMITTEE ON MEDICAL RESEARCH

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INDEXED

RECOMMENDATIONS OF THE 20TH MEETING OF THE PAHO|ACMR

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RECOMMENDATIONS OF THE 20TH MEETING OF THE PAHO/ACMR

1. Diarrheal Diseases

1.1 It was recommended that:

a) A progress report of the activities of this SWG be presented at the next meeting of the ACMR.

b) The results of the forthcoming meeting of the SWG be circulated to all ACMR members.

c) A strong emphasis should be placed on operational and HSR aspects in the program as a whole and in any projects which were being planned or funded.

d) Efforts should be made to increase the number of epidemiologists in the area and to foster the training of scientists concerned with the problem.

1.2 Action Taken

Because of the lack of time available at the 21st ACMR meeting, an oral presentation regarding the activities of the SWG has not been planned. However, a report of the first meeting of the PAHO SWG on Diarrheal Diseases held during 1981 is attached for consideration.

As is shown in "PAHO research in progress", projects on research on Diarrheal Diseases funded within the region followed the guidelines established by the PAHO SWG which puts strong emphasis on the operational and HSR aspects of the program. Strong efforts have been made to increase the awareness of epidemiologists in the countries by encouraging their participation in the National Diarrheal Disease Control Program Committee. Inclusion of epidemiologists in specific research activities has been strongly

recommended by the secretariat and invariably endorsed by the National Programme Managers. Guidelines to be followed for those interested in undertaking epidemiological research in diarrheal disease control have been widely distributed in the region and are attached.

2. Health Services Research

2.1 It was recommended that:

a) There should be a change in focus vis a vis HSR. PAHO should try to select a few categorical programs and introduce HSR into these programs in an evaluative or operational mode instead of insisting on the formulation of a vertical HSR program.

b) Efforts should be made to attract some of the academic community into health oriented research activities and focal points should be identified to promote harmony in HSR capabilities.

c) The present subcommittee on HSR should cease to function but the topic of HSR should be constantly before the ACMR.

2.2. Action Taken

As a base for development of a proposal on a regional program on "Drug management and supply" for Latin America and the Caribbean, an operational analysis on Posts and Health Centers was made in the Dominican Republic, Ecuador, Honduras, Panama and Peru. These studies identified several deficiencies in different aspects of the operation such as, selection of items to be bought, distribution and utilization of drugs. A methodology to be incorporated in instructional modules was developed for the self-evaluation of those involved in these activities.

In the Maternal and Child Health Care program, activities concerning the risk approach have been implemented. Strong support for this was obtained from the scientific and academic communities not only in the development of tools and methods, but also in the training aspects. In particular, CLAP has developed a methodology for identification of risk factors that is being applied in 50 maternity hospitals of 12 countries in the region.

A plan was developed in Mexico concerning HSR as a component of the program designed for providing health services to the marginal urban areas.

An inventory of health services researchers on the U.S.-Mexican border has been developed.

Through visits of the secretariat, strong efforts have been made to promote in the academic community the concept that HSR activities are needed to improve primary health care services. Studies of that sort will only be possible if a core of scientific personnel is available. It was suggested that students should participate in health science research studies as prerequisite for graduation. Also emphasized was the need for interdisciplinary teams in accordance with the nature of the problems to be tackled.

At a workshop attended by professors of operational research and health management, held in Caracas, Venezuela, the purpose of the teaching of operational research in the undergraduate, graduate and post-graduate levels in programs concerning health management was discussed. Recommendations were made regarding the contents of the curriculum and the bibliography to be used.

3. Social Sciences related to HSR

3.1 It was recommended that:

a) The scientific subcommittee should continue its activities and complete its work in one year.

b) The subcommittee should complete its work on the development of the inventory on social science health research, and specifically, related to social and economic research on malaria. It should continue to develop the conceptual and research framework for the research by the social sciences in relation to malaria as well as examine the state of field work and epidemiological research being done on malaria.

3.2 Action taken

The scientific working group on social science health research has completed a Latin American bibliography on Social Sciences applied to health which will be circulated to major libraries and schools of public health in the region. A review of social and economic factors affecting the transmission and the control of malaria was also prepared, identifying those factors which may foster more effective planning and the organization of existing control programs.

The Report of the Working Group presented at this meeting (item 5 of the agenda) summarizes: 1) the current situation relating to malaria in the Region; 2) the present position of social science research in connection to this disease; 3) social and economic factors which affect its transmission and its control presented as a working conceptual framework; 4) the experience of malaria control programs in three nations which illustrates the direct application and the relevance of the principles identified in the conceptual framework; and, 5) the major conclusions and the recommendations of the Working Group.

4. PAHO guidelines and review procedures for the protection of human subjects in medical research

4.1 It was recommended that:

a) The ACMR members be circulated with the full documentation of the procedures used by the PAHO review committee.

b) This item be kept on the agenda and be discussed at the next meeting by which time the final report of the WHO/CIOMS group would be available for study and discussion.

4.2 Action Taken

The PAHO guidelines and review procedures for research invloving human subjects were developed by the Secretariat and approved by the Regional Director and the PAHO Review Committee for Research involving Human Subjects was established at Headquarters.

The following documents are presented for the information of the PAHO Advisory Committee on Medical Research:

a) PAHO guidelines and review procedures for research involving human subjects.

b) Draft of forms to be included in all proposals for research to be conducted and/or supported by PAHO which involves experimentation using human subjects. These forms are to be completed by the principal investigator indicating that an appropriate local committee has reviewed and approved the research activities involving human subjects (assurance/certification/declaration of protection of human subjects) and providing all necessary information on the characteristics of the project in order that PAHO/Review Committee on Research Involving Human Subjects (RCRIHS) could review it. (Application for a research project to be reviewed by the PAHO RCRIHS).

c) proposed international guidelines for biomedical research involving human subjects.

d) XIVth CIOMS round table conference on Medical Ethics and Medical Education.

5. Regional activities vis-a-vis the Special Program for Research and Training in Tropical Diseases

5.1 It was recommended that:

a) Efforts should be made through PAHO to stimulate interest and promote participation in the TDR program.

b) Members of the Committee should be circulated with the TDR regional profile.

c) A report on the TDR should be presented at the next meeting of the ACMR.

d) Consideration should be given to increasing the involvement of the region specifically in that part of the program relating to Chagas' disease which was found only in the Region.

e) Efforts should be made to achieve better coordination of actions between PAHO and WHO headquarters in relation to this program.

5.2 Action Taken

Members of the committee have been circulated with the TDR regional profile and a report on TDR activities in the region has been presented at the Pan American Conference on Health Research Policies.

An effort has been made by the secretariat to promote participation of scientists of the region in collaborative research projects not only in Chagas' disease, which is only found in the Region, but also in the other diseases targetted by the program.

A meeting sponsored by TDR on standardized protocols for chemotherapy of Chagas' disease was held in the PAHO office. Furthermore, the secretariat located in Washington participated in steering committee meetings of the Scientific Working Groups on Chagas' disease, Leishmaniasis, and Malaria as well as in the meetings of the Research Strengthening Group of TDR.

6. Nutrition

6.1 It was recommended that:

a) Systematic support should be given to the training of researchers in nutrition and health in the countries.

b) Promote, support and strengthen scientific and technological exchange in the field of nutrition between the countries of the Region.

c) Promote, facilitate and support dialogue and interchange between personnel involved in research, planning, and administration of programs of health and nutrition..

d) Channel some resources from external sources to the development of action-oriented research in those fields related to the consumption and utilization of nutrients.

e) Stimulate and support research according to the following priorities: 1) Operational research, especially in relation to the effective and systematic incorporation of a discrete component of nutrition within the primary health care package; 2) Applied research, directed towards the possibility of utilizing the existing health services for the prevention and control of the nutrition infection complex; 3) Basic research on nutrition and its relationship with infection, parasitic infestation as well as its effects on the individual in terms of social and biological functioning.

6.2 Action Taken

Two projects were initiated in the Region. The first one in Colombia is related to the determinants of child feeding practices and their inprovement through primary health services in a rural community in the Department of Cundimarca, Colombia. This is a joint venture between the State Health Department and the Javeriana University. In the first stage of this project that has been already completed, a comprehenisve diagnosis of the socio-cultural and economic situation of the community involved was carried out. The second phase of the project will give a complete understanding of the dynamics of feeding practices, particularly related to the infant and young child.

The second project was initiated in Mexico by the National Institute of Health Sciences and Technology of The Child (Sistema Nacional para el Desarrollo Integral de la Familia, DIF). The purpose of this project is the design, testing and evaluation of health and nutrition indicators to be used by primary health care workers.

Two to three new research projects are expected to be established if a funding search proves to be successful. Preliminary talks with possible funding agencies are underway.

A preliminary guideline for the design of research protocols, the organization and management of action-oriented research in nutrition was prepared and it is being submitted to the ACMR (item 6 of the agenda).

7. Mental Health Research

7.1 It was recommended that:

a) There should be a regional initiative in this field.

b) Dr. Hamburg be requested to convene a study group to explore the area as it related peculiarly to the Region and to prepare the background material necessary to allow a decision to be taken as to whether there should be a regional research program and how it should be implemented.

7.2 Action Taken

A report on the subject has been prepared by Dr. Hamburg and it is being presented at this meeting (item 7 of the agenda).

8. Acute Respiratory Infections

8.1 It was recommended that a study group be set up to examine the state of research in this area and the feasibility of a regional program to deal with acute respiratory infections in children.

8.2 Action Taken

A meeting chaired by Dr. Robbins, with the participation of several experts on the subject, was held at PAHO in order to establish the areas in which research could make the most positive impact. A report on this meeting is being presented at the ACMR (item 4 of the agenda).

A broad project on research in Acute Respiratory infections has been prepared and is attached for your consideration.

9. Cardiovascular Diseases Research

9.1 It was recommended that PAHO staff working in this area make a presentation during the 21st meeting on the research being done in this field.

9.2 Action Taken

A report made by the secretariat has been prepared and will be presented at this meeting (item 9 of the agenda).

10. Environmental Problems and Their Relation to Health

10.1 It was recommended that for the 21st meeting CEPIS be invited to make a presentation which would address the issue of interdisciplinary collaboration in health research.

10.2 Action Taken

The Director of CEPIS will make a presentation at the 21st meeting (item 10 of the agenda).

REPORT OF THE FIRST MEETING OF THE
PAHO SCIENTIFIC WORKING GROUP ON
DIARRHOEAL DISEASES (SWG/DD)

(Washington, D.C., 15-16 June, 1981)

CONTENTS

1. SUMMARY

The First Pan American Health Organization (PAHO) Scientific Working Group Meeting on Diarrhoeal Diseases (SWG/DD) took place at PAHO Headquarters on 15-16 June, 1981. Seven scientists from as many Member Countries met with several PAHO Secretariat members to review Regional Diarrhoeal Diseases Control (CDD) Program research activities to date, to consider new technical advances in the field and to update existing priorities for Regionally administered CDD research. After an introductory address by PAHO Director Dr. Héctor R. Acuña, the participants met in small working groups followed by plenary sessions. The recommendations subsequently formulated by the SWG/DD will provide the framework by which a newly formed, out-of house Steering Committee for CDD Research will set priorities for research grant proposals from within the Region of the Americas; review and evaluate those submitted for PAHO/WHO CDD Program funding and make appropriate recommendations.

2. TERMS OF REFERENCE

2.1. To review the "research review mechanism" outlined by the PAHO Interdivisional Working Group on Diarrhoeal Diseases.

2.2. To review new and existing knowledge regarding diarrhoeal diseases.

2.3. To designate areas where further research is needed.

2.4. To review previous research priorities and establish new ones.

2.5. To recommend approaches to managing Regional CDD research activities that should be adopted with due regard to feasibility and cost.

2.6. To prepare a clear Regional research plan in the context of program needs.

3. OPENING REMARKS by Dr. Héctor R. Acuña, PAHO, Director

(abstract)

The Director welcomed the participants, pointing out their collective expertise highly qualified them to chart the Organization's course of action as regards diarrhoeal diseases research. In highlighting the high priority PAHO has traditionally accorded diarrhoeal diseases, the Director quoted a portion of the acceptance speech he delivered when assuming the Directorship in 1975[1] in which he called for increased efforts to eliminate this "age-old problem." Since then, recalled the Director, the WHO Global Program for the Control of Diarrhoeal Diseases

(CDD) has been initiated, complementing ongoing Regional efforts, and activities have been steadily intensifying. The work to be undertaken by the group, added the Director, will help the Organization deal with an ever increasing flow of CDD research proposals, in the process contributing significantly to the achievement of "Health for All by the Year 2000."

4. DESCRIPTION OF THE CDD PROGRAM

The policy and technical bases of the global CDD Program were described. Begun in May, 1978 in response to Resolution 31.44 of the World Health Assembly, the Program reflects the Organization's increased commitment both to primary health care (PHC) and to the goal of Health for All by the Year 2000.[2,3] A number of key technical breakthroughs have dramatically improved the feasibility of controlling diarrhoeal diseases. These include the recognition of several new diarrhoeal pathogens, new understanding of the pathogenesis of diarrhoea and, especially, the refinement of oral rehydration therapy (ORT) and demonstration of its high efficacy in the management of acute diarrhoeal dehydration.

The CDD Program has two components: health services delivery and research. The former seeks to integrate the four basic program strategies into existing PHC systems. These strategies are: a) improved case treatment, utilizing ORT and proper dietary management; b) improved maternal and child care practices; c) improvement of water supplies and basic sanitation, and d) enhanced epidemiological surveillance.

In the Region, 30 countries have participated in sub-Regional CDD meetings and seminars to date, 25 have named national CDD program managers, 12 have held national CDD courses and seminars and 19 have prepared or are preparing national "plans of action."

Whereas to date country-level activities have been largely concentrated on developing national CDD programs or plans of action, training, information dissemination and operational research are now becoming increasingly important.

With the growing interest of both investigators and the donor community, activities in connexion with the second CDD Program component, research, are rapidly expanding.

In the initial planning phase, emphasis was placed on reviewing the available knowledge and determining operational (health services) and basic (biomedical) research priorities for the Program.[4] Between August 1978 and March 1980, nine global groups were convened on a one-time basis, with the participation of 64 scientists from 19 developing and 8 developed countries, to review knowledge in the following areas: immunity and vaccine development; epidemiology and etiology of acute diarrhoeal

diseases; clinical management of acute diarrhoea; child care practices related to diarrhoeal diseases; and environmental health in relation to diarrhoeal diseases prevention. During the same period, regional groups were convened in all six WHO regions to set out regional research priorities, primarily in operational research areas most related to the development of national CDD programs. In the Americas, initial priorities were identified by the PAHO Multidisciplinary Study Group on Diarrhoeal Diseases which met in 1979 in Washington, D.C.[5] The present meeting is, therefore, the second such Regional forum to consider CDD research needs in the Americas.

During 1980 a 5-year global CDD research management plan was conceived. Basically, the plan provides for basic, biomedical research to be administered on the global level by three Scientific-Working Groups (SWG) while Regional SWGs determine operational, (health services delivery) research matters.[6] Each Regional SWG, moreover, must approve an out-of-house peer review mechanism in which a panel of qualified scientists critiques and approves Regional research proposals.

The rationale for decentralizing CDD operational research is two-fold: it allows closer matching of research activities to actual country program needs and meets donor community conditions for increased funding.

5. COLLABORATION WITH THE INTERNATIONAL DRINKING WATER SUPPLY AND SANITATION DECADE

An overview of the Organization's plans and activities in connexion with the International Drinking Water Supply and Sanitation Decade was presented. Although comparatively one of the most advanced Regions in terms of environmental infrastructure development there are large imbalances in the availability of potable water and basic sanitary facilities throughout Latin America and the Caribbean. To illustrate, whereas 80% of the Region's urban population has access to safe water supplies, the figure for rural areas is only 34%. Regarding latrines, the figures are 45% and only 3-4%, respectively. Key problem areas include poor coordination between Ministries of Health and Ministries of Public Works; use of inappropriate equipment; poor infrastructure maintenance; low community involvement; and lack of "software" for manpower training. Human resources are seen as the limiting factor to improving the situation and, correspondingly, manpower training is one area in which CDD program imput is sorely needed.

In view of the massive ongoing and proposed infrastructure investments in this sector, the Organization is playing a complementary role by focusing on institutional strengthening, the development of human resources and community participation.

6. RESEARCH NEEDS

As of 1 April 1981, the Headquarters Secretariat had received some 326 formal proposals or letters of intent seeking support for research. An analysis of the first 263 received indicated that 157 related primarily to bacterial enteric infections (of which 48 were from the Region for the Americas), 62 primarily to viral diarrhoeas (28 from the Americas), 18 to drug development and management (6 from the Americas), and 26 to miscellaneous categories (10 from the Americas). A number of these proposals were considered to fall within the area of competence of regional SWGs and were forwarded to the appropriate regional offices.

Of these proposals and enquiries, some 55% were from investigators in developed countries and 43% from investigators in developing countries. The remainder involved collaborative research between workers in both developed and developing countries.

The total number of proposals approved for funding as of 1 April amounted to 19. Of these, 12 were for bacterial enteric infections (6 from the Americas), 4 for viral diarrhoeas (2 from the Americas), and 3 for drug development and management (all 3 from the Americas).

With program implementation underway, emphasis on Regional-level research is shifting from clinic-based trials to operational field studies. Eleven clinical trials in five Member Countries have been completed over the past three years with PAHO assistance, yielding valuable therapeutic and etiological findings and, in the process, building up regional research expertise.

Operational research supported by CDD funding is currently in progress in Jamaica, Guatemala, El Salvador, Mexico, Guyana and Ecuador. Additional operational proposals are now under consideration for funding.

Practically speaking, operational studies are in many countries the only means of generating baseline data - and establishing realistic targets - for subsequent, comprehensive national CDD programs. PAHO encourages and upon request provides both technical and financial support to such studies because they offer a means of testing various program delivery strategies while simultaneously providing services at the community level.

As expressed in several global and regional fora, the CDD Program's research component must be "goal-oriented." On the Regional level, therefore, research priorities should closely mirror actual program needs. Keeping in mind that a correlary to this aim is the strengthening of Regional institutions' research capabilities, special efforts should be made to identify and support developing country investigators and to stress the TCDC approach wherever practicable.

Research priorities for the CDD program have been identified by several groups over the past four years, (e.g., WHO/CDD Technical Advisory Groups, Global Advisory Committees on Medical Research (GACMRs), UNICEF-WHO Joint Committee on Health Policy, PAHO Regional ACMRs, PAHO Multidisciplinary Study Group on Diarrhoeal Diseases). In light of perceived current program needs the Regional Secretariat identified the following areas for consideration by the group:

a) Optimal strategies and approaches to integrating CDD activities within existing PHC systems;

b) Determination of CDD program cost-effectiveness;

c) Simplified management information systems for improved monitoring and surveillance capabilities;

d) Alternative packaging, quality control and distribution methods for locally produced ORS;

e) Behavioral studies to examine "knowledge-attitudes-practices" determinants of target populations as regards diarrhoeal diseases;

f) Efficacy and impact of ORT in different settings; (e.g., natural disasters, refugee populations; high altitudes, etc.).

g) Refinement of community organizational and promotional strategies;

h) Innovative approaches to developing and utilizing audio-visual materials, both for manpower training and public health education;

i) Development of integrated curricula and evaluation of various manpower training strategies;

j) Feasibility and cost-effectiveness of various low-cost water and sanitation interventions at the community level;

k) Survey and evaluation of local traditional diarrhoeal remedies;

l) Alternative approaches to national CDD program evaluation on all levels.

7. RESEARCH RECOMMENDATIONS

After considering the preceding information in plenary the participants met in small working groups. Among the group's general recommendations was that the CDD Program should inventory all CDD-related research ongoing in the Region - both PAHO-supported and other - and, using

the CDD information system, should inform each country of the findings on a regular basis. The specific research recommendations they developed along with relative time frames, are presented below.

7.1 Clinical Research Priorities

7.1.1 Studies on the genesis of chronic diarrhoeas, and development of appropriate practical therapeutic modalities, when associated with malnutrition (≤ 3 years).

7.1.2 Evaluation of practical, locally appropriate feeding practices as an adjunct to treatment during rehydration, maintenance and recovery phases of diarrhoea, including (≤ 3 years):

a) appropriate caloric concentration
b) frequency of feeding
c) types of food given
d) effects on appetite
e) effects on purging rates
f) weight gain
g) lactose intolerance.

7.1.3 Evaluation of the clinical significance of vomiting and practical methods to control it in different settings (i.e., home, health center, hospital, etc.), (1 year).

7.1.4 Evaluation of the clinical and biochemical aspects of current and new ORS formulations, which may be developed to improve product stability or for use in special circumstances, such as (2 years):

a) high altitude
b) malnourished children
c) neonates.

7.1.5 Investigation of the effect of early domiciliary use of ORS or locally available fluids on the clinical course of simple uncomplicated diarrhoeas (2 years).

7.2 Laboratory Research Priorities

7.2.1 Longitudinal studies on the natural history of diarrhoeal pathogens prevalent within the Region, particularly rotavirus and enterotoxigenic E. coli, (ETEC) (3-5 years);

a) epidemiology (i.e., relative incidence, modes of transmission, seasonality);

b) host factors (i.e., defense mechanisms);

c) environmental and other factors.

7.2.2 Recognition of new agents implicated in the genesis of infections diarrhoeas (3-5 years):

a) bacterial (i.e., campylobacter, yersinia, vibrios, new types of EPEC);

b) viruses, (i.e., Norwalk agent, astrovirus, calcivirus, adenovirus).

7.2.3 Reassessment of the actual roles of traditional pathogens (i.e., Shigella, Salmonella, E. histolytica), especially in populations not well studied in the past (≤ 2 years).

7.2.4 Characterization of the different factors in human milk which may confer protection against specific agents, (≤ 2 years).

7.2.5 Determination of the relationships between serum, breastmilk, saliva and duodenal antibodies in protection against diarrhoeal pathogens, (≤ 2 years).

7.3 Operational/Behavioral Research Priorities

7.3.1 Comparison of outcomes, (such as clinical, reinfection intervals, behavioral changes, etc.) of diarrhoeal cases when CDD activities are performed primarily by (2 yrs.):

a) mothers at home
b) primary health care workers (ambulatory)
c) traditional fixed facility staff.

7.3.2 Evaluation of the efficacy, reliability and cost-effectiveness with which the following CDD functions are performed by mothers, PHC workers and fixed facility staff (3-5 years):

a) detection of risk factors in both patients and families (i.e., malnutrition, concomitant infections, socioeconomic factors);

b) proper treatment and/or referral of cases;

c) delivery of health education to clients;

d) case reporting and detection of outbreaks;

e) integration of CDD activities with other PHC functions;

f) provision of patient follow-up.

7.3.3 Systematic exploration for effective methods to use ORS - both the product and delivery system - as a vehicle for health promotion in particular settings (≤2 years).

7.3.4 Development and testing of different materials and methods for training and continuing education of all levels of health manpower in the prevention and treatment of diarrhoeal diseases (3 years).

7.3.5 Comparison of the contents and effectiveness of various community-level health education measures and delivery systems in reducing incidence and assuring proper treatment of diarrhoeal diseases (3 years).

7.3.6 Examination of "knowledge-attitudes-practices" (K-A-P) determinants of diarrhoeal diseases in target populations, especially as regards the following (3 years):

7.3.6.1 Environmental factors

a) Water protection, treatment, storage, consumption and utilization.

b) Food storage, handling, preparation and consumption patterns.

c) Methods and practices of waste disposal, especially excreta.

7.3.6.2 Child care practices and personal hygiene

a) Personal and domestic hygiene practices.

b) Child feeding practices, emphasizing breastfeeding and preparation of weaning foods.

7.3.6.3 Utilization of health delivery services

a) Recognition and importance of diarrhoea and dehydration.

b) Behavioral responses in the home to diarrhoea, vomiting and abdominal pain.

c) Utilization of health services - both indigenous (traditional) and allopathic - for treatment of diarrhoeal diseases.

d) Investigation of factors affecting the acceptability of CDD activities performed by different categories of health workers.

8. REFERENCES

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5. Recommendations of the 1979 Meeting of the Multidisciplinary Study Group on Diarrhoeal Diseses, PAHO Document CE84/15, April 1980, Annex IV.

6. Report of the Second Meeting of the Technical Advisory Group. Unpublished document WHO/CDD/80.2 (1980), pp. 22-23.

ANNEX

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NOTES FOR INVESTIGATORS PLANNING TO UNDERTAKE EPIDEMIOLOGICAL RESEARCH IN DIARRHOEAL DISEASE CONTROL*

CONTENTS

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INTRODUCTION

Epidemiology is a public health speciality concerned with the community and the environmental aspects of human disease. Epidemiological studies may be descriptive (dealing with data collected to define the natural occurrence of the disease or condition in question), analytical (in which naturally occurring "cases" are assembled and compared with naturally occurring "controls"), or experimental (when some intervention is deliberately introduced by the investigator). Such studies always deal with the collection and analysis of numbers (i.e., they are quantitative), and have as their purpose the identification of disease causation (or "risk factors"). The ultimate goal of an epidemiological study is to find means of prevention (of morbidity or mortality).

These notes and comments have been prepared to assist health workers who are planning to conduct community-based, risk-factor or cause-oriented research. They are not comprehensive, and do not cover all situations, answer all questions, or provide the sole basis for the planning and writing of a research protocol. Rather, they are intended to provide certain fundamental guideposts and to point out certain pitfalls that must be avoided. The reader is urged to consult one or more of the standard textbooks on epidemiology. The personal advice or services of a professional statistician will be useful and will often prove essential, and consultation with an experienced epidemiologist, if available, will be most helpful.

A protocol for an epidemiological research study should consist of detailed, defined amplifications of these major headings: Purpose and Significance of the Investigation, Review of Relevant Background, Overall Study Design, Methods of Data Collection, Methods of Data Analysis, and Feasibility. The writing of a research protocol is an essential planning step for the investigator; in the process of converting general ideas into a specific work plan, he or she sharpens the research objectives, identifies data requirements, anticipates data sources and the arrangements necessary to make use of them, considers methods of analysis, and uncovers inconsistencies and other problems that must be resolved. The points for consideration outlined in the following sections should be helpful in this process.[1]

1. PURPOSE AND SIGNIFICANCE OF THE STUDY

These should be stated clearly but briefly and should leave no doubt as to why the study should be undertaken, what additional knowledge will have been accumulated at its successful conclusion, and how this new knowledge will increase understanding and/or contribute to the ability to prevent, control, or manage diarrhoeal diseases. If the study is to be a descriptive one, the population(s), place(s), and time-frame(s) involved (who, where, when) should be specified. If the study is analytical or experimental, the research hypothesis should be stated, and it should be indicated whether this has general applicability (a biological or social phenomenon affecting all people) or is of purely local significance (affecting only certain people, places, times, or circumstances).

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[1] They will also satisfy the requirements of Sections II.1 and II.2 of the research proposal form of the WHO Diarrhoeal Diseases Control (CDD) Programme.

2. REVIEW OF RELEVANT BACKGROUND

This should provide the knowledge base upon which the research proposal is built; it should be as complete as necessary for the reader's understanding, but no more extensive than necessary. The uncertainties in our understanding or the gaps in knowledge that the proposed project is supposed to fill should be identified.

3. OVERALL STUDY DESIGN

A carefully considered summary statement of the general approach to be used in the study provides a skeleton framework upon which appropriate research methodology must be built. The general nature and approach of the study should be stated first, followed by details of how it is to be constructed and conducted. This is discussed in more detail below, using examples of descriptive, analytical, and experimental studies.

3.1 Descriptive study

In a descriptive study the investigator's role is limited to that of observer and data collector; he is merely a reporter of "natural" occurrence. The group under study may be the entire population of a particular geographical area and the period of observation could be a given point in time, or the past year, or the year to come; alternatively, the study group may be a recruited panel of persons, families, or villages who agree to provide information and/or specimens during a future period of time. The detailed description of an epidemic outbreak is a familiar example. A descriptive study produces counts of events, which are then related to the entire study group (or to subgroups), and expressed as rates or proportions. A "longitudinal study" is one in which observation is continuous over a period of time; it produces data on the duration of occurrences as well as counts of them. It is important to note that the observer does nothing to influence these results, and there is no "control" group; he only makes comparisons among subgroups within the study or between his study and similar studies elsewhere.

3.1.1 Examples:[1]

(1) "Seasonal variations in diarrhoeal morbidity and mortality in contrasting geographical zones of country A"

"This descriptive study will be based on detailed weekly surveillance data collected by specially trained village health workers (VHWs) over a period of two years, in all villages in District X (a hot, "wet" delta area) and in District Y (a cool, dry plateau area). Accurate census data will be collected just before and immediately after the study period. In a random sample of diarrhoea cases laboratory studies will be carried out. Incidence and mortality rates will be calculated by age, sex, and season, and rates by etiological agent will be estimated. The rates for the two Districts will be compared and the effect of climate on seasonal variations in diarrhoeal disease incidence will be noted".

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[1] These examples, and the others given in following sections, are hypothetical; they were specially written for this document for the purpose of illustration.

(2) "Intra-familial transmission of rotavirus (RV)"

"This will be a longitudinal study of the "natural" transmission of RV within volunteer but otherwise unmodified households (HH). Index children will be selected from among babies born in the local hospital. Baseline blood specimens will be collected from each HH member, including an umbilical cord specimen from the newborn. Subsequently, heel-prick blood samples will be collected every three months from the index babies and faecal samples from each HH member; all specimens will be studied to detect evidence of RV infection. All episodes of diarrhoea in index children will be investigated by examination of stool specimens. When RV infection is found, all members of that HH will be bled, and faecal samples will be collected from them all every second day for two weeks, at which time a follow-up blood sample will be collected. At the end of two years the study of that HH will be terminated. Incidence rates of infection and reinfection will be calculated by age, sex, and status within the family, and the duration of excretion will be recorded".

3.1.2 Important concepts and definitions

Data sources (i.e., case numerator): Consider whether cases or deaths or both are to be counted. Will case data come from hospitals, field surveillance, laboratories, or existing records? What is the quality of these data?

Population at risk (i.e., population denominator): Is the total population or parts of it (defined sub-groups) most appropriate, and what is the source and quality of the available data?

Size of population: Consider the statistical concept of sample variance, i.e., the larger the groups the better the estimated rates.

Rates (incidence or prevalence) or proportions: Which is the most appropriate?

- Incidence rate: new cases occurring during a specified period of time, in a specified place and population, divided by the population at risk, and multiplied by some unit of population such as 1000 (e.g., "The incidence rate of shigellosis among children below 5 years of age in District X during 1978 was 40 per 1000".).

- Prevalence rate: all cases present at some specified point in time, in a specified place and population, divided by the population at that time, and multiplied by some unit of population such as 1000 (e.g., "A survey conducted in Village Y on 15 May 1980 showed that the prevalence rate of malnutrition among infants was 15 percent".).

- Proportion: sub-divisions of a total group, often expressed as percentages (e.g., "In the epidemic of food poisoning in City Z, 60 percent of the cases were female and 40 percent male".).

Place component: "Place" must be precisely defined.

Time component: Define time parameter(s), including duration of observation.

Other circumstances: It may be necessary or useful to include relevant information about the environment, weather, nutrition, animals, etc. Are laboratory studies and data needed?

3.2 Analytical studies

In this type of study, the investigator deliberately selects participants on the basis of a carefully defined characteristic(s), for the purpose of examining the statistical association of a possible cause and an apparent effect. For this purpose it is necessary to have two groups of participants, one with the characteristic(s) (the "subjects" or "cases") and the other lacking it (the comparison or "control" group). It is essential to keep in mind that, by definition, cause leads to effect (usually a disease, in epidemiological studies), and therefore cause must come first in time! When designing an analytical study protocol, and interpreting its results, two troublesome causes of misinterpretation must be borne in mind - "confounding" and "intervening" variables. These are complex and subtle, and should be reviewed in an epidemiology textbook. They may be briefly defined as follows:

- Confounding variable: any factor that is intimately associated with the study factor, such that either (or both) may be the "cause" of the disease under investigation (e.g., poor sanitation and poor nutrition are associated; which is the "cause" of the severe diarrhoea which is being studied?).

- Intervening variable: any factor that may be intermediate between the study factor as a "cause" and the disease (effect) under investigation (e.g., does breast milk itself provide something to protect the infant from diarrhoeal disease, or does breast feeding simply protect the infant from a breast milk substitute prepared with contaminated water which exposes him or her to diarrhoeal disease?).

There are three types of analytical study (prospective, retrospective, and concurrent), each with advantages and disadvantages. Some studies may incorporate more than one type of element (or even of epidemiological description) and the following should be understood as illustrating basic principles rather than establishing fixed limits.

3.2.1 Prospective (cohort study) approach

This consists of a comparison, during a period of time, of one group that is exposed to a "cause" under study with another group that is not exposed (the "control"). Its purpose is to calculate the incidence rates in the two groups, and then to compare the two rates to calculate "relative risk" (see below, 5.2).

Example: "The effect of breast feeding on the frequency and severity of diarrhoeal disease"

"This prospective study is designed to test the hypothesis that breast feeding reduces the frequency and severity of acute diarrhoeal attacks in infants. For this purpose healthy, well-nourished infants having equivalent socioeconomic status and sanitary environment will be recruited for study, at 1 - 3 months of age, from the family registers of home-visiting Health Aides. Volunteers will be divided into three comparable groups: (a) those who have been breast fed exclusively and will continue so for at least the next three months, (b) those who have been fed exclusively on artificial formula (from at least two weeks after birth) and subsequently other foods, and will continue that feeding, and (c) those who have been receiving and will continue with a mixed diet of breast milk and other foods. They will be visited at home every second week, height and weight will be charted, and detailed records will be kept of the occurrence, severity, and duration of episodes of diarrhoea until the babies' first birthday. Incidence rates of diarrhoea and relative risks will be calculated, and proportionate distributions by duration and severity of episodes will be made and correlated with growth".

Advantages and disadvantages

Advantages: There is least likelihood of serious bias (see below, 4.4) since the participants are under continuous observation and both cause and disease effect can be determined with accuracy. Incidence rates and relative risks can be calculated directly.

Disadvantages: It is necessary to have a causal hypothesis to start with, and then observation must extend over the required time before results are available. The disease being studied must occur frequently enough that a sufficient number of cases may be expected in a study group of feasible size. These are usually costly studies, especially when large groups are necessary for diseases of low incidence.

3.2.2 Retrospective (case-control study) approach

This is a comparison, "looking backward" in time, of one group having the disease (effect) with another group ("control") not having the disease, to determine relative proportions which had been exposed to possible causes. A familiar example of a retrospective study is the investigation of an outbreak of "food poisoning", where cases and persons who did not become ill are asked about foods they did and did not eat at a banquet or a picnic. Its purpose is to detect association and calculate relative risk (see below, 5.1 and 5.2). Incidence rates cannot be calculated directly from this type of study because it does not begin with a "population at risk".

Example: "The etiological significance of infection with supposed pathogens of diarrhoeal disease"

"This retrospective study is designed to investigate the etiological significance of the "currently recognized" agents of diarrhoeal disease. A group of patients with acute diarrhoea and a matched control group of

healthy persons will be studied, to determine the rates of infection with each "pathogen". For each patient selected from Hospital X, a healthy person living nearby and of the same age, sex, and socioeconomic level will be selected - both by random procedures. Faecal samples will be collected for laboratory study to detect bacteria, viruses, and parasites that have been associated with diarrhoeal disease in the past. It is assumed in this study that the onset of infection with any agent that is found preceded the onset of diarrhoea. After agent-specific infection rates have been determined for both groups, the statistical significance of associations and relative risk will be calculated. A relative risk significantly greater than 1 will be interpreted as indicating that the infectious agent is truly associated as a cause of diarrhoea. As time and facilities permit, additional "new" etiological agents of diarrhoeal disease will be searched for".

Advantages and disadvantages

Advantages: The investigator does not need to start with a specific causal hypothesis, but may search for one among several. A retrospective study may take much less time than a prospective study, because the time between cause and effect has already elapsed. These studies are feasible even for diseases in which cases occur infrequently.

Disadvantages: The investigator cannot know or anticipate the intermediate happenings between cause and effect, since they were not under observation. He cannot calculate incidence rates (risk), only relative risk.

3.2.3 Concurrent (cross-sectional study) approach

In its simplest form, a study of this type is based on a survey, in which information about a disease (or other "effect" of interest) and its possible cause is obtained at the same point in time. It has two objectives. Its primary (analytical) purpose is to categorize a population into four groups - (a) with both disease and the factor(s) under study, (b) with disease/without factor(s), (c) without disease/with factor(s), and (d) without either disease or study factor(s) - in order to calculate statistical association. Its secondary (essentially descriptive) purpose is to produce information about the proportions of people, in a representative sample of a population, who have the two characteristics being studied.

Example: "The effect of health knowledge on breast feeding practice"

"This concurrent study is designed to test the hypothesis that knowledge about the health advantages of breast feeding (presumed to be the result of a health education programme) is associated with a higher prevalence of breast feeding. It will be based on a survey of mothers of infants about 5 months of age. Women in Village Z, which has a health education coverage rate of about 50%, will be asked two questions (among others):

(a) Are you breast feeding your baby?

(b) Do you know any reason why it is better for your baby to be breast fed rather than to be fed "pap" or from a bottle?

The resulting data will be used to prepare a four-fold table based on two characteristics: breast feeding (yes/no) and the answer to the second question (yes/no), to determine whether a significantly greater number of women practice breast feeding if they know its health benefits than if they do not. The data will also permit the investigator to learn the prevalence rates of breast feeding at about 5 months of age and of mothers' understanding of its advantages, both of which are important in evaluating health education activities".

Advantages and disadvantages

Advantages: This is the quickest and least expensive type of study.

Disadvantages: Difficulties in interpretation result from: (a) other, unsuspected characteristics or events may be the true cause of the association found (e.g., if the study example above showed an inverse relationship between breast feeding and health knowledge, it could have been because women living nearest the market town where the health centre was located (and where the health education was provided) had greatest access to commercial milk formula - an example of a "confounding variable"), and (b) cause and effect may be difficult to separate (not a problem in the study example given, but if diarrhoea and poor nutritional state were found to be associated, which was cause and which effect?).

3.3 Experimental (intervention) study

This is essentially a prospective study, carried out in experimental and control groups, with the important difference that the investigator deliberately introduces the factor under study. Every effort must be made to eliminate all variables except the one under investigation, i.e., the experimental and control groups must be as alike as possible in all ways other than the procedure that is applied to the experimental subjects. The experimental study is most familiar in the form of controlled clinical, drug, and vaccine trials. Since the investigator is actively intervening, ethical considerations are of great importance.

3.3.1 Example of an experimental study based on an opportunity which presents itself in a field programme:

"The effect of readily available, abundant, sanitary water supplies on diarrhoeal diseases incidence"

"This 'experimental' study takes advantage of an approved, funded programme to provide sanitary deep wells to 10% of the villages in District W during the next year. All villages in the District will be classified by size, economic status, distance from currently used surface waters, and previous diarrhoeal disease incidence rates. When a well is to be constructed, the village selected will be matched by two other villages with the same characteristics. Intensive surveillance for diarrhoeal diseases by specially trained VHWs will begin one month before construction starts, in all three

villages of the "set", and will continue for two years thereafter. As additional wells are constructed, additional village "sets" will be added to the study. The object is to calculate incidence rates in the villages supplied with wells and in controls, and to determine differences."

3.3.2 Advantages and disadvantages

Advantages: A well designed experimental study provides the best evidence of the role of a cause (or prevention or cure) of a disease.

Disadvantages: Expense, unless an opportunity is exploited such as in the example; then, it has all the characteristics of a prospective study.

4. SOME CONSIDERATIONS IN DATA COLLECTION

Certain principles are applicable regardless of study design, others are relevant only to specific study approaches. The investigator should consider the applicability of the following, and describe in detail the procedures to be used for data collection.

4.1 Definitions and characteristics of study population

Definition of a case: Should one include: all cases, only deaths, or only survivors; a specific etiological diagnosis, a specific clinical syndrome, or the general disease pattern; clinical diagnosis only or with laboratory confirmation; acute or chronic cases (to be defined); new or continuing cases; first episodes only, recurrences or recrudescences (defined); sub-clinical "cases"? What minimum professional qualification is necessary to make the diagnosis (e.g., physician, nurse, VHW)?

Characteristics of a case: The investigator should obtain as much information as is necessary about: age, sex, race, occupation, education, religion, socioeconomic status, medical history, nutrition, travel, etc. Note, however, that too much irrelevant data may clutter a study and make analysis unnecessarily burdensome; the investigator must exercise judgement as to what is likely to be important.

Source of cases: Are cases to be chosen at random (see below, 4.3) or by some selective procedure, and from a routine reporting system, active surveillance, hospitals, other treatment facilities, laboratory reports, surveys, or birth and death registers? How reliable and complete are the records? Remember the "iceberg phenomenon" - the tip of the iceberg (deaths) is most easily found, severe cases go to hospital, milder cases will be found in health centres or at home, and sub-clinical cases are not detectable without laboratory aid.

Definition of denominator (population at risk): This may be the entire population from which cases may arise, or a component defined by characteristics such as age, sex, occupation, etc. Consider duration of residence, and population movement and changes over time. Is the population ascertained by the investigator or from existing records (collected when and by whom)?

Comparability of cases and populations: When a characteristic (such as age) is known to affect the disease or other result, the groups to be compared must be alike in that characteristic. This may be accomplished by statistical weighting (or adjustment) after the data have been collected, or by "matching" the cases and controls selected for analytical or experimental studies. Note, however, that when case-control characteristics have been matched by the investigator, no inferences may be made about that characteristic after the study has been completed (e.g., if cases have been matched by age, the effect of age cannot be studied).

4.2 Characteristics of place and time

Place: Consider the detail needed - country, area, specific locality; urban-rural; altitude, terrain, environment; housing, population density. Maps may be helpful, both for providing detailed data and for plotting the location of cases.

Time: It may be measured from minutes to decades; what is necessary for this study? Note seasonal and annual variations, migration and population movement.

Other characteristics: Sanitation, weather, insects, animals, habits and customs, etc. Are they relevant?

4.3 Random selection

This means that each person (or place or thing) in a group has an equal opportunity to be selected out of that group, regardless of how the group may be defined (e.g., a sample of 4-year old male children in city X, or of villages of less than 1000 population with tubewells in region Y). Random selection may be assured by numbering all people, villages, or laboratory cultures, or the grids on a map, and then using a table of random numbers for unbiased selection. Other procedures are acceptable (such as the toss of a coin, or using the serial numbers on paper money) so long as both personal preference or systematic procedures (such as choosing the first case to appear each morning at a clinic) are avoided. Random selection is an important element in avoiding bias.

4.4 Bias

Bias results from any act or procedure, whether known or unknown to the investigator, that will affect the result in an artificial (i.e., not biological or sociological) manner. Bias may result in grossly incorrect and invalid research findings and conclusions. The principal types of bias are :

Selection bias: non-random selection (see above, 4.3), especially self-selection by the cases, controls, villages, etc. Hospital cases are always biased - by self-selection, severity, distance, etc.

Bias of disproportions: When the incidence rates of a disease (such as diarrhoea) differ markedly by some variable (such as age), the overall rate for a population is affected by the age distribution. If two whole

populations which differ in age distribution are compared, the one with the greater proportion of young children will be disproportionately affected by their high incidence rates. This distortion is avoided by comparing only age-specific rates or by population standardization (i.e., statistical "adjustment").

Observer or interviewer bias results, for example, when the observer knows which is a case and which a control, and inevitably treats them differently. It also results from a poorly designed questionnaire or an interviewer who asks "leading" questions. It is best avoided by keeping the interviewer "blind" as to which is case and which control, and by the use of objective (e.g., laboratory) test results.

Respondent bias results when the subject knows the "correct" answer. Avoid it by keeping the respondent "blind" and by objective tests. The optimal study is "double-blind" - i.e., neither the observers nor the respondents know which are cases and which are controls.

"Drop-out" and "refusal" bias: Persons who decline to participate, or who leave a study prematurely are, almost by definition, different from those who do not. Refusal bias is difficult to avoid except by random allocation among volunteers only; volunteers should never be matched with non-volunteers. A study of the characteristics of drop-outs may suggest how they differ from those who continue, and to what extent the final study group may validly represent the entire population.

4.5 Laboratory considerations

Almost all the points mentioned above with respect to people and places - definition, case characteristics, sources of data, denominator, bias - apply equally to laboratory results. In addition, consider: training of staff and quality of laboratory equipment, availability of specific procedures, quality of specimens and timing of their collection for laboratory study, different meanings of agent recovery and serological tests, confirmation of diagnosis, repeat testing, primary vs. reinfection, carriers, etc.

4.6 Statistical considerations

Since epidemiological studies are always quantitative, statistical handling of the data is necessary. With respect to data collection, the following must be considered:

Sample size requirements

Since study results need to be analyzed statistically, the study groups must be sufficiently large to reach the desired level of statistical "significance". They should not be larger than necessary, however, to avoid unnecessary expense. This almost always requires that a decision be made on sample size at the stage of protocol development, before the study begins.

A statistician can calculate the sample sizes needed for various research purposes if the investigator can provide him with certain estimates and the level of statistical confidence that is needed to rule out mere chance. For two-sample studies (analytical and experimental studies or where two rates are being contrasted in descriptive studies), the statistician must be told the differences anticipated between the groups to be compared (or the smallest difference that will have practical significance) as well as the "confidence level" required (usually 95% or 99%, with much larger groups needed for the latter). For a sample survey, he must know the prevalence rate anticipated and the range of rates (i.e., the precision of the rate) that the investigator can accept as useful for his purposes. If the investigator has no information on which to base estimates (of group differences or survey results), it will be necessary to undertake limited pilot studies or surveys in order to obtain estimates. The pilot study results are not "lost"; they may be incorporated into the larger study if the methods used are not changed.

To estimate the sample size required, the statistician thus works from estimated results and tolerable ranges to the number of subjects needed. This is illustrated in the following table for simple random sampling, with 95% probability. Note that the investigator may specify the precision needed, but that sample size increases as precision improves.

Estimated prevalence rate	Size of samples needed for indicated ranges around prevalence rate (with 95% probability)		
	± 10%	± 5%	± 2%
10%	36	144	900
30%	84	336	2100
50%	100	400	2500

When two rates are to be compared, the calculation is more complicated because of the need for precision in both survey results, as well as to permit the statistician to ensure that either a difference or no difference between the two results can be identified with confidence.

Size of a "control" group

When the cases of a disease being studied are numerous and readily available, the case and control groups should generally be equal in size (and both adequate in size, as mentioned above). When cases are not numerous (as in certain of the less common diarrhoeal diseases, or those requiring sophisticated laboratory diagnosis), statistical analysis is strengthened by having two or even three controls for each case.

4.7 Classification errors

Even though it is commonly assumed, the reciprocal misdiagnosis of cases and controls is not self-compensating; such misclassification always reduces the chance of demonstrating a difference that is truly present. Extreme effort and care must therefore be taken to ensure accurate diagnosis.

4.8 Survey and questionnaire design

Survey design

For a survey to produce valid results, the population sample must be representative of the whole. In theory, the best way to achieve this is by simple random sampling - in which each ultimate unit of study (a person, a house, or some other object) is numbered, and a sample is picked by a table of random numbers. This is rarely feasible, and usually would be very inefficient since the sample would include a true proportion of all classes of people whereas research interest is often concentrated on only one or a limited number of classes.

Instead, some system of stratification can be devised whereby an entire population or area is subdivided stepwise into smaller groupings which have some internal uniformity and which include a known proportion of the entire population. Then, each stratum can be sampled with different but known probability of selection; this approach is called "stratified random sampling". The results of the survey may be reported as specific prevalence rates for each subsample, and if an overall, total population rate is wanted, appropriate adjustment calculations are made to weight all subsamples to fair and equal representation.

An important logistical consideration in survey design is the feasibility of locating and reaching each individual person (or house, etc.) selected from a survey stratum; if the subjects have been selected as individuals by a truly random method, they are likely to be widely dispersed and isolated. A compromise is available, called "cluster sampling". In this method, all of the children in a household, for example, are selected as a group. The groups must be selected in a random fashion that gives each such group an equal opportunity for selection, but the individuals are not independent and are more likely to resemble each other (especially for a disease transmitted from person-to-person) than the subjects would be who are selected by a simple random procedure. This sometimes rules out the use of cluster sampling, and the method usually increases the sample size required.

These two approaches to sampling only illustrate the complexity of truly valid survey sampling; there are many other problems, and solutions to them. When planning a survey, the inexperienced investigator should consult a statistician with sampling experience.

Questionnaire design

This is a sophisticated skill, and should be undertaken only by someone with experience. Only a limited number of relevant questions should be asked. Problems relate to the phrasing and ordering of questions, the inclusion of confirmatory questions, coding of responses for subsequent analysis, and the overall length of the questionnaire. A pretest or "pilot" trial of a questionnaire is almost always desirable before a final commitment is made.

4.9 Data handling

This must be planned and arranged for at the time of protocol development. Hand tabulation and analysis are suitable and may be preferable for smaller studies and those with limited data sets, but if computer processing is thought to be necessary, the availability of suitable equipment ("hardware"), the format of data for computer entry (including coding), computer programming ("software"), and the analytical procedures to be used must all be considered.

4.10 Ethical considerations

Adequate procedures must be incorporated into the protocol to ensure the health and safety of study participants. Note that the withholding of an "accepted" remedy or prophylactic may be as unethical as the administration of a possibly hazardous new one. Subjects must be reasonably informed of the nature and implication of the study, and an "informed consent" form may have to be signed. The participants must be free to withdraw from the study at anytime they wish to do so. For the protection of both study participants and investigators, all research protocols dealing with human subjects should be reviewed and approved by an Ethical Review Committee.

5. SOME CONSIDERATIONS IN DATA ANALYSIS

The statistical procedures to be used for the analysis of data must be specified in the protocol, in detail; it is not sufficient to plan "data to be analysed by standard statistical methods". A competent statistician should be consulted if the investigator does not have the necessary skills.

Several general principles should be kept in mind:

5.1. Statistical association

This simply means that two characteristics have been found together more frequently that one could expect on the basis of chance alone. Biological causality requires other types of evidence in addition, including plausibility consistent with current understanding. Furthermore, a statistician calculates statistical association from the data provided to him; he may not be able to judge their quality and whether certain poorly collected or invalid data should be discarded. Only the investigator can do that, and conclusive interpretation is his responsibility.

5.2 Relative risk

This is a mathematical statement of the relationship between the rates found in two study groups. If, for example, children in village M have an incidence rate of 5 diarrhoeal episodes per year and those in village P experience only 2 episodes per year, the relative risk for village M (in relation to village P) is 2.5. In retrospective (case-control) studies, where incidence rates cannot be calculated, relative risk can be estimated by an indirect calculation (for which a textbook or statistician should be consulted). A relative risk of 1 means that no difference has been found between the two study groups.

5 3 Inferences

Inferences about causation derived from a study are, in a strict sense, limited to the study population; caution must be used in extrapolating them to other population groups. For example, the results of a study among malnourished infants in one country may not apply to well-nourished or older children in that country, or to children in other countries. Furthermore, one study does not "prove" causation; consistent conclusions must be obtained by different investigators, in different settings.

5.4 Efficiency and effectiveness analyses

Risk/benefit, cost/benefit, and cost/effectiveness analyses may be of great importance, and should be considered in addition to epidemiological descriptions and inferences about transmission, causation, etc.

5.5 Hypothetical conclusions

The conclusions the investigator expects to derive from the study should be specified in advance. That is, he should be able to make a statement such as "if the proposed hypothesis is supported we shall conclude that _____; if it is rejected by this study we shall conclude that _____". This does not rule out alternative conclusions if the study produces totally unexpected results.

6. FEASIBILITY

The translation of a good research idea into a practical research project requires much more than the availability of adequate funding. The principal investigator must be assured that: permission to undertake the work has been given by all relevant governmental, organizational, and institutional authorities; needed equipment, including laboratory and computer facilities, are available for use; skilled personnel, including such special competence as statistical expertise, can be found; the numbers of individual cases, controls, or other study subjects are adequate; the time frame is reasonable and there is a reasonable probability that the study subjects will continue under observation for the time required; and the logistical plans for subject recruitment, travel, specimen collection, etc. are practicable.

PAHO GUIDELINES AND REVIEW PROCEDURES FOR RESEARCH INVOLVING HUMAN SUBJECTS

1. Background

Recognizing that medical progress throughout history has and will continue to require human experimentation, there has been during the past several decades a growing concern over the adoption of measures that assure the safe and responsible involvement of human subjects in all types of biomedical experimentation.

Concern regarding international aspects of bioethics and human rights has been voiced by WHO's governing bodies (Resolution EB55.R65). PAHO Advisory Committee on Medical Reasearch at the 13th, 19th, 20th meetings held in 1974, 1980 and 1981 respectively drew attention to the importance of the ethical issues within the context of biomedical research.

2. General Guidelines

The PAHO Committee for Research Involving Human Subjects (PAHO CRIHS) is at Headquarters to provide a mechanism for the assessment of ethical implications of research projects. In addition, similar committees are established at PAHO centers in which research involving human subjects is carried out.

Until WHO officially adopts the general guidelines and principles being developed in collaboration with CIOMS, these committees are guided by the principles established by the Helsinki Declaration of the World Medical Association (attached as Annex 1) and by the Standards of Conduct for Research carried out by or under the auspices of the World Health Organization. In addition, committees are instructed to comply with principles, practices, and rules applicable within the country where the

research is carried on.

3. Terms of Reference

All PAHO-sponsored research, whether the Organization is directly responsible by conducting the study or indirectly by providing financial support or technical cooperation, is subject to ethical review by the field as well as Headquarters committees. As to the type of research, the review requirements extend not only to clinical pharmacology and drug trials, but to all forms of clinical research including studies in the area of therapy, diagnosis, prevention or behavioral sciences including collection, storage and dissemination of information relating to individuals.

The PAHO committees must take into consideration that an ethical review of research proposals constitutes a mechanism for the protection of the individual subject; an important protection for the investigator and for the granting agency; and an important element for the protection of a nation, particularly in the developing world. These committees review all proposals to assess ethical implications, such as:

a) the dangers, if any, to the subject's health as a consequence of the proposed investigation;

b) the inviolability of his/her rights as an independent and free individual;

c) the appropriateness of the methods used to obtain informed consent, either verbal or written and if such consent seems appropriate;

d) the risks and potential benefits of the investigations, with

respect to medical progress and national interests; and

e) compliance with principles, practices and rules within the country or countries where research projects are to be carried out.

4. Membership

The Core Committee at Headquarters will comprise of 6 members and may include PAHO staff; clinical researchers, staff from international organizations, the diplomatic or scienrific community; or any other Washington-based public or private institution with links with institutional health programs. The Committee will be served by a chairman and a secretary appointed by the PAHO Director. The members will also be designated by the PAHO Director on the recommendation by the chairman, Technical Units or government bodies. In addition, the Secretary will maintain an updated list of other individuals from throughout the Region who may be invited to serve on an ad-hoc basis to review proposals of their expetise. The list may include scientific specialists, lay people from the community, religious leaders, hospital administrators, nurses, dentists, sociologists, psychologists, lawyers, and others.

As to the field or regional centers review committees, it is recommended that the core group be composed of two staff members who are independent of the project or of the Principal Investigator and three other individuals derived from outside the organization and representing social, governmental and clinical research groups.

Members should be appointed for periods of two years.

5. Review of the Proposal

The proposals should be reviewed at a meeting so that all members may offer and discuss their different points of view. In exceptional circumstances the review of the proposals may be conducted by mail. The Headquarters RCRIHS will meet every two months. The field or center committees should schedule their meetings well in advance of the due dates for the review of the proposals at Headquarters. The number of sessions per year should reflect the needs of the individual center.

The agenda will include an annual progress review of each ongoing study previously approved as well as all new proposals involving human subjects. Proposals seeking PAHO sponsorship, whether conducted in the field or at Headquarters' installations or in independent isntitutions, must provide, if man is an experimental subject, sufficient detail so as to make possible the sound assessment of ethical implications, such as:

1) A description of the characteristic of the proposed subject population and the rationale for using in this population special subjects, such as fetuses, pregnant women, children, the mentally disabled, prisoners, or other subjects whose ability to give voluntary informed consent may be in question.
2) An assessment of any potential risks - physical, psychological, social, legal or other - and of the likelihood and seriousness of such risks. If methods of research create potential risks, a description of other methods, if any, that were considered and why they will not be used.

3) A description of consent procedures to be followed, including how and by whom documentation of informed consent will be obtained.
4) The procedures (including confidentiality safeguards) for protecting against or minimizing potential risks and an assessment of their likely effectiveness.
5) An assessment of the potential benefits to be gained by the individual subject, as well as of the benefits which may accrue to society in general as a result of the planned work.
6) An evaluation of the risk- benefit ratio.
7) When physical or psychological risks to human subjects are involved, a statement on the extent to which the principal investigator will be responsible for their medical care, and how potential subjects will be selected from a population available.

The applications forwarded to the HRERC will also include the written approval of the field or center review committee stating the criteria and guidelines followed as well as a summary of the conclusions.

Finally, recognizing that prime responsibility for the welfare of subjects involved in medical research rests with the institutions undertaking the studies and the appropriate governmental authorities, the current WHO Manual provisions require that, before supporting any research activity, technical units ensure that the proposal has been authorized by national health authorities and that it has been reviewed by an appropriate committee either at the institutional or governmental level, which will be carefully

6. Informed Consent

"Voluntary consent" is a principle adopted by all codes of ethics and has, throughout the years, remained unchallenged. The definition of "informed consent", however, has proven to be a highly debated issue, particularly in regard to its validity. Until clearer guidelines are established, the PAHO Review Committees in assessing this issue will focus on the appropriateness of the process whereby the experimental subject is informed before he signs the consent form.

7. Committees' Decision

The PAHO CRIHS Committees are advisory panels to the Director of the field office or regional center, and in the case of the Headquarters Committee they advise the PAHO Director.

Their conclusions recommend approval, rejection or discontinuation of a research proposal involving human subjects.

8. Review Procedures

I When the proposal is originated in the field or at PAHO centers:

1) The originator of the proposal submits it to the field or center committee.

2) Field, centers or headquarter committees review the application as to the safeguard and right of human subjects involved in the research.

2.a) If such safeguards have not been considered or are unsatisfactory, the proposal is returned to the originator

of the proposal for the necessary amendments.

2.b) If the safeguards put forth are accepted, the proposal is channeled to the Secretary of the PAHO Headquarter's Committee with the clearance report.

3) When the cleared research proposal reaches Washington, the Secretary studies it and takes the following steps:

3.a) If no human subjects are involved in the proposed study, he gives clearance to continue the processing of the application through the corresponding offices.

3.b) If human subjects are involved, but the information is insufficient, he writes to the originator of the proposal requesting him to submit the needed clarifications.

3.c) If the documentation is complete, he sends the documentation to all the core Committee members and, if necessary, to those selected from the ad-hoc list to be consulted by mail, and schedules the review for the next session.

4. After consideration of the project by the Headquarters Committee:

4.a) If the Committee endorses the project, the Secretary gives clearance to continue the processing of the application.

4.b) He returns the proposal to the originator through the center or field committees if the guarantees, given by the latter, are not accepted or endorsed.

II When the proposal is originated at Headquarters or the first step of the administrative procedure for processing it is at

Headquarters the proposal should be chanalized through the secretary of the committee and the following steps should be taken:

1) If no human subjects are involved in the proposed study, he gives clearance to continue the processing of the application through the corresponding offices.

2) If human subjects are involved:

   2.a) If the information provided is insufficient, he writes to the originator of the proposal requesting him to submit the needed clarifications.

   2.b) If safeguards and rights of human subjects involved in the research have not been considered or are unsatisfactory, the proposal is returned to the originator for the necessary amendments.

   2.c) If the documentation is complete, or when it is complete, he sends the documentation to all the core Headquarters Committee members and to those selected from the ad-hoc list, and schedules the review for the next session.

3) After consideration of the project by the Headquarters Committee:

   3.a) If the Committee endorses the project, the secretary gives his clearance to continue the processing of the application through the appropriate offices.

   3.b) If the committee do not accept or endorse the project, it is returned to the originator of the proposal. This proposal might be received again at a future committee meeting

provided the objections raised by the committee have been answered.

3.c) If the safeguards put forth are accepted, the secretary gives his clearance to continue the processing of the application through the appropriate offices.

9) Current composition of the 'PAHO Review Committee for Research Involving Human Subjects' at Headquarters is as follows:

Dr. George Alleyne (Chairman)
Chief, Research Promotion
Coordination Unit
Division of Human Resources
and Research
Pan American Health Organization

Dr. Jorge Litvak
Chief, Division of Disease
Prevention and Control
Pan American Health Organization

Dr. Franklin Neva
Chief, Laboratory of Parasitic
Diseases
National Insitute of Health
Building 5, Room 114
9000 Rockville Pike
Bethesda, Md. 20205

Dr. Jorge Osuna
Chief, Health Care Delivery
Division of Comprehensive
Health Services
Pan American Health Organization

Dr. Jorge Ríos
Chairman
Department of Medicine
George Washington University
Medical Center
2150 Pennsylvania Ave. NW
Washington, D.C. 20037

Dr. José Romero Teruel
Chief, Fellowships and Research
Services
Division of Human Resources
and Research
Pan American Health Organization

Dr. Gabriel Schmuñis (Secretary)
Division of Human Resources
and Research
Pan American Health Organization

Declaration of Helsinki

Recommendations guiding medical doctors in biomedical research involving human subjects

Adopted by the Eighteenth World Medical Assembly, Helsinki, Finland, 1964, and revised by the Twenty-ninth World Medical Assembly, Tokyo, Japan, 1975

Introduction

It is the mission of the medical doctor to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the doctor with the words, "The health of my patient will be my first consideration", and the International Code of Medical Ethics declares that, "Any act or advice which could weaken physical or mental resistance of a human being may be used only in his interest."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies *a fortiori* to biomedical research.

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

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without direct diagnostic or therapeutic value to the person subjected to the research.

Special 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.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every doctor in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Doctors are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

[1] *WHO Chronicle*, **19**: 31-32 (1965).

I. Basic principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance.

3. Biomedical 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 his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interest of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Doctors should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Doctors should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the doctor is obliged to preserve the accuracy of the results. Reports on experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The doctor should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the doctor should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a doctor who is not engaged in the investigation and who is completely independent of this official relationship.

11. In the case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical research combined with professional care (clinical research)

1. In the treatment of the sick person, the doctor must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method.

4. The refusal of the patient to participate in a study must never interfere with the doctor-patient relationship.

5. If the doctor considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (1, 2).

6. The doctor can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-therapeutic biomedical research involving human subjects (non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the doctor to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers—either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

PAN AMERICAN HEALTH ORGANIZATION
Pan American Sanitary Bureau, Regional Office of the
WORLD HEALTH ORGANIZATION

DRAFT

APPLICATION FOR A RESEARCH PROJECT TO BE REVIEWED BY THE PAHO COMMITTEE FOR RESEARCH INVOLVING HUMAN SUBJECTS

A. General Information

1. Project to be executed ☐ and/or financially supported by PAHO by contract ☐; grant ☐; training grant ☐; fellowship ☐; other ☐.
2. Research activity to be conducted by PAHO staff or with collaboration of PAHO Staff; in which funds will be requested from any other agency ☐.
3. Project Title

4. Name of principal investigator:

5. Name and address of the institution:

Telephone Number:

6. Name of co-investigator(s): (State also their address(es) if they do not belong to the same institution as the principal investigator).

B. General Questionnaire

1. Project involves the use of: *

- ☐ Experimental drug(s)
- ☐ Radioactive agents
- ☐ Non-therapeutic research
- ☐ Fetal research
- ☐ Other: .....
  .....
- ☐ Non approved use for an approved drug(s)
- ☐ Experimental surgical procedure
- ☐ Behavioural research
- ☐ Placebo
- ☐ Deception of subjects

* Check the pertinent ones.

2. Expected duration of the study:

3. Expected duration of the study on each individual subject:

4. Subjects information:

a) Type and number of subjects to be studied (e.g. normal controls, patients with specific diseases).

b) Age range:

c) Sex: .....Males .....Females .....Both

d) Will pregnant women be included in the study? ....Yes ....No.

e) If subjects included in the study are either children, pregnant women, mentally retarded or legally restricted groups of if it includes fetal research, clearly specify the need to use these particular individuals.

f) Specify the established criteria for the selection of subjects (patients and controls).

g) Will the subject's physician also be the investigator?

h) Specify the established criteria for exclusion of subjects (patients and controls).

i) Compensation:
Monetary: ....No ....Yes. Amount $..... Timing .....
Reimbursement of expenses: ....No ....Yes
..... Type and amount.

5. Location of study

☐ Outpatient ☐ Inpatient ☐ Other

6. Laboratory studies

Will any tests be performed which are not routinely included as part of the work up for these types of patients? .... Yes .... No. List:

7. What measures will be taken to protect the confidentiality of the information?

8. Who will request the participation of the subjects in the study and in what manner will the consent be obtained?

9. If the protocol involves risk of the subjects what measures will be taken if an injury which is proximately caused by the experiment occurs on the patients? Will the patients receive free medical care? Are the patients going to be adequately compensated?

C. Proposal

1. Introduction (Abstract of the background, nature and reasons of the proposed study, including its significance).

2. Specific aims (Outline what you intend to learn from the proposed study).

3. Experimental protocol (Outline the studies to be performed in the individuals/patients, describing any special procedures).

Risks and potential benefits.

1. Risks. (Evaluate the risks involved. Document if necessary and possible, with literature references. Include a statement about what precautions will be taken to minimize these risks).

2. Potential benefits. (State the rationale to believe that the potential benefits to patients or society obtained from this study outweigh the risks).

3. Informed consent. (Attach a copy of the form proposed to be used as well as a description of all materials used to advise subjects of potential risks and benefits to be expected)

D. Authorization of competent national health authority.

This study has been approved by:

NAME

TITLE

ADDRESS & TELEPHONE

DATE

PLACE OF APPROVAL

I have reviewed this protocol and evaluated the scientific merit and potential value of the proposed study as well as the measures for protecting human subjects involved and I approved it.

Main authority of the Institution:

Name _____

Title _____

Date _____

Place _____

The undersigned accepts all responsibility for assuring protection of the rights and welfare of human subjects used in this study and agrees to hold PAHO harmless from any claims related to this study.

Principal Investigator's name:

_____

Date _____

Place _____

NOTE: Any changes must be promptly reported to the Institutional Review Board and PAHO.

PAN AMERICAN HEALTH ORGANIZATION

Pan American Sanitary Bureau, Regional Office of the

WORLD HEALTH ORGANIZATION

DRAFT

PROTECTION OF HUMAN SUBJECTS ASSURANCE/CERTIFICATION/DECLARATION

☐ PAHO conducted ☐ PAHO collaboration

☐ Grant ☐ Contract

☐ Trainee/Fellow ☐ Other

☐ Original ☐ Follow-up ☐ Revision ☐ New ☐ Renewal ☐ Continuation

STATEMENT OF POLICY: Safeguarding the rights and welfare of human subjects at risk in research activities conducted and/or supported by PAHO is the responsibility of the institution which receives or is accountable to PAHO for the funds awarded for the support of the research activity in accordance with appropriate national codes of ethics or legislation, or in their absence the Declaration of Helsinki of the World Medical Association. In order to provide for the adequate discharge of this institutional responsibility, it is the policy of PAHO that no research activity involving human subjects, to be conducted and/or supported by PAHO, shall be undertaken unless an appropriate committee, at the institutional or governmental level reviews and approves such research activity, and the institution submits to PAHO a certificate of such review and approval

1. TITLE OF PROPOSAL OR RESEARCH ACTIVITY:

2. PRINCIPAL INVESTIGATOR/TRAINEE/FELLOW:

3. DECLARATION THAT HUMAN SUBJECTS EITHER WILL OR WILL NOT BE INVOLVED

☐ A. No individuals who might be considered human subjects, including those from whom organs, tissues, fluids, or other materials will be derived, or who could be identified by personal data, will be involved in the proposed research activity. (If no human subjects will be involved, check this box and proceed to Item 7. Proposals determined by PAHO to involve human subjects will be returned.

☐ B. Human subjects who will be involved in the proposed research activity include:

☐ minors ☐ fetuses ☐ abortuses ☐ pregnant women ☐ prisoners

☐ mentally retarded ☐ mentally disabled, or ☐ none of the previous

Give name of institution and name and address of official(s) authorizing access to any subjects in facilities not under direct control of the applicant or offering institution.

Use following report format for each institution other than grantee or applicant with responsibility for human subjects participating in this research activity: (Attach additional report sheets as necessary).

INSTITUTIONAL AUTHORIZATION FOR ACCESS TO SUBJECTS

- Subjects: Status (wards, residents, employees, patients, etc.)_____

Number _____ Age range _____

Name of Official (please print) _____

Title _____ Telephone _____

Name and address of cooperating institution _____

_____

_____

Date _____ Place _____

_____

4. DECLARATION OF ASSURANCE STATUS/CERTIFICATION OF REVIEW

The signer certifies that all research activities in this application proposing to involve human subjects have been reviewed and approved by this Institution's (or governmental) institutional review board in a meeting convened on the date of _____

The institutional Review Board consists of the following members: (Indicate those involved in the review of this research activity).

NAME	TITLE	SPECIALTY
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

When requested, the Institution will submit to PAHO documentation and certification of such reviews and procedures as may be required for implementation of this assurance to the proposed project or activity.

THE INSTITUTIONAL REVIEW BOARD HAS DETERMINED, AND THE INSTITUTIONAL OFFICIAL SIGNING BELOW CONCURS THAT THE RESEARCH ACTIVITY:

☐ CONFORMS TO THE PRINCIPLES SET FORTH IN THE DECLARATION OF HELSINKI, AND/OR (mark one)

☐ CONFORMS TO APPLICABLE NATIONAL ETHICAL OR LEGAL REQUIREMENTS OF THE COUNTRY WHERE THE RESEARCH ACTIVITY WILL BE PERFORMED.

5. NAME AND ADDRESS OF INSTITUTION

6. TITLE OF INSTITUTIONAL OFFICIAL TELEPHONE NUMBER

7. SIGNATURE OF INSTITUTIONAL OFFICIAL DATE

PLACE

ENCLOSE THIS FORM WITH THE PROPOSAL