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PAHO GUIDELINES AND REVIEW SYSTEM FOR PROTECTION OF HUMAN RIGHTS IN MEDICAL INVESTIGATIONS

CONTENTS

PAHO GUIDELINES AND REVIEW SYSTEM FOR PROTECTION OF HUMAN RIGHTS IN MEDICAL INVESTIGATIONS*

I. INTRODUCTION

The history of medicine reveals how in essence all medical progress implies, and has always implied, human experimentation, insofar as each therapeutic procedure, new drug or surgical technique has to be tested for the first time on human beings, often after exhaustive animal experiments have led to a virtual certainty of its safety.

As regards human experimentation, the Helsinki Declaration of the World Medical Association has been very widely acclaimed as establishing the basic ethical principles that should govern research involving human subjects, although this Declaration does not and was not intended to cover all the situations that may eventually emerge in the broad field of human experimentation.

Insofar as suitable animal models are not available for some kinds of prophylactic or therapeutic research, and because therapeutic interventions have become progressively more effective, the criteria for their adoption and for safeguarding the interests of the patients have become progressively more stringent.

Within the several points covered by the various codes of Ethics which are concerned with the protection of human rights of individuals as subjects of research, the obtention of "voluntary consent" is regarded as a basic principle which remains absolutely unchallenged. Others terms used in the same connection are "Free consent" and "informed consent". However in particular circumstances of research being conducted in communities with low levels of social and economic development, the obtention of "informed consent" may involve difficulties inasmuch as certain types of research which are readily accepted in this communities might be openly rejected in others were the levels of education and self-determination are considerably higher.

Although advances in knowledge of the means and techniques by which disease may be combatted and health promoted must be pursued, ethical considerations have to comtemplate the real possibilities for the application of better knowledge for the improvement of health conditions among the communities from which such knowledge is derived.

It is worthwhile noting that the growing concern over human rights and standards for human experimentation which is taking place in countries with more advanced legislation and social policies in these matters, is not paralleled in less developed countries.

In view of the above and considering recent resolutions of the United Nations General Assembly (3218 XXIX) and the World Health Assembly (WHA 23.41) the Pan American Sanitary Bureau has stablished Policy and Procedural Guidelines for the Protection of the Rights of Individuals as Subjects of Research.

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*Prepared by Dr. Jorge Osuna, Department of Health and Population Dynamics, Pan American Health Organization, Washington, D.C., USA.

II. POLICY AND PROCEDURAL GUIDELINES FOR THE PROTECTION OF THE RIGHTS OF INDIVIDUALS AS SUBJECTS OF RESEARCH

For the purposes of this guide human experimentation is defined as any investigation in which the subject studied is man or his derivative products. Such as definition would include not only the individual either as a healthy entity or as a patient but also the use of such items as man's body fluid samples, clinical history content, certificates, and expressions of opinion which it has been deemed essential to collect in order to achieve the objectives of an investigation.

The investigator involved with experimentation in man at basic, clinical, sociological or other levels mut adhere to principles of conduct that will safeguard the health, welfare, privacy and the basic human rights of all subjects participating in an investigation.*

1. Objectives

In recognition of the increasing importance of research as a component of public health progress and of the essentiality of studies in man if science is to contribute to his progress, the Pan American Health Organization deemed it of importance to outline structures and processes used in reviewing research proposals which it sponsors, with specific reference to those aspects of the investigations in man that involve the ethics of the scientist and the rights of the individuals he uses as subjects. It is intended to comply with principles, practices and rules applicable within the country where research projects are being carried out.

2. Procedures

In addition to such fundamental information as is required of granting agencies - background, statement of problem, design, purpose, methods, procedure, personnel, locale, equipment, budget, etc. - all proposals seeking PAHO sponsorship, whether conducted in field or Headquarters installations or in independent institutions, must provide, if man is an experimental subject, sufficient detail so as to make possible the sound assessment of ethical implications, such as: i) the dangers, if any, to the subject's health as a consequence of the proposed investigation, ii) of the inviolability of his rights as an independent and free individual, iii) the appropriateness of the methods used to obtain informed consent, either verbal or written if such consent seems appropriate, iv) the risks and potential benefits of the investigations, and v) compliance with principles practices and rules within the country or countries where research projects are to be carried out.

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*See "Declaration of Helsinki" adopted by the World Medical Association in 1964 for criteria guiding the medical profession.

a. Principal Investigator

The principal investigator must supply the Research Ethics Review Committee with an estimate of the health risks to the individuals involved in the investigation and with the provisions made to minimize them. When testing new or unusual therapeutic, prophylactic, ionizing, surgical or other procedures in which the dangers to human health are known to be high or are likely to be high on the basis of existing knowledge or animal experimentation, he must obtain by noncoercive means the informed consent of the subjects. He must, as evidence of the subjects' willingness to serve in the experiment, give proof that the subject is free to terminate his participation at any time without prejudice or untoward consequences to him.

The principal investigator will obtain the guidance of a Committee of his associates appointed by the institution in which he works to lend independent support and approval to the investigational methodology he has selected for his studies so as to have wider assurances of the ethical use of human beings. For institutions such as the Institute of Nutrition of Central America and Panama, the Pan American Zoonoses Center, the Caribbean Food and Nutrition Intitute, and the Latin American Center for Perinatology and Human Development, it is necessary that a single committee of independent associates be constituted in each installation to guide principal investigators in that institution, and in turn to provide the Research Ethics Review Committee with their deliberations and conclusions with respect to the required assurances.

b. Research Ethics Review Committee

A Research Ethics Review Committee, chaired by the Deputy Director of the Pan American Health Organization, has been constituted from among individuals in the organizational components of PAHO to advise the Director on whether specific research proposals presented to it adhere to policy with respect to the safeguard of the rights to which human subjects are entitled. It will review proposals containing detailed assurances of compliance with policy and having the approval of a committee of independent associates of the investigator.

The Committee will inform the investigator of its recommendations, of the required frequency of progress reports and will identify those provisions of the protocol which may not be altered without Committee approval.

The Research Ethics Review Committee will exercise continuing review of on-going research projects and may authorize visits by an appropriate member of the Committee or by a delegate whenever necessary.

Representation of the Committe is formed from those departments of the Organization and preferably through those staff members who are

intimately acquainted with procedural aspects of the investigations in the subject of their competence. If under certain circumstances or for special investigations, such experts are not available from the PAHO staff, a consultant with the appropriate scientific background may be called upon on an ad hoc basis to provide the necessary assessment. The administrative components of PAHO is also represented on the Committee by a senior staff ember.

For the purpose of reviewing policy, practices and procedures, the committee will meet two times each year. It will meet as often as necessary, on call of the Chairman, to review specific research projects proposed by individual staff members or by one of the Field Committees.

Both the "Declaration of Helsinki" and "the Standars of Conduct for Rresearch carried out by or under the auspices of WHO" should guide the Committee in the discharge of their responsibilities.

3. Conclusion

Although the above policy guidelines do not attempt to specify all the criteria and all the considerations which bear upon studies in man, the Pan American Health Organization and the scientists participating in such investigations assume broad obligation with respect to the desirability and necessity of initiating such studies and with respect to the adequacy of all practices used in achieving the studies' objectives.

III. SUGGESTIONS FOR FUTURE ACTION

To ensure that stated procedures for the protection of human rights in medical investigation are applied to the fullest possible extent, the Organization should contribute to the perfectioning of relevant policies and procedures at the country level. Some of the specific aspects are as follows.

1. Development of National Policies and Legislation:

a) The constitution of National Boards on Medical Research at the highest possible level within the goverments, should be promoted and their functions and responsibilities should be regulated.

b) The dimensions of the problem in each country, should be assesed by means of a thorough revision of on-going research in which human subjects is involved.

c) Exchange of information and documentation, should be facilitated through meetings, consultation and distribution of written materials.

2. The constitution of Institutional Committees, has to be formulated. in order to comply with minimum requirements, such as:

a) Number of persons that should compose the Committee.

b) Diversity of backgrounds and expertise that should be represented in the Committee.

c) Official representation of the Ministry of Health and or other goverment bodies in theCommittee.

d) Relationship of Committee members with the Institution.

e) Procedures to be followed by the Committee in the initial and continued review of applications, proposals and activities.

f) Procedures to be follow by the Institution to provide advice and counsel to activity directors an investigators with regard to the Committee's action and to insure an adequate flow of information between project executives and the Committee and monitoring of unanticipated problems.

g) Ways and means for coordination between the Committe and the administrative echelons in order to make sure that the decissions of the Committee receive due consideration in the implication of projects.

3. The problem of "informed consent" should receive further clarification, specially when studies involve children, pregnant women, illiterate and underprivileged as subjects of research.

4. Better definitions of what may constitute small risks, such as blood sampling, psycological testing and other inconveniences such as hospitalization, should be pursued.

5. Finally, ethical considerations should be concerned not only with what may constitute a health risk or potential harm to the integrity of the individual, but also with the relevancy of specific studies to the particular health needs and problems of the community in which research takes place.

IV. ANNEXES

1. Membership in the PAHO Research Ethics Review Committee

2. Membership in Institutional Committees -

   CEPANZO
   CCAP
   CFNI

3. Membership in INCAP's Research Ethics Review Committee

4. Normas Generales y Mecanismos para Proteger a Sujetos Humanos en Estudios Realizados por el INCAP.

5. "Informed Consent Form" INCAP.

6. "Informed Consent Form" INCAP.

7. Research Ethics Review Committee - Working mechanisms.

8. WHO - Guidelines for Research Involving Human Subjects.

9. Declaration of Helsinki.

PAHO RESEARCH ETHICS REVIEW COMMITTEE (RERC) HQS

Chairman: Dr. Charles L. Williams, Jr.

Alternate: Dr. Mauricio Martins Da Silva

Secretary: Dr. Jorge Osuna

Alternate: Dr. Carlos H. Daza

Members	Alternate
Dr. Pedro Acha, AH	Dr. Harold Hubbard, AH
Eng. Edmundo Elmore, ES	Dr. Efrain Ribeiro, ES Dr. Vicente Witt, ES
Dr. James O. Bond, CD	Dr. Merlin L. Brubaker, CD Dr. Kuang Chi Liang, ME Dr. Jorge Litvack, HP
Dr. Jose Luis Garcia Gutierrez, ST	Dr. Morris L. Yakowitz, ST
Dr. Richard A. Prindle, PD	Dr. Sumedha Khanna, PD Dr. Jorge Rosselot, PD
Mr. William Childress, BF	Mr. James Milan, BUD
Dr. Gladys Conly, ME	

RESEARCH ETHICS REVIEW COMMITTEE (RERC)

CEPANZO

Members

Dr. Alberto Cuba Caparó	Chief of Pathology Unit
Dr. Victor Varela-Diaz	Chief of Immunology Unit
Dr. Héctor López Adaros	Chief of Epidemiology Unit

C L A P

Members

My. Enrique Boix (SM.M)	Director, Hospital de Clínicas
Dr. Hector Artucio	Director Asistente del Hospital de Clínicas
Dra. Silvia Carrara de Sica	Adjunto a la Dirección, del Hospital de Clínicas

C F N I

Members

Dr. R. Cook	Director, CFNI
Dr. J. M. Gurney	
Dr. A. C. K. Antrobus	

I N C A P

RESEARCH ETHICS REVIEW COMMITTEE

Members

Dr. Carlos Tejada	Director, INCAP
Dr. José Aranda Pastor	Physician, specialized in Epidemiology Member, Division of Applied Nutrition
Dr. Fernando Viteri	Physician, specialized in Internal Medicine and Physiology, Chief of Division of Biomedics
Dr. Robert Kein	Psychologist, Chief, Division of Human Development
Dr. Miguel Guzmán	Statistician, with previous training in Biochemistry, Chief, Division of Statistics
Dr. Ivan Beghin	Physician, specialized in Public Health Nutrition, Chief, Division of Applied Nutrition
Dr. Luis Octavio Angel	Physician, specialized in Public Health, member, Division of Education and Director of the graduate course in Public Health with Emphasis in Nutrition and Child Health
Dr. Juan José Urrutia	Physician, specialized in Pediatrics and infectious diseases, member, Division of Microbiology
Dr. Víctor Mejía Pivaral	Social Anthropologist, member, Division of Human Development
Dr. Edgar Braham	Biochemist, specialized in Applied Nutrition, member, Division of Agrdiculture and Food Sciences and Director of the graduate programs in Food Sciences and Animal Nutrition

NORMAS GENERALES Y MECANISMOS PARA PROTEGER A SUJETOS

HUMANOS EN ESTUDIOS REALIZADOS POR EL INCAP

El Instituto de Nutrición de Centro América y Panamá (INCAP) tiene entre sus actividades programas de investigación. Estos programas tienen entre sus objetivos generales los siguientes:

a) Lograr una mejor comprensión de los problemas nutricionales de la población del área, su magnitud, su severidad, sus factores responsables y sus efectos.

b) Buscar soluciones a los problemas detectados, que sean aplicables dentro de las condiciones prevalentes en el área.

c) Evaluar, en condiciones naturales la factibilidad, eficiencia y posibles efectos secundarios de medidas que se estimen recomendables para el control de problemas nutricionales; y

d) Obtener información básica no disponible, y que sea necesaria para estudios cuyos objetivos figuren dentro de los tres anteriores.

En la mayoría de estos estudios se hace necesario realizar investigaciones y llevar a cabo observaciones en sujetos humanos; Esto plantea un problema de ética de los investigadores en el que se debe dar especial atención a proteger los derechos humanos de los individuos sujetos a estudio. Además de este problema fundamental, de responbilidad moral, existen circunstancias por las cuales investigadores del Instituto deben ser particularmente cuidadosos en relación con este asunto. Entre ellos cabe mencionar los siguientes:

a) Que en su calidad de Organismo Internacional el INCAP debe respetar las leyes y otras reglamentaciones de los países en que trabaja.

b) Que gran parte de los fondos que recibe para sus programas de investigación provienen de fuentes externas y que tiene por lo tanto la responsabilidad de no comprometer a esos organismos, instituciones o individuos que apoyan sus trabajos; y

c) Que con frecuencia se tienen que emprender estudios que involucran a individuos o poblaciones de quienes es prácticamente imposible obtener previamente un consentimiento a su participación en los estudios, que asegure al investigador una verdadera y clara comprensión de parte de ellos de lo que se les está pidiendo. Las razones de esto son de diversa índole, pero son fundamentalmente debidas a las características socio-culturales, de educación y de comprensión de la ciencia de los miembros de dichas poblaciones; así como a la naturaleza misma de algunos de los estudios.

Ante estas circunstancias el INCAP y cada uno de sus investigadores han sido siempre muy celosos de los principios éticos que deben seguir en el

desarrollo de sus investigaciones. Ha existido lo que podríamos llamar un código implícito y sistemas internos de control y no se han llevado a cabo investigaciones en las que se pueda poner en duda su solidez moral. Se considera, sin embargo, que es necesario y conveniente que los principios de ética, en todo tipo de estudios, pero especialmente en investigaciones con humanos se establezcan claramente por escrito y que el mecanismo de control sea formalmente institucionalizado. Esos son los objetivos de este documento.

A) NORMAS GENERALES QUE DEBEN REGIR LAS INVESTIGACIONES EN EL INCAP O EN LAS QUE FUNCIONARIOS DEL INCAP PARTICIPEN:

1) Los estudios en humanos deben ser realizados únicamente si no es posible obtener la información deseada usando animales de experimentación.

2) Debe evitarse llevar a cabo investigaciones o procedimientos de estudio en individuos sanos cuando existan o se prevean posibles riesgos para la salud de los individuos involucrados.

3) Los procedimientos de investigación o tratamientos experimentales aplicados a individuos enfermos deberán ser evaluados en comparación con los mejores métodos o tratamientos conocidos hasta ese momento. Deberán ser de beneficio para el paciente en cuestión o para otros enfermos. En este último caso debe evitarse someter al paciente a riesgos injustificados en base a los beneficios esperados como consecuencia de la investigación.

4) En el caso de sujetos, sanos o enfermos, en que sea necesario llevar a cabo procedimientos o tratamientos que no conllevan un riesgo previsto significativo para la salud, ni incomodidad de trascendencia para su bienestar; se deberá valorar cualquier riesgo o incomodidad en relación con los beneficios esperados para ellos mismos o para otros individuos.

5) En cualquier caso de una investigación ya iniciada si se considera que su continuación puede ser perjudicial para la salud y el bienestar del sujeto, o la comunidad, debido a factores directamente relacionados o nó con la investigación, esta se deberá descontinuar.

6) Siempre deberán hacerse los mayores esfuerzos para informar adecuadamente acerca de los procedimientos y objetivos de la investigación a los individuos sujetos a estudio, a los padres o tutores legales de niños pequeños o de personas con incapacidad de tomar decisiones apropiadas referentes a su propio bienestar, y a las autoridades responsables en caso de instituciones o comunidades; cualquier estudio podrá realizarse sólo previa aceptación de parte de ellos, sin que medie ninguna medida coercitiva. Dentro de lo posible esta aceptación deberá obtenerse por escrito y debidamente firmada.

B) MECANISMO DE CONTROL

Desafortunadamente todas y cada una de las normas indicadas en la sección anterior están sujetas a un criterio o juicio que no es absoluto: las situaciones no son siempre claramente éticas o no éticas. En estas circunstancias, se considera que es inadecuado dejar las decisiones sólo en manos de los investigadores y es necesario, para la protección y beneficio de los sujetos, de la institución, y de los investigadores asegurarse que se esté usando el mejor criterio. Por lo tanto se considera necesaria la existencia de un grupo de personas, con suficientes conocimientos, reconocida competencia científica y rectitud moral que controle la efectiva y razonable aplicación, en la forma más estricta posible, de las normas anteriormente señaladas y de otros principios fundamentales de ética y responsabilidad moral y legal que no se hubiera podido prever. Para ese proposito, se establece en el INCAP un Comité de Resguardo de los Derechos Humanos y de Etica Profesional, que será responsable de revisar y aprobar o nó, todo proyecto de investigación en el que particpen humanos como sujetos experimentales o de estudio.

El Comité estará formado por:

a) 5 profesionales del INCAP y 5 suplentes. Estos últimos servirán para reemplazar a los miembros titulares que tengan responsabilidad como investigadores en el proyecto considerado o en caso de ausencia de los titulares; por lo menos dos de los miembros del Comité deberán ser métidocs.

b) Un representante nombrado por el Ministerio de Salud Pública y Assistencia Social de Guatemala; y,

c) Un representante del Colegio de Médicos y Cirujanos de Guatemala.

La aprobación previa por este Comité es necesaria para que se lleve a cabo cualquier proyecto de investigación o cualquier tipo de estudio en que participen sujetos humanos, en los cuales el INCAP sea directamente responsable o participen oficialmente funcionarios del INCAP. El Comité, después de las consultas que considere necesarias, podrá dar o nó su aprobación al mismo. El Comité deberá presentar el informe de sus deliberaciones y conclusiones para cada proyecto en un acta escrita y firmada que será enviada a la Dirección del Instituto. La Dirección, en base al informe del Comité autorizará o nó la ejecución del proyecto.

En caso de que después de aprobado un proyecto, los investigadores consideren necesario modificar el diseño, hacer cualquier cambio en la metodología o introducir nuevas técnicas o procedimientos será necesario que estos proyectos sean revisados y aprobados por el Comité en forma similar a la aprobación de un nuevo proyecto.

La Dirección del Instituto será el enlace entre el Comité y los investigadores y tendrá la responsabilidad de asegurar la continuidad del proceso de control.

Finalmente, se considera importante señalar que, independientemente de cualquier sistema que se establezca, en último término la seguridad y el bienestar de los humanos que participen como sujetos experimentales, o de estudio, en proyectos de investigación, depende de la competencia y de las cualidades morales y éticas de los investigadores y del personal técnico bajo su supervisión. Los profesionales del INCAP deben permanecer conscientes de esta situación y de la gran responsabilidad que sobre ellos pesa, como hasta ahora estamos seguros ha ocurrido.

Este documento será sometido a la aprobación del Director de la Oficina Sanitaria Panamericana y del Consejo de INCAP para que tenga validez reglamentaria.

SAMPLE

"INFORMED CONSENT FORM" - INCAP

Dear Sir:

As was explained to you personally, the procedure that you accepted to have done to you consists in swallowing a very thin probe until it reaches your stomach and intestines. So that the probe does not affect the swallowing process, you are going to gargle beforehand with a medicine that puts the throat to sleep for an hour. After having swallowed the first part of the probe, you will not have to make any further effort, the probe will continue by itself until it comes out in your stools.

The probe will be in place for 1 or 2 days. As it is very thin, it is not going to cause you any nuisance and you will be able to eat normally. During this time we will take small quantities of intestinal juice to see if you have microbes or parasites. If we find some bad microbe or parasite, we will give you the medicine you need.

While this test lasts you will remain in the INCAP hospital. So that your stay in the hospital should not cause you to lose money, you will be paid the daily salary prescribed by law for the time spent in the hospital.

Having understood the content of this document and in testimony that you are in agreement for this procedure to be carried out, we ask you to sign this page.

_____ _____

Name Date

SAMPLE

"INFORMED CONSENT FORM" - INCAP

Dear Sir:

The study with which you are collaborating has as its objective the determination of whether you are digesting your food or not. The results will not only benefit you but will also help us to develop programs oriented towards the betterment of the state of health of people living in the coasted area of Guatemala.

To be able to complete this study, it is necessary that you be in INCAP's rural ward for_____ days. In this ward you will be given several sugars, as well as meals containing tortillas, black beans or eggs. Besides that your stools and urine will be collected and you will be asked to breathe into a special tube that is used for obtaining breath samples. By examining the urine, stool and breath samples, we will know whether you are digesting your food or not. Also blood will be extracted from the vein twice to find out if you have anemia and need vitamins.

During your stay in the ward, a complete medical check will be made (physical examination, blood, stool and urine analyses) to see if you show evidence of having some disease. If necessary treatment will be given to you.

So that your stay in the ward should not represent any economic hardship for you, you will be paid the daily salary determined by law for the time that you remain in the ward.

Having understood the content of this document and in testimony that you have agreed to take part in this study, we ask you to sign this page.

_____ _____

Name Date

PROPOSED WORKING MECHANISM FOR THE
PAHO RESEARCH ETHICS REVIEW COMMITTEE (RERC)

1. Research worker submits his proposal to field RERC.

2. Field RERC reviews the application as to the safeguard and right of human subjects involved in the research.

   2A. If such safeguards have not been considered or are unsatisfactory, the proposal is returned to the research worker for necessary amendments.

   2B. If the safeguards put forth are accepted, the proposal is channeled to PAHO Headquarter's RERC Hqts with a clearance report.

3. When the cleared research proposal reaches Washington, RERC Htqts' Secretary studies it and takes the following steps:

   3A. If no human subjects are involved in the proposed research project he sends it to the FIN Office (FIN) for further action.

   3B. If human subjects are involved the proposal is submitted to RERC Hqts for review.

4. After consideration of the project, RERC Hqts

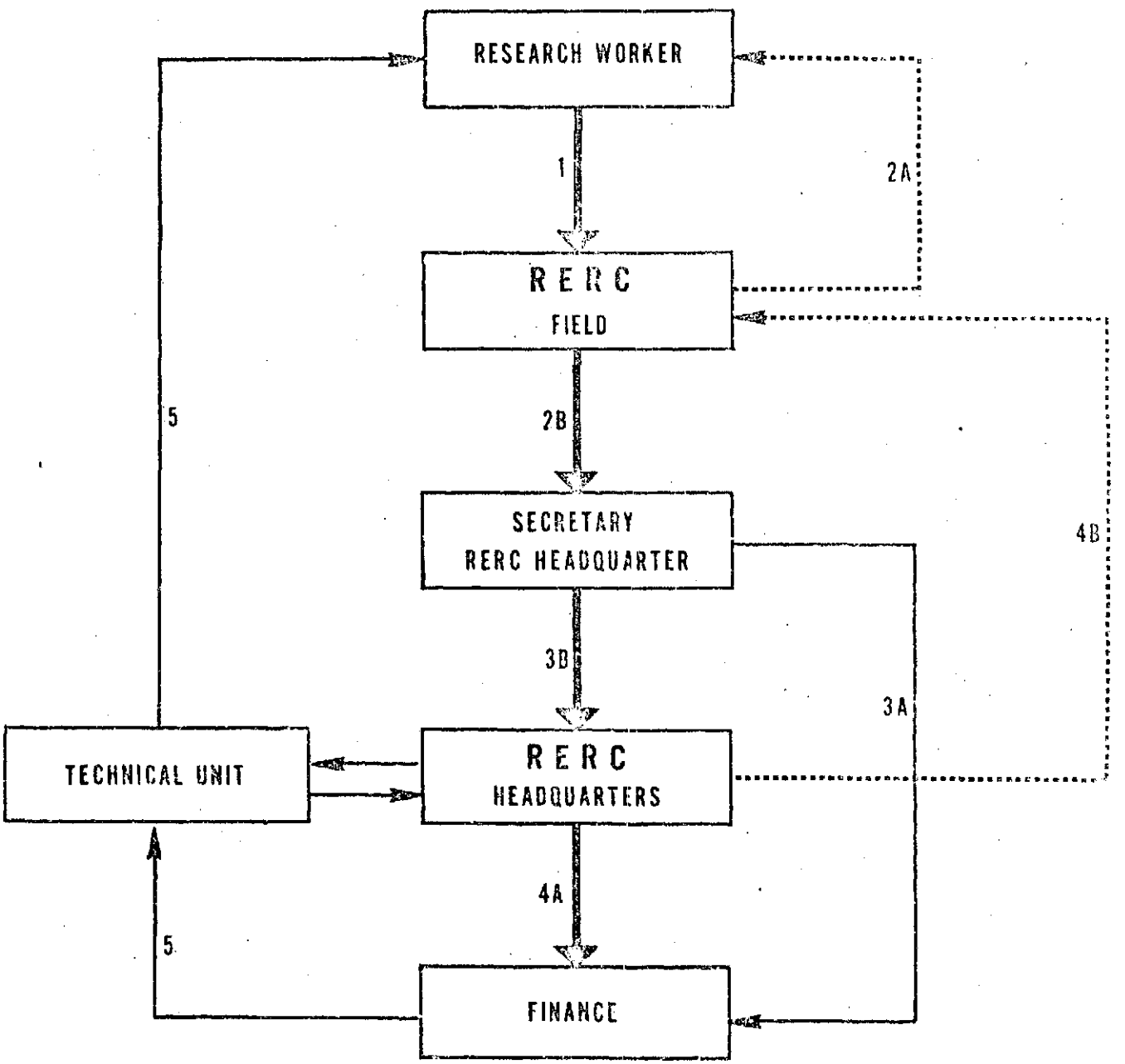
   4A. Sends the research proposal to FIN for final action if it endorses or accepts field RERC's clearance.

   4B. Returns the proposal to the research worker through field RERC if the guarantees given by the latter and not accepted or endorsed.

5. Once funds (or the lack of them) for the research proposal have been identified, the appropriate technical unit informs the applicant of the outcome of his request.

NOTE: FIN will be instructed not to process any research proposal that does not have RERC Hqts' clearance.

PAHO RESEARCH ETHICS REVIEW COMMITTEE



GUIDELINES FOR RESEARCH INVOLVING HUMAN SUBJECTS

As is already known, the Director-General has set up a Secretariat Committee on Research involving Human Subjects (SCRIHS). The actual membership, as decided by the Director-General, includes the following members:

Chairman:	Dr. H. Mahler, ADG
Secretary:	Dr. J. de Moerloose, Chief, HL
Members:	Dr. V. Fattorusso, Director, PTX Mr. F. Gutteridge, Director, LEG Dr. K. W. Newell, Director, RECS Dr. I. Barrai, Chief, HG Dr. D. C. Cameron, Chief, DRD Dr. W. C. Cockburn, Chief, VIR Dr. H. C. Goodman, Chief, IMM Dr. A. Manuila, Chief, PT Dr. W. H. P. Seelentag, Chief, RHL

It was decided that SCRIHS should issue Guidelines for Research Involving Human Subjects that would serve the different Divisions and units of the Organization, and indicate the position and responsibility of WHO whenever research in human subjects is concerned. A copy of the Guidelines is attached.

The attention of Divisions and units is drawn to the fact that, whenever problems arise which might involve difficult ethical decisions, the individual cases should be referred to SCRIHS.

28 April 1971

(Signed)
H. Mahler, ADG
Chairman of SCRIHS

(Prepared by Dr. J. de Moerloose) RC. 28 April 1971

RESEARCH INVOLVING HUMAN SUBJECTS

Standards of conduct for research carried out by or under the auspices of WHO

Preliminary Remarks

When WHO, either on its own initiative or in co-operation with other institutions concerned with research, has to face the problem of experimentation on man, we can be practically certain that the experiments will be conducted in countries where there is no national legislation or code of ethics on the subject, for there are very few countries possessing such legislation or a code of that nature. The only examples that can be cited are a few countries such as the United States of America, the United Kingdom, France and the Netherlands. The United States of America* stands alone in having formulated legislation regarding experimentation on man, and even so it concerns only clinical trials of pharmaceutical preparations. In the Netherlands, the ethical rules drawn up by the Netherlands Medical Association are based on the final analysis to the Helsinki Declaration (1964)*. It is therefore only in the few countries mentioned above that, in the event of experiments being conducted on man, WHO finds itself under the obligation to comply with the standards laid down in the codes of ethics which they have formulated.

Where national codes of ethics are lacking, it is WHO's duty to comply with the provisions of the only international instrument at present known to us namely those of the Helsinki Declaration, supplemented by Article 7 of the International Covenant on Civil and Political Rights adopted by the United Nations General Assembly on 16 December 1966. Article 7 provides that no one shall be subjected without his free consent to medical or scientific experimentation. This being the position, it follows that WHO cannot formulate, for the experiments on man which it intends to conduct in its Member Countries, any standards that would be fundamentally different from those of the Helsinki Declaration. At the very most, it may be said that the Organization is entitled to prescribe stricter rules!

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*A further, recent exception is provided by Austria, where the Federal Ministry of Social Affairs has issued "Guidelines for the testing of new drugs on human beings".

Obviously, however, by the nature of its mission and because of the prestige it enjoys throughout the world, WHO has a duty to be especially prudent when initiating or co-operating in experiments on man. It should be recalled in this connection that for some years past the public opinion of certain countries has been rendered particularly sensitive on this point, so we are liable to run into great difficulties if research on man is undertaken imprudently or without providing for all the necessary precautions. It is even arguable that WHO is more vulnerable in that respect than isolated investigators or national research institutions. It also seems to us that we must be particularly careful not to publish papers (we have already come under criticism for this) which describe experiments conducted on man, with or even without WHO's assistance, in which elementary ethical principles have not been adhered to.

No doubt the provisions of the Helsinki Declaration are imperfect and some of its principles may well need revision and amplification. We know, however, that any attempt to improve it and even, taking the mostoptimistic view, the publication of an ideal code of ethics would at the most provide only a guide for concrete cases of experimentation on man. In every specific case of experimentation the interplay of the various factors that must be considered may be of such complexity that even the best code of ethics cannot be applied. To draw a parallel, we might say that the position in regard to experimentation on man is similar to the position in regard to diseases, as expressed by the adage that "there are no diseases, but only sick persons". It is a fact that for every concrete case of experimentation we have to evaluate, from the ethical point of view, the significance of various factors such as consent, the risk, the benefit anticipated from the experiment the qualifications of the investigator and the type of person undergoing the experiment, and the distinction between pure research and research into treatment methods conducted on a patient or a group of patients. It is thus extremely difficult in certain cases to give a definite opinion as to whether the rules of ethics are being observed. Our conclusion must therefore be that if any doubt remains as to the ethical justification for an experiment, the investigator must consult his peer group and, in those cases where special committees are set up, refer to them for advice. The committees which are set

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up must be independent of the investigator or research group. It is for this reason, in fact, that the Director-General of WHO has decided to establish a committee within the Organization. With regard to the utopian concept of a code of ethics concerning experimentation on man one last conclusion can be drawn - namely, that it would be extremely dangerous to try to enact laws on the subject, for their rigid provisions might have the effect of paralysing research.

Essential Points Covered by the Various Codes of Ethics

1. Consent

All the ethical codes without exception require the consent of the person subjected to the experiment. None of the various codes give, however, any satisfactory definition of the term "consent". On the other hand, a number of qualifying adjectives are utilized, all of which give an idea of what consent must be or ought to be under ideal conditions. References are made to "true consent", "informed consent", "free consent" and sometimes also "valid consent". It seems clear that in order to be "valid" consent must be informed and free. The facts prove, however, that "informed" consent is extremely rare: many experiments nowadays are so complex that their true nature and their consequences or their risks can be understood only by qualified experts. Particular caution is therefore necessary with experiments conducted on children or minors, or on mentally deficient or retarded persons. In some countries, indeed, any authorization that may be given by their legal representatives or by their parents is considered as invalid. The validity of the consent is also open to question if the experiment is conducted on persons who by their position are subjected to some degree of duress. This applies, for example, to prisoners, students, or the staff of medical care institutions, or where the "volunteer" is tempted by the promise of material or financial advantages. Certain categories of person must also be ruled out as potential subjects for experimentation, e.g. the new-born, infants and pregnant women, the incurable, the moribound, or the old. In such cases any experimentation, even with prior consent, should be banned. Also bound up with the concept of consent is the possibility for the subject of the experiment to put an end to it at any time. This condition, which was already included in the Nuremberg code, seems extremely unsatisfactory since very often it may be too late to decide to stop the experiment.

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From the foregoing, it would therefore seem that ideal conditions for consent are seldom realized in practice. And yet the existence of such conditions is one of the essential prerequisites. An importance consequence of this situation is that the burden of responsibility under imperfect conditions of consent must necessarily be shifted on to the investigator. He alone can understand what consent implies and what are the risks and possible benefits of the experiment. That, too, is the reason why both the Nuremberg code and the Helsinki Declaration require that the experiment should be conducted by particularly well qualified investigators. They must be aware that experimentation on man has to be preceded by laboratory research or animal studies to the fullest extent possible.

2. Risks and benefits of the experiment

Every experiment on man entails a certain risk which must be evaluated in relation to the potential benefits. Experiments from which it is clear that the benefit will be nil or very small cannot be undertaken. For the same reason, the repetition of experiments that have already been carried out must be avoided. It is therefore important that the investigator should find out whether or not the experiment has already been carried out. Experiments may entail risks for the physical or mental personality of the individual. The risks of disability may be very small or serious, temporary or permanent. It is recognized that if there are any risks of serious ill effects from the experiment, it cannot be undertaken even on volunteers, and this applies *a fortiori* where there is a danger of death: if risks of such a nature exists, the investigator must conduct the experiment on himself.

Within the sphere of WHO's activities, certain experiments may in the short or long run affect directly not only the person or persons subjected to them, but also the environment and hence categories of person other than those undergoing the experiment, because of more or less remote repercussions and consequences. This aspect of the problem must also, of course, be considered by the investigator.

It has been thought necessary to justify certain risks to which one or more individuals are subjected by reference to the interests of and benefits to society. This argument, in cases where the experiment entails harmful or adverse consequences, for example, cannot be used, for it has no validity. Some codes also consider as illicit any experiments entailing risks of serious suffering.

3. Nature of the experiment

The Helsinki Declaration, like other codes, draws a distinction between experiments of a therapeutic nature and those concerned only with research. In the case of non-therapeutic experiments, it is recognized that they can be undertaken equally well either on volunteers or on sick persons. In the case of experiments conducted on sick persons there must be strict observation of the precepts of medical ethics: it would be in complete contradiction with medical principles not to have as one's primary objective the treatment of a patient. Very special consideration must be given to this question whenever it is proposed to conduct tests with new treatment or diagnostic methods whose results are uncertain, whereas conventional methods have proved effective.

In the present state of scientific knowledge, where a solution is wanted quickly to the problem being investigated, special precautions must be taken in the case of controlled clinical trials or blind or double-blind methods. In the case of controlled clinical trials, on sick persons for example, the effect of excluding from the benefits of treatment a control group, with or without the consent of the patients concerned, can be particularly prejudicial. The same is true when the objective is to determine the effect of certain preventive measures, such as vaccine, for example. These considerations are still more strongly applicable in the case of blind or double-blind methods.

Important Remarks

It has been mentioned in a number of cases that poorly designed experiments, or experimental designs which are not clearly described, present particular problems. This is also the case of SCRIHS. Some experimentation projects have had to be refused or postponed on this ground. It is therefore essential to present a clear description of the experimental schemes on which ethical judgement is requested.

Moreover, it is essential that any significant changes in an experimental project be referred to SCRIHS.

DECLARATION OF HELSINKI - World Medical Association (1964)

Recommendations Guiding Doctors in Clinical Research

It is the mission of the doctor to safeguard the health of the people. His knowledge and conscience are dedicated to the fulfillment 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 device which could weaken physical or mental resistance of a human being may be used only in his interest." 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 each doctor in clinical research. 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.

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

I. Basic Principles

1. Clinical research must conform to the moral and scientific principles that justify medical research and should be based on laboratory and animal experiments or other scientifically established facts.

2. Clinical research should be conducted only by scientifically qualified persons and under the supervision of a qualified medical man.

3. Clinical research cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

4. Every clinical research project should be preceded by careful assessment of inherent risks in comparison to forseeable benefits to the subject or to others.

5. Special caution should be exercised by the doctor performing clinical research in which the personality of the subject is liable to be altered by drugs or experimental procedure.

Declaration of Helsinki

II. Clinical Research Combined with Professional Care

1. In the treatment of the sick person, the doctor must be free to use a new therapeutic measure, if in his judgment it offers hope of saving life, re-establishing health, or alleviating suffering. If at all possible, consistent with patient psychology, the doctor should obtain the patient's freely given consent after the patient has been given a full explanation. In case of legal incapacity, consent should also be procured from the legal guardian; in case of physical incapacity, the permission of the legal guardian replaces that of the patient.

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

III. Non-Therapeutic Clinical Research

1. In the purely scientific application of clinical 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 clinical research is being carried out.

2. The nature, the purpose and the risk of clinical research must be explained to the subject by the doctor.

3a. Clinical research on a human being cannot be undertaken without his free consent after he has been informed; if he is legally incompetent, the consent of the legal guardian should be procured.

3b. The subject of clinical research should be in such a mental, physical and legal state as to be able to exercise his power of choice.

3c. Consent should, as a rule, be obtained in writing. However, the responsibility for clinical research always remains with the research worker; if never fails on the subject even after consent is obtained.

4a. The investigator must respect the right of each individual to safeguard his personal integrity, especially if the subject is in a dependent relationship to the investigator.

4b. At any time during the course of clinical research the subject or his guardian should be free to withdraw permission for research to be continued. The investigator or the investigating team should discontinue the research if, in his or their judgment, it may, if continued, be harmful to the individual.