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APPLIED RESEARCH IN THE AFRICA CHILD SURVIVAL INITIATIVE

Lessons Learned from the ACSI-CCCD Project 1982 - 1993

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Public Health Service
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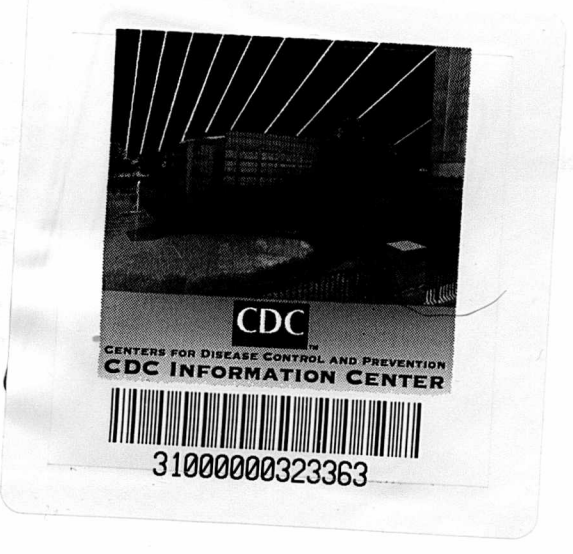

ABBREVIATIONS

AAAS	American Association for the Advancement of Science
ACSI	Africa Child Survival Initiative
A.I.D.	Agency for International Development
AIDS	Acquired Immunodeficiency Syndrome
ALRI	Acute Lower Respiratory Tract Infection
AQ	Amodiaquine
ARHEC	African Regional Health Education Center (Nigeria)
ARI	Acute Respiratory Infection
BUCENS	Bureau of the Census
BCG	Bacillus Calmette-Guerin (immunization against TB)
CAR	Central African Republic
CCCD	Combatting Childhood Communicable Diseases
CDC	Centers for Disease Control
CDD	Controlling Diarrheal Diseases
CEIS	Computerized EPI Information System (WHO software program for EPI)
CEC	Continuing Education Committee
CEU	Continuing Education Unit
CHRD	Commission on Health Research for Development
CHU	University Hospital Center (Togo)
CHW	Community Health Worker
CIOMS	Council for International Organizations of Medical Sciences
CRPF	Chloroquine-Resistant Plasmodium falciparum
CQ	Chloroquine
DHS	Demographic and Health Surveys
DMPGE	Department of Preventive Medicine and Endemic Diseases (CAR)
DPRS	Department of National Health Planning, Research and Statistics
DPT	Diphtheria, Pertussis, Tetanus
DTU	Diarrhea Training Unit
DTP	Diphtheria, Tetanus, and Pertussis (same as DPT)
EIR	Entomologic Inoculation Rate
EIS	Epidemic Intelligence Service
ENHR	Essential National Health Research
EPI	Expanded Program on Immunization
EPIINFO	Epidemiologic Information program (a database and statistics program for microcomputers)
EZ	Edmonston-Zagreb Measles Vaccine
FBA	Facility-based Assessment
FMOH	Federal Ministry of Health (Nigeria)
HEALTHCOM	Communication for Child Survival Project
HIS	Health Information Systems
HIV	Human Immunodeficiency Virus
HSA	Health Service Area (Lesotho)
IEC	Information, Education, Communication

IHPO	International Health Program Office
IMR	Infant Mortality Rate
INSP	National Institute of Public Health (Cote d'Ivoire)
IOM	Institute of Medicine
IRB	Institutional Review Board
IUGR	Intra-uterine Growth Retardation
KAP	Knowledge, Attitude, and Practices
LBW	Low Birth Weight
LGA	Local Government Area (Nigeria)
MCH	Maternal and Child Health
MMRP	Mangochi Malaria Research Project
MOH	Ministry of Health
MQ	Mefloquine
NCID	National Center for Infectious Diseases (CDC)
NIH	National Institutes of Health
NMR	Neonatal Mortality Rate
NNT	Neonatal Tetanus
OCCGE	Organisation de Coordination et de Cooperation Pour la Lutte Contre les Grandes Endemies
OPRR	Office for Protection from Research Risks
OPV	Oral Polio Vaccine
ORS	Oral Rehydration Salts
ORT	Oral Rehydration Therapy
ORTU	Oral Rehydration Therapy Unit
PHAL	Private Health Association of Lesotho
PHC	Primary Health Care
PRICOR	Primary Care Operations Research Project
PRITECH	Technologies for Primary Health Care Project
P/S	Pyrimethamine-Sulphadoxine
REACH	Resources for Child Health Project
SANRU	Santé Rural (Rural Health Project, Zaire)
SHDS	Strengthening Health Delivery Services Project
SSS	Salt and Sugar Solution
STD	Sexually Transmitted Diseases
TB	Tuberculosis
TBA	Traditional Birth Attendant
TT	Tetanus Toxoid
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
VHW	Village Health Worker
VDRL	Venereal Disease Research Laboratory (a serologic test for Syphilis)
WFS	World Fertility Surveys
WHO	World Health Organization
WHO/AFRO	WHO Africa Regional Office
ZSPH	Zaire School of Public Health

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INTRODUCTION

This document is one of several publications reviewing a decade of applied research experience in the **Africa Child Survival Initiative-Combatting Childhood Communicable Disease** (ACSI-CCCD) **Project**, supported by the **U.S. Agency for International Development** (USAID). A compendium of ACSI-CCCD-sponsored research, a companion piece to this document, gives greater detail about some of the individual research projects undertaken by this project.

This publication examines lessons learned during the course of the project that might offer insights to policy- makers involved in the promotion or conduct of research in a public health setting. During the course of 12 years' experience in some 13 African countries, those involved with the project have gained a great deal of insight and experience with the opportunities and limitations of conducting public health research in developing countries. It is that experience that this document hopes to synthesize into a framework that might guide future efforts.

This document is offered with a few caveats:

1. Although this document spans a wide range of countries and experiences, there is probably a significant bias toward the perspective of the donor agencies, largely because of easier access to documentation and personnel.

2. The framework of the ACSI-CCCD Project within which this research was done is also an important consideration: Although the CCCD Project included a substantial amount of research, it was not by definition a "research" project, but rather a child survival intervention. Thus, it also included numerous service delivery components, including training, program assistance, and logistical support. Within this framework, the primary role of CCCD research was to identify and solve problems constraining the achievement of project objectives. In this respect, it cannot be compared to a project (donor funded or otherwise) that has the singular objective of promoting or producing research. The authors acknowledge this multiple role, but also believe that this was one of the project's strengths.

3. Because the intent of this document is a critical self-assessment of the ACSI-CCCD program, it sometimes gives a disproportionate emphasis to constraints and limitations that affected the research activity. On the other hand, the paper presents relatively few examples of many concrete program benefits that evolved from CCCD research. This should not detract from the considerable achievements of that project. Those achievements are perhaps better addressed in the companion document to this review -- a compendium of CCCD applied research -- and in several other end-of-project documents that evaluate the contribution of individual program components (e.g., malaria control and Expanded Programme on Immunization support activities). A complete listing of these documents is available on request (see footnote on page 42).

A note on abbreviations and conventions: At its outset, the ACSI-CCCD Project was known simply as the CCCD project (Combatting Childhood Communicable Diseases). The prefix Africa Child Survival Initiative was added in 1986 and the project became known as ACSI-CCCD (although it was often still commonly called "the CCCD Project"). Both terms may be used interchangeably in this document.

In some instances the document may also use terms that may not currently be preferred--for example, traditional birth attendants (TBAs). In general, we have not tried to change or update terminology used in specific studies.

BACKGROUND AND METHODS

This document is based on an extensive review of some 250 applied research projects carried out in 18 countries during the course of the ACSI-CCCD Project. There were three main components to the analysis:

1. **Review of documents**, including published and unpublished studies, project proposals, source documents, preliminary and final reports, correspondence, minutes of meetings, trip reports, and annual, quarterly and monthly reports.

2. **Interviews** with CDC principals, counterpart investigators, Ministry of Health (MOH) personnel, program managers, and administrators from other donor-supported research programs.

3. **Site visits** to two CCCD-supported countries involved in substantive research activities, Nigeria and Zaire, in 1990.

The actual process of identifying specific activities as research projects also required that a certain amount of redefinition be done, since countries and project personnel often differed considerably in what they classified as a research project. In general, this assessment did not include routine outbreak investigations or routine surveillance activities as research. Moreover, multiple activities that related to a single problem or research question were generally consolidated as a single project for the purpose of this analysis, although they were often listed as multiple activities in project documents.

The initial investigation that gave rise to this report was an in-depth review done in 1990; it examined the role of African investigators in the ACSI-CCCD Project (Joseph, 1990). That earlier assessment used an extensive document review and also included site visits to review operational research sites and activities in Zaire and Nigeria. Structured interviews and a brief questionnaire were used to identify major strengths and limitations of the respective research projects in these countries. In Zaire, sites included local and donor- supported research institutions, as well as the Zaire School of Public Health. In Nigeria, six sites were visited throughout the country, including four sponsoring universities, and interviews were held with investigators and members of the research review committee, as well as other MOH and project personnel.

Whereas the 1990 review was focused almost exclusively on the benefits to counterpart African researchers and institutions, this 1992 evaluation was expanded to include all research activities carried out under the aegis of ACSI-CCCD. It was also broadened to include an assessment of the role of CCCD research in advancing program objectives and public health goals of the project itself.

The current evaluation has used many of the findings of the 1990 assessment, as well as updating the record with research carried out in the intervening years. The study has again made an extensive use of document reviews and structured interviews with individual researchers, project principals, and others involved in promoting research or implementing its findings.

Included in these activities were four focus-group discussions--one with malaria program managers held in Atlanta in November 1992, and three conducted in Dakar in March 1993 at the Sixth Consultative Meeting of the ACSI-CCCD Project. Two of the three Dakar groups were held among counterpart investigators and program managers; the third group was held with experienced investigators actively involved in promoting research and building research capacity in Africa. A number of individual interviews with project counterparts were also conducted during this period.

These methods cannot be expected to reliably document every individual experience with applied research in the ACSI-CCCD project. However, they *have* allowed identification of a surprising number of consistent themes, as well some overall strengths and weaknesses noted by various respondents. While there are numerous limitations to a retrospective evaluation such as this, a few deserve specific mention:

1. Studies that were aborted or terminated at an early stage are under-represented. Although there is considerable benefit in examining failures as well as successes, studies or projects that were not pursued to completion often had only brief documentation. It was also generally not feasible to meet with authors of unapproved proposals or studies that were prematurely terminated, except in a few significant instances.

2. Because the costs of applied research activities were often contained within the general project operating budget, or overlapped other areas of operations, accurately evaluating the cost of research activities was not possible, except in a few instances.

3. Finally, the methods used here are largely, but not exclusively, qualitative. In dealing with a research program as diverse in scope and nature as CCCD's, such an assessment is probably the best that can be achieved by a retrospective review of a 12-year period.

CHAPTER 1

THE ROLE AND NATURE OF RESEARCH IN PUBLIC HEALTH PROGRAMS

"Data must be recognized as a valuable resource, more valuable in direct proportion to their relevance, validity and timeliness."

H.R. Hapsara (1992)

1.1 Definition of Research and its Role in Public Health

1.1.1 Definition of Research

The definition of "*research*" that this document has adopted is intentionally broad. The decision to be inclusive rather than exclusive was made to demonstrate that a continuum exists among different methods applied to problem solving in the public health field, whether called surveillance, research, or evaluation. A convenient reference point for defining research is the 1979 Belmont Report (of the National Commission for the Protection of Human Subjects). It defines research as:

> "...an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge."

A more pointed description, emphasizing the applied nature of health research, classifies it as "**the use of scientific methods to analyze health situations, identify problems, and solve them,**" a process whose objective is "science-based, knowledge-based decision making at all levels of health services (Lucas, 1993)." The main characteristics we have used to define research, therefore, are the following:

1. It contributes to general knowledge.
2. It uses scientific method.
3. It addresses a stated hypothesis (i.e., answers a research question).

1.1.2 Definition of applied, or "operational," research

Reduced to its most basic components, the role of applied research can be stated in two simple rules:

1. Research is undertaken to discover <u>something not already known</u>; and,
2. Research is meant to provide answers <u>for some purpose</u>.

Rule 1 is relevant because it proscribes research from being done where information is otherwise obtainable. In general, however, deficiencies in the research environment usually coexist with deficiencies in information management. Thus, programs with inadequate methods for directing data to those who need it often initiate "research" to provide data that may already be available, but are simply not accessible. In short, inefficient data and information management often lead to inefficient research, (that is, research that duplicates available information).

Rule 2 -- that research is meant to provide answers for a purpose -- is relevant simply because it relates research to some potential user. Despite the intellectual appeal of "research for research's sake," most research in public health is undertaken with potential or actual applications in mind (although these may not always be clearly defined). In practice, research is often directed at two audiences. In the first instance, it fulfills a local need that may be satisfied by limited distribution of a written or verbal report of findings to a few key decision makers. The second audience is the wider academic community, public health community, or population at large, however defined. If one accepts the definition of research as a contribution to generalized knowledge, then dissemination beyond the immediate user is implicit. Whether that intended audience should be malaria researchers, health workers, the general public, or the international community often depends on the nature and importance of the findings.

Two factors are responsible for much of the duplication that often pervades research environments. One is lack of access to information sources. This can often be traced to poor dissemination of prior research and to deficient libraries and data systems. The other factor is an unwillingness to use "someone else's" results, due to lack of confidence in others' results, or to real or imagined differences in the populations. Unfortunately, although most researchers accept in principle the need for making research findings widely available, there are a number of obstacles to meeting this goal:

Conceptual obstacles: Many researchers interpret appropriate dissemination as one of two options only--an article published in a journal, or a presentation at a conference. Both have shortcomings, such as timeliness or limited audiences, which are particularly relevant in developing countries (see box).

Financial constraints: Funding is often not available in public health or research programs for adequate dissemination, except for journal publication or local meetings.

Logistical constraints: Research reports are often presented in a format unsuitable for wide dissemination. For example, the form of a final report is often too lengthy and technical for wide distribution. In addition, many authors often have neither the experience nor inclination to use other outlets of dissemination, such as lay publications or radio.

In considering a "program of research," this document assumes that such a program is intended to provide more than research results. That is, it assumes that some degree of training, skills transfer, capacity building or institutional strengthening is at least a partial objective of the research program. Because the ACSI-CCCD Project fell within this domain (and because the project often measured itself by what capacity it left behind), the role of counterpart individuals and institutions occupies a significant focus in this assessment. These counterparts were the numerous program managers of CCCD target intervention programs (in immunization, diarrheal disease and malaria) as well as academic researchers in universities, and ministry of health personnel in other capacities.

BOX 1.1.2

GETTING THE MESSAGE OUT: THE ISSUE OF JOURNAL PUBLICATION

Although the scientific community has traditionally placed great emphasis on publication in peer-reviewed journals as the principal measure by which scientific research is validated, there are at least two major limitations of this approach that are of particular relevance to developing countries--timeliness and limited distribution. In one illustrative example, the authors looked at 24 CCCD-supported studies documenting chloroquine resistance of Plasmodium falciparum and in vivo sensitivity to alternative drugs. The average period from study completion to journal publication in these studies was 2 years, with a range of 1 to 4 years. Although these periods are not atypical for journal publication, the status of chloroquine resistance was a rapidly evolving one and had often changed considerably by the time publications appeared. Admittedly, local response to these research findings was seldom dictated by publication. On the other hand, the useful life of the journal recommendations for secondary data users was extremely short.

For topics whose status is rapidly changing (e.g., malaria or AIDS), journal publication may not fulfill the need for rapid dissemination. Although in the CCCD experience, journal publication did provide a useful means for developing research discipline, it is often not the best medium for "getting the message out," particularly if the goal is wide and timely local distribution.

In the ACSI-CCCD Project, several alternatives to peer-reviewed journals were tried:

- *For expeditious international publication of changing developments, the WHO's Weekly Epidemiological Report and the CDC's own Morbidity and Mortality Weekly Report (MMWR) have been used as outlets.*
- *Where documentation of the research effort has been a primary concern, the project has used annual and quarterly reports of the CCCD Project, although these seldom numbered more than several hundred copies.*
- *For wider coverage (2,000 to 3,000 copies), the ACSI-CCCD Project also engaged in a concerted effort with ministries of health to initiate and sustain national epidemiologic bulletins at the local level. These have been locally produced and printed with the use of microcomputer graphics and desk-top publishing programs. Although these have had extraordinary initial success in several countries (e.g., Zaire, Nigeria, and Burundi), ongoing evaluation will be needed to gauge the practical usefulness of these publications and their capacity for sustainability.*
- *The CCCD technical director in Atlanta published a monthly communication called "R&D Feedback." This brief document was sent to all CCCD countries and partner agencies, as well as selected other persons and institutions. It included each month a brief note of commentary and a copy of a recently published study or report deemed important by the director. Over its lifetime, it included publications based on many CCCD OR studies, as well as important articles from diverse other sources. Because it was sent expeditiously through US government mail to CDC field assignees, it became a timely mechanism through which major articles were rapidly shared with CCCD national counterparts.*

1.2 The Problem of Data and Information Management

In general, the problem of research and research capacity cannot be separated from the question of information management as a whole. In the area of research there are usually two complementary problems relating to information management. The first relates to physical unavailability of data;

there simply are not enough data. This is the most familiar complaint heard from researchers and program managers. A second problem is the appropriateness of available data. This could be characterized as the gap between "**data**" and "**information**" -- or the problem of synthesizing useful information for decision making from what data there are. This in turn may be influenced by the quality or accuracy of the data available and their suitability for the intended purpose. Most sources readily admit to the first of these being a problem. A more recent issue involves data quality or representativeness, either of which can which can make research "unusable."

1.2.1 Availability (existence) of data

The lack of health data in developing countries is so widely documented that it will be discussed only briefly here. Among the more commonly cited problems are the lack of vital event (births and deaths) registration and reliable census data. Mortality rates--including indices such as infant and under 5 mortality--are inevitably based on retrospective estimates, and in many cases vary widely with the method or model chosen. Morbidity recording is often similarly deficient. Although most countries can produce a ranking of the top 5 or 10 hospital diagnoses (and can indicate what percentage of all hospital admissions these represent), the denominator for these totals is often unknown, and rates or trends often cannot be determined. Health problems that are not diseases may not be recorded at all. Morbidity data that are available are generally hospital data, whereas few countries have reliable community-level statistics. Where such community data are available, they often consist of scattered data from more accessible urban or peri-urban areas. Often deficiencies in health information systems are associated with comparable deficiencies in management information systems.

1.2.2 Accessibility of existing data

Accessibility relates both to locally produced data and to sources of regional or international research data. When the status of information services in developing countries is examined, it is immediately apparent that the numbers and the costs of publications, journals, and other information sources are burgeoning. As a result mainly of cost (compounded in many countries by currency exchange restrictions), medical collections and libraries in the developing world have deteriorated (Bruer et al., 1981). This has created tremendous gaps in the information available to academic researchers. On the other hand, the availability and diminishing costs of microcomputer technology have created opportunities for the rapid evolution of information services in the developing world that would have been unthinkable less than a decade ago. Much of this technology is readily available in the private sector in most developing countries.

In considering the problems of access and use of data and information, the interest of the researcher is two-fold: 1) access to the broad body of knowledge represented by international journals and publications; and 2) timely access to accurate data on local health issues or problems of importance. Whereas one is important to define the state of the art, the other is important to define the status quo. Unfortunately, library and research resources are often inadequate to this task. In many cases, even when equipment is available, chronic shortages of supplies and spare parts may prevent these resources from functioning effectively. In 1990, the **American Association for the Advancement of Science** (AAAS) reviewed 106 libraries in 28 African countries, focusing mainly on microcomputer technology. At that time only 48 libraries had a computer, and only 11 (10%) offered on-line

searches. Even where this service was available, libraries reported difficulties supplying full- text articles for researchers (usually because of expense). Of 16 libraries with CD-ROM data bases, only 4 indicated that they had funding for continuing their subscriptions in the future. Similar findings can be described for most African countries. Although recent programs have been developed to alleviate some of these needs (e.g., the **AAAS Journal Distribution Program**[1] and CD-ROM Initiative, and the **SatelLife** communications program[2]), these external assistance programs do not usually provide support for indefinite periods.

1.2.3 Appropriateness of available data

The belief that African and other developing countries have no research capability is a misconception. For example, a review of the Medline data base from 1965 to 1993 by the authors identified at least 141 journal publications from Nigeria on malaria alone, 102 of these (72%) by Nigerian authors. Review of citations and abstracts suggests that about 25 of these are case histories, reviews or basic descriptive studies. The majority comprise original research, including 36 clinical trials and approximately 30 basic biomedical research studies. By any measure these indicate considerable depth and breadth of indigenous research.

In 1988, the **Commission on Health Research for Development** (CHRD) similarly found an appreciable amount of scientific literature being produced worldwide--16,220 publications whose first authors lived in developing countries (or 5.6% of all publications).[3] It concluded that "there is an active health research community in developing countries--small by the standards of industrial countries, but productive in spite of many handicaps" (CHRD, 1990). However, simply considering the quantity of research generated may be misleading in terms of the usefulness of that research. The same commission notes, for example, that research quality in developing countries often tends to be "marginal," through lack of oversight, access to journals, and appropriate peer review. This uncertain quality, they note, often limits confidence in the usefulness of research results (CHRD, 1990). The issue of research quality (or data quality, to take the wider view) is particularly relevant in the context of limited resources, since "bad" data often cost as much as "good" data to collect and analyze, yet may not be usable because of questionable reliability.

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[1]The AAAS's Sub-Saharan Africa Journal Distribution Program started in 1985. It provides over 3,500 subscriptions to almost 200 journals in the sciences and humanities to some 200 universities and research libraries in 38 countries. Contact address is: **AAAS Sub-Saharan Journal Distribution Program, Directorate for International Programs 1333 H Street, N.W. Washington D.C. 20205**

[2]SatelLife is a nonprofit organization supporting the establishment of regional and international health communications networks in Africa through affordable satellite technology. It sponsors, in collaboration with the IDRC (Canada), the operation of the HealthNet Information Service in Africa. Contact address is **Dr. Charles Clements, Executive Director, 126 Rogers Street, Cambridge, MA 02142.**

[3] The CHRD, an "independent international initiative" was formed in 1987, and authored the 1980 report "Health Research: Essential Link to Equity in Development." The Commission was subsequently superseded by the Task Force on Health Research for Development, and in March 1993, by the Council on Health Research for Development (COHRED). For a number of years, it has published the newsletter "ENHR Forum." Contact address is: **COHRED Secretariat, c/o UNDP, Palais des Nations, CH-1211, Geneva 10, Switzerland.**

BOX 1.3.1

A SELECTIVE APPROACH TO RESEARCH: AN ANALOGY

Analogy is a poor tool for scientific proof, but it is often an effective tool for scientific explanation. In a broad sense, the health research environment is analogous to a mechanic fixing a car or reassembling an engine. To fit the parts together, screws and bolts of various sizes, strengths and thread widths are necessary. One mechanic may have a bucket full of assorted screws and bolts. As he attempts to assemble each part he reaches into the bucket at random, seeking a bolt that "looks like the right one." Testing by trial and error, he sooner or later matches the correct bolt to the correct part. This is an apt metaphor for a program manager trying to implement a program based on ad hoc data and a miscellany of research studies undertaken by independent investigators. In circumstances where data are incomplete (that is, some of the nuts and bolts are missing) the process is even more inefficient, he may need to search through the whole "bucket" of miscellaneous research studies and data sources, only to find that there is no appropriate "nut or bolt" (i.e., no data appropriate to his immediate need). Or he may try to assemble a critical part using three bolts instead of five.

On the other hand, a more efficient worker might inventory his nuts and bolts beforehand, assigning each to a place in a tray according to size, thread width, and the like. To assemble his engine, he could then match his engine parts, and, determining that a certain assembly required three 1/2" bolts, proceed rapidly with the process. If his inventory identified certaine parts as missing, he could more easily determine how much was missing and whether the missing parts were critical or not. Similarly, the program manager who inventories information needs and the resources available is able to selectively commission specific problem-based research according to his immediate data needs.

Indeed, in program planning making decisions based on incomplete data is often a risk. On the other hand, programs seldom have the luxury of having all the data they need and thus they must often make decisions based on incomplete information. Each aspect of this process is made easier and more efficient when the decision maker has some control (whether direct or indirect) over the nature and scope of research undertaken, and some ability to make a priori decisions as to what research is undertaken.

A second factor determining the usefulness of research is the representativeness of the data--or the quality of information derived from data, rather than the quality of the actual data. An illustrative example is provided by Kirkwood (1991) in **Disease and Mortality in Sub-Saharan Africa**. In reviewing sources of data for Control of Diarrheal Diseases (CDD) programs, she reports finding a total of 27 research studies for Nigeria -- 20 WHO/CDD morbidity surveys, 2 longitudinal studies, 3 analyses of hospital statistics, and 2 analyses of registered deaths. Despite their quantity, she concludes: "Even these did not give a complete picture of either diarrheal morbidity or mortality in Nigeria." All the WHO/CDD surveys, she notes, were done in urban areas, and only one study looked at a range of risk factors (Kirkwood, 1991). This example illustrates a common data problem encountered by the ACSI-CCCD Project during its 12 years -- the lack of a clear strategy linking research and research findings to action. In other words, problem-oriented or problem-based research in the context of a research agenda is often lacking.

1.3 Matching Data to Data Needs: Problem-Based Research

Why is problem-based or problem-oriented research needed? Why have a research agenda? Both questions are answered in part by the above example. In the absence of clear problem identification

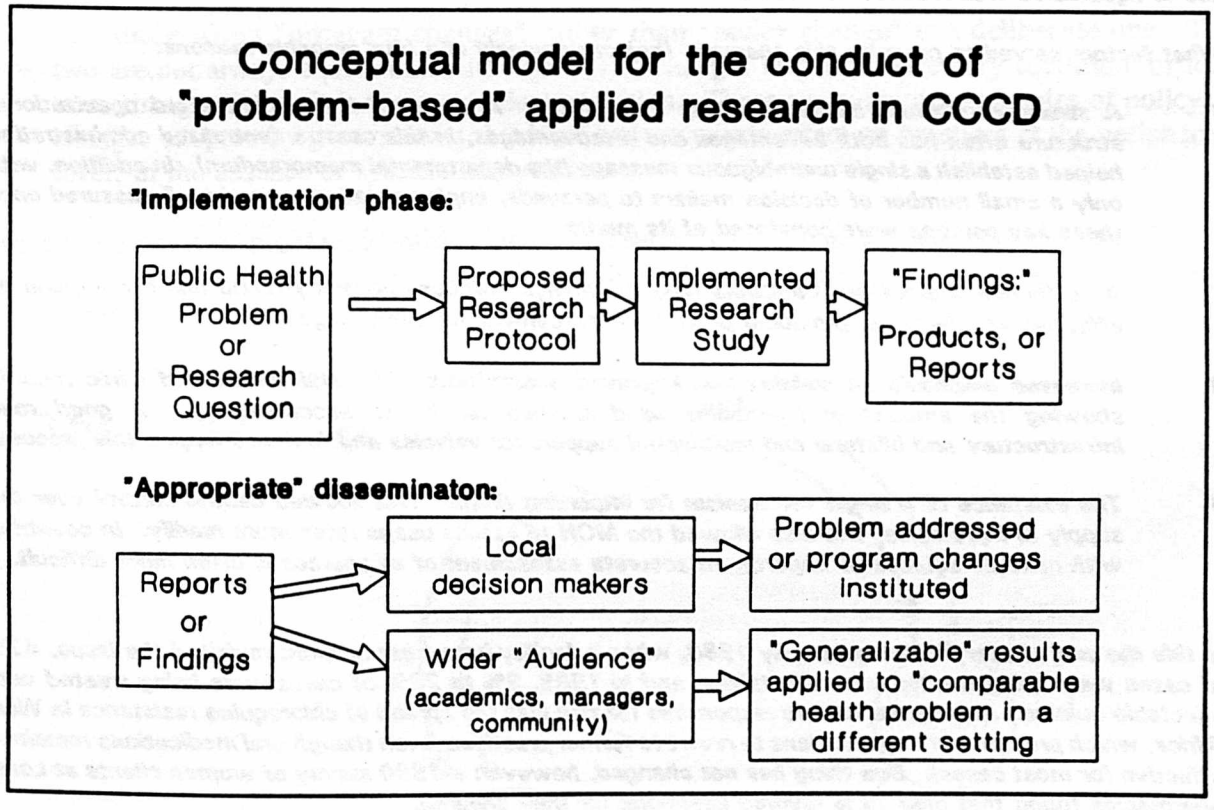
and a specific problem-driven approach to research, the resulting mismatch between the needs of programs and the priorities of individual researchers makes the process inefficient, even if it is eventually successful.

1.4 Problem-Based Research: Decision Making in a Public Health Context

"There are important differences between medical and other scientific research," noted Henry Miller, Vice Chancellor of the University of Newcastle upon Tyne, in the 1970 John Snow Memorial Lecture delivered at the Royal College of Surgeons (Miller, 1971). His comment on the predilection in medicine for basic research and laboratory science is particularly relevant:

> "Concentration on the laboratory makes it easy to forget that medical research is essentially directed to a human need, and has a social function beyond the mere satisfaction of the investigator's curiosity. It begins with an unsolved problem... and it ends with the successful application of an effective solution of the problem in the same situation." (Miller, 1971).

Although Miller was mainly referring to clinical research, what he says is equally true in public health. Conceptually, the evolution of the research process from problem to solution is shown in the figure below.



BOX 1.4.1

GETTING FROM "HERE" TO "THERE": TRANSFORMING RESULTS INTO MEANINGFUL CHANGES

What factors are responsible for transforming research findings into meaningful program changes? Why do some research findings lead to major changes while others languish in desk drawers? And why does some research successfully make the transition to written policy, yet never become implemented? There are a number of reasons why research may or may not be effectively used. One instructive example relates to the use of injectable antimalarials in Togo.

The overuse of injectable drugs in that country (as in other developing nations) existed for some time, and was not unknown to policymakers. In 1983, a survey in the Plateaux and Maritime regions found that injections were used in 56% of cases of malaria treatment; in 1984, a CCCD/MOH survey in the Plateaux Region found injectables were used in 66% of children under 5 years old. This in itself was not news. Where this investigation went further than prior studies was in its investigation of underlying reasons. A community survey revealed that only 10% of mothers favored injections over pills as the preferred treatment for their children. When this question was repeated in a health facility survey, mothers gave the same answer--only 9% preferred injections. On the other hand, another survey revealed that 69% of clinicians believed that mothers preferred injections--a belief that the study clearly refuted. This and other findings spurred Togo's malaria program to address the issue as a priority through: 1) issuing a departmental memorandum (lettre circulaire) addressing the issue; 2) increasing the emphasis on oral medication in health worker training; and 3) increasing attention to the issue in supervisory visits. By 1986, a survey found the use of injectables was reduced to 18% of cases treated.

What factors served to promote this change? Project principals cite four probable reasons:

1. ***A strong centralized decision-making mechanism:*** *Although a highly centralized oganizational structure often has both advantages and disadvantages, in this case, a centralized administration helped establish a single unambiguous message (the departmental memorandum). In addition, with only a small number of decision makers to persuade, implementation was virtually assured once these key persons were convinced of its merits.*

2. ***An effective alternative:*** *Clinicians who did change practices generally found oral chloroquine as effective as injections, providing positive reinforcement for the change.*

3. ***Increased emphasis on training and improved supervision:*** *The maintenance of clinic records showing the amount of injectables used allowed for better accountability. A good road infrastructure and bilateral and multilateral support for vehicles and fuel also helped this process.*

4. ***The existence of a single mechanism for importing drugs:*** *This allowed central control over the supply of injectables, and also allowed the MOH to assess usage rates more readily. In countries with multiple sources of imports, an accurate assessment of all sources is often more difficult.*

Is this the end of story? Not quite. By 1988, when a facility-based assessment revisited the issue, 47% of cases were being treated with injectables, and in 1989, 9% to 28% of cases were being treated with injectable quinine. Among the factors responsible for this was the spread of chloroquine resistance in West Africa, which prompted many clinicians to revert to former practices (even though oral medications remained effective for most cases). One thing has not changed, however: a 1990 survey of women clients at Lome pharmacies found that only 12% favored injections for their children.

There are a number of observations that evolve from this model:

- **The process does not begin with initiation of research.** Research may in fact be only one of many possible approaches to addressing operational problems in public health programs. Other options may include using comparable data from elsewhere (analogy), routine data collection, expert consensus, induction (arguing from the particular to the general), and deduction (arguing from the general to the particular). (See also MacClure, 1985; and Silverman, 1981.) In general, it is an implicit responsibility of researchers to ensure that data meeting the program's information needs are not already available before initiating research.

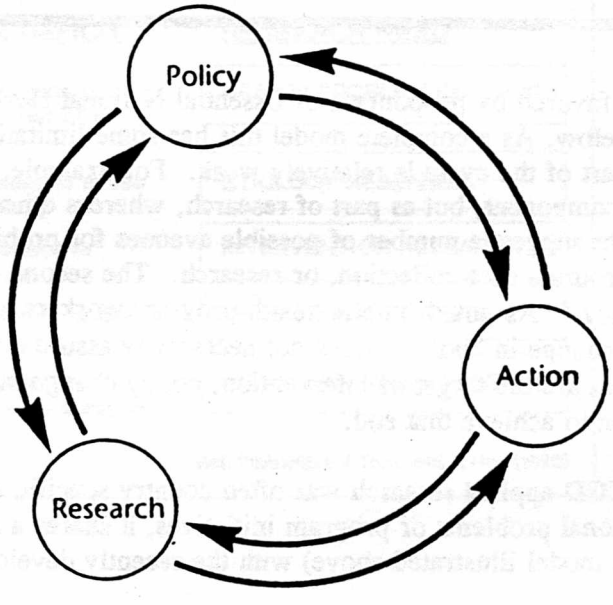
- **The process does not end with research findings or results.** Although common wisdom often assumes that good research will find its way into implementation, experience suggests otherwise, and the need for "advocacy" and appropriate dissemination is implicit.

- **Identifying the problem and formulating a research question are processes in themselves.** Countries asked to identify research priorities often generate a list of diseases or health problems rather than clearly defined research questions. The main failing of this approach is that it offers little insight into the "information need" related to each problem, and therefore little guidance as to whether the problem is amenable to a research solution. Or, as Miller notes, "One of the real difficulties of direction is that the social importance of a problem has no relation to its ripeness for solution" (Miller, 1971).

- **The designation "program changes" rather than "policy change" is a deliberate one.** The two are not always equivalent. Although policy changes may be a necessary condition for long term changes, often it is not a sufficient condition. There are numerous examples of policy changes adopted by governments that have had very little effect on practices at the peripheral level, in the absence of specific interventions.

Because the process of problem identification and research is a dynamic one (and the process of generating research in response to problems is iterative), the model can also be seen as a continuous loop, linking research policy and action.

The ENHR Loop



BOX 1.4.2

ESSENTIAL NATIONAL HEALTH RESEARCH (ENHR) — A CHRONOLOGY AND SUMMARY

> *"The linkage between research and the utilization of research needs to be strengthened (through greater) participation of research users in setting the objectives and timetable for research projects [and through more effective communication of results] to potential users." (CHRD, 1990)*

The concept of ENHR grew out of an "independent international initiative" launched in 1987 as the ***Commission on Health Research for Development****. This group of 12 commissioners, including 8 from developing countries, conducted an exhaustive evaluation of the state of health research in developing countries, which culminated in the 1990 report, Health Research: Essential Link to Equity in Development (CHRD, 1990).*

The ***Task Force on Health Research for Development*** *was established as the follow-up entity to the CHRD in 1990, empowered to explore the feasibility of ENHR, and to further the recommendations of the commission. Under this task force, the policies of the CHRD were crystallized into a concrete strategy governing ENHR. This embodied a goal of "promoting health and development on the basis of equity and social justice" and a mode of operation involving:*

- *multidisciplinary and intersectoral research;*
- *inclusion of researchers, providers and community representatives in planning, promoting and implementing research programs; and*
- *effective mechanisms to close the gap between research and application.*

The "content" of ENHR was envisioned to include traditional research methods such as epidemiology and social and behavioral research, but its focus was to be on the poor and disadvantaged. The task force also identified a generic process for implementation of ENHR, involving seven common elements: 1). promotion and advocacy; 2). an ENHR mechanism; 3). priority setting; 4). capacity building and strengthening; 5). networking; 6). financing; and 7). evaluation.

The task force ended its mandate in 1993, handing over its mission to the successor, the ***Council on Health Research for Development*** *(COHRED), a nongovernmental institution whose objective is to "promote, facilitate, support and evaluate the ENHR strategy."*

This is the model favored by proponents of Essential National Health Research, a program described in greater detail below. As a complete model this has some limitations. Its emphasis on problem identification as part of the cycle is relatively weak. For example, it includes problem identification not as a separate component, but as part of research, whereas others would argue that problem identification might suggest a number of possible avenues for problem solving -- surveillance, a literature search, routine data collection, or research. The second drawback of this model is the emphasis on "policy." As noted, public health program workers and researchers have increasingly recognized that a change in "policy" does not necessarily assure a change in practices. Where it is actual practices that are the target of intervention, policy change may be neither a necessary nor sufficient condition to achieve that end.

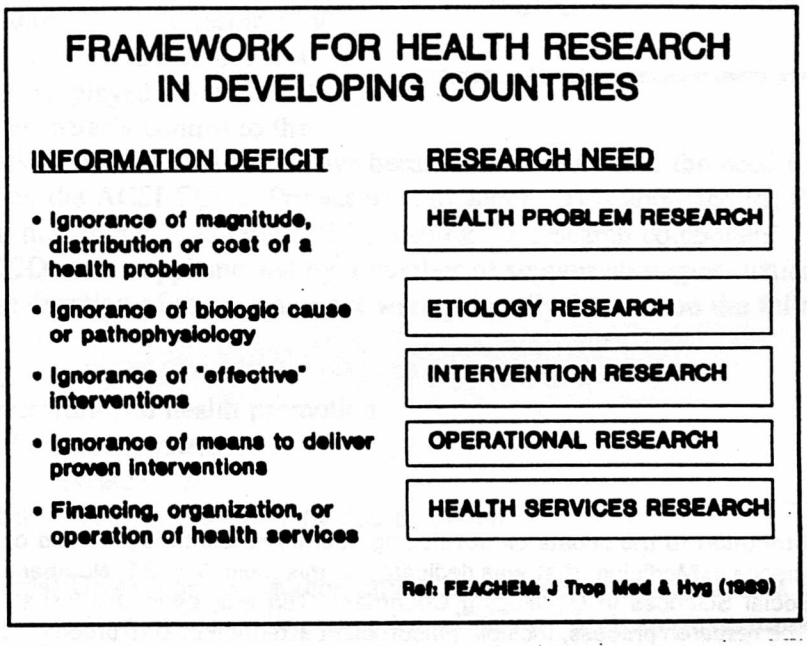
Because ACSI-CCCD applied research was often country specific and very strongly linked to immediate operational problems or program initiatives, it shares a number of goals (as well as a preference for the model illustrated above) with the recently developed initiative of **Essential**

National Health Research (ENHR), whose principal objective is "science-based, knowledge-based decision making at all levels of health services" (Lucas, 1993). The product of an independent international initiative begun in 1987, ENHR has been described as an "intersectoral multidisciplinary approach" to problem solving, intended to "establish a dynamic relationship among policy, action and research sectors (Task Force on Health Research for Development, 1991)."

The **Commission on Health Research for Development** (CHRD) which coined the phrase "Essential National Health Research," attempted to categorize the role of research in a systematic review of 10 countries, dividing the discipline into **"country-specific research"** and **"global research."** It noted that as a general rule, country-specific research should be closely linked to action, and to consumers, policymakers, and the community, whereas global research issues and long-term scientific advances may require "greater independence and autonomy from the pressing needs of action" (CHRD, 1990). It also observed that the results of country-specific research are usually location-specific and therefore have limited transferability from country to country. Directly related to this effort, the CHRD identified the need for countries to develop systematic methods for establishing research priorities. These priorities should be able to address the concerns and interests of policy and decision makers, communities and researchers, rather than being "narrowly constructed along disciplinary lines, and... predominantly oriented toward medical technology (Task Force on Health Research for Development, 1991)."

1.5 Defining Research Priorities

An important effort to correlate the range of information needs and research priorities of developing countries within a logical framework is contained in the work of Feachem et al. (1989) in a background document for the CHRD. Within this framework, information deficits in developing countries can be classified into five categories; each is addressed by a particular type of research. The five categories are illustrated in the figure below.



Of particular importance to this evaluation is the authors' observation that "**there is a natural sequence implied" within this framework.** They state, for example, that "**operational research will, in general, come after considerable progress in aetiology, health problem, and intervention research.**" Feachem et al. also noted that, in terms of establishing priorities for one health problem in relation to others, reliable data on the magnitude, distribution (and perhaps costs) are required. Since such data are typically lacking or incomplete in most developing countries, "health problem research" (i.e., basic epidemiologic, demographic or sociological research) is essential.

Two additional points should be noted about this model:

(1) Although there is clearly a hierarchical order to the classification, health problems are rarely static, and programs may have to revert to additional basic research or health problem research as situations change.

(2) These "categories" of research are not necessarily mutually exclusive. A large scale intervention, for example, might include not only intervention research, but also operational research or cost-benefit analysis.

To a considerable degree, the above model appears to represent quite accurately the situation prevailing in most of the CCCD Project countries evaluated, although in general the CCCD Project did not consciously document its research priorities within such a framework.[1]

[1] An important contribution to the debate on developing country research is provided by a special 1992 issue of the journal Social Science in Medicine, that was dedicated to this topic (Vol. 35, Number 11.: Building Research Capacity for Health Social Sciences in Developing Countries). Ten articles in this issue examine many of the concerns confronting the research process, including insufficient attention paid to problem identification, the need for emphasis on presenting results in an accessible and useful form," and the threat of "scientific colonialism" in developing country research (Trostle, 1992).

CHAPTER 2

THE AFRICA CHILD SURVIVAL INITIATIVE

2.1 Origins

The ACSI-CCCD Project was initiated in 1981 as the Combatting Childhood Communicable Diseases Project (CCCD). In 1982 and 1983, the first bilateral project agreements were signed in Zaire, Liberia, and Togo. These were followed eventually by 10 more bilateral country projects.

The ACSI-CCCD Project was initially proposed following the Declaration of Alma Ata in 1978, and in response to WHO's request for increased technical cooperation in support of Primary Health Care (PHC) programs in Africa. When first planned, the project made allowances for support of two vertical programs--CDD and the EPI. This strategy was based on the assumption that these were two areas where "**proven cost-effective interventions**" existed that could be applied with some guarantee of success in sub- Saharan Africa. Malaria control was soon added as a third target intervention, primarily in response to insistence from African MOHs. This was done despite the fact that there was no equivalent assurance of a "proven intervention" for that disease. Control of acute respiratory infection was also added to CCCD, but at a much later stage; it also played a much smaller role. The addition of malaria control to the package of interventions in CCCD is instructive because it demonstrated the need for flexibility and responsiveness, which the ACSI-CCCD Project tried to adopt. This approach (of flexible responsiveness) also had appreciable influence in shaping the research component. The three target interventions of CCCD were supplemented by a number of support strategies, which changed slightly in emphasis over the duration of the project, but were primarily focused on the following activities:

USAID Bilateral CCCD Projects 1982 - 1993

COUNTRY	STARTED	ENDED
Zaire	1982	1991
Togo	1983	1993
Liberia	1983	1990
C.A.R.	1984	1992
Lesotho	1984	1991
Malawi	1984	1988
Rwanda	1984	1988
Congo	1984	1987
Swaziland	1984	1991
Guinea	1985	1991
Côte d'Ivoire	1985	1991
Burundi	1985	1993
Nigeria	1986	1993

- **training,**
- **health education and health promotion,**
- **health information systems,**
- **operational research, and**
- **sustainability and cost recovery (added in 1987).**

As stated in the original USAID project authorization, these interventions placed a major focus on capacity building, and were intended to "**increase the ability of African governments to prevent and control childhood communicable disease** (CCCD Annual Report, FY 1983)."

2.2 Objectives

One important feature of the ACSI-CCCD Project, which later had a marked impact on its research agenda, was the list of "measurable objectives" it established for specific reductions in mortality, morbidity, and other areas. Although some of the objectives were subsequently modified or adjusted, the initial project goals of CCCD were very much defined by five impact objectives. One of these was for overall mortality reduction, and four were related to cause-specific morbidity or mortality. These objectives were:

1. to reduce the mortality rate of children under 5 by 25%,

2. to reduce neonatal tetanus mortality by 25%,

3. to reduce measles morbidity and mortality by 50%,

4. to reduce mortality caused by diarrhea and dehydration by 25%; and

5. to reduce malaria mortality in children under 5 by 25% in areas where presumptive treatment of fever is operational.

(Annual Report, 1983)

A number of sub-objectives were also stated, identifying targets for coverage or behavioral change. The revised targets for these indices were:

COVERAGE	
Immunization at 1 year	80%
Tetanus toxoid at term	60%
EFFECTIVE CASE MANAGEMENT	
At health facilities	
Diarrhea	90% correct
Malaria	90% correct
In the community	
Diarrhea	50% correct
Malaria	50% correct

(Annual Report 1988-89)

Although these objectives provided useful guidance for developing specific work plans, the assumption that these were "readily measurable objectives" proved to be much more problematic, as will be shown. Specific sub-objectives for the research component of CCCD were also established in the original project paper. These are identified in the relevant section below.

2.3 Scope of the ACSI-CCCD Project

During its project life, ACSI-CCCD directly supported a total of 13 country projects for variable periods. It also included a number of countries that were not bilateral signatories (e.g., Kenya, Zimbabwe, and The Gambia); these countries received assistance indirectly through activities of the regional epidemiologists or through individual research support. Thus, research projects were actually supported in 18 countries.

Over time, (and out of concern for spreading its resources too thinly), the CCCD Project progressively decreased its involvement in non-bilateral countries and concentrated activities in the 13 countries in which it had in-country staff and support. (With respect to research, there were a few notable exceptions--primarily Kenya and Malawi).

The main implementing agency for the CCCD Project was the **Centers for Disease Control and Prevention** (CDC), an agency within the U.S. Public Health Service. Within the CDC, the **International Health Program Office** (IHPO) had the primary responsibility for the CCCD Project. There were also substantive inputs from CDC's Division of Immunization and the Malaria Branch in the Division of Parasitic Diseases.

Although CDC played the main role in implementing the ACSI-CCCD Project, other collaborating institutions, nongovernmental agencies, and individual contractors were used at various times to provide support functions or specific project components in various countries. For example, the U.S. Bureau of the Census collaborated on specific demographic projects. **HEALTHCOM** (The Communications for Child Survival Project) provided social marketing and formative research support in Malawi, Lesotho, Nigeria, and Zaire. Other USAID-funded projects also cooperated with CCCD in various countries. These included:

- **PRITECH** (Technologies for Primary Health Care Project)
- **REACH** (Resources for Child Health Project)
- **PRICOR** (Primary Care Operations Research Project).

As an operational note, these agencies or institutions were often supported directly out of USAID-Washington, and the degree of coordination with CCCD country activities often varied. In addition to local collaboration, the ACSI-CCCD project also cooperated at various levels with a number of international agencies. Through several arrangements, coordination with other international development agencies and research bodies was supported in several countries. Some of the cooperating and collaborating agencies included:

- **British Overseas Development Agency** in the Gambia
- French **Fonds d'Aide et Cooperation** in the Congo
- **UNICEF** (extensive collaboration in virtually every CCCD country)
- **WHO/African Regional Office** (extensive collaboration in-country as well as separate regional support for intercountry training and Health Information Systems (HIS) activities)
- **OCCGE** (Organisation de Coordination et de Coopération pour la Lutte Contre les Grandes Endémies) in Burkina Faso

2.4 Administrative Structure of the ACSI-CCCD Project

Although there was no universal operating mechanism for all CCCD bilateral projects, in-country activities generally involved at least one resident technical officer and a variable complement of other technical assistants, depending on country needs and the project's capabilities. Over time, in-country epidemiologists were assigned, on a regional or national basis, to six countries -- Malawi, Zaire, Côte d'Ivoire, Burundi, Burkina Faso (OCCGE), and Nigeria.

In project countries, operating relationships with MOHs varied. In countries where CCCD's role included substantial responsibility for one or more vertical programs (e.g., EPI in Zaire), there was considerable operational overlap between the ministry and the CCCD program; national MOH program managers for these components often operated directly out of program offices. In general, a close operational relationship with the MOH was favored. Where feasible, the CCCD Project operated physically within the MOH. Where this was not physically possible (because of limitations of space, for example), it still maintained close operational ties with the MOH, through the ministry's appointment of a counterpart CCCD national coordinator and individual program managers.

In general, therefore, functioning of the project was closely tied to an active process of collaboration with the MOH and its program managers in the CCCD focus areas (malaria, diarrheal disease, and EPI). This working relationship also played a significant role in defining two important aspects of CCCD research: policy relevance, and utilization of research findings.

Although all CCCD projects established operating relationships with MOHs, not all bilateral projects were as closely tied to day-to-day operations of ministries. In a large decentralized system such as Nigeria, the project eventually restricted its involvement in some activities (e.g., training, CDD, and EPI) to a limited number of focus states, while other activities (such as strengthening of HIS) continued to collaborate with ministries at a national level.

In its relationships within USAID, the CCCD Project had a complex organization; some parts of its program and budget were assigned to regional activities and some to country-specific ones. There was a similar dual relationship between the local USAID mission and USAID in Washington. Significant changes in the degree of local mission involvement (versus centralized management) also occurred over the life of the project. Over time, the general effect of this evolution was a decreased emphasis on regional activities and a greater focus on the country-specific level.

Fiscal responsibility for the CCCD Project had a similarly complex structure, which also evolved over the life of the project. In general, such fiscal responsibility remained with the CCCD Project in each country, and the project technical officer retained a fair degree of autonomy in individual funding decisions (within the limits of the agreed-upon work plan). The initial operation of regional research committees and research promotion was budgeted as one of five inter-country activities (that is, funded from a regional budget); by contrast, individual country programs frequently conducted their own research or special projects under their own operating budgets. Several large-scale studies that were considered central to project-wide objectives (e.g., the Mangochi Malaria Research Project, and the Mortality and Use of Health Services surveys) were also funded as separate items by USAID-Washington.

2.5 Goals, Objectives and Strategies of CCCD Research

2.5.1 The goals of CCCD Applied Research

The original **goals** set forth for CCCD research were as follows:

1. To increase national ability to effectively adapt known prevention and control techniques to reduce childhood communicable disease mortality and morbidity in African children.

2. To identify and solve operationally important problems in the prevention and control of childhood communicable diseases in Africa.

(Project Description and Work Plan for Fiscal Years 1983-1984)

At the time of its inception, these goals of the "operations research" component (as it was then called) seemed clear enough. Because the target diseases that CCCD hoped to address were all ones with proven interventions, it was assumed that the problems that would need to be addressed would be largely operational--for example, the best way to deliver interventions or to document effectiveness.

2.5.2 Objectives and Strategies

The two primary **objectives** of ACSI-CCCD research were as follows:

1. **Identify and solve operational problems limiting the achievement of CCCD targets and objectives.**

2. **Develop African capability to conduct operational research.**

(1985 Annual Report)

There was, however, an unforeseen complication to the joining of these objectives. Although the two objectives chosen are not inherently at conflict with each other or mutually exclusive, their emphases differ. The first is more focused on results, while the second is more concerned with development of human resources, that is, training. Since information needs were frequently so fundamental that they were indispensable to program planning or implementation, the training needs implicit in developing local researchers were often secondary to the need for obtaining usable results. This was an unanticipated consequence.

The strategy that the project hoped to use to achieve these objectives was:

1) to identify and encourage institutions and investigators,

2) to solicit and review proposals,

3) to support at least 10 projects per year,

4) to provide technical support, and

5) to assist dissemination and use of results.

This concept and strategy became the operational research component of CCCD. Whereas the dual objectives represent ideals, this model encountered two obstacles in practical terms. The first was that the foundation of existing research capacity on which to build was much less than expected. The second was that the project itself would exert a considerable demand for research data that were often indispensable to program planning and implementation. This often limited the project's ability to invest in research training or skills building, and tipped the balance more towards product delivery. The extent to which these two considerations reshaped the priorities that the research component was able to address is discussed at some length in subsequent sections.

CHAPTER 3

THE ACSI-CCCD EXPERIENCE IN APPLIED RESEARCH

3.1 Background

Over the course of its 12-year existence (1981 to 1993) the ACSI-CCCD Project has undertaken a considerable number of research activities, spanning a wide range of disciplines and levels of complexity. Although this evaluation identified over 250 studies, the number is likely even greater, since many studies initiated at the local level were not necessarily well documented at the central level. In addition, this review did not generally include routine outbreak investigations or many surveillance activities.

In general, ACSI-CCCD research activities fell within three domains:

1. **A formal review mechanism:** This involved solicitation for proposals, review committees, and small-scale grant awards (US$5,000-US$10,000). It was the mechanism for the East/Southern Africa Regional Review Committee (1982-1986) and the Nigeria Research Review Committee (1987 to present).

2. **Locally initiated problem-oriented research:** This usually meant small-scale epidemiologic studies or problem identification. These were usually undertaken at the initiative of the local CCCD office or MOH, with varying levels of local participation and occasional external collaboration.

3. **Large-scale collaborative studies:** Such collaborations occurred between principals from CDC, MOH, and in-country CCCD personnel. These usually involved considerable input and collaboration in protocol development by Atlanta-based staff and formal ethical review by an Institutional Review Board (IRB). They were often financed under a separate budget from Atlanta, Washington, or regional funds (e.g., MMRP, Edmonston Zagreb [EZ] vaccine trials).

Initially, it was the first of these activities (the review committee mechanism) that was called the "operational research" component and that was the principal vehicle for the promotion of research capacity in the host countries. Although CCCD country programs were continually conducting research of their own, this was often classified as routine programmatic activities or "special studies." This separation did have the advantage of preserving the budget allocation for "operational research" promotion as a separate entity. On the other hand, it also served to obscure the contribution that local and collaborative research made to project activities.

In reality, about 30% of the more than 250 studies reviewed were initiated under the umbrella of review committees, whereas the majority of investigations were funded and implemented under other mechanisms.

3.2 The Operational Research Component of ACSI-CCCD

As noted above, the operational research component of CCCD was only one element of the project's activities in research, but the main one targeting African research capacity. From its inception, the operational research component became strongly identified with the research review committee mechanism. The FY 1983 work plan set forth a plan for two regional committees, specifying their composition and the procedures for their operation, including a provisional list of research priorities. The plan also stipulated that research projects under the mechanism meet the requirements of the U.S. Government for the protection of human subjects, as well as those of the host country, and it proposed a 6-year projection of activities. Of the two regional committees, one would be sited in Côte d'Ivoire and would cover West Africa; the other would be sited in Malawi, and would cover East, Central, and Southern Africa.

The principal elements of this research strategy were to be the same for both regional committees and included the following:

- Review committees would meet at least twice yearly.
- Committees would include MOH personnel, university researchers, USAID and WHO personnel, and persons from "non-health-related fields."
- The CCCD epidemiologist would serve as secretary to the committee.
- Projects would be supported to a maximum of US $10,000.
- Projects of more than $10,000 would be referred to the CCCD steering committee for review.
- Review committees would assure the protection of human subjects, while field epidemiologists would submit approved proposals to the CDC IRB for human subjects clearance.
- Field epidemiologists would review and assist projects "where appropriate," with the assistance of committee members "where feasible."

(Annual Report, FY 1983)

The intent of this strategy was to allow for speedy review of proposals, local approval of funding, and appropriate ethical and financial oversight. With some qualifications, it was quite successful at achieving those specific goals. In other respects, its record was mixed. Of the two regional committees initially proposed, only the East/Southern Africa committee achieved functional status, and its actual output in terms of successful projects was limited.

In both regional mechanisms and the later national committee in Nigeria, the demands on the CCCD program of managing the formal research component were considerable. In the East/Southern Africa Regional Committee, time demands on the epidemiologist eventually led to exclusion of non-bilateral countries from the research program, and in Nigeria, probably contributed to the need to transfer responsibility for operation of the committee to the federal MOH. In Zaire, a national mechanism,

BOX 3.2.1

AFRICAN INVESTIGATOR RESEARCH UNDER THE REVIEW COMMITTEE MECHANISM

The studies that follow are two of the more successful examples of small-scale African investigator research initiated under the operational research component of the ACSI-CCCD Project.

EVALUATION OF HOME-BASED ORS, CÔTE D'IVOIRE. (SHAW et al., 1986)

This prospective study examined mothers' retention of how to prepare one of three recommended formulas for home-based ORS: salt-sugar, rice-water, or guava leaf solutions. Instruction was fairly elaborate. Groups of 10 to 20 received 10-30 minutes of instruction, followed by demonstration of ORS preparation and distribution of printed materials. A sample of solution prepared by each mother at home was collected one day after mothers received instruction and was analyzed for sodium, potassium, osmolarity, and reducing sugars.

Among the more important findings of this study were the following: 1) Procurement of utensils and materials for home preparation of ORS was not a major problem, but a great diversity of implements and materials was noted; 2) the measured weight of sugar cubes found in homes was usually 4g or 4.5g, rather than the 5g assumed by the recommended formula; and 3) nearly one in three mothers prepared a solution that had too high a sodium concentration, despite specific training just one day before the sampling.

This study's findings had considerable importance in Côte d'Ivoire's reevaluation of its national policy on promotion of home-based ORS. It was used to justify a number of program recommendations (by UNICEF and others) that the "policy of using both ORS packets and home solutions be retained, but that considerably more emphasis be placed on packet use in facilities." In subsequent years, as the supply of ORS packets improved, the country was able to increasingly emphasize the use of ORS packets in preference to salt and sugar solutions (SSS).

****

KAP IN CHILDHOOD DIARRHEA, MULANJE. (MALENGA et al., 1986)

This was a questionnaire survey of mothers in Mulanje district, an area of development by the Rural Piped Water Project (RPWP). Several findings are relevant. Although 95% of mothers had heard of SSS, only 14% could recall the formula correctly. Secondly, 93% of mothers had heard of SSS from the hospital or health center, but only 0.1% heard of it from the radio. Only 23% of households owned a radio. Finally, only 28% of households had sugar for making SSS, and few had all the necessary utensils.

These findings were presented to the MOH in November 1986 and figured prominently in development of a diarrheal disease policy/program. They were also the basis for later investigations under the auspices of CCCD and HEALTHCOM activities in Malawi (targeted at developing appropriate messages for diarrheal disease control, and means for their dissemination, as well as providing appropriate utensils for home preparation).

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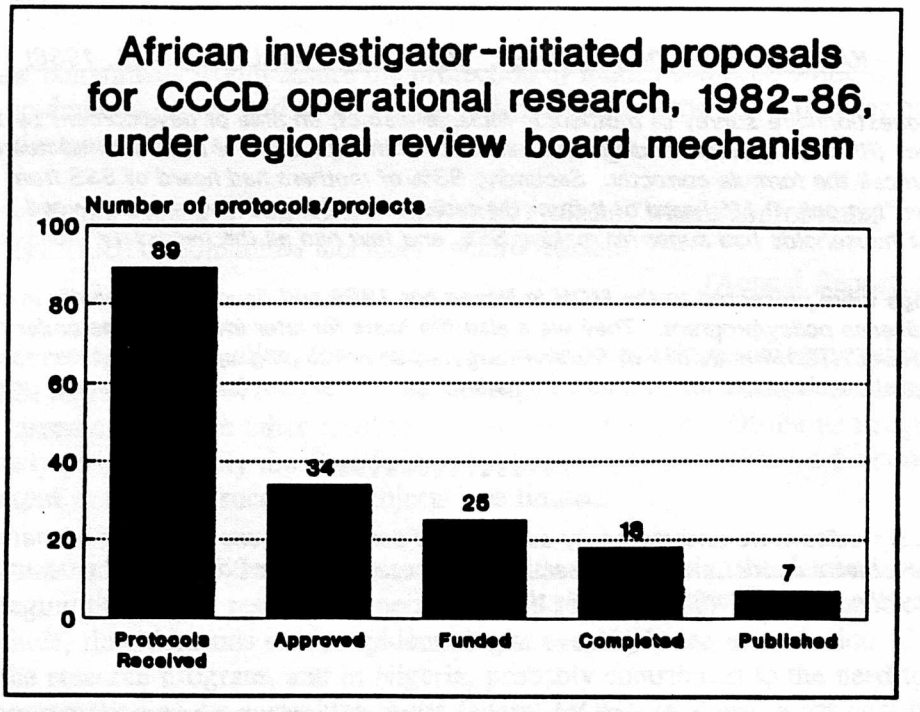
Both of these studies were undertaken by senior MOH personnel – one a director of maternal and infant services, the other a district medical officer. In both cases the effect on national programs was strongly influenced by the investigator's role within the MOH.

set up after the end of the regional activity, succeeded in producing guidelines and soliciting a few proposals, but CCCD political and management problems obstructed more significant achievements in formalizing the national operational research activity. In Togo, the national committee made only modest headway until a full-time research associate -- responsible for coordinating and expediting sponsored research -- was appointed. Review of formal and informal evaluations suggests that administrative management has been a continually challenging task. This is particularly true with respect to project supervision, technical review, and data analysis, but was also true with respect to more mundane matters, such as notifying committee members, assigning protocols for review, directing correspondence to potential researchers, and coordinating the photocopying of protocols and reports.

As initially conceived, much of this support and assistance was to have come from either members of the review committee (as mentors or preceptors) or supporting institutions with which researchers were affiliated. Often, however, neither option materialized and the field epidemiologist was burdened with supervision. When the research infrastructure is limited (for example, copy machines are scarce), this should not be surprising. But these limitations were probably underestimated by the project and undoubtedly contributed to the frustrations of the regional epidemiologists with the inordinate time demands it placed on them. When the ACSI-CCCD Project ended its regional activities in 1986, many country programs limited their research activities to data essential for program implementation and did not continue a formal research program. Nevertheless, these country projects often engaged in informal and sometimes very productive collaborations with local researchers. In Nigeria, with the benefit of the previous regional experience, and in Togo, with a less-ambitious program of research and a full-time coordinator, the CCCD Project was more effective in managing the review committee mechanism. Although the CCCD project had generally modest goals for the research sponsored by review committees, some of these studies had considerable impact on local policies or programs. Two early studies in diarrheal disease are good examples (see box).



Under the original mechanism for promotion of African investigator research, the two regional committees in East/Southern Africa and West Africa received 89 proposals from 1982 to 1986, approved 34, and funded 25. Of these, 18 were completed, and 7 published.

BOX 3.2.2

SPECTRUM OF ACSI-CCCD APPLIED RESEARCH, 1982 - 1993

Of some 265 studies undertaken with ACSI-CCCD support from 1982 to 1993, approximately 17% were small-scale studies initiated locally (by in-country project staff or counterparts); 28% were generated by research review committees; and 55% were larger collaborative efforts involving Atlanta staff or cooperating institutions. Of the total, malaria studies accounted for 37%;, immunization studies 22%, and diarrheal disease 19%.

STUDY FOCUS	***EXAMPLES***
EPI/ IMMUNIZATION	*- Coverage Surveys* *- Serosurveys* *- Facility surveys of sterilization practices* *- Knowledge, attitude and practice (KAP) surveys* *- "Missed opportunities" studies* *- Evaluation of vaccination campaigns* *- Vaccine trials and efficacy studies*
CDD/ DIARRHEAL DISEASE	*- KAP studies of mothers and health care workers* *- Analysis of ORS/SSS solutions* *- Facility surveys of ORS and health education practices* *- Facility-based morbidity* *- Risk factors for diarrheal disease* *- Formative research on purging practices*
MALARIA	*- In vivo sensitivity studies* *- Survey of fever treatment practices* *- Impregnated bed net studies* *- Drug quality control testing*
MORTALITY ASSESSMENT	*- Facility-based mortality studies* *- Mortality and Use of Health Services surveys* *- Preceding birth technique (PBT studies)*
HEALTH SERVICES RESEARCH	*- Revolving drug fund (RDF) feasibility study* *- Cost effectiveness of ORT and EPI programs* *- Economic impact of disease*
EVALUATION RESEARCH	*- Facility surveys of health care worker practices* *- Pre and post-intervention evaluation of training methods* *- Multipurpose community surveys*

3.3 The Regional Research Review Committee for East, Central and Southern Africa

Of the two regional committees set up by the CCCD Project, the East/Southern Africa Regional Review Committee was the more successful. Its actual achievements in absolute numbers were modest, however, and demonstrate some of the difficulties inherent in the undertaking. The **East/Southern Africa Regional Review Committee** was established in 1983 with the arrival of the CCCD regional epidemiologist in Malawi. In its first year, it established guidelines, research priorities, and protocol review procedures. A regional review committee was established with 10 eminent members from seven countries, plus the CCCD regional epidemiologist. Studies were to be funded to a maximum of $US 10,000. Technical review and approval of protocols would be provided at annual meetings of the review committee, and ethical review would be provided by CDC, pending establishment of an acceptable local mechanism for ethical review. A chronology of activities is summarized in the accompanying box.

Several reviews of the regional research activity were carried out during the program's lifetime. In general, they endorsed the relevance and the value of the activity to CCCD objectives. However, they also found that the scale of the effort generally overwhelmed the resources available.

Unfortunately, the recommendations made in several periodic reviews of the entire ACSI-CCCD Project do not appear to have offered a consistent direction to the operational research effort. This factor may have contributed to some ambiguity of purpose in operational research efforts.

Observations made in the **1983 mid-term evaluation** of the CCCD project (North et al., 1983) noted progress in identifying research priorities but "few linkages to local institutions," and recommended continuation of operational research as "an ad-hoc adjunct of the CDC epidemiologists in strengthening individual African researchers." This report also recommended that operational research pay particular attention to improving national capabilities to do research, but noted that "it is unrealistic to expect all submitted protocols will be of outstanding quality." It further recommended that "simplicity and likelihood of project completion should be emphasized." The need for specific skills and training in the planning and conduct of research appears not to have been addressed. With respect to institutionalization of the process, it recommended:

> The responsibility for OR should be decentralized as much as possible. Plans for any long-term, intercountry institutionalization, including the OR review committees, should be reviewed with WHO/AFRO (North et al., 1983).

The report also stressess the pivotal role of institutional capacity building, noting:

> The opportunities for helping to develop national epidemiological institutional capabilities should be encouraged from the outset of any AID-funded program.

The **1985 evaluation** (ISTI, 1985) reinforced the opinion that operational research efforts "should be focused on studies directly related to general or specific operational problems encountered." It noted, however, that "this will require some reorientation of field staff in order to identify ways in which focused research could resolve implementation problems." It particularly noted the inadequacy of field supervision and advised the use of short-term consultants "to the extent feasible."

BOX 3.3.1

CHRONOLOGY OF RESEARCH ACTIVITIES FOR THE EASTERN, CENTRAL AND SOUTHERN AFRICA RESEARCH REVIEW COMMITTEE

1983	NOV	KENYA	*CCCD operational research 6-day workshop, nine participants.*
		ZIMBABWE	*CCCD 5-day workshop, six participants.*
	DEC	KENYA	*East/Southern Africa ad hoc Operational Research Advisory Group Committee Meeting, formative group – 9 of 13 invited members present representing CDC, regional MOHs, UNICEF, the WHO Regional Office (WHO/AFRO) and REDSO. Guidelines and draft brochure produced and developed. Of 18 proposals submitted, 12 were eventually approved and 8 projects were completed to final report.*
1984	MAR	TOGO	***First CCCD Consultative Meeting, Lome.***
		MALAWI	*Project Agreement signed.*
	MAY	MALAWI	*CCCD-sponsored 5-day OR workshop, Mangochi; 15 participants.*
	OCT	LESOTHO	*East/Southern Africa OR Review Meeting, Maseru. Twenty-three proposals reviewed; 11 approved; 5 completed to final report.*
1985	MAR	MALAWI	***Second CCCD Consultative Meeting, Lilongwe.***
	JUN-OCT		*External Evaluation of East/Southern Africa Regional Research Program by Dr. B. Frank Polk (Rwanda, Burundi, Kenya), and Dr. James Chin (Malawi, Zimbabwe, Lesotho, Swaziland).*
	OCT	SWAZILAND	*East/Southern Africa OR Review Meeting. Twenty-one proposals submitted; 5 approved; 3 completed to final report. The committee advised preview of proposals by a subcommittee before full committee review and endorsed continued review of proposals from anglophone West African countries.*
	DEC	USA	*Washington D.C. meeting with USAID adopts policy to exclude non-bilateral countries from OR activity.*
1986	NOV	CONGO	***Third CCCD Consultative Meeting, Brazzaville.***
1987	JAN	MALAWI	*HEALTHCOM Workshop in Formative Research for Health Educators.*
	SEP	MALAWI	*Mangochi Malaria Research Project (MMRP) study begun.*
1988	NOV	CÔTE D'IVOIRE	***Fourth ACSI-CCCD Consultative Meeting, Yamoussoukro.***
	MAY		*End of E/S Africa Regional project activity; balance of funds deobligated.*

Also in 1985, a comprehensive review of all sponsored research projects was undertaken by two consultants -- Dr. James Chin of the University of California, Berkeley, and Dr. B. Frank Polk of Johns Hopkins University, School of Hygiene and Public Health, Baltimore. This evaluation provided the most comprehensive view of the research component to date. It found that the quality of protocols and research was mixed, and that the time and assistance available to researchers were

generally "very inadequate." It agreed that investigators were generally lacking in experience and resources for data management and analysis, "but also need more ongoing support vis-a-vis protocol development and problem solving... including inspection of data and ongoing dialogue." This evaluation was also the first to seriously question the effectiveness of the mechanism itself as the best method to build research capacity. It comments:

> Perhaps the most efficient (if not the most effective) solution would be to complement each of the existing field epidemiologists in Africa with another experienced investigator who would work more closely with the grant recipients at all stages of the research process. In a sense, the nature of the funding might well become more similar to contracts than to grants. Accordingly, I would suggest that areas of research be 'prioritized' and that interested investigators be more directed in what AID and CDC would like accomplished (Polk, 1985).

The **1986 External Evaluation** (LaForce et al., 1986) addressed issues from an altogether different perspective, placing notable importance on publication of studies, authorship of papers, and the like. This evaluation noted the general lack of success of West Africa operational research efforts. One reason it gave was "the lack of training of potential African investigators in research methodology." It also included a strong recommendation to use the Health Services Research Course (WHO/AFRO, 1983) developed by the **Strengthening Health Delivery Services** (SHDS) regional project as a means of providing training in the preparation of research grants.[1]

The sum of these appraisals, although difficult to abstract, seems to be an acknowledgment that the activity was producing major benefits, but required a far greater investment in training and support than it was afforded. A second theme was that the effort would benefit if more concrete linkages were established to immediate project objectives.

A number of specific issues and questions generated by the experience of CCCD with the East/Southern Africa Regional Review Committee are worthy of comment:

1. **Sustainability:** Although several evaluations recommended that the program explore options for WHO/AFRO to become the reviewing body and secretariat for CCCD operational research, this option did not materialize, in part because of reservations held by committee members themselves. In the absence of such a reviewing body or other acceptable regional structure, the sustainability of the project was never a realistic feasibility, and the activity ceased at the end of the regional epidemiologist's contracted assignment.

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[1] The SHDS course on research methods and protocol development was in fact used in at least two training workshops--one in Nigeria in September 1988 and another in Togo. The course was later substantially revised and adapted by its author and a technical working group, supported by the WHO Programme on Health Systems Research and the International Development Research Center. The course is the basis of a two-part volume, Designing and Conducting Health Systems Research Projects, in the five-volume Health Systems Research Training Series (Brownlee et al., 1992). As noted by the authors, this revision builds considerably upon the original SHDS course by recognizing "the need to support course participants beyond the point of developing a research proposal, through the phases of fieldwork, data analysis, and report writing." Contact address: **International Development Research Centre, PO Box 8500, Ottawa, Ontario, Canada K1G 3H9.**

2. **Funding:** One logistical problem in the operation of the regional committee was the number of currencies involved. Disbursements were made in Kenyan shillings, Zimbabwe dollars, Malawi kwacha, U.S. dollars, and so on. Because exchange rates often fluctuated considerably, budgets were often unpredictable. A second complication was the formula for disbursement. Researchers were initially disbursed funds according to a 30:30:40 formula: 30% upon completion of an acceptable protocol, 30% upon completion of specified interim goals (e.g., training of interviewers and completion of a certain percentage of interviews), and 40% upon completion of the project and submission of a final report. Although this is a reasonable formula, it presumes that the researcher (or sponsoring institution) is able to fund a part of operational costs in the interim and be reimbursed upon project completion. This is sometimes an unrealistic assumption in developing countries, and the arrangement did cause some hardship and operational difficulties. These were generally more severe when projects involved field studies, which usually depended heavily on the cost of gasoline and transportation. In response to researchers' and committee members' concerns, the committee adopted a 50:50 formula in 1984, allowing 50% payment at initiation of the research and 50% "upon completion of an acceptable interim progress report."

3. **Dissemination:** This was an acknowledged weakness of the project. As with other aspects of this activity, this seems to have been more a consequence of inadequate resources than of a lack of inspiration. As early as October 1983, the project initiated a quarterly epidemiologic bulletin, The CCCD Bulletin, intended to disseminate the results of research on communicable diseases in Africa. A subscription was to be available free of charge through the local USAID office or U.S. embassy. Although this effort was rather short-lived, it is worthy of note for two reasons. It was an early acknowledgment that journal publication alone was not a sufficient means for disseminating research findings. Secondly, it proposed to build on existing resources for local dissemination.

3.4 West Africa Regional Operational Research

The regional research program in West Africa was far less successful than its East African counterpart. In one research committee meeting in March 1985, twelve proposals were reviewed and four approved. Of these, three were completed and one published. In general, the number of submissions received by the West African program was small, although the completion rate was high for funded studies. Of 11 approved projects, 9 were completed and 4 published. One reason cited for the low response to this activity was "the lack of training of potential African investigators in research methodology." Another reason was insufficient time for the field epidemiologist to devote to the activity, a similar situation to the one that existed in the East Africa region (LaForce, 1986). Whatever the reasons, this activity achieved only modest results, lacked a clear plan to institutionalize the component, and was eventually dissolved prematurely.

3.5 The Nigeria Research Review Committee

The Nigerian Operational Research Review Committee was an attempt by the ACSI-CCCD Project to profit from the experience of the previous regional committees. It was established in 1987 as a national committee, thus avoiding the pitfalls of managing and coordinating research efforts in multiple countries. Nigeria offered several advantages over other countries for a research promotion activity. It had an extensive academic community, with numerous regional universities and medical schools; an established track record of individual research by a number of prominent Nigerians; and a MOH supportive of promoting relevant national research. It also had some of the drawbacks of the regional mechanism -- it included a wide geographic area and a large population; and its currency was unstable for much of the period. At about this time the federal MOH in Nigeria was also in the process of formulating a fairly comprehensive policy on health research (see box).

Of particular relevance in the Nigeria operational research effort was a deliberate attempt to have the research committee represent three separate interests--those of academic researchers, MOH decision makers, and regional PHC coordinators. Whereas such committees have traditionally included the first two groups, the inclusion of persons responsible for program implementation was a relatively new step. In the case of the Nigeria committee, it offered major advantages, but also evoked some criticism.

The committee as originally formed, had nine members appointed by the federal MOH. Members were to serve for a period of 3 years, with a chairperson elected annually. Committee meetings were scheduled quarterly, and project proposals were to be obtained through an ongoing solicitation publicized through a booklet of research guidelines distributed to universities and state MOHs. As with the prior research activities, a target of 10 research projects per year was envisioned. The CCCD Project epidemiologist served as a nonvoting secretary to the committee until March 1990; those responsibilities were subsequently assumed by the national staff. Projects were supported to the equivalent of approximately US $5,000. (The local currency equivalent had to be readjusted several times over the project's life because of currency devaluation.) Funds were disbursed to investigators through their supporting institution, usually a university or local government agency.

The committee comprised three academics, three regional PHC coordinators, and representatives of the two ministries and one national institute concerned with research. The presence of two separate ministries with responsibilities for health research created a curious situation. Although the **Federal Ministry of Science and Technology** possessed a specific mandate for promoting and managing national research (and its **Department of Medical and Natural Sciences** expressly addressed medical research), that ministry was rather remote from the day-to-day operational activities of the **Ministry of Health.** Locating the research activity within the Ministry of Science and Technology was therefore not widely endorsed, and was in fact, generally felt to be at cross-purposes with making the research responsive to immediate operational needs and readily available to local policymakers. It was decided at an early stage, therefore, that the MOH rather than the Ministry of Science and Technology should hold primary responsibility for the research committee, although the director of the Department of Medical and Natural Sciences in the Ministry of Science and Technology remained a committee member.

The other body concerned with national health research -- the **National Institute of Medical Research** -- was a semi-independent body (under the umbrella of the Ministry of Science and

BOX 3.5.1

NIGERIA NATIONAL HEALTH RESEARCH POLICY AND STRATEGY
Source: Federal Ministry of Health National Health Policy, October 1988

Priorities for health service and biomedical research shall be reviewed in collaboration with the Ministry of Education, Science and Technology. Mechanisms shall be devised to promote support and coordinate research activities in the high-priority areas and to strengthen the research capabilities of national institutions to enable them to undertake these essential tasks.

11.1 In collaboration with the Federal Ministry of Education, Science and Technology, the Ministry of Health shall review:

(a) The priorities for health services and biomedical research in Nigeria. Particular attention will be paid to practical, problem-solving activities including the assessment of health technologies that are being selected for use in the health services;

(b) The scope and content of activities in the field of biomedical and health services research at academic and other institutions;

(c) Mechanisms for promoting and financing research activities that are judged to be of high priority, and coordinating the activities of the various scientists and institutions involved;

(d) The training of research scientists, technicians and other support staff especially in the priority disciplines where there are marked shortages, e.g., epidemiology, medical biologists, etc.;

(e) The strengthening of ministries of health and other institutions to enhance their capabilities to undertake relevant research.

11.2 Biomedical and health services research shall cover the following areas:

(a) Epidemiological research: to identify the major health problems and their determinants in different parts of the country and in different segments of the population;

(b) Operational research: to test the efficacy of health technologies and various methods of applying them in the local situation;

(c) Development research: to develop new, improved tools for the prevention, treatment and control of diseases of local importance. This will include traditional medical practices so that useful ones can be incorporated into the health care system and the practitioners can be persuaded to abandon the use of any agents or procedures (including traditional surgical operations) which are shown to be unacceptably dangerous.

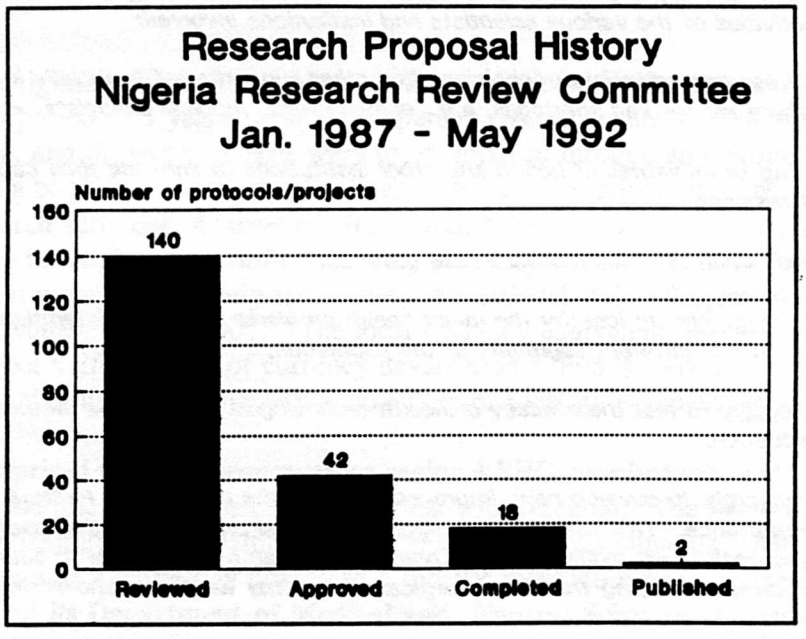
(d) Basic biomedical research: to broaden fundamental knowledge of the biological and other sciences relevant to health.

11.3 The highest priority shall be accorded to epidemiological and operational research in support of primary health care programmes.

11.4 The role of the ministries of health in research: In order to ensure that the priority problems in health shall be identified and addressed, and that the research results shall be adopted and applied, the ministries of health shall be closely involved in the planning, execution and evaluation of the research activities.

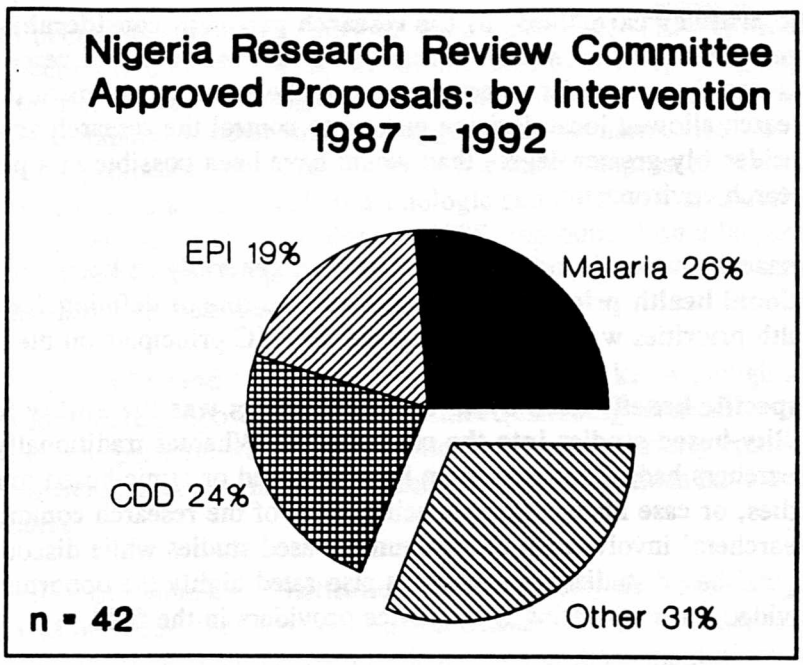
Technology), and was the immediate successor of the **Medical Research Council of Nigeria**. With its own director, it was mandated to conduct research and coordinate research activities in human health problems in the country (Essien, 1990). In practical terms, it dealt mainly with biomedical research. There also appeared to be considerable duplication of responsibilities in some of these agencies.

Within the MOH, two main players influenced the direction and operating philosophy of the committee to a great deal -- the **Department of Primary Health Care** and the **Department of National Health Planning, Research and Statistics** (DPRS). The relationship between the Department of Primary Health Care and the research activity was deliberately strong — with the conscious intent of promoting the implementation of research as well as the conduct of research. This was also reflected in the presence of four PHC members on the committee -- the national director and three zone coordinators. The DPRS was established after a ministerial reorganization in 1989, as part of a national initiative to make the planning process much more responsive and accountable to individual ministries. Although continuing to maintain a close operational relationship with the Department of Primary Health Care, the status of the review committee subsequently became more formally established within the jurisdiction of DPRS.



With the benefit of experience from the prior regional efforts, the CCCD Project and the Nigeria Research Review Committee were able to achieve a number of successes. As of May 1992, the program had reviewed 140 protocols and approved 42 studies. Of these, 18 had been completed, and 2 published. This does not include CCCD-supported research sponsored under other mechanisms (e.g., the malaria surveillance network).

Of the approved studies, malaria and diarrheal disease studies each composed about one-quarter of the total; EPI-related studies accounted for a slightly smaller proportion (19%). Almost half of these studies were straightforward descriptive studies or questionnaire surveys; an equal number involved more complex study designs and methods.



The research program was also able to sponsor several related activities in building research capacity:

- a 1988 training workshop in research methods,
- several dissemination workshops,
- presentations at various ACSI-CCCD consultative meetings, and
- installation of CD-ROM capability for MEDLINE and POPLINE computer searches at the national medical library.

Several strengths of the program were identified from project documents and interviews with researchers and committee members. They included the following:

1. **The CCCD research activity, as constituted, played an unique role in the promotion of research in Nigeria.** That uniqueness was due to the ability of researchers to submit proposals to a local body, receive timely feedback, discuss questions of implementation, and receive funding, all at the local level.

2. **The local nature and focus of the activity also allowed the process to be responsive to local priorities.** This favored the consideration of problems of immediate relevance, and readily applicable solutions. The representation on the research review committee of persons from three disciplines (PHC coordinators, academics, and Federal Ministry of Health principals) allowed an exceptionally productive amount of communication and interaction to occur. This generally ensured that the results of studies were able to reach policymakers in a timely fashion. Committee members generally had a broad and current knowledge of ongoing activities, the results obtained, and the implications for policy. Periodic meetings of zonal and local PHC coordinators also served as forums for discussion and dissemination of relevant results. As expected, the responsiveness at the local or zonal level was more readily influenced than policy at the federal level.

3. **The primary care "bias" of the research program considerably strengthened the involvement of that sector in managing its own data and research.** Although this was also the cause for some resentment, the strict commitment to problem-based research allowed local decision makers to control the research agenda to a considerably greater degree than would have been possible in a purely academic research environment.

4. **Research pursued under the project was generally in keeping with local and national health priorities.** In particular, the role of defining "relevance" to local health priorities was vigorously upheld by PHC principals on the committee.

5. **A specific benefit cited by several researchers was the ability to extend facility-based studies into the community.** Whereas traditionally, university researchers had often focused on hospital-based or clinic-based morbidity, descriptive studies, or case histories, the specific focus of the research committee actively favored researchers' involvement in community-based studies while discouraging hospital-based studies. Researchers also rated highly the opportunity the program provided for cooperating with service providers in the field.

6. **The most frequently cited individual benefit to researchers was experience in protocol development, whereas the greatest benefit received was "practical experience in executing projects."** Although most researchers believed they gained some skills in data management and analysis, this was also one of the areas in which both researchers and committee members felt the project needed more emphasis.

7. **Researchers generally appreciated the limitations of the project's sponsorship role:** Most saw the program's role as one of providing inexperienced researchers with the ability and confidence to apply elsewhere for subsequent (larger) grants.

8. **Investigators generally had very high praise for the review process, the guidance received from preceptors, and the "responsiveness" of the process.** Committee members were generally more conscious of inadequate supervision as a problem than were researchers. A recurrent theme in review meetings was the need for "intensifying the monitoring of approved studies." It appears that investigators fared best when able to take advantage of additional resources in their own academic community or institution (formally or informally).

Some shortcomings were also identified:

1. **The diverse composition of the research committee – one of its principal strengths – was also the most frequent target of criticism.** Comments were often based on the belief that some committee members were not skilled enough in research methods to critique proposals adequately. Although to some extent this may have been simply an expression of traditional academic prejudices, it was generally acknowledged by committee members that some proposals would benefit from external review when the experience of members might be limited. In general, however, the sum total of skills and competencies within the committee was adequate to address most of the proposals received.

2. **Of 140 protocols submitted, only 42 were approved.** This represents a relatively high rejection rate (70%) for a program intended to develop fledgling researchers and basic research skills. Although in theory this could have been due to very stringent acceptance standards, other findings suggest that the main cause was a relatively low standard of protocols submitted. There was a widely expressed need for greater training in basic statistical and epidemiologic skills, as well as a desire to see the protocol development training, done in 1988, reproduced on a larger scale. (The original workshop had 21 participants.) Both investigators and committee members acknowledged the weakness in methodologic skills.

3. **Dissemination beyond the immediate users was weak.** Although a number of suggestions were proposed by the committee (including publication of a local compendium, periodic workshops, publication in the quarterly epidemiology bulletin, and presentations at international conferences), these options have been slow to materialize.

4. **The ability of sponsoring institutions to adequately assist investigators with statistical or laboratory support varied considerably.** In some cases, high demand on limited facilities often caused problems even at those institutions with "adequate" support.

5. **Two concerns that existed in the prior regional activity were also present in Nigeria.** First, adequately monitoring and supervising projects over a wide geographic area still proved difficult. Secondly, the activity still commanded a considerable amount of time and effort from the CCCD epidemiologist (much of which was concerned with routine administrative matters rather than training or skills transfer).

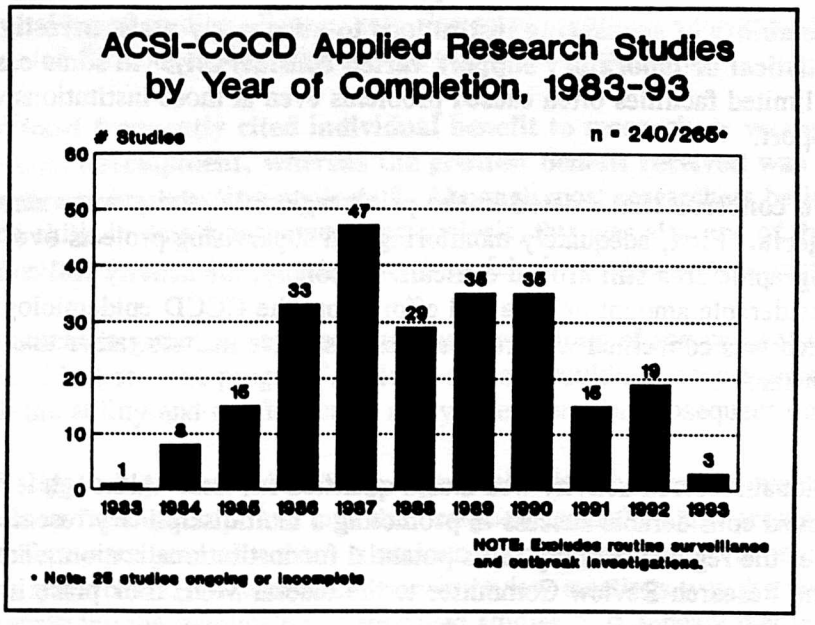
The Nigeria operational research activity was thus a qualified success. Although it faced some constraints, it achieved considerable success in promoting a multidisciplinary research agenda. It was also an advance over the regional activity in its potential for institutionalization. Transfer of responsibility for the Research Review Committee to the federal MOH took place in 1991.

3.6 Other Individual Country Efforts

A number of other countries also tried to establish local mechanisms for review and promotion of small-scale research. In Zaire, Burundi, and Rwanda, these efforts resulted in local guidelines and workshops, but were not truly functional in the manner of the previous examples cited. In Togo, the program was initiated with a protocol development workshop in 1988, but faltered until a full-time research associate was assigned to coordinate research activity. Of 11 studies generated by local investigators, at least 9 were successfully completed; one is ongoing. Although it was not possible to accurately judge the impact of these completed studies on policy or programs at the local level, the program appears to have achieved considerable success as a promotional activity.

3.7 CCCD Special Studies and Intramural Research

Although more attention may have been paid to the operational research component as a discrete entity, the CCCD Project's own intramural research and special studies often played an equal or greater role in developing research capacity. Whereas the specific objective of promoting African research capacity was assigned to the operational research component, a substantial role in the conduct of project research had also been envisioned for field epidemiologists -- work plans for field epidemiologists included a 35% time expenditure for research activities and an additional 30% on regional consultations. Over the course of the ACSI- CCCD Project, technical officers were also involved to a variable degree in intramural research, largely dependent on their particular interests and individual background. Although these research activities did not envision capacity building as a direct product, it was assumed that some benefit would result from the collaboration of local counterparts on project activities. In reality, the benefit was probably much more than imagined. Moreover, since project-initiated research and local problem-solving activities accounted for 60% to 70% of the total research carried out under the ACSI-CCCD Project, their impact should not be minimized.



What was the nature of these special studies? Initially, much of this research was concerned with obtaining baseline data for project activities and program planning. Although later included in operational research activities, much of it was, in fact, what Feachem has termed **"health problem research"** -- intended to define the "magnitude, distribution or cost" of a health problem (Feachem et al., 1989). This was particularly evident in the research studies generated during the first 2 years of individual country projects. For example, of 48 special studies initiated from 1983 to 1984, 19 were KAP or practice surveys, 15 were epidemiologic studies attempting to define disease morbidity, mortality or trends, and 5 were surveys incorporating both disease epidemiology and KAP elements. Only 9 studies were related to an intervention, the impact of an intervention, or disease etiology. This experience illustrates clearly two of Feachem's concerns: 1) the dearth of available baseline data in developing countries, and 2) the necessity of having fundamental data before more advanced studies can be profitably undertaken.

BOX 3.7.1

SPECTRUM OF RESEARCH UNDERTAKEN DURING FY 1983 AND FY 1984, ACSI-CCCD PROJECT: "SPECIAL STUDIES"

TYPE OF STUDY	*# STUDIES*	*EXAMPLES*
KAP studies or practice surveys	*19*	*- Home treatment of fever survey, Togo* *- Record review at 4 sites for fever treatment practices, Togo* *- Knowledge and use of SSS, Kinshasa* *- Feasibility of vaccinating sick children, Kinshasa* *- Maternal and Child Health practices, Côte d'Ivoire*
Epidemiologic	*15*	*- Register survey of measles studies in Lome, Togo* *- Geographic analysis of mortality data, Kinshasa* *- Lameness survey, rural and urban Zaire*
Combined KAP and epidemiology	*5*	*- Mortality and Use of Health Services surveys, Zaire, Togo, Liberia* *- 75-household community survey for local-area monitoring, Uganda* *- Mortality and preventive practices at prenatal clinics, Kinshasa*
Etiology or intervention studies	*9*	*- Chloroquine resistance studies, Kinshasa and Mbuji-Mayi* *- Study of chloroquine-associated pruritus, Karonge and Dwangwa;* *- Effectiveness of diarrhea messages, Kinshasa*

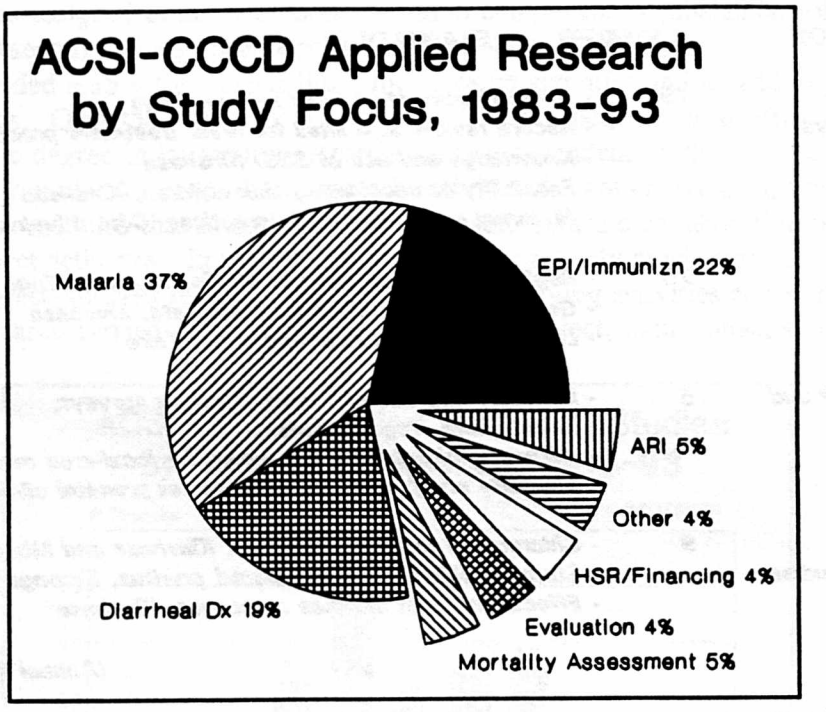
(Annual Report FY 1984)

3.8 Spectrum and Quantity of Applied Research in CCCD

Eventually, CCCD-initiated research did span the entire spectrum of research identified by Feachem, from health problem research to health services research. In general, the progression also followed a hierarchical order: epidemiologic studies and baseline KAP studies formed a substantial part of initial project activities, whereas evaluation studies, cost-effectiveness studies, and financing became more important priorities toward the end of the CCCD Project life. The project did, however, maintain a deliberate bias for problem-oriented research throughout its existence. The full spectrum of applied research projects undertaken by the CCCD Project is better addressed in the companion compendium to this document. The compendium provides detail regarding many of the specific research activities in which the project engaged. However, the general scope of activities undertaken is illustrated in the accompanying box, which provides information concerning the two early project years, 1983 and 1984 (see box 3.7.1).

Overall, and throughout its 11 years of implementation, the ACSI-CCCD project sponsored at least 265 individual applied research studies. Approximately 106 of these had Africans as principal investigators, and at least 39 more listed Africans as co-principal investigators or second authors. Excluding reviews and summary articles, at least 89 articles were published in peer-reviewed journals, and many presentations were made at a large variety of conferences, including 6 consultative meetings held between 1984 and 1993.

The range of topics comprising the focus of the 265 implemented research projects is represented in the adjacent figure. Over 75% of all studies were devoted to the three target intervention areas (vaccination, diarrheal disease, malaria), whereas about one quarter concerned other interventions (e.g., ARI, 5%) or support strategies and methodologies (17%).



The representation of countries in the CCCD research effort largely reflected the level of technical expertise present. In general, the countries which accounted for the greatest numbers of studies were those with a CCCD epidemiologist -- Nigeria, Malawi, Zaire, and Côte d'Ivoire. However, a number of smaller countries (for example, Togo and the Central African Republic) did pursue an appreciable amount of research activity without a resident epidemiologist.

Two summary points should be noted about the CCCD research effort:

1. **Much of the research activity in CCCD was basic problem-definition (or "health problem research" in Feachem's typology) or operational research.** It was directly program-driven, and addressed issues of concern in multiple countries.

2. **From its inception, the CCCD Project adopted a broad approach to information, data, and research.** Country work plans included both research capacity building and strengthening of HIS and surveillance systems as complementary strategies. Both approaches were usually developed concurrently. Bilateral projects started to implement surveillance activities from the start -- establishing sentinel surveillance where feasible, testing the effectiveness of existing surveillance, and simplifying disease reporting. These dual strategies -- ad hoc research and ongoing surveillance -- were intended to provide immediate answers for immediate program needs (through short-term research projects), while simultaneously initiating a more sustainable solution (through established disease surveillance).

BOX 3.8.1

A SUSTAINED PROGRAM OF DATA FOR DECISION MAKING USING RESEARCH AND SURVEILLANCE IN MALAWI'S MALARIA POLICY

ACSI-CCCD's involvement with malaria control in Malawi covered a broad scope of activities from 1984 to 1993, although the bilateral project formally ended there in 1988.

Establishing baselines--using available data: *A considerable portion of initial program activity in Malawi was based on studies of existing data. Although not as intellectually challenging an approach as original research, it provided a wealth of information on rising rates of inpatient morbidity, case fatality, and malaria-related mortality. The value of this approach was enhanced by a relatively good system of existing inpatient reporting. It was also an approach continued throughout the project.*

Filling in gaps--supplementing available data: *Not all baseline information was available from existing data. Specific surveys were required to estimate community prevalence of febrile illness, to determine home and facility practices for the treatment of fever, and to assess community access to services. From 1985 to 1986, the project and MOH initiated numerous community surveys that established incidence estimates for febrile illness, and facility-based surveys that assessed the quality of treatment by health workers. Community surveys revealed that only 15% of mothers had access to radios, and antenatal clinic surveys showed that only 30% of antenatal patients took chemoprophylaxis. Training assessments and performance tests of health workers identified specific deficiencies in treatment practices that could be addressed by directed training. Exit interviews with mothers evaluated the effectiveness of patient education.*

Efficacy and effectiveness--drug sensitivity surveillance: *In 1984, in response to confirmed reports of chloroquine resistance, the government of Malawi and the CCCD Project established national sentinel surveillance of chloroquine resistance. Using six sites to monitor in vivo parasitologic and clinical response, the malaria program tracked the declining effectiveness of chloroquine and evaluated the effectiveness of alternative drugs. The program was able to monitor development of a decreasing clinical response to chloroquine in 1990, and to identify the superior effectiveness of pyrimethamine-sulfadoxine in alleviating anemia. In addition to evaluating clinical and parasitologic response in children, studies also examined antimalarial effectiveness in chemoprophylaxis programs for pregnant women.*

Getting something for "almost nothing"--modifying the vaccination coverage survey: *By adding a limited number of questions on community treatment practices to the national vaccination coverage survey in 1986, the MOH and CCCD Project were able to derive national estimates for community treatment practices (e.g., 10% for home treatment of malaria), without much additional cost.*

Going one step further--sentinel surveillance of clinical practices: *To supplement morbidity reporting, the MOH and CCCD Project in 1986 established a network of 12 sentinel health facilities where pediatric outpatient staff routinely collected information on home treatment of illness from mothers accompanying sick children. Prevalence data for practices such as home treatment of fever (15%-16%) and home use of SSS (40%-47%) were available for comparison with national or local rates derived from coverage surveys.*

Integrated interventions--testing community-based approaches: *In response to MOH initiatives to broaden community-based control and prevention, the CCCD Project and MOH initiated research to assess "the situation beyond the clinics"--traditional birth attendants (TBAs), merchants and drug-sellers, local healers, and use of individual personal protective measures. Through the HEALTHCOM project, it initiated an intervention study that demonstrated that TBAs could be used as an acceptable source of community treatment for malaria. With HEALTHCOM and a local drug company, a pictorial treatment chart was developed to promote correct dosage regimens for chloroquine treatment of malaria.*

Going "two" steps further--a large scale prospective study: *In an attempt to identify a rational approach to chemoprophylaxis in pregnancy, the MMRP was initiated in 1987. Prospectively following a cohort of 4,220 pregnant women, it showed mefloquine to be superior to chloroquine in clearing placental parasites and reducing the incidence of low birth weight.*

The current status: *The development of policy from these sources of data has been exemplary. In response to the failing effectiveness of chloroquine, the policy has developed cautiously but assuredly to select and promote pyrimethamine-sulfadoxine as the first-line drug for malaria treatment in young children. Since 1992, the malaria program has moved systematically to implement the policy nationally and to monitor compliance with the new guidelines. The program has also sought to ensure that adequate supplies of the new drug are made available to health facilities.*

What remains to be done? *While policy development has progressed admirably in Malawi, progress from policy to practice has sometimes lagged. Efforts to provide malaria treatment at the community level have not been widely employed. As late as 1991, various reports noted that treatment practices in villages, clinics, and hospitals varied from place to place despite widespread availability of guidelines. Although research capacity has been considerably strengthened in clinical and epidemiologic skills, social and behavioral input into program implementation has been relatively weak and unsustained. Future research plans include intervention studies evaluating the feasibility and effectiveness of bed nets, alternative regimens for chemoprophylaxis in pregnancy, and improved methods for the diagnosis of malaria.*

3.9 Program Benefits of ACSI-CCCD Research

Apart from the capacity building, which was part of CCCD's research mandate, the direct value of CCCD-supported applied research to the ACSI-CCCD program and to MOH was considerable. Because this is covered extensively in a number of individual publications detailing the impact of various CCCD components,[1] it will not be exhaustively reviewed. However, one model, which provides an instructive example of how data can be used in an integrated and systematic fashion, is Malawi's program of malaria-related research (see box 3.8.1).

[1] A full listing of the over 30 papers and documents in this ARTS (Analysis, Research, and Technical Support) series, as well as copies of individual publications, is available from the ACSI-CCCD Technical Coordinator, International Health Program Office, Centers for Disease Control and Prevention, Atlanta GA 30333, or from the Office of Analysis, Research and Technical Support, Africa Bureau, U.S. Agency for International Development, Washington DC, 20523.

CHAPTER 4

AFRICAN INVESTIGATOR INVOLVEMENT IN ACSI-CCCD RESEARCH

4.1 Role of African Investigators

The role of African investigators in CCCD applied research has varied greatly. Review of available research reports and evaluations has identified six levels of involvement by African investigators:

1. **African investigator research initiated within a formal research framework:** These were studies initiated by African investigators, approved through a formal process of protocol submission and review, and administered and executed by the local investigator. This level applies mainly to the projects executed through the East/Southern Africa Research Review Committee and operations of the Nigeria Research Review Committee.

2. **Informal review and approval of African investigator research:** In many instances, a less-formal process occurred. A local researcher would propose an investigation to the epidemiologist or CCCD technical officer and be funded after a less-formal review process, which may have involved submission of a protocol for comments to CDC principals in Atlanta.

3. **Collaborative studies with CDC:** Occasionally, local researchers were major collaborators in CCCD studies in a country and were involved not only in executing the field investigation but also in developing and revising the study protocol.

4. **African participation in field investigations:** In many local studies (usually initiated by the CCCD field epidemiologist or technical officer), local co-investigators assisted in executing the study in the field. While it is doubtful that this would appreciably increase capacities for independently undertaking research, it generally contributed a great deal to familiarity in handling data.

5. **Thesis research of Africans studying abroad:** A small number of Africans studying abroad (usually U.S. doctoral or Master of Public Health students choosing to do thesis research in their native country) were assisted by a CCCD grant. An external evaluator in 1985 recommended that CCCD actively promote this option.

6. **Combined training/field study:** The prototype of this category is the series of studies and training sessions conducted by CDC's Malaria branch (with CCCD, WHO, and OCCGE collaboration) on in vivo drug sensitivity. The basic protocol for field study was a modification of WHO protocols devised by CDC principals. Modifications and site selection for individual countries were usually agreed upon through consultation with local principals and carried out in conjunction with a

training workshop that focused on specific technical skills. Preliminary data analysis was an integral part of the workshop. Developing preliminary recommendations from the study findings was also a requisite part of the exercise, accomplished before the workshop concluded. While this model offered little training in protocol development and review to general participants, it did emphasize an appropriate approach to analyzing data and the use of study results to derive appropriate policy recommendations. Development of a publishable document was usually a collaboration of one or two local principals with CDC and CCCD personnel.

4.2 Benefits to African Researchers and Institutions

From its inception, the ACSI-CCCD Project recognized that there would be a substantial need for data to guide and measure the progress of its interventions. Among the obstacles to this goal (as stated in the original project document), were "the scarcity of qualified biomedical researchers and the lack of institutions capable of supporting biomedical research." To address this, the CCCD project's objectives included:

- strengthening African institutions,
- increasing the individual capabilities of African professional staff (Chin, 1985).

Thus, there were always two dimensions to the goal of increased research capacity -- one reflecting individual benefit to researchers, the other focused on institutional strengthening.

A concerted attempt was made to evaluate the benefits to African researchers and institutions of ACSI-CCCD applied research activities (including but not limited to the formal operational research component). The findings enumerated here reflect the results of numerous individual interviews with participating researchers, focus-group interviews with researchers and program managers, and country visits to review research programs in Nigeria and Zaire. An "expert" group of experienced researchers with experience outside the CCCD program was also convened. This process had three main findings: 1) individual benefits to researchers were considerable, 2) the contribution to the effective use of research (by programs and program managers) was also appreciable, and 3) the contribution to creating a sustainable environment for research was more modest.

In polling counterpart researchers and program managers, several consensus themes were identified:

1. Most counterparts were relatively new to the field of applied research. They noted that the emphasis on problem-based research was a relatively recent phenomenon compared to previous research activities in Africa, which were generally the work of individuals, usually sited in medical schools, and not closely related to programs.

2. They also noted that there had often been previous local efforts aimed at promoting research. Frequently these did not function well because of lack of trained personnel (human resources), lack of financing, and commitment of the MOH.

3. Policymakers and MOH personnel strongly endorsed local problem-based research. Academics and internationally based researchers also endorsed this need but were less inclined to call it research. Overall, the need for research (however defined) within the public health sector of developing countries was widely accepted.

4.3 Individual Benefits to African Researchers

The total number of individual researchers involved with CCCD research projects is difficult to judge. Although 115 African investigators are named as principal investigators in various projects, not all of these were successfully completed. Moreover, some investigators involved in secondary roles on large-scale CCCD projects undoubtedly had more research involvement than some named as principal investigators for small-scale studies costing $5,000.

In concrete terms, the ACSI-CCCD program can boast of some 88 original research studies initiated by 83 African investigators that were supported by CCCD through one of 4 research review committees (East/Southern Africa Regional Committee; West Africa Regional Committee; Nigeria Research Review Committee; or Togo Research Review Committee) under the formal program of research promotion. There were also 39 projects (by 32 African researchers) initiated with full or partial project support under other mechanisms. For example, investigators participating in malaria surveillance networks in Nigeria, Malawi, and Zaire. In addition, at least 80 African researchers are cited in project documents or published reports as co-investigators or collaborators in other ACSI-CCCD research. (This may be an underestimate, since collaborators are frequently unnamed in informal project reports.)

A note of caution is warranted -- for several reasons, simply counting numbers of studies, investigators, or even publications as measures of program success may be misleading (although peer-reviewed publication does offer some measure of credibility). These are process indicators; although they are important, there is a need for impact and outcome indicators as well.

A number of specific benefits accrued to researchers and program managers associated with the CCCD program. A few researchers associated with CCCD received long-term training (such as MPH or PhD degrees) in American institutions -- some through CCCD directly, and some through other mechanisms. Other benefits identified by investigators and program managers included:

1. **Accessibility.** The single characteristic of the research program that researchers consistently identified as valuable and unique to ACSI-CCCD) was the "accessibility" of the program. By this was meant its ability to develop and submit protocols locally (in the case of research review committees), receive timely feedback, work on modifications, consult freely with preceptors, clarify anticipated questions, obtain relevant journal articles, and procure funding locally. In addition, many investigators felt strongly that a locally constituted board of experts was better able to determine the relevance or importance of a proposal, as well as appreciate local constraints. The most important feature of the research program was not simply the availability of financial support therefore, but the local focus and scope of the effort.

2. **Interaction with experts.** Investigators who worked on collaborative ventures also felt that there was exceptional, immediate benefit gained by local interaction with technical experts. Thus, the presence of in-country technical officers, epidemiologists, or both was considered a particular CCCD strength. This was even more acutely felt in smaller countries with fewer academic resources or research institutions. In this respect, there was explicit concern that the provision of technical assistance by short-term or medium-term consultants was not equivalent to an in-country presence.

3. **Workshops.** Investigators who attended one of several CCCD research workshops gave qualified endorsements of this process. They saw the workshops as extremely useful for gaining experience in protocol writing, and for learning the procedure of putting together a research proposal (problem identification, writing a problem statement, budgeting, and the like). However, they felt strongly that workshops were not a substitute for an interactive process of collaboration on an actual research project, and that workshops were too often held in a vacuum, without definite plans for follow-up. The expert group of experienced researchers expressed this even more strongly. One contributor noted: "Workshops, by themselves, even if they are well done, are useless without follow-up!"

4. **The solicitation-review process.** There was qualified endorsement of the formal solicitation- review mechanism used by the Nigeria and East/Southern Africa Operational Research Review Committees. However, it was acknowledged that some of this mechanism's practical limitations (for example, membership of the committees, and the size of eligible awards) needed to be addressed for more effective operation.

5. **Mentoring.** There was a strong sentiment that the "mentor" relationship of working jointly on the evolution of a research project was generally the most fruitful mechanism for skills transfer in both large and small countries. This sentiment was consistent across both donor agencies and African counterparts. Counterparts generally felt that they had been significantly involved in CCCD research activities (including generating or shaping research activity and in implementation). Most felt they had benefitted from the experience.

6. **Supervision and oversight.** Individual benefit derived from the CCCD project varied. In general, both research quality and the benefit derived by the researcher reflected the effectiveness of supervision and oversight of research efforts. Where close oversight or collaboration occurred (as in Malawi, Togo, and Zaire, and in much of the research in Nigeria), the perceived benefits of the research experience were greatest.

7. **Experience in specific methods.** Individual benefits appeared to be greatest in disciplines or methodologies which were most clearly aligned with CDC's own interests and expertise. These included epidemiologic research, disease outbreak investigation, case-control studies, and surveys of communities and health facilities.

Suggestions for maximizing benefits: To continue to maximize benefits, researchers argued for more training, a more directed approach to research capacity building, and continued support of small-scale researchers. Counterparts as well as experienced researchers generally felt that training was the first priority of a program promoting research. "It is not possible to do effective research without adequately trained people," was a common refrain. Virtually all respondents agreed that basic skills in data management, statistics, and epidemiologic principles were weak. Many counterparts and experienced researchers argued for a more directed approach to research capacity building: While acknowledging that all MOH personnel can benefit to some extent from research experiences, they also noted a need for a skilled person(s) to be a core resource for research activity. Priority for personnel training should be given to people "actually doing that type of work." There is a definite need, they asserted, for long-term training. There was also a concern, among the expert

group, that the public health estalishment was not appropriately using the skills of researchers once they have been trained (that is, there was a fear that they were under-utilized). The need for continued support of small-scale researchers was highlighted. Local program managers who had acquired some experience in small operational research projects needed some autonomy and funding to allow individual initiatives to work. Without this, they noted, skills deteriorate and enthusiasm wanes.

4.4 Institutional Benefits

The influence of the CCCD Project on institutional strengthening was much more variable. Strengthening of traditional academic research institutions was not initially a conspicuous objective of CCCD research efforts. This was because 1) CCCD was generally more interested in specific problem-solving than academic research; and 2) relatively few capable institutions had a strong interest in public health research.

A number of institutional benefits were derived from ACSI-CCCD:

1. In Nigeria the institutional benefits appeared to be twofold -- aiding the establishment of a framework for research promotion, and improving institutional research capacity in the various collaborating institutions and universities, through provision of reagents, supplies, technical assistance, and the like. Another such tangible was the provision of CD-ROM on-line search capabilities provided to the National Medical Library. In general, however, although CCCD gave several countries some experience in running a formal review mechanism, it did not leave institutionalized review mechanisms behind in most of those instances, with the exception of Nigeria.

2. Research capabilities of other institutions were often indirectly strengthened through CCCD support of HIS and disease surveillance. Provision of computers and software to ministries and PHC offices at various levels enhanced these institutions' capabilities for both routine surveillance and periodic research. Involvement of universities in national malaria surveillance networks generally strengthened individual institutions; it also improved cooperative relationships with MOHs.

3. There were many additional benefits to individual institutions and programs. Research components were included in short courses in health education at the Zaire School of Public Health and the Africa Regional Health Education Centre in Nigeria. In Zaire, a number of health programs were beneficiaries of close working relationships with CCCD. Among these were the rural health project SANRU (Santé Rurale), and the urban program Santé Pour Tous.[1]

[1] The authors acknowledge special indebtedness to two individuals whose reflections on their experience with operational research in Zaire provided considerable assistance for this document--Dr. Sambe Douale, formerly of the SANRU project, and Lauren Greenberger of the PRICOR project in Zaire. Their work with the Zaire School of Public Health and the PRICOR operational research project in Zaire furnished us with many insights on practical aspects and policy implications of operational research.

4. In Malawi, there was appreciable success in developing institutional capabilities in malaria research. Building on research experience developed during drug sensitivity surveillance from 1984 to 1987, the program was able to implement the MMRP and a number of follow-up projects from 1987 to 1992. Plans have also been developed for continuing consolidation of research capabilities in the establishment of satellite field research stations and a program of training in research.

5. Although there was some collective experience gained from the experiments with regional research committees, the institutional benefit of this effort was limited. Lack of a strong regional sponsoring body or a mechanism for ongoing support were two reasons why the benefits of these efforts were not sustained beyond the short term.

In each of these examples (as well as the individual benefits previously cited), the CCCD experience tends to reinforce the finding that the strength of a research program such as CCCD's depends not so much upon the sophistication of research, as upon its relevance. Moreover, the integration of a research program into a wider program of service delivery and program assistance may contribute to the mutual strengthening of several components, although this may also necessitate compromises.

4.5 Balancing Product Delivery and Capacity Building

Mention has already been made of the competing objectives of ACSI-CCCD applied research -- the need for usable results versus the need to build capacity and train indigenous researchers.

The 1990 CHRD report also comments on this dichotomy. It notes that building and sustaining research capacity generally includes at least four components:

1. individual competence,
2. institutional infrastructure,
3. incorporation of research into policy formulation, and
4. participation in global health research (CHRD 1990).

With respect to foreign donor involvement in health projects, however, the CHRD report also makes particular mention of what it sees as a common failing of donor-assisted research -- that it often does not contain a research institution-building component. Learning from such research, it notes, "usually accrues more to donor agencies than to developing countries, and often much of the actual work is undertaken by foreign consultants rather than national researchers."

In absolute terms, that was partly true of ACSI-CCCD applied research. The majority of research projects were undertaken with CDC staff as principal investigators. On the other hand, a significant proportion of studies were undertaken by African principals, and in many others, the contributions of African collaborators were substantial. Throughout its existence, the ACSI-CCCD Project generally recognized the need for leaving research capacity in place. However, in operating under the dual constraints of a relatively modest budget and its (often immediate) need for critical program information, the project was often constrained in practice from what it had endorsed in theory since its inception.

4.7 CCCD's Contribution to the "Effective Use of Data"

One consequence of CCCD research that was deliberately omitted from the individual benefits listed above was the role of CCCD in **"demystifying" research**. Described as one of the "prescient" aspects of CCCD, this was one of the most widely endorsed aspects CCCD activities.

Program managers and other ministry personnel were generally the first to note that involvement with the CCCD project had considerably enhanced their confidence in using data and research for problem solving. This was revealed in focus groups with malaria program managers in 1992, in groups with other program managers and researchers in 1993, and in individual interviews with both administrators and beginning researchers. Although difficult to quantify, this enhanced capacity of persons who were not professional researchers to relate better to a research environment was so widely and clearly enunciated by counterparts that it must be seen as a substantial achievement in strengthening MOHs. In particular, program managers acknowledged that the CCCD program helped ministries put the "tool" of research in the hands of many people, allowing them to use the research method as a "management tool" for more appropriate decision making.

In practical terms, some of the tangible benefits achieved through collaborations were skills in identifying problems, methods to define problems, experience in the preparation of a protocol, and confidence building to enable program managers to undertake their own initiatives in "problem-solving research." In Togo, for example, one program manager noted that its program was able to use fewer consultants in later years of the project because local personnel were able to do more.

Project counterparts also contended that the project, by "demystifying research," had demonstrated that research was "no longer something that only academics in universities were entitled to claim." They also felt that even if administrators or program managers were not able to undertake a great deal of research themselves (because of time constraints or competing priorities), they were still better able to interact in a research environment (with universities and academics) because of their CCCD experience.

Several concrete examples of policy applications support these conclusions.

> **Zaire:** Data were used in program implementation. Drug-sensitivity testing helped establish sulfadoxine-pyrimethamine as the second-line drug for treatment of uncomplicated malaria. Studies showing inaccurate preparation of SSS caused re-evaluation of the strategy for promotion of home-based rehydration solutions. Epidemiologic studies of measles in Kinshasa showed significant incidence below the recommended immunization age of 9 months, leading to a re-examination of immunization policy and trials of an alternative vaccine (EZ). In a debate with the Ministry of Health over the utility of chloroquine prophylaxis in first and subsequent pregnancies, program managers were able to support their recommendations to the minister with concrete findings.
>
> **Central African Republic:** Facility-based studies of health care worker performance were pivotal in discussions with UNICEF about plans for an accelerated "campaign" of vaccination activities, providing a clear opportunity to justify the MOH position on such training. Despite this, later events led to the donor's demands prevailing. Nevertheless, the opportunity to use the research findings was still considered a successful use of data for policy.

Togo: Successive rounds of drug-sensitivity testing guided the evolution of malaria policy by allowing the MOH to evaluate the effectiveness of chloroquine at 10 mg/kg and 25 mg/kg. KAP studies helped guide decisions on the most effective methods for health worker training, by comparing performance with different teaching methods. By its use of findings to support recommendations to the ministry, this research gave greater credibility (and justification) to a training initiative, where changes of established procedures were proposed. As one respondent phrased it, "If you need to convince people to change, you need data."

Several respondents also felt that, despite data to the contrary, decisions were sometimes made for political expediency rather than being driven by research results. In spite of this drawback, there was no desire to abandon the process; rather, there was a very strong consensus that "this is the way to go," despite occasional setbacks from the political arena.

CHAPTER 5

PRIORITY SETTING AND RESEARCH AGENDAS

5.1 Research Priorities of Review Committees

Priorities in the CCCD operational research component were initially established from an ad hoc list drawn up by the Evaluation and Research Division of IHPO. This list was used in guidelines for the East/Southern Africa Regional Review Committee and was subsequently adopted with modifications by other research review committees. This process had two weaknesses:

- First, it did not establish a dynamic process for determining research priorities, but simply established a one-time inventory of topics; and
- Secondly, the priorities were essentially donor determined rather than negotiated.

To establish a suitable agenda, the process should generally include three steps:

1. First, the major health problems or research questions must be identified.
2. Then, the problems need to be prioritized according to the importance of each and the feasibility of finding a research solution.
3. Finally, a strategy to address questions and to implement solutions must be developed, including the matching of research to existing or potential resources.

Although the guidelines for the operational research under the review committees identified a wide range of important health problems, no attempt was made to rank or prioritize them (undoubtedly out of concern for "limiting" research options). In addition, review of submitted protocols showed that the policy implications that *were* envisioned for individual projects were often only broadly or vaguely defined (e.g., "...to contribute to existing knowledge," or "...to provide the basis to plan appropriate strategies"). In this context, therefore, the program should realistically be viewed mainly as a training exercise in research skills. It would probably be unfair, therefore, to expect it to have a substantial effect on policy or programs.

It should also be noted that, although the chosen guidelines were quite broad, there *were* a few occasions when protocols were rejected because they did not conform to the CCCD guidelines, although these proposals often did deal with major local health problems (such as guinea worm, nutrition and acute respiratory infections). Although a negotiated set of priorities cannot by itself eliminate all such debates, an agreed-upon set of priorities will likely do much to make such decisions more acceptable to researchers.

In a 1986 assessment, evaluators of the CCCD project also endorsed this view. While acknowledging that the list of research topics set by CCCD had "great relevance to CCCD", they also noted:

> A clearer statement of research priorities is needed from African program managers. The evaluation team suggests that CCCD use the annual consultative meeting as a forum to discuss research priorities (LaForce et al., 1986).

In fact, at the 1986 consultative meeting, this process was initiated with appreciable success by one component of CCCD -- the immunization activity (see box 5.1.1). Although this mechanism did provide useful guidance for the conduct of EPI-related research in CCCD, it was never formally embraced as a mechanism for agenda setting by the CCCD program as a whole.

5.2 Other Mechanisms for Priority Setting

In addition to the formal mechanism used by the immunization program and the approach taken at the inauguration of the CCCD Project, several other methods were used over the years to determine the nature of research undertaken by the project.

1. Informal consensus: Individual technical officers generally had appreciable latitude in determining project work plans and activities on a short-term basis. Regional epidemiologists had an even greater freedom of choice. During the process of negotiating annual work plans with local counterparts, the local CCCD project was often able to identify specific programmatic issues that could be addressed by research. If capabilities within the country allowed it, the research could be initiated locally. If the technical officer or counterparts felt that technical assistance was necessary, resources at the CDC could be requested. In practice, this might be provided by IHPO, the Division of Immunization, Enteric Diseases, Special Viral Pathogens, or any other office with the required expertise.

2. Regional meetings: These were a means for technical officers or counterparts to identify common program concerns and request assistance or guidance from CDC principals. These included annual project-wide staff meetings for CCCD staff and six biennial conferences for CCCD staff and African counterparts. At these forums, technical officers and CDC researchers could propose specific problem-based research to answer program questions. A number of operational issues were identified through this mechanism -- for example, declining use of ORT corners, high dropout rates in EPI programs, and low coverage for maternal tetanus immunization. Regional meetings were also used by the respective branches in CDC to present agendas of proposed research priorities to field staff and other CCCD principals.

3. Global research priorities: Several global forums have periodically identified priority research issues for their programs. One of the best known of these is the EPI Global Advisory Group. Often CCCD's agenda for research was highly influenced by these global priorities. In many respects, the CCCD Project was an ideal vehicle for such research: it encompassed a broad range of countries and geographies, and information derived from successful research could be used in other bilateral countries as well as the host country. Moreover, the availability of regional funding from a central budget meant that a single-country allocation would not have to support an entire large-scale project.

BOX 5.1.1

A METHOD FOR IDENTIFYING RESEARCH PRIORITIES IN EPI

As part of ACSI-CCCD activities in Africa, IHPO and CDC's Division of Immunization agreed in 1987 to collaborate in providing epidemiologic assistance to immunization-related activities in the CCCD Project. One of the first tasks undertaken as part of this collaboration was to identify EPI-related research priorities that would be part of the joint IHPO-DOI work plan over the next 2 years. A list of 17 projects was compiled from preliminary discussions with colleagues working in the CCCD Project. The importance and design of each project were briefly described. The list was then distributed for review to colleagues with expertise in the EPI. Reviewers were asked to rate each proposal on a priority scale from 1 to 10, to comment on the proposals, and to suggest any high-priority proposals that were not on the list. Forty-one reviewers returned the list of proposed projects with ratings and comments. Twenty-two reviewers were CDC staff or worked for the CCCD Project. The remaining 19 worked for African MOHs, WHO, or universities. A listing of the six highest ranked and four lowest ranked (and average rating on a scale of 1 to 10) is provided below. No additional project was suggested more than once.

Highest Rank	***Average Rating***
1. Identification and evaluation of the reasons for non-utilization and under-utilization of vaccination services and the demonstration of a strategy for increasing use.	*8.1*
2. A study of the impact of using all health center contacts as opportunities to vaccinate children.	*7.7*
3. Evaluation of the impact of a two-dose measles vaccine schedule.	*7.5*
4. Measuring the impact of vaccination on the incidence of measles.	*7.4*
5. Identifying and evaluating a strategy for vaccinating women of childbearing age with tetanus toxoid.	*7.3*
6. A study of the impact of therapeutic vitamin A on case fatality rates of children hospitalized for measles.	*7.1*

Lowest Rank	***Average Rating***
14. A comparative immunogenicity trial of two doses of acellular versus three doses of whole cell pertussis vaccine.	*5.4*
15. Assessment of the cost and effectiveness of using a vaccination strategy of special immunization days to raise coverage and reduce disease incidence.	*5.3*
16. Comparison of the serologic efficacy of two and three doses of tetanus toxoid.	*4.9*
17. Demonstration of the impact of giving measles vaccination at school entry.	*4.7*

Source: Proceedings of the Fourth Consultative Meeting, ACSI-CCCD, Yemoussoukro March 24-31, 1988.

The agenda was extensively discussed with African colleagues at the Fourth Consultative Meeting and generated great interest. Individual national interest in specific topics was identified, and a number of studies proposed in collaboration with local researchers. Of the top 10 priorities, 7 were initiated in one or more countries, with technical support and assistance from the CCCD Project.

4. **"Piggyback" research:** On occasion, ongoing research afforded an opportunity to conduct additional research without major additional cost. This "opportunistic" research often yielded useful secondary data. For example, field trials of several confirmatory tests for urinary chloroquine, assessment of mothers' histories of fever, and electron microscopic studies of placental malaria were all initiated as secondary investigations to other research.

Although the above mechanisms all offer some link between the problems identified by public health programs and research undertaken, with the exception of the EPI-related process they do not ensure that the research program effectively addresses the felt needs of individual countries or country programs. Neither do these mechanisms establish a clear national agenda by which various parties implementing research may be coordinated and controlled.

These two concerns have increasingly become the focus of ENHR initiatives in developing countries. Although such initiatives are a relatively recent phenomenon, they have been enthusiastically embraced in Africa. A significant step in this direction was made at an African conference on ENHR held in Uganda in 1992 (see box 5.3.1).

5.3 Developing Country Perspectives on the Need for a Research Agenda

The topic of setting priorities in research is not a new one. However, concrete measures to address the need for a research agenda are relatively recent initiatives in international health. In 1989, a Nigerian conference on **"Priorities and Process for Health Research in Nigeria"** offered one such perspective. Noting that "external sources have been singularly responsible for the bulk of support for research programmes in the health sector," while local governments devote an "insignificant proportion" of budgets, one commentator questioned whether African governments can hope to harness beneficial research efforts and limit unethical ones in such a setting.

As a solution, he proposed the following:

> It is essential for recipient nations to ensure that such funds are disbursed on projects that are 1) considered to be of priority and therefore justifiable on the grounds of relevance, 2) theoretically and methodologically sound, and 3) ethical, and in which indigenous manpower is used. This in effect means that recipient countries must set priorities in health care research and must develop the appropriate framework within which the external agencies can fund research (Erinosho, 1990).

Although observers are sometimes surprised by the revelation, the above perspective is often shared by donor agencies. These agencies have many times been equally vocal about the lack of clear guidance on research priorities in developing countries. In general, if there has been discord between developing country priorities and donor priorities (and there often has been), two factors that are clearly within the control of developing countries frequently contribute to the situation: 1) the affinity of academics (even in developing countries) for basic research; and 2) the lack of a clear, indigenous research agenda.

Focus groups and interviews with African researchers and program managers (as well as others experienced in promoting research capacity), uncovered a number of points regarding research agendas in donor-sponsored programs.

BOX 5.3.1

ESSENTIAL NATIONAL HEALTH RESEARCH IN AFRICA -- THE KAMPALA CONFERENCE

In April 1992, an international conference on ENHR was held in Kampala, Uganda, under the sponsorship of the International Development Research Centre of Canada and the Task Force on Health Research for Development. Of 46 attendees, there were 39 African participants and 14 African countries represented.

*Discussion of **priority setting** identified the following factors as relevant: magnitude of the health problem; its seriousness, groups at risk, socioeconomic burdens, feasibility of control, availability of resources, and acceptability by the community.*

*Discussion of **resource needs** included identification of the following priorities: training in research methodology; collaborative research activities; strengthening of existing institutions; effective monitoring and evaluation of the research process; a realistic focus, taking into account the available time span for research; attractive conditions of service for researchers; long- term support; credit and recognition; wide dissemination; and a close relationship with health consumers.*

*It was recommended that the **targets of dissemination** should be scientists, policymakers, health workers, communities and donors. Political interference, censorship, "packaging problems," and lack of manpower were identified as **possible obstacles**. The recommended **avenues for dissemination** included scientific journals, conferences, briefings, organized community-based meetings and mass media messages, and in- service training for health workers.*

*In discussions of future mechanisms, the **role of donor support** was seen as advocacy and support of implementation of ENHR; technical assistance in capacity building and training; support for national and regional meetings and networking activities; assisting international information exchange; and providing an operational umbrella for the international secretariat.*

This conference also played a "landmark" role in establishing the mandate for a continuing international mechanism for facilitating the ENHR strategy. This mechanism was eventually embodied in the COHRED, established as a successor body to the Task Force on Health Research for Development in March 1993.

Although it was widely recognized that development agencies often "have their own agenda," researchers and program managers did **not** necessarily see an **inherent** conflict between that fact and their own administrative priorities. However, they did feel that separate agendas can occasionally result in "imposed" projects, for which country participants feel absolutely no ownership. It would be very difficult for such projects to have meaningful influence on national programs or policy, regardless of the quality of the science involved.

For research to have influence at the MOH level, it was believed that it should involve persons who can influence implementation. "You cannot be in charge of a program and be a passive onlooker... *and* be expected to use the results!" was one significant comment. Although negotiated research priorities were, in fact, a traditional strength of the CCCD Project, the few exceptions were readily identified by counterparts.

In general, program managers recognized that differing agendas were often an intrinsic part of doing business in donor-assisted programs, acknowledging that donors had not only political and policy concerns at stake, but also training needs, opportunities for professional advancement, and individual academic interests. Despite this, they expressed considerable confidence that a suitable set of priorities could be negotiated between donor-assisted programs such as CCCD and local programs.

Most counterparts also expressed the belief that the research priorities of developing countries *are* generally known to program managers, even when not explicitly embodied in work plans. What was needed, then, was simply a process for identifying and prioritizing these ideas, whether through convening a national workshop/conference, Delphi methods, or other means. In terms of a national research agenda, it was felt that internal coordination of research agendas (among different vertical programs), and external coordination with donors were both needed. Counterparts also believed strongly that research must be grounded in some clear local need, even if it also provided information for wider global questions.

CHAPTER 6

ETHICAL OVERSIGHT, HUMAN SUBJECTS, AND INSTITUTIONAL REVIEW BOARDS (IRBs)

6.1 General Ethical Principles

For the ethical conduct of research in a program such as the ACSI-CCCD Project, there are two areas for consideration. The first is a universal set of principles that should govern the conduct of research, whatever the setting. The second is the consideration of factors specific to the international setting and to the nature of collaborations involving external sponsorship of research. Two specific concerns are associated with the latter: 1) the difference in cultures between the donor and recipient, and 2) the constraints of government sponsorship of research (in this case, the U.S. Government).

In practical terms, the nature of collaborative research in an international setting requires that the ethical principles governing those activities meet the requirements of both countries involved. Fortunately, there is relatively little divergence among the ethical standards established for research in the major industrial countries, or between those standards and the more recently established consensus standards established under the auspices of the United Nations. This is in large part because of common origins. These principles emerged after World War II in the **1947 Nuremberg Code**, the **1964 Helsinki Declaration**, and its subsequent revisions.

In the United States, much of the impetus for codifying the principles of ethical research also developed after the Nuremberg trials of the 1950s. However, two specific and well-publicized issues added additional weight to the demands for clear ethical guidelines during the 1970s (see Brandt, 1978; Jones, 1981; Rothman, 1982; and Edgar, 1992): The first of these (and the most important in influencing policy) was the so-called **"Tuskegee Study"** of untreated syphilis, in which rural black men with syphilis went untreated for 40 years. The second controversy (which had a similar but less publicized impact) was the so-called **"Willowbrook Study,"** involving hepatitis experiments at an institution for the mentally retarded.

Both studies, once publicized, revealed a surprising lack of oversight and attention to ethical concerns during long-term research studies. Both involved vulnerable subpopulations at particular risk of being exploited for research purposes -- rural black men, "mostly poor and uneducated," in the case of the Tuskegee study, and institutionalized patients in the case of Willowbrook.

It was largely in response to public outrage surrounding the publicizing of the Tuskegee study that the **1974 National Research Act (P.L. 93-348)** was passed, and with it, the commission established that would set forth the basic ethical principles for human subjects research. This commission was the **National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research,** and it met from 1974 to 1978.

Two of the more relevant documents which define the ethical standards for health-related research in the United States are the **Belmont Report** (1979), and the **Code of Federal Regulations 45 CFR 46–The Protection of Human Subjects** (1983). The latter initially applied to research funded by the Department of Health and Human Services, but was extended in 1991 to research sponsored by other U.S. Government agencies.

The 1991 amendment also included a specific provision governing research in foreign countries. It allowed procedures operating in those countries to be substituted for U.S. requirements when "the procedures are at least equivalent to those provided in this policy."

Whereas these documents enumerate the legal principles and regulatory requirements governing research, far more detailed guidance is provided by the **Office for Protection from Research Risk** of the National Institutes of Health in its Institutional Review Board Guidebook, **Protecting Human Research Subjects** (OPRR, 1993). A short but detailed guide is also provided by the DHHS publication, **Guidelines for the Conduct of Research within the Public Health Service** (DHHS, 1992). This publication also provides useful guidance on issues such as authorship, publication practices, and supervision of trainees.

As highlighted by the Belmont Report, three principles should underlie all research involving human subjects--respect for persons, beneficence, and justice.

- **Respect for persons:** This requires that persons be able to decide for themselves whether or not to participate in research, and, if incapable as, for example, with children, that their rights be protected against harm or abuse. This is the principle upon which informed consent is based.

- **Beneficence:** This requires that the risks imposed by research must be justified by benefits. It requires that risks be minimized in all cases.

- **Justice:** This is a particularly relevant principle in the context of international collaborative research. It requires that "research should not unduly involve persons from groups unlikely to be among the beneficiaries of the subsequent applications of the research." Like beneficence, this is often a value judgment, which requires weighing benefits and examining alternatives. Consideration of this principle is one of the functions of an ethical review committee or IRB.

In the international context, the principle guidance for ethical research has been provided by the several revisions of the **1964 Helsinki Declaration** (1975, 1983, 1989) and by guidelines derived from those principles, released as proposed guidelines in 1982 by the **Council for International Organizations of Medical Sciences** (CIOMS), and in finalized version (after a 10-year period of comment and revisions), as the **International Guidelines for Biomedical Research Involving Human Subjects**, (CIOMS, 1993). In addition, the CIOMS recently developed and published specific guidelines for epidemiologic studies, based on findings of a 1990 conference and "a series of extensive consultations with experts in many countries and organizations" (CIOMS, 1991). Although these guidelines were not intended to supersede other ethical standards, they addressed specific situations relevant to epidemiologic studies. One of the WHO personnel serving as an advisor and consultant to that project was a former regional epidemiologist in the early years of the ACSI-CCCD Project. A brief chronology of these milestones is shown in the accompanying box (see box 6.1.1).

BOX 6.1.1
REGULATIONS AND CONVENTIONS GOVERNING HUMAN SUBJECTS RESEARCH: A CHRONOLOGY

1947: The Nuremberg Code. *A set of ethical standards drafted to judge physicians and scientists who conducted medical experiments on concentration camp prisoners.*

1964: The Declaration of Helsinki. *The International Code of Ethics for Biomedical Research.*

1971: U.S. National Guidelines on Biomedical Research, *precursor to the 1974 National Research Act*

1972: "Syphilis Victims Got No Therapy." *News reports in the popular media provoke outrage concerning the Tuskegee Syphilis Study, leading to termination of the research, begun in 1932. Subsequent initiatives prompt passage of the 1974 National Research Act.*

1973: American Psychological Association Guidelines *on the Conduct of Social and Biobehavioral Research.*

1974: National Research Act (P.L. 93-348). *"The Secretary shall by regulation require that each entity that applies for a grant or contract... submit assurances that it has established... a board (to be known as an* ***Institutional Review Board****) to review biomedical and behavioral research involving human subjects."*

1975: Helsinki II. *A revision of the 1964 Helsinki Declaration -- the International Code of Ethics for Biomedical Research. "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."*

1979: The Belmont Report: *Ethical Guidelines for the Protection of Human Subjects of Research published. It identified three basic principles of ethical research -- respect for persons, beneficence and justice.*

1981: Code of Federal Regulations 45 CFR 46: Protection of Human Subjects. *"Basic" regulations governing human subjects research became final on January 16, 1981. Revised in 1983, and 1991 it sets standards for the protection of human research subjects, including additional protections pertaining to research involving fetuses, pregnant women, and in vitro fertilization; prisoners as medical subjects; and children as subjects in research.*

1982: Proposed International Guidelines for Biomedical Research Involving Human Subjects. *Issued by the CIOMS, these are guidelines for the application, particularly in developing countries, of the principles of the Declaration of Helsinki (Revised in 1992).*

1986: "Decision Making About Human Subjects Review Requirements" Guidelines. *Revision of Human Subjects Review process at CDC, Atlanta. Investigations to determine the cause or extent of a current health problem in the community are "the public health equivalent of individual doctor-patient situations" and do not require IRB approval. However, "adequate care should be taken to protect the rights and welfare of individuals involved."*

1991: International Guidelines for Ethical Review of Epidemiological Studies. *CIOMS, Geneva. "The requirement that proposals for epidemiological studies be submitted to independent ethical review applies irrespective of the source of the proposals -- academic, governmental, health-care, commercial or other."*

1991: Common Federal Policy for the Protection of Human Subjects. *Sets forth as a "Common Rule" the requirements for the protection of human subjects (extending ethical standards established in 45 CFR 46 to other departments and agencies of the federal government).*

1993: International Guidelines for Biomedical Research Involving Human Subjects. *Released by CIOMS. Final revision of 1982 guidelines.*

Among the documents cited, the Helsinki Declaration and the Belmont Report bear certain similarities since they identify the general principles that govern ethical research. The International Guidelines and Federal Code, on the other hand, identify specifics derived from those principles -- for example, the nature and composition of IRBs. The full texts of the Belmont Report, the Code of Federal Regulations 45 CFR 46, and the CIOMS Guidelines are included as appendices to this document.

For much of the life of the ACSI-CCCD Project, the international consensus regarding research was relatively ill-defined. Although, in general, there was clear agreement on underlying principles, there was generally less familiarity in individual countries with how these principles should be embodied in practice (for example, the nature and composition of IRBs, protection of vulnerable populations, and standards for informed consent).

6.2 Implications for Collaborative and Sponsored Research

In developing country research, there is often more agreement on ethical principles than on the logistical issues relating to the implementation of ethical standards. In the ACSI-CCCD experience, a number of practical issues arose that are relevant to similar programs. In general, these were related to three main areas: 1) the composition and functioning of IRBs, 2) delays and logistical problems in the review process, and 3) the intrusion of political considerations into "the scientific arena."

When the CCCD operational research component was initially proposed, provision of a local mechanism for ethical review was clearly identified as a priority. The mechanism proposed was that "authorization be obtained" for the regional research review committees to serve as branches of the CDC IRB. In the interim, proposals would be required to undergo institutional review at CDC before being funded. Incorporating ethical review into the research review committees proved problematic mainly because of the stipulated membership requirements of IRBs.

In the case of the ACSI-CCCD Project, the attempt to make the review committee responsible for both technical review and ethical review was a departure from the norm. The more common arrangement in industrial countries is for technical review to be carried out by one body and ethical review by another (after the study has passed technical review).

In general, many ACSI-CCCD projects fell within the categories of **"exempt" research** (e.g., routine questionnaire surveys not addressing sensitive or confidential issues and not collecting personal identifiers; e.g., retrospective record reviews not involving personal identifiers) or were **"minimal risk" studies**, qualified for **"expedited review"** (no significant risks or confidentiality concerns).

> **Exempt research:** This is research that does not require any institutional ethical review. For U.S.-supported research, the categories are defined by U.S. federal regulations, and include 1) research in educational settings involving normal educational practices; 2) educational testing; 3) research involving survey or interview procedures, except when the responses deal with sensitive personal behavior, are potentially damaging to the individual and are recorded in such a way that the individuals can be identified; 4) research involving observation of public behavior; and 5) research involving the study of existing, publicly available data.

Minimal risk studies: Such studies do not meet the conditions of exempt research. However, because they entail little additional risk, they generally do not have to be reviewed by the entire IRB, and can usually be reviewed by an expedited process.

One of the more important functions of institutional review applies where new information becomes available during the course of a study. Whether this information comes from the study itself or from other sources, it is the investigator's responsibility to bring this information to the attention of the IRB if it is likely to have a bearing on the risks or benefits of a study. In this respect, IRB permission to conduct a specific study is always subject to review if circumstances change.

This has happened on a few occasions in ACSI-CCCD. In one instance, amodiaquine was dropped from a clinical trial evaluating chemoprophylactic agents in pregnancy, following published reports of adverse effects. In a contrasting example, a trial of vitamin A in measles was discontinued when strong evidence of the intervention's effectiveness was suggested by published reports. In this case the question was whether it was ethical to *withhold* the beneficial intervention from the controls, rather than one of *submitting* subjects to an adverse intervention. In both circumstances, proper ethical review of the changing circumstances required premature termination of the research. Each of these instances provided useful experiences for counterparts.

In a small number of cases, political concerns also influenced what research could be undertaken. One limitation commonly imposed was on the handling of blood samples. A small (but significant) number of projects had to be aborted because countries that did not have specific local laboratory capabilities would not allow blood samples to be taken out of country. When the results of such studies represented important information for programmatic decisions, these limitations presented an interesting ethical dilemma -- a choice between decision making with incomplete data and respect of sovereignty. In reality, the question was largely academic, because the CCCD project was required to always respect the wishes of host governments in such matters. But in a larger sense, a project may occasionally have to decide whether limitations on its objectivity or ability to operate are of a nature that interferes substantially with its scientific mission.

In the CCCD experience, difficulties were most often caused when clear standards did not exist or were not known beforehand. This suggests that identification of such norms and limitations should be a priority for researchers in international collaborations, particularly in situations where a country's concerns and sensitivities are predictable (for example, with respect to AIDS-related research).

6.3 Publication and Authorship

Ethical protections that address the rights of research subjects are now a fairly well-established convention, both in the United States and internationally. Ethical protections that address the rights and responsibilities of researchers are less well established.

What are some of the concerns in question? In 1989, the Institute of Medicine (IOM) in Washington D.C., largely in response to some well-publicized instances of scientific misconduct and fraud, issued a committee report, **The Responsible Conduct of Research in the Health Sciences** (IOM, 1989). Unlike the previously mentioned reports, which dealt largely with human subjects, this one addressed the conduct of researchers themselves. It noted that most universities and research institutions depended on a system of "self-regulation... and individual researchers' professional standards" to

ensure ethical conduct. It found that few universities or academic institutions had any explicit standards for responsible research practices. Formal oversight was also rare. Moreover, the IOM found that research communities as a whole generally tolerated "too many substandard practices." Finally, this group identified several real and potential areas of abuse. One was that "pressure to publish" and emphasis on the number of publications (rather than their quality) have generally given rise to a number of questionable practices including:

- "honorary authorship" or "gift authorship";
- repetitive publication of short-term research results;
- fragmenting studies into many parts resulting in "multiple, overlapping and trivial papers";
- neglect of young researchers by peers and mentors;
- inadequate training and supervision; and
- sequestering or withholding of research data from peers and colleagues.

The IOM report also cited a number of "distasteful" practices that compromise research integrity even though they may not constitute actual misconduct. These include:

- misuse of statistics,
- selective interpretation of data,
- incomplete acknowledgment of contributions from colleagues or trainees, and
- incomplete or inaccurate publication.

In its conclusions, the IOM report infers that sloppy or careless research policy and practices may, in the long run, cause more damage than deliberate fraud or misconduct. Among the IOM's findings, two stand out as particularly relevant to international collaborations. The first concerns inadequate training and supervision. Although, in the CCCD experience, limited training and supervision were more consequences of geography and limited personnel resources than pressure to publish, the report does point out that inadequate supervision and monitoring during the implementation phase of a study can lead to sloppy or fraudulent data. The IOM places the responsibility for this squarely on the sponsors of research and supervisors, rather than on researchers. The second concern relates to authorship. To its credit, the ACSI-CCCD Project (and the CDC divisions involved) did have an informal policy by which the principal collaborating scientist for a research project generally had to be cited as a co-author if a CDC principal was first author. However, because of the nature of the CCCD Project itself, there generally was at least one counterpart scientist (whether a researcher or program manager) who had substantive input into the planning, development, or execution of in-country research. In some instances the project went further. In the case of supported malaria research, for example, CDC's Malaria Branch actively encouraged in-country researchers to assume first authorship of many of its publications. Of 56 malaria-related publications, 22 list Africans as first authors (including the main chloroquine-resistance studies done in Malawi, Nigeria, Zaire, and Côte d'Ivoire); 16 others list an African as second or third author.

Among the specific recommendations of the IOM report, a number are probably relevant to the ACSI-CCCD experience and similar programs of collaborative research:

> **Formal guidelines on ethical research.** Such guidelines should be developed, including specifications for retention of primary data (3 years is the usual suggestion), standards for training and supervision, and specific policies and procedures for responding to allegations of misconduct.

Formal authorship policies. Authorship credit should be based only on substantial contributions to ALL of the following: (a) conception and design, or analysis and interpretation of data; (b) drafting the manuscript or revising it critically for important intellectual content; and (c) final concurrence with the version published (International Committee of Medical Journal Editors, 1988). These recommendations are already part of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

A reassessment of institutional rewards for publication. This was proposed with the intention of decreasing the importance of the *number* of publications in professional advancement, and increasing the relative value of research "quality."

CHAPTER 7

CONCLUSIONS

This review was able to identify a number of specific strengths of the ACSI-CCCD program of research, as well as a few limitations and weaknesses.

7.1 General Conclusions

1. The program of research was able to fulfill its two main objectives: solving problems impeding the achievement of project goals, and building African research capacity.

2. African researchers generally appreciated the opportunity afforded to collaborate with foreign "experts." This process was effective and operated well in practice. It also compared favorably with other bilateral and multilateral funded research. There also seemed to be a consensus that the country counterparts did have a significant input into the formulation stage of defining and developing research topics.

3. There were several specific advantages of the mechanism that the ACSI-CCCD Project used in conducting research. These included the following: 1) generally close cooperation with the MOH; 2) responsiveness of research to specific policy questions; 3) generally very good communication lines between programs and the persons determining the appropriate priorities for research; 4) generally good communications between different vertical programs (e.g., EPI and malaria) through regular staff meetings (under the umbrella of CCCD); and 5) a "problem-oriented" approach to research, allowing direct links to implementation and application of results.

4. Logistically, a major advantage of the CCCD program was the ability of in-country personnel to make decisions on funding of research.

5. There was appreciable transfer of skills as a result of the programs of applied research carried out within the ACSI-CCCD Project.

6. The greatest perceived benefit of CCCD research was in improving the ability of MOHs to use data from all sources (surveillance, research, or routine monitoring) more effectively.

7.2 Research Agendas and Priority Setting

1. Most countries in which CCCD had bilateral projects did not have a clear research agenda to determine specific research priorities. Health research was frequently undertaken on an *ad hoc* basis often determined by the availability of donor funds.

2. ACSI-CCCD assistance helped identify specific program issues that could be addressed by targeted research.

3. It was generally easier to identify specific research priorities in CCCD because, in general, the same team of persons was engaged in program implementation and service delivery as was involved in selecting appropriate topics for research.

4. The ability of the ACSI-CCCD to set a meaningful research agenda was enhanced by the availability of resources with which to carry out priority research.

7.3 Usefulness of Research -- Its Impact on Policy and Practices

1. There was a broad consensus that the results of CCCD research were practical and useful to programs.

2. African counterparts most often cited examples of country-specific, problem-based research as applications of CCCD research that were most useful to their programs.

3. The usefulness of research initiated under the review committee mechanism and its potential for program impact were often limited by uneven quality and lack of wide dissemination.

4. The direct effect of research findings on programs or policy was often tempered by political or social considerations. Although research recommendations did not always have the desired outcome, researchers and program administrators remained strongly committed to the research process.

5. Although research-based policy changes have been encouraging, there has not always been a corresponding change in actual practices at the peripheral level.

7.4 Capacity Building

1. The role of CCCD in capacity building was generally greatest in developing individual research capacity. CCCD's role in strengthening institutional capacity was more limited.

2. Institutional benefit to MOHs was generally greater than to academic institutions.

3. Individually, a number of countries did generate compelling benefits to academic institutions through collaborative research. This was probably greatest in Nigeria and Zaire.

4. Institutional benefits were generally twofold -- supporting a framework for research and providing supplies and materials.

5. A specific benefit of ACSI-CCCD to program managers and ministries of health was its role in "demystifying" research and creating an environment that fostered decision making based on "hard data." The use of research as a management tool had both individual and institutional benefits.

6. The role of research capacity building was sometimes subsumed into the immediate need for producing data or results for the ACSI-CCCD Project, particularly where studies were needed to address specific obstacles to program effectiveness.

7.5 Mechanisms

1. "Mentoring" through research collaborations has generally proven to be the most consistent mechanism for research capacity building in large and small countries.

2. The impact of the review committee mechanism as a means to promote research has been mixed. It is probably most suitable for larger countries with fairly well-established academic communities.

3. Drawbacks associated with the research committee process include problems ensuring adequate supervision and guidance for projects, uneven research quality, and inadequate dissemination.

4. There are a number of logistical problems that make regional coordination of research difficult. This mechanism is most likely to be effective if supported by a strong regional body and ongoing means to sustain it.

7.6 Operational Issues and Concerns

1. Differing priorities between funding agencies and developing countries were acknowledged by most counterparts, but were not generally seen as insurmountable obstacles.

2. Research projects were most likely to gain ready acceptance by counterparts when they dealt with clearly identified priorities of the MOH or individual programs. However, even when there was not a clear link between immediate program goals and research, acceptance was favored by involving country counterparts at an early stage of the project's development.

3. Projects were least likely to gain acceptance when they were introduced as an accomplished fact, when they did not have clear and direct links to existing programs, and when there was an imbalance between the levels of participation of foreign consultants and local investigators.

7.7 Follow-up and Continuity

1. The consensus among program counterparts was that CCCD had proven itself, not only in terms of research but also in product delivery and program support.

2. There was equal concern, in view of this success, about the ending of the regional CCCD Project.

3. Although the CCCD Project achieved significant gains in program support, it was generally recognized that longer term strategic planning, and active rather than reactive engagement, required that significant local capacity be in place. In general, the project had not fully achieved this at the time it ended.

4. In general, participants in ACSI-CCCD research from all perspectives saw the continuing need for a program of technical assistance in research (problem-based research, in particular). It was generally believed that this should be multidisciplinary, include significant in-country support, allow for regional initiatives (to address problems of interest to more than one country), and incorporate longer term training to a more substantial degree than pursued by CCCD.

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APPENDIX 1.

THE BELMONT REPORT

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

April 18, 1979

SUMMARY

On July 12, 1974, the National Research Act (Pub. L. 93-348) was signed into law, there-by creating the **National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.** One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles. In carrying out the above, the Commission was directed to consider:

(i) the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine,

(ii) the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects,

(iii) appropriate guidelines for the selection of human subjects for the participation in such research and

(iv) the nature and definition of informed consent in various research settings.

The Belmont Report attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations. It is the outgrowth of an intensive four-day period of discussions that were held in February 1976 at the Smithsonian Institution's Belmont Conference Center supplemented by the monthly deliberations of the Commission that were held over a period of nearly four years. It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects. By publishing the Report in the Federal Register, and providing reprints upon request, the Secretary intends that it may be made readily available to scientists, members of Institutional Review Boards, and Federal employees. The two-volume Appendix, containing the lengthy reports of experts and specialists who assisted the Commission in fulfilling this part of its charge, is available as DHEW Publication No. (OS) 78-0014, for sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

Unlike most other reports of the Commission, the Belmont Report does not make specific recommendations for administrative action by the Secretary of Health, Education, and Welfare. Rather, the Commission recommended that the Belmont Report be adopted in its entirety, as a statement of the Department's policy. The Department requests public comment on this recommendation.

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Ethical Principles and Guidelines for Research Involving Human Subjects

Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime Trials, the Nuremberg code was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype of many later codes[1] intended to assure that research involving human subjects would be carried out in an ethical manner.

The codes consist of rules, some general, others specific, that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted.

Three principles, or general prescriptive judgments, that are relevant to research involving human subjects are identified in this statement. Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects. These principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.

This statement consists of a distinction between research and practice, a discussion of the three basic ethical principles, and remarks about the application of these principles.

A. Boundaries Between Practice and Research

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called "experimental" when the terms "experimental" and "research" are not carefully defined.

For the most part, the term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals.[2] By contrast, the term "research" designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The face that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project.[3]

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

B. Basic Ethical Principles

The expression **"basic ethical principles"** refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect for persons, beneficence and justice.

1. *Respect for Persons*. Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.

However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequences. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

2. ***Beneficence***. Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm and (2) maximize possible benefits and minimize possible harms.

The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of

obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients "according to their best judgment." Learning what will in fact benefit may require exposing persons to risk. The problem posed by these imperatives it to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures.

The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children—even when individual research subjects are not direct beneficiaries. Research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that presents more than minimal risk without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

3. ***Justice***. Who ought to receive the benefits of research and bear is burdens? This is a question of justice, in the sense of "fairness in distribution" or "what is deserved." An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property on the basis of which burdens and benefits should be distributed. These formulations are (1) to each person an equal share, (2) to each person according to individual need, (3) to each person according to individual effort, (4) to each person according to societal contribution, and (5) to each person according to merit.

Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently these questions have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularly flagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project, long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised positions,

or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

C. Applications

Applications of the general principles to the conduct of research leads to consideration of the following requirements: informed consent, risk/benefit assessment, and the selection of subjects of research.

1. ***Informed Consent***.—Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied.

While the importance of informed consent is unquestioned, controversy prevails is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

Information. Most codes of research establish specific items for disclosure intended to assure that subjects are given sufficient information. These items generally include: the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc.

However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care. It may be that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary or their care not perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.

A special problem of consent arises where informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to indicate to subjects that they are being invited to participate in research of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified only if it is clear that (1) incomplete disclosure is truly necessary to accomplish the goals of the research, (2) there are no undisclosed risks to subjects that are more than minimal, and (3) there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator.

* ***Comprehension***. The manner and context in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice.

Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities. Investigators are responsible for ascertaining that the subject has comprehended the information. While there is always an obligation to ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension.

Special provision may need to be made when comprehension is severely limited—for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (e.g., infants and young children, mentally disabled patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.

The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest.

* ***Voluntariness***. An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable.

Unjustifiable pressures usually occur when persons in positions of authority or commanding influence — especially where possible sanctions are involved — urge a course of action for a subject. A continuum of such influencing factors exists, however, and it is impossible to state precisely where justifiable persuasion ends and undue influence begins. But undue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitled.

2. ***Assessment of Risks and Benefits***.—The assessment of risks and benefits requires a careful arrayal of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

The Nature and Scope of Risks and Benefits. The requirement that research be justified on the basis of a favorable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons. The term "risk" refers

to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm.

The term **"benefit"** is used in the research context to refer to something of positive value related to health or welfare. Unlike "risk," "benefit" is not a term that expresses probabilities. Risk is properly contrasted with harms rather than risks of harm. Accordingly, so-called risk/benefit assessments are concerned with the probabilities and magnitudes of possible harms and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm, and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked.

Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society). Previous codes and Federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society if the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interest other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research.

The Systematic Assessment of Risks and Benefits. It is commonly said that benefits and risks must be "balanced" and shown to be "in a favorable ratio." The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the following considerations: (i) Brutal or inhumane treatment of human subjects is never morally justified. (ii) Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures. (iii) When research involved significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject—or, in some rare cases, to the manifest voluntariness of the participation). (iv) When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits. (v) Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

3. ***Selection of Subjects.***— Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.

Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research on to some patients who are in their favor or select only "undesirable" persons for risky research. **Social justice** requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators and treated fairly in the course of research. Thus injustice arises from social, racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if IRBs are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting, they can consider **distributive justice** in selecting research subjects.

Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research subjects if more advantaged populations are likely to be the recipients of the benefits

One special instance of injustice, results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

Notes:

[1]Since 1945, various codes for the proper and responsible conduct of human experimentation in medical research have been adopted by different organizations. The best known of these codes are the Nuremberg Code of 1947, the Helsinki Declaration of 1964 (revised in 1975), and the 1971 Guidelines (codified into Federal Regulations in 1974) issued by the U.S. Department of Health, Education, and Welfare Codes for the conduct of social and behavioral research have also been adopted, the best known being that of the American Psychological Association, published in 1973.

[2]Although practice usually involves interventions designed solely to enhance the well-being of a particular individual, interventions are sometimes applied to one individual for the enhancement of the well-being of another (e.g., blood donation, skin grafts, organ transplants) or an intervention may have the dual purpose of enhancing the well-being of a particular individual, and, at the same time, providing some benefit to others (e.g., vaccination, which protects both the person who is vaccinated and society generally). The fact that some forms of practice have elements other than immediate benefit to the individual receiving an intervention, however, should not confuse the general distinction between research and practice. Even when a procedure applied in practice may benefit some other person, it remains an intervention designed to enhance the well-being of a particular individual or groups of individuals; thus, it is practice and need not be reviewed as research.

[3]Because the problems related to social experimentation may differ substantially from those of biomedical and behavioral research, the Commission specifically declines to make any policy determination regarding such research at this time. Rather, the Commission believes that the problem ought to be addressed by one of its successor bodies.

APPENDIX 2.

PROTECTION OF HUMAN SUBJECTS

CODE OF FEDERAL REGULATIONS
45 CFR 46

Revised as of March 8, 1983

PART 46——PROTECTION OF HUMAN SUBJECTS

Subpart A——Basic HHS Policy for Protection of Human Research Subjects

Sec.

Subpart B——Additional Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women, and Human In Vitro Fertilization

Sec.

Subpart C——Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

Sec.

Subpart D——Additional Protections for Children Involved as Subjects in Research

Sec.

Authority: 5 U.S.C. 301; sec. 474(a), 88 Stat. 352 (42 U.S.C. 2891-3(a)).

Subpart A——Basic HHS Policy for Protection of Human Research Subjects

Source: 46 FR 8386, January 26, 1981, 48 FR 9269, March 4, 1983.

§ 46.101 To what do these regulations apply?

(a) Except as provided in paragraph (b) of this section, this subpart applies to all research involving human subjects conducted by the Department of health and Human Services or funded in whole or in part by a Department grant, contract, cooperative agreement or fellowship.

(1) This includes research conducted by Department employees, except each Principal Operating Component head may adopt such nonsubstantive, procedural modifications as may be appropriate from an administrative standpoint.

(2) It also includes research conducted or funded by the Department of Health and Human Services outside the United States, but in appropriate circumstances, the Secretary may, under paragraph (e) of this section waive the applicability of some or all of the requirements of these regulations for research of this type.

(b) Research activities in which the only involvement of human subjects will be in one or more of the following categories are **exempt** from these regulations unless the research is covered by other subparts of this part:

(1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), if information taken from these sources is recorded in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

(3) Research involving survey or interview procedures, except where all of the following conditions exist: (i) responses are recorded in such a manner that the human subjects can be identified, directly or through identifiers linked to the subjects, (ii) the subject's responses, if they became known outside the research, could reasonably place the subject at risk of criminal or civil liability or be damaging to the subject's financial standing or employability, and (iii) the research deals with sensitive aspects of the subject's own behavior, such as illegal conduct, drug use, sexual behavior, or use of alcohol. All research involving survey or interview procedures is exempt, without exception, when the respondents are elected or appointed public officials or candidates for public office.

(4) Research involving the observation (including observation by participants) of public behavior, except where all of the following conditions exist: (i) observations are recorded in such a manner that the human subjects can be identified, directly or through identifiers linked to the subjects, (ii) the observations recorded about the individual, if they became known outside the research, could reasonably place the subject at risk of criminal or civil liability or be damaging to the subject's financial standing or employability, and (iii) the research deals with sensitive aspects of the subject's own behavior such as illegal conduct, drug use, sexual behavior, or use of alcohol.

(5) Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

(6) Unless specifically required by statute (and except to the extent specified in paragraph (i)), research and demonstration projects which are conducted by or subject to the approval of the Department of Health and Human Services, and which are designed to study, evaluate, or otherwise examine: (i) programs under the Social Security Act, or other public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.

(c) The Secretary has final authority to determine whether a particular activity is covered by these regulations.

(d) The Secretary may require that specific research activities or classes of research activities conducted or funded by the Department, but not otherwise covered by these regulations, comply with some or all of these regulations.

(e) The Secretary may also waive applicability of these regulations to specific research activities or classes of research activities, otherwise covered by these regulations. Notices of these actions will be published in the *Federal Register* as they occur.

(f) No individual may receive Department funding for research covered by these regulations unless the individual is affiliated with or sponsored by an institution which assumes responsibility for the research under an assurance satisfying the requirements of this part, or the individual makes other arrangements with the Department.

(g) Compliance with these regulations will in no way render inapplicable pertinent federal, state, or local laws or regulations.

(h) Each subpart of these regulations contains a separate section describing to what the subpart applies. Research which is covered by more than one subpart shall comply with all applicable subparts.

(i) If, following review of proposed research activities that are exempt from these regulations under paragraph (b)(6), the Secretary determines that a research or demonstration project presents a danger to the physical, mental, or emotional well-being of a participant or subject of the research or demonstration project, then federal funds may not be expended for such a project without the written, informed consent of each participant or subject.

§ 46.102 Definitions.

(a) "Secretary" means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom authority has been delegated.

(b) "Department" or "HHS" means the Department of Health and Human Services.

(c) "Institution" means any public or private entity or agency (including federal, state, and other agencies).

(d) "Legally authorized representative" means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

(e) **"Research" means a systematic investigation designed to develop or contribute to generalizable knowledge.** Activities which meet this definition constitute "research" for purposes of these regulations, whether or not they are supported or funded under a program which is considered research for other purposes. For example, some "demonstration" and "service" programs may include research activities.

(f) **"Human subject"** means a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information. **"Intervention"** includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. **"Interaction"** includes communication or interpersonal contact between investigator and subject. "Private information" includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identify of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

*(g) **"Minimal risk"** means that the risks of harm anticipated in the proposed research are not greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

(h) **"Certification"** means the official notification by the institution to the Department in accordance with the requirements of this part that a research project or activity involving human subjects has been reviewed and approved by the Institutional Review Board (IRB) in accordance with the approved assurance on file at HHS. (Certification is required when the research is funded by the Department and not otherwise exempt in accordance with § 46.101(b)).

§ 46.103 Assurances.

(a) Each institution engaged in research covered by these regulations shall provide written assurance satisfactory to the Secretary that it will comply with the requirements set forth in these regulations.

(b) The Department will conduct or fund research covered by these regulations only if the institution has an assurance approved as provided in this section, and only if the institution has certified to the Secretary that the research has been reviewed and approved by an IRB provided for in the assurance, and will be subject to continuing review by the IRB. This assurance shall at a minimum include:

(1) A statement of principles governing the institution in the discharge of its responsibilities for protecting the rights and welfare of human subjects of research conducted at or sponsored by the institution, regardless of source of funding. This may include an appropriate existing code, declaration, or statement of ethical principles, or a statement formulated by the institution itself. This requirement does not preempt provisions of these regulations applicable to Department-funded research and is not applicable to any research in an exempt category listed in § 46.101.

(2) Designation of one or more IRBs established in accordance with the requirements of this subpart, and for which provisions are made for meeting space and sufficient staff to support the IRB's review and recordkeeping duties.

(3) A list of the IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, member of governing panel or board, stockholder, paid or unpaid consultant. Changes in IRB membership shall be reported to the Secretary.[1]

(4) Written procedures which the IRB will follow (i) for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (ii) for determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; (iii) for insuring prompt reporting to the IRB of proposed changes in a research activity, and for insuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the subject; and (iv) for insuring prompt reporting to the IRB and to the Secretary[1] of unanticipated problems involving risks to subjects or others.

(c) The assurance shall be executed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by these regulations, and shall be filed in such form and manner as the Secretary may prescribe.

(d) The Secretary will evaluate all assurances submitted in accordance with these regulations through such officers and employees of the Department and such experts or consultants engaged for this purpose as the Secretary determines to be appropriate. The Secretary's evaluation will take into consideration the adequacy of the proposed IRB in light of the anticipated scope of the institution's research activities and the types of subject populations likely to be involved, the appropriateness of the proposed initial and continuing review procedures in light of the probable risks, and the size and complexity of the institution.

(e) On the basis of this evaluation, the Secretary may approve or disapprove the assurance, or enter into negotiations to develop an approvable one. The Secretary may limit the period during which any particular approved assurance or class of approved assurances shall remain effective or otherwise condition or restrict approval.

(f) Within 60 days after the date of submission to HHS of an application or proposal, an institution with an approved assurance covering the proposed research shall certify that the application or proposal has been reviewed and approved by the IRB. Other institutions shall certify that the application or proposal has been approved by the IRB within 30 days after receipt of a request for such a certification from the Department. If the certification is not submitted within these time limits, the application or proposal may be returned to the institution.

§ 46.107 IRB membership.

(a) Each IRB shall **have at least five members, with varying backgrounds** to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members' backgrounds including consideration of the racial and cultural backgrounds of members and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, including but

not limited to subjects covered by other subparts of this part, the IRB shall include one or more individuals who are primarily concerned with the welfare of these subjects.

(b) No IRB may consist entirely of men or entirely of women, or entirely of members of one profession.

(c) Each IRB shall include at least one member whose primary concerns are in nonscientific areas; for example: lawyers, ethicists, members of the clergy.

(d) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

(e) No IRB may have a member participating in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

(f) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of complex issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

§ 46.108 IRB functions and operations.

In order to fulfill the requirements of these regulations each IRB shall:

(a) Follow written procedures as provided in § 46.103(b)(4).

(b) Except when an expedited review procedure is used (see § 46.110), review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting.

(c) Be responsible for reporting to the appropriate institutional officials and the Secretary[1] any serious or continuing noncompliance by investigators with the requirements and determinations of the IRB.

§ 46.109 IRB review of research.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by these regulations.

(b) An IRB shall require that information given to subjects as part of informed consent is in accordance with § 46.116. The IRB may require that information, in addition to that specifically mentioned in § 46.116, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.

(c) An IRB shall require documentation of informed consent or may waive documentation in accordance with § 46.117.

(d) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

(e) An IRB shall conduct continuing review of research covered by these regulations at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.

§ 46.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

(a) The Secretary has established, and published in the *Federal Register*, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list will be amended, as appropriate, through periodic republication in the *Federal Register*.

(b) An IRB may review some or all of the research appearing on the list through an expedited review procedure, if the research involves no more than minimal risk. The IRB may also use the expedited review procedure to review minor changes in previously approved research during the period for which approval is authorized. **Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson** from among members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure set forth in § 46.108(b).

(c) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

(d) The Secretary may restrict, suspend, or terminate an institution's or IRB's use of the expedited review procedure when necessary to protect the rights or welfare of subjects.

§ 46.111 Criteria for IRB approval of research.

(a) In order to approve research covered by these regulations the IRB shall determine that all of the following requirements are satisfied:

(1) **Risks to subjects are minimized:** (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) **Risks to subjects are reasonable in relation to anticipated benefits,** if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). **The IRB should not consider possible long-range effects of applying knowledge gained in the research** (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) **Selection of subjects is equitable.** In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted.

(4) **Informed consent will be sought** from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by § 46.116.

(5) **Informed consent will be appropriately documented** in accordance with, and to the extent required by § 46.117.

(6) Where appropriate, the research plan makes **adequate provision for monitoring the data collected to insure the safety of subjects.**

(7) Where appropriate, there are adequate **provisions to protect the privacy of subjects and to maintain the confidentiality of data.**

(b) Where some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as persons with acute or severe physical or mental illness, or persons who are economically or educationally disadvantaged, appropriate additional safeguards have been included in the study to protect the rights and welfare of these subjects.

§ 46.112 Review by institution.

Research covered by these regulations that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

§ 46.113 Suspension or termination of IRB approval of research.

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the Secretary.[1]

§ 46.114 Cooperative research.

Cooperative research projects are those projects, normally supported through grants, contracts, or similar arrangements, which involve institutions in addition to the grantee or prime contractor (such as a contractor with the grantee, or a subcontractor with the prime contractor). In such instances, the grantee or prime contractor remains responsible to the Department for safeguarding the rights and welfare of human subjects. Also, when cooperating institutions conduct some or all of the research involving some or all of these subjects, each cooperating institution shall comply with these regulations as though it received funds for its participation in the project directly from the Department, except that in complying with these regulations institutions may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort.

§ 46.115 IRB records.

(a) An institution, or where appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:

(1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.

(2) Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB, the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.

(3) Records of continuing review activities.

(4) Copies of all correspondence between the IRB and the investigators.

(5) A list of IRB members as required by § 46.103(b)(3).

(6) Written procedures for the IRB as required by § 46.103(b)(4).

(7) Statements of significant new findings provided to subjects, as required by § 46.103(b)(5).

(b) The records required by this regulation shall be **retained for at least 3 years after completion of the research,** and the records shall be accessible for inspection and copying by authorized representatives of the Department at reasonable times and in a reasonable manner.

§ 46.116 General requirements* for informed consent.

Except as provided elsewhere in this or other subparts, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

(a) Basic elements of informed consent. Except as provided in paragraph (c) or (d) of this section, in seeking informed consent the following information shall be provided to each subject:

(1) **A statement that the study involves research,** an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;

(2) A **description of any reasonably foreseeable risks** or discomforts to the subject;

(3) **A description of any benefits** to the subject or to others which may reasonably be expected from the research;

(4) A **disclosure of appropriate alternative procedures** or courses of treatment, if any, that might be advantageous to the subject;

(5) A statement describing the extent, if any, to which **confidentiality** of records identifying the subject will be maintained;

(6) For research involving more than minimal risk, an explanation as to whether any **compensation** and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

(7) An explanation of whom to contact for **answers to pertinent questions** about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and

(8) **A statement that participation is voluntary,** refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;

(3) Any additional costs to the subject that may result from participation in the research;

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and

(6) The approximate number of subjects involved in the study.

(c) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent provided the IRB finds and documents that:

(1) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) programs under the Social Security Act, or other public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and

(2) The research could not practicably be carried out without the waiver or alteration.

(d) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

(1) The research involves no more than minimal risk to the subjects;

(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;

(3) The research could not practicably be carried out without the waiver or alteration; and

(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

(e) The informed consent requirements in these regulations are not intended to preempt any applicable federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.

(f) Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state, or local law.

§ 46.117 Documentation of informed consent.

(a) Except as provided in paragraph (c) of this section, informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person singing the form.

(b) Except as provided in paragraph (c) of this section, the consent form may be either of the following:

(1) A written consent document that embodies the elements of informed consent required by § 46.116. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed; or

(2) A "short form" written consent document stating that the elements of informed consent required by § 46.116 has been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the "short form."

(c) An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:

(1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or

(2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

In cases where the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

§ 46.118 Applications and proposals lacking definite plans for involvement of human subjects.

Certain types of applications for grants, cooperative agreements, or contracts are submitted to the Department with the knowledge that subjects may be involved within the period of funding, but definite plans would not normally be set forth in the application or proposal. These include activities such as institutional type grants (including bloc grants) where selection of specific projects is the institution's responsibility; research training grants where the activities involving subjects remain to be selected; and projects in which human subjects' involvement will depend upon completion of instruments, prior animal studies, or purification of compounds. These applications need not be reviewed by an IRB before an award may be made. However, except for research described in § 46.101(b), no human subjects may be involved in any project supported by these awards until the project has been reviewed and approved by the IRB, as provided in these regulations, and certification submitted to the Department.

§ 46.119 Research undertaken without the intention of involving human subjects.

In the event research (conducted or funded by the Department) is undertaken without the intention of involving human subjects, but it is later proposed to use human subjects in the research, the research shall first be reviewed and approved by an IRB, as provided in these regulations, a certification submitted to the Department, and final approval given to the proposed change by the Department.

§ 46.120 Evaluation and disposition of applications and proposals.

(a) The Secretary will evaluate all applications and proposals involving human subjects submitted to the Department through such officers and employees of the Department and such experts and consultants as the Secretary determines to be appropriate. This evaluation will take into consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the proposed research to the subjects and others, and the importance of the knowledge to be gained.

(b) On the basis of this evaluation, the Secretary may approve or disapprove the application or proposal, or enter into negotiations to develop an approvable one.

§ 46.121 Investigational new drug or device 30-day delay requirement.

When an institution is required to prepare or to submit a certification with an application or proposal under these regulations, and the application or proposal involves an investigational new drug (within the meaning of 21 U.S.C. 355(i) or 357(d)) or a significant risk device (as defined in 21 CFR 812.3(m)), the institution shall identify the drug or device in the certification. The institution shall also state whether the 30-day interval required for investigational new drugs by 21 CFR 312.1(a) and for significant risk devices by 21 CFR 812.30 has elapsed, or whether the Food and Drug Administration has waived that requirement. If the 30-day interval has expired, the institution shall state whether the Food and Drug Administration has requested that the sponsor continue to withhold or restrict the use of the drug or device in human subjects. If the 30-day interval has not expired, and a waiver has not been received, the institution shall send a statement to the Department upon expiration of the interval. The Department will not consider a certification acceptable until the institution has submitted a statement that the 30-day interval has elapsed, and the Food and Drug Administration has not requested it to limit the use of the drug or device, or that the Food and Drug Administration has waived the 30-day interval.

§ 46.122 Use of federal funds.

Federal funds administered by the Department may not be expended for research involving human subjects unless the requirement of these regulations, including all subparts of these regulations, have been satisfied.

§ 46.123 Early termination of research funding: evaluation of subsequent applications and proposals.

(a) The Secretary may require that Department funding for any project be terminated or suspended in the manner prescribed in applicable program requirements, when the Secretary finds an institution has materially failed to comply with the terms of these regulations.

(b) In making decisions about funding applications or proposals covered by these regulations the Secretary may take into account, in addition to all other eligibility requirements and program criteria, factors such as whether the applicant has been subject to a termination or suspension under paragraph (a) of this section and whether the applicant or the person who would direct the scientific and technical aspects of an activity has in the judgment of the Secretary materially failed to discharge responsibility for the protection of the rights and welfare of human subjects (whether or not Department funds were involved).

§ 46.124 Conditions.

With respect to any research project or any class of research projects the Secretary may impose additional conditions prior to or at the time of funding when in the Secretary's judgment additional conditions are necessary for the protection of human subjects.

Subpart B——Additional Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women, and Human in Vitro Fertilization

Source: 40 FR 33528, Aug. 8, 1975, 43 FR 1758, January 11, 1978, 43 FR 51559, November 3, 1978

§ 46.201 Applicability.

(a) The regulations in this subpart are applicable to all Department of Health, Education, and Welfare grants and contract supporting research, development, and related activities involving: (1) The fetus, (2) pregnant women, and (3) human *in vitro* fertilization.

(b) Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will in any way render inapplicable pertinent State or local laws bearing upon activities covered by this subpart.

(c) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

§ 46.202 Purpose.

It is the purpose of this subpart to provide additional safeguards in reviewing activities to which this subpart is applicable to assure that they conform to appropriate ethical standards and relate to important societal needs.

§ 46.203 Definitions.

As used in this subpart:

(a) "Secretary" means the Secretary of Health, Education, and Welfare and any other officer or employee of the Department of Health, Education, and Welfare to whom authority has been delegated.

(b) "Pregnancy" encompasses the period of time from confirmation of implantation (through any of the presumptive signs of pregnancy, such as missed menses, or by a medically acceptable pregnancy test), until expulsion or extraction of the fetus.

(c) "Fetus" means the product of conception from the time of implantation (as evidenced by any of the presumptive signs of pregnancy, such as missed menses, or a medically acceptable pregnancy test), until a determination is made, following expulsion or extraction of the fetus, that it is viable.

(d) "Viable" as it pertains to the fetus means being able, after either spontaneous or induced delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heart beat and respiration. The Secretary may from time to time, taking into account medical advances, publish in the Federal Register guidelines to assist in determining whether a fetus is viable for purposes of this subpart. If a fetus is viable after delivery, it is a premature infant.

(e) "Nonviable fetus" means a fetus *ex utero* which, although living, is not viable.

(f) "Dead fetus" means a fetus *ex utero* which exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord (if still attached).

(g) "*In vitro* fertilization" means any fertilization of human ova which occurs outside the body of a female, either through admixture of donor human sperm and ova or by any other means.

§ 46.204 Ethical Advisory Boards.

(a) One or more Ethical Advisory Boards shall be established by the Secretary. Members of these board(s) shall be so selected that the board(s) will be competent to deal with medical, legal, social, ethical, and related issues and may include, for example, research scientists, physicians, psychologists, sociologists, educators, lawyers, and ethicists, as well as representatives of the general public. No board member may be a regular, full-time employee of the Department of Health, Education, and Welfare.

(b) At the request of the Secretary, the Ethical Advisory Board shall render advice consistent with the policies and requirements of this Part as to ethical issues, involving activities covered by this subpart, raised by individual applications or proposals. In addition, upon request by the Secretary, the Board shall render advice as to classes of applications or proposals and general policies, guidelines, and procedures.

(c) A Board may establish, with the approval of the Secretary, classes of applications or proposals which: (1) Must be submitted to the Board, or (2) need not be submitted to the Board. Where the Board so establishes a class of applications or proposals which must be submitted, no application or proposal within the class may be funded by the Department or any component thereof until the application or proposal has been reviewed by the Board and the Board has rendered advice as to its acceptability from an ethical standpoint.

(d) No application or proposal involving human *in vitro* fertilization may be funded by the Department or any component thereof until the application or proposal has been reviewed by the Ethical Advisory Board and the Board has rendered advice as to its acceptability from an ethical standpoint.

§ 46.205 Additional duties of the Institutional Review boards in connection with activities involving fetuses, pregnant women, or human in vitro fertilization.

(a) In addition to the responsibilities prescribed for Institutional Review Boards under Subpart A of this part, the applicant's or offeror's Board shall, with respect to activities covered by this subpart, carry out the following additional duties:

(1) Determine that all aspects of the activity meet the requirements of this subpart;

(2) Determine that adequate consideration has been given to the manner in which potential subjects will be selected, and adequate provision has been made by the applicant or offeror for monitoring the actual informed consent process (e.g., through such mechanisms, when appropriate, as participation by the Institutional Review board or subject advocates in: (i) Overseeing the actual process by which individual consents required by this subpart are secured either by approving induction of each individual into the activity or verifying, perhaps through sampling, that approved procedures for induction of individuals into the activity are being followed, and (ii) monitoring the progress of the activity and intervening as necessary through such steps as visits to the activity site and continuing evaluation to determine if any unanticipated risks have arisen);

(3) Carry out such other responsibilities as may be assigned by the Secretary.

(b) No award may be issued until the applicant or offeror has certified to the Secretary that the Institutional Review Board has made the determinations required under paragraph (a) of this section and the Secretary has approved these determinations, as provided in § 46.120 of Subpart A of this part.

(c) Applicants or offerors seeking support for activities covered by this subpart must provide for the designation of an Institutional Review Board, subject to approval by the Secretary, where no such Board has been established under Subpart A of this part.

§ 46.206 General limitations.

(a) No activity to which this subpart is applicable may be undertaken unless:

(1) Appropriate studies on animals and nonpregnant individuals have been completed;

(2) Except where the purpose of the activity is to meet the health needs of the mother or the particular fetus, the risk to the fetus is minimal and, in all cases, is the least possible risk for achieving the objectives of the activity.

(3) Individuals engaged in the activity will have no part in: (i) Any decisions as to the timing, method, and procedures used to terminate the pregnancy, and (ii) determining the viability of the fetus at the termination of the pregnancy; and

(4) No procedural changes which may cause greater than minimal risk to the fetus or the pregnant woman will be introduced into the procedure for terminating the pregnancy solely in the interest of the activity.

(b) No inducements, monetary or otherwise, may be offered to terminate pregnancy for purposes of the activity.

[40 FE 33528, Aug. 8, 1975, as amended at 40 FR 51638, Nov. 6, 1975]

§ 46.207 Activities directed toward pregnant women as subjects.

(a) No pregnant woman may be involved as a subject in an activity covered by this subpart unless: (1) The purpose of the activity is to meet the health needs of the mother and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or (2) the risk to the fetus is minimal.

(b) An activity permitted under paragraph (a) of this section may be conducted only if the mother and father are legally competent and have given their informed consent after having been fully informed regarding possible impact on the fetus, except that the father's informed consent need not be secured if: (1) The purpose of the activity is to meet the health needs of the mother; (2) his identity or whereabouts cannot reasonably be ascertained; (3) he is not reasonably available; or (4) the pregnancy resulted from rape.

§ 46.208 Activities directed toward fetuses in utero as subjects.

(a) No fetus *in utero* may be involved as a subject in any activity covered by this subpart unless: (1) The purpose of the activity is to meet the health needs of the particular fetus and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or (2) the risk to the fetus imposed by the research is minimal and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

(b) An activity permitted under paragraph (a) of this section may be conducted only if the mother and father are legally competent and have given their informed consent, except that the father's consent need not be secured if: (1) His identity or whereabouts cannot reasonably be ascertained, (2) he is not reasonably available, or (3) the pregnancy resulted from rape.

§ 46.209 Activities directed toward fetuses ex utero, including nonviable fetuses, as subjects.

(a) Until it has been ascertained whether or not a fetus ex utero is viable, a fetus ex utero may not be involved as a subject in an activity covered by this subpart unless:

(1) There will be no added risk to the fetus resulting from the activity, and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means, or

(2) The purpose of the activity is to enhance the possibility of survival of the particular fetus to the point of viability.

(b) No nonviable fetus may be involved as a subject in an activity covered by this subpart unless:

(1) Vital functions of the fetus will not be artificially maintained,

(2) Experimental activities which of themselves would terminate the heartbeat or respiration of the fetus will not be employed, and

(3) The purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

(c) In the event the fetus *ex utero* is found to be viable, it may be included as a subject in the activity only to the extent permitted by and in accordance with the requirements of other subparts of this part.

(d) An activity permitted under paragraph (a) or (b) of this section may be conducted only if the mother and father are legally competent and have given their informed consent, except that the father's informed consent need not be secured if: (1) his identity or whereabouts cannot reasonably be ascertained, (2) he is not reasonably available, or (3) the pregnancy resulted from rape.

§ 46.210 Activities involving the dead fetus, fetal material, or the placenta.

Activities involving the dead fetus, macerated fetal material, or cells, tissue, or organs excised from a dead fetus shall be conducted only in accordance with any applicable State or local laws regarding such activities.

§ 46.211 Modification or waiver of specific requirements.

Upon the request of an applicant or offeror (with the approval of its Institutional Review Board), the Secretary may modify or waive specific requirements of this subpart, with the approval of the Ethical Advisory Board after such opportunity for public comment as the Ethical Advisory Board considers appropriate in the particular instance. In making such decisions, the Secretary will consider whether the risks to the subject are so outweighed by the sum of the benefit to the subject and the importance of the knowledge to be gained as to warrant such modification or waiver and that such benefits cannot be gained except through a modification or waiver. Any such modifications or waivers will be published as notices in the *Federal Register*.

Subpart C——Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

Source: 43 FE 53655, Nov. 16, 1978

§ 46.301 Applicability.

(a) The regulations in this subpart are applicable to all biomedical and behavioral research conducted or supported by the Department of Health, Education, and Welfare involving prisoners as subjects.

(b) Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will authorize research involving prisoners as subjects, to the extent such research is limited or barred by applicable State or local law.

(c) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

§ 46.302 Purpose.

Inasmuch as prisoners may be under constraints because of their incarceration which could affect their ability to make a truly voluntary and uncoerced decision whether or not to participate as subjects in research, it is the purpose of this subpart to provide additional safeguards for the protection of prisoners involved in activities to which this subpart is applicable.

§ 46.303 Definitions.

As used in this subpart:

(a) "Secretary" means the Secretary of Health, Education, and Welfare and any other officer or employee of the Department of Health, Education, and Welfare to whom authority has been delegated.

(b) "DHEW" means the Department of Health, Education, and Welfare.

(c) "Prisoner" means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

(d) "Minimal risk" is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

§ 46.304 Composition of Institutional Review Boards where prisoners are involved.

In addition to satisfying the requirements in § 46.107 of this part, an Institutional Review Board, carrying out responsibilities under this part with respect to research covered by this subpart, shall also meet the following specific requirements:

(a) A majority of the Board (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the Board.

(b) At least one member of the Board shall be a prisoner, or a prisoner representative, with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one Board only one Board need satisfy this requirement.

§ 46.305 Additional duties of the Institutional Review Boards where prisoners are involved.

(a) In addition to all other responsibilities prescribed for Institutional Review Boards under this part, the Board shall review research covered by this subpart and approve such research only if it finds that:

(1) The research under review represents one of the categories of research permissible under § 46.306(a)(2);

(2) Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weight the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;

(3) The risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers;

(4) Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides to the Board justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;

(5) The information is presented in language which is understandable to the subject population;

(6) Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and

(7) Where the Board finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

(b) The Board shall carry out such other duties as may be assigned by the Secretary.

(c) The institution shall certify to the Secretary, in such form and manner as the Secretary may require, that the duties of the Board under this section have been fulfilled.

§ 46.306 Permitted activities involving prisoners.

(a) Biomedical or behavioral research conducted or supported by DHEW may involve prisoners as subjects only if:

(1) The institution responsible for the conduct of the research has certified to the Secretary that the Institutional Review Board has approved the research under § 46.305 of this subpart; and

(2) In the judgment of the Secretary the proposed research involves solely the following:

(A) Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

(C) Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction and sexual assaults) provided that the study may proceed only after the Secretary has consulted with appropriate experts including experts in penology medicine and ethics, and published notice, in the *Federal Register*, of his intent to approve such research; or

(D) Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary has consulted with appropriate experts, including experts in penology medicine and ethics, and published notice, in the *Federal Register*, of his intent to approve such research.

(b) Except as provided in paragraph (a) of this section, biomedical or behavioral research conducted or supported by DHEW shall not involve prisoners as subjects.

Subpart D——Additional Protections for Children Involved as Subjects in Research

§ 46.401 To what do these regulations apply?

(a) This subpart applies to all research involving children as subjects, conducted or supported by the Department of Health and Human Services.

(1) This includes research conducted by Department employees, except that each head of an Operating Division of the Department may adopt such nonsubstantive, procedural modifications as may be appropriate from an administrative standpoint.

(2) It also includes research conducted or supported by the Department of Health and Human Services outside the United States, but in appropriate circumstances, the Secretary may, under paragraph (e) of § 46.101 of Subpart A, waive the applicability of some or all of the requirements of these regulations for research of this type.

(b) Exemptions (1), (2), (5) and (6) as listed in Subpart A at § 46.101(b) are applicable to this subpart. Exemption (4), research involving the observation of public behavior, listed at § 46.101(b), is applicable to this subpart where the investigator(s) does not participate in the activities being observed. Exemption (3), research involving survey or interview procedures, listed at § 46.101(b) does not apply to research covered by this subpart.

(c) The exceptions, additions, and provisions for waiver as they appear in paragraphs (c) through (i) of § 46.101 of Subpart A are applicable to this subpart.

§ 46.402 Definitions.

The definitions in § 46.102 of Subpart A shall be applicable to this subpart as well. In addition, as used in this subpart:

(a) "Children" are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.
(b) "Assent" means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

(c) "Permission" means the agreement of parent(s) or guardian to the participation of their child or ward in research.

(d) "Parent" means a child's biological or adoptive parent.

(e) "Guardian" means an individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care.

§ 46.403 IRB duties.

In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all applicable sections of this subpart.

§ 46.404 Research not involving greater than minimal risk.

HHS will conduct or fund research in which the IRB finds that no greater than minimal risk to children is presented, only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in § 46.406.

§ 46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being only if the IRB finds that:

(a) The risk is justified by the anticipated benefit to the subjects;

(b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and

(c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in § 46.408.

§ 46.406 Research involving greater than minimal risk and no prospect of direct benefit to the individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that:

(a) The risk represents a minor increase over minimal risk;

(b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;

(c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and

(d) Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in § 46.408.

§ 46.407 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

HHS will conduct or fund research that the IRB does not believe meets the requirements of §§ 46.404, 46.405, or 46.406 only if:

(a) The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and

(b) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either: (1) That the research in fact satisfies the conditions of §§ 46.404, 46.405, or 46.406, as applicable, or (2) the following:

(i) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health of welfare of children;

(ii) The research will be conducted in accordance with sound ethical principles;

(iii) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in § 46.408.

§ 46.408 Requirements for permission by parents or guardians and for assent by children.

(a) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. In determining whether children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate. If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accord with § 46.116 of Subpart A.

(b) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine, in accordance with and to the extent that consent is required by § 46.116 of Subpart A, that adequate provisions are made for soliciting the permission of each child's parents or guardian. Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research to be conducted under §§ 46.404 or 46.405. Where research is covered by §§ 46.406 and 46.407 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

(c) In addition to the provisions for waiver contained in § 46.116 of Subpart A, if the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may waive the consent requirements in Subpart A of this part and paragraph (b) of this section, provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with federal state or local law. The choice of an appropriate mechanism

would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit of the research subjects, and their age, maturity, status, and condition.

(d) Permission by parents or guardians shall be documented in accordance with and to the extent required by § 46.117 of Subpart A.

(e) When the IRB determines that assent is required, it shall also determine whether and how assent must be documented.

§ 46.409 Wards.

(a) Children who are wards of the state or any other agency, institution, or entity can be included in research approved under §§ 46.406 or 46.407 only if such research is:

(1) Related to their status as wards; or

(2) Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

(b) If the research is approved under paragraph (a) of this section, the IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

NOTICES

HUMAN SUBJECTS

Minimum Criteria Identifying the Viable Fetus

On March 13, 1975, regulations were published in the Federal Register (40 FE 11854) relating to the protection of human subjects in research, development, and related activities supported by Department of Health, Education, and Welfare grants and contracts. These regulations are codified at 45 CFS Part 46.

Elsewhere in this issue of the Federal Register, the Secretary is amending 45 CFR Part 46 by, among other things, adding a new Subpart B to provide additional protections pertaining to research, development, and related activities involving fetuses, pregnant women, and in vitro fertilization.

Section 46.203(d) of Subpart B provides inter alia as follows:

The Secretary may from time to time, taking into account medical advances, publish in the Federal Register guidelines to assist in determining whether a fetus is viable for purposes of this subpart.

The notice is published in accordance with § 46.203(d). For purposes of Subpart B, the guidelines indicating that a fetus other than a dead fetus within the meaning of § 46.203(f) is viable include the following:
an estimated gestational age of 20 weeks or more and a body weight of 500 grams or more.

FEDERAL REGISTER, VOL 40, AUGUST 8, 1975

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[1]Reports should be filed with the Office for Protection from Research Risks, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland 20205.

APPENDIX 3.

RESEARCH ACTIVITIES WHICH MAY BE REVIEWED THROUGH EXPEDITED REVIEW PROCEDURES

Research activities involving no more than minimal risk and in which the only involvement of human subjects will be in one or more of the following categories (carried out through standards methods) may be reviewed by the Institutional Review Board through the expedited review procedure authorized in 46.110 of 45 CFR part 46.

1) Collection of: hair and nail clippings, in a nondisfiguring manner; deciduous teeth; and permanent teeth if patient care indicates a need for extraction.
2) Collection of excreta and external secretions including sweat, uncannulated saliva, placenta removed at delivery, and amniotic fluid at the time of rupture of the membrane prior to or during labor.
3) Recording of data from subjects 18 years of age or older using noninvasive procedures routinely employed in clinical practice. This includes the use of physical sensors that are applied either to the surface of the body or at a distance and do not involve input of matter or significant amounts of energy into the subject or an invasion of the subject's privacy. It also incudes such procedures as weighing, testing sensory acuity, electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, diagnostic echography, and electroretinography. It does not include exposure to electromagnetic radiation outside the visible range (for example, x-rays, microwaves).
4) Collection of blood samples by venipuncture, in amounts not exceeding 450 milliliters in an eight-week period and no more often than two times per week, from subjects 18 years of age or older and who are in good health and not pregnant.
5) Collection of both supra- and subgingival dental plaque and calculus, provided the procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques.
6) Voice recordings made for research purposes such as investigations of speech defects.
7) Moderate exercise by healthy volunteers.
8) The study of existing data, documents, records, pathological specimens, or diagnostic specimens.
9) Research on individual or group behavior or characteristics of individuals, such as studies of perception, cognition, game theory, or test development, where the investigator does not manipulate subjects' behavior and the research will not involve stress to subjects.
10) Research on drugs or devices for which an investigational new drug exemption or an investigational device exemption is not required.

Source: 46 FR 8392
1/26/81

APPENDIX 4.

International Ethical Guidelines for Biomedical Research Involving Human Subjects

Prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO)

THE GUIDELINES

Informed Consent of Subjects

Guideline 1: Individual informed consent

For all biomedical research involving human subjects, the investigator must obtain the informed consent of the prospective subject or, in the case of an individual who is not capable of giving informed consent, the proxy consent of a properly authorized representative.

Guideline 2: Essential information for prospective research subjects

Before requesting an individual's consent to participate in research, the investigator must provide the individual with the following information, in language that he or she is capable of understanding:

- that each individual is invited to participate as a subject in research, and the aims and methods of the research;
- the expected duration of the subject's participation;
- the benefits that might reasonably be expected to result to the subject or to others as an outcome of the research;
- any foreseeable risks or discomfort to the subject, associated with participation in the research;
- any alternative procedures or courses of treatment that might be as advantageous to the subject as the procedure or treatment being tested;
- the extent to which confidentiality of records in which the subject will be maintained;
- the extent of the investigator's responsibility, if any, to provide medical services to the subject;
- that therapy will be provided free of charge for specified types of research-related injury;
- whether the subject or the subject's family or dependants will be compensated for disability or death resulting from such injury; and
- that the individual is free to refuse to participate and will be free to withdraw from the research at any time without penalty or loss of benefits to which he or she would otherwise be entitled.

Guideline 3: Obligations of investigators regarding informed consent

The investigator has a duty to:

- communicate to the prospective subject all the information necessary for adequately informed consent;
- give the prospective subject full opportunity and encouragement to ask questions;
- exclude the possibility of unjustified deception, undue influence and intimidation;
- seek consent only after the prospective subject has adequate knowledge of the relevant facts and of the consequences of participation, and has had sufficient opportunity to consider whether to participate;

- as a general rule, obtain from each prospective subject a signed form as evidence of informed consent; and
- renew the informed consent of each subject if there are material changes in the conditions or procedures of the research.

Guideline 4: Inducement to participate

Subjects may be paid for inconvenience and time spent, and should be reimbursed for expenses incurred, in connection with their participation in research; they may also receive free medical services. However, the payments should not be so large or the medical services so extensive as to induce prospective subjects to consent to participate in the research against their better judgment ("undue inducement"). All payments, reimbursements and medical services to be provided to research subjects should be approved by an ethical review committee.

Guideline 5: Research involving children

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

- children will not be involved in research that might equally well be carried out with adults;
- the purpose of the research is to obtain knowledge relevant to the health needs of children;
- a parent or legal guardian of each child has given proxy consent;
- the consent of each child has been obtained to the extent of the child's capabilities;
- the child's refusal to participate in research must always be respected unless according to the research protocol the child would receive therapy for which there is no medically-acceptable alternative;
- the risk presented by interventions not intended to benefit the individual child-subject is low and commensurate with the importance of the knowledge to be gained; and
- interventions that are intended to provide therapeutic benefit are likely to be at least as advantageous to the individual child-subject as any available alternative.

Guideline 6: Research involving persons with mental or behavioural disorders

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

- such persons will not be subjects of research that might equally well be carried out on persons in full possession of their mental faculties;
- the purpose of the research is to obtain knowledge relevant to the particular health needs of persons with mental or behavioural disorders;
- the consent of each subject has been obtained to the extent of that subject's capabilities, and a prospective subject's refusal to participate in non-clinical research is always respected;
- in the case of incompetent subjects, informed consent is obtained from the legal guardian or other duly authorized person;

- the degree of risk attached to interventions that are not intended to benefit the individual subject is low and commensurate with the importance of the knowledge to be gained; and
- interventions that are intended to provided therapeutic benefit are likely to be at least as advantageous to the individual subject as any alternative.

Guideline 7: Research involving prisoners

Prisoners with serious illness or at risk of serious illness should not arbitrarily be denied access to investigational drugs, vaccines or other agents that show promise of therapeutic or preventive benefit.

Guideline 8: Research involving subjects in underdeveloped communities

Before undertaking research involving subjects in underdeveloped communities, whether in developed or developing countries, the investigator must ensure that:

- persons in underdeveloped communities will not ordinarily be involved in research that could be carried out reasonably well in developed communities;
- the research is responsive to the health needs and the priorities of the community in which it is to be carried out;
- every effort will be made to secure the ethical imperative that the consent of individual subjects be informed; and
- the proposals for the research have been reviewed and approved by an ethical review committee that has among its members or consultants persons who are thoroughly familiar with the customs and traditions of the community.

Guideline 9: Informed consent in epidemiological studies

For several types of epidemiological research individual informed consent is either impracticable or inadvisable. In such cases the ethical review committee should determine whether it is ethically acceptable to proceed without individual informed consent and whether the investigator's plans to protect the safety and respect the privacy of research subjects and to maintain the confidentiality of the data are adequate.

Guideline 10: Equitable distribution of burdens and benefits

Individuals or communities to be invited to be subjects of research should be selected in such a way that the burdens and benefits of the research will be equitably distributed. Special justification is required for inviting vulnerable individuals and, if they are selected, the means of protecting their rights and welfare must be particularly strictly applied.

Guideline 11: Selection of pregnant or nursing (breastfeeding) women as research subjects

Pregnant or nursing women should in no circumstances be the subjects of non-clinical research unless the research carries no more than minimal risk to the fetus or nursing infant and the object of the research is to obtain new knowledge about pregnancy or lactation. As a general rule, pregnant or nursing women should not be subjects of any clinical trials except such trials

as are designed to protect or advance the health of pregnant or nursing women or fetuses or nursing infants, and for which women who are not pregnant or nursing would not be suitable subjects.

Confidentiality of Data

Guideline 12: Safeguarding confidentiality

The investigator must establish secure safeguards of the confidentiality of research data. Subjects should be told of the limits to the investigators' ability to safeguard confidentiality and of the anticipated consequences of breaches of confidentiality.

Compensation of Research Subjects for Accidental Injury

Guideline 13: Right of subjects to compensation

Research subjects who suffer physical injury as a result of their participation are entitled to such financial or other assistance as would compensate them equitably for any temporary or permanent impairment or disability. In the case of death, their dependants are entitled to material compensation. The right to compensation may not be waived.

Review Procedures

Guideline 14: Constitution and responsibilities of ethical review committees

All proposals to conduct research involving human subjects must be submitted for review and approval to one or more independent ethical and scientific review committees. The investigator must obtain such approval of the proposal to conduct research before the research is begun.

Externally Sponsored Research

Guideline 15: Obligations of sponsoring and host countries

Externally sponsored research entails two obligations:

- An external sponsoring agency should submit the research protocol to ethical and scientific review according to the standards of the country of the sponsoring agency, and the ethical standards applied should be no less exacting than they would be in the case of research carried out in that country.

- After scientific and ethical approval in the country of the sponsoring agency, the appropriate authorities of the host country, including a national or local ethical review committee or its equivalent, should satisfy themselves that committee or its equivalent, should satisfy themselves that the proposed research meets their own ethical requirements.

NOTE: The guidelines reproduced above are taken from the 1993 CIOMS publication **"International Ethical Guidelines for Biomedical Research Involving Human Subjects"** (Price: Swfr. 10.-) and include the complete text of all 15 guidelines. Although only the actual guidelines are reproduced here (for reasons of space), the cited publication also includes, in addition to the above text, extensive commentary on each guideline, and several appendices. Three related CIOMS publications of potential interest to readers are listed below:

CIOMS. International guidelines for ethical review of epidemiological studies. Geneva: CIOMS, 1991. (Price: Swfr. 6.-)

Bankowski Z, Bryant JH, Last JM. Ethics and epidemiology: International guidelines. Proceedings of the XXVth CIOMS Conference; Geneva, 7-9 Nov 1990. (Includes text of guidelines as well as conference presentations; 163 pages, plus annexes. Price: Swfr. 25.-).

Bankowski Z, Bryant JH, Last JM. Ethics and research on human subjects: International guidelines. Proceedings of the XXVIth CIOMS Conference; Geneva, 5-7 Feb 1992. (Includes entire text of guidlines and commentaries, as well as conference presentations; 228 pages, plus annexes. Price: Swfr 25.-).

CIOMS publications may be obtained directly from CIOMS, c/o World Health Organization, Avenue Appia, 1211 Geneva 27, Switzerland. Both CIOMS and WHO publications are distributed by the World Health Organization, Distribution and Sales Unit, Avenue Appia, 1211 Geneva 27, Switzerland and are available from booksellers through the network of WHO sales agents. A list of these agents may be obtained by writing to the above address.