Informed Consent: From Good Intentions to Sound Practices

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A Report of a Seminar

24–25 May 2001
Population Council
New York, NY

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Cover and text printed on recycled paper in the USA

Acknowledgments

We are grateful to Ronald Bayer, Arthur Caplan, Bette-Jane Crigger, Saran Da Ly, Judith Fortney, Anrudh Jain, Elof Johansson, Robert Levine, S'phindhile Magwaza, Mary McCabe, Therese McGinn, Katie Paine, Ok Pannenborg, Rachael Pine, John Santelli, Suniti Solomon, Kimberly Thompson, John Townsend, and Ellen Weiss for their thoughtful presentations that served as the foundation for this seminar. We also thank all the seminar participants for their willingness to join us in a lively discussion about this critical subject.

Thanks to members of the Robert H. Ebert Program on Critical Issues in Reproductive Health for their participation in planning the seminar, and especially to Beverly Winikoff, who gave invaluable insight into the conceptualization of the seminar and who offered comments on several drafts of this report. We also thank Kelly Blanchard, Heidi Jones, Nancy Sloan, and Janneke van de Wijgert for their review and suggestions on earlier drafts of this report. We are grateful to Jared Stamm for his meticulous copyediting and to Elise Mandel for her excellent proofreading. Special thanks to Virginia Kallianes for organizing the seminar and for preparing this manuscript for publication.

We greatly appreciate the support of the John D. and Catherine T. MacArthur Foundation and the William and Flora Hewlett Foundation for the seminar and this publication.

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INTRODUCTION

This report is a summary of presentations and discussions at a seminar entitled "Informed Consent: From Good Intentions to Sound Practices." This two-day seminar brought together 65 individuals from nine countries on 24–25 May 2001 to discuss challenges of informed consent in research. (See appendixes for the seminar agenda and a list of the participants.) The seventh in a series of seminars held every two years, this meeting was sponsored by the Population Council's Robert H. Ebert Program on Critical Issues in Reproductive Health. Topics of past seminars have included abortion research; sexually transmitted infections (STIs) in field programs; and the interaction of rights, technologies, and services.

The underlying premise of this seminar was that even when those who sponsor and conduct research start with good intentions, they may have difficulty translating them into practice. The goal of the meeting was to put informed consent into historical and contemporary perspective and to explore ways that the barriers to effective implementation can be overcome. This report is based entirely on the content of the speakers' presentations and the lively discussions that ensued.

A BRIEF HISTORY OF INFORMED CONSENT

The idea of informed consent sounds straightforward because the term has become so well-known to those concerned about ethics in medical research. The familiarity of the term, however, belies the elusiveness of the concept and the difficulty of its implementation. An explanation for why implementing informed consent is so challenging may be embedded in the term itself: one of its components—information—comes from one source (researcher/provider) and the other—consent—comes from another (participant/patient). This "dyadic relationship" is difficult to predict and control and, as in any relationship requiring communication, leaves much room for misunderstanding.

The emphasis placed on informed consent in medical practice and in research is relatively new, having emerged in the last half of the twentieth century. Its origins are rooted in a history of abuse. Indeed, it was reaction to past abuses that prompted the codification of ethical principles for the conduct of research on human subjects in recent decades.

Historians differ on how much informed consent was exercised in medical practice in the nineteenth century and before. Some suggest that physicians showed little regard for patients' views or rights. Others argue that physicians in earlier medical traditions did exhibit respect for patients' knowledge and autonomy. On closer examination of the evidence, however, it appears that even those providers who offered their patients information and sought their consent did so because they believed it would confer some therapeutic benefit, not because they saw it as the patient's right. Only in the last several decades has informed consent become central to medical practice in the United States and Europe, reflecting a growing commitment in broader society to the right to autonomy and to the rights of the vulnerable.

Informed consent in research has its own unique history, going back to the 1930s in the United States, when courts upheld the importance of knowledgeable consent in medical research. It was the outrage at the cruelty of Nazi experimentation with human subjects, however, that led to the creation of ethical codes for research, including informed consent.[1] The first principle of the Nuremberg Code asserts that voluntary, competent, informed, and comprehending consent is "absolutely essential" in research.[2] This monumental step was nonetheless limited in its application as a practical guide to research ethics.

Despite the outcry against Nazi experimentation, abuse in medical research continued. A 1962 review of state laws in the United States revealed that not a single state had a statute that required doctors to inform patients receiving experimental drugs of their right to informed consent.[3] In 1966, Henry Beecher, a leading thinker in the field of research ethics, published an article in the *New England Journal of Medicine* citing 22 cases of unethical practices in research.[4] These included a study in which live cancer cells were injected into patients with dementia without their knowledge or consent at the Jewish Chronic Disease Hospital in Brooklyn, New York.

In the 1960s, further efforts were made to clarify and codify the concept of informed consent. In 1964, the World Medical Association issued the Declaration of Helsinki, which asserted the requirement of informed consent for all non-therapeutic research (i.e., research for purposes of investigation).[5] In contrast, in the case of therapeutic research or research conducted by a clinician investigating possible benefits of a treatment for a sick patient, the declaration said that consent should be sought "consistent with patient psychology"—to be determined by the physician.

In 1966, in reaction to the Jewish Chronic Disease Hospital scandal, the U.S. Food and Drug Administration (FDA) issued clear requirements for informed consent in research.[6] In the same year, the U.S. Surgeon General created a policy that required anyone who received funds for research involving human subjects from the Public Health Service to submit their research for institutional review, with specific attention to informed consent.[7]

Yet abuse continued. In 1972, the world of medical research was stunned by revelation of the Tuskegee syphilis experiment. For some 40 years, researchers had been following the progression of syphilis in several hundred African-American men. They had withheld treatment

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1 Ironically, the United States had itself conducted medical research with human subjects without such consent during World War II, using the exigencies of war to justify experimentation with psychiatric hospital patients in the search for a dysentery vaccine and for anti-malaria drugs.

2 Alemania. 1951. *Trials of War Criminals Before the Nuernberg Military Tribunals Under Control Council Law no. 10*, Nuernberg, October 1946, April 1949, vol. 2, pp. 181–182. Washington, D.C.: U.S. Government Printing Office.

3 Bayer, Ronald. "Informed consent: Lessons of the past, a guide to the future?" seminar presentation.

4 Beecher, Henry K. 1966. "Ethical and clinical research," *The New England Journal of Medicine* 274(24):1354–1360.

5 *World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*, adopted by the 18th World Medical Association (WMA) General Assembly, Helsinki, Finland, June 1964; amended most recently by the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000.

6 U.S. Food and Drug Administration. 1966. "Consent for use of investigational drugs on humans: Statement of policy," Part 130: New Drugs. *Federal Register* 31 (August 30).

7 U.S. Public Health Service, Division of Research Grants. 1966. "Clinical investigations using human subjects," statement of policy, Policy and Procedures Order no. 129.

from these men, even after penicillin was proven effective to treat syphilis in the late 1940s. By the time the study was exposed, many of the men had died of the disease or related problems, their partners had been infected, and several of their children had been born with the disease. A quarter of a century after Nuremberg, this event shook the foundations of the medical research community and led to the creation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The work of this U.S. federal advisory body from 1974 to 1978 resulted in the Belmont Report,[8] which asserted three principles as central to research, the first of which is at the heart of informed consent:

- Respect for persons—individuals should be treated as autonomous agents, and persons with diminished autonomy are entitled to protection;
- Beneficence—possible benefits should be maximized and possible harms minimized; and
- Justice—those who realize the benefits of research should share in its burdens.

The Belmont Report was followed by other commissions, and in 1986 the "Common Rule" was proposed. Based on an existing 1981 policy of the Department of Health and Human Services (DHHS), this regulation was extended to all U.S. government agencies. Codified in 1991, the "Common Rule" finally put into place a comprehensive regulatory framework for human research in the United States.[9]

The recent history of informed consent in medical research is one that is dominated by events in the United States. What relevance does it have for research conducted elsewhere, especially in developing countries, where cultural, social, economic, and medical conditions may be extremely different? Some have suggested that the concept of first-person informed consent, primarily developed in the context of the civil rights struggles in the United States, is not relevant for much of the developing world and that its application may be an imposition from the outside, a sort of "ethical imperialism."[10]

An analysis of the thinking behind these claims appeared in *The New England Journal of Medicine* in 1992.[11] The authors, Carel IJsselmuiden and Ruth Faden, identified and analyzed three common arguments regarding why informed consent is not appropriate or does not apply in Africa:

- It is culturally inappropriate because individuals are not autonomous;
- The subjects are not "competent" or the communication difficulties are insurmountable; and
- Urgency makes informed consent requirements unreasonable (i.e., informed consent slows down the search for solutions to urgent health problems).

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[8] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1978. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. DHEW publication no. (OS) 78-0012. Washington, D.C.: U.S. Government Printing Office.

[9] Department of Health and Human Services, National Institutes of Health, Office for Protection from Research Risks. 1991. Code of Federal Regulations, Title 45, Public Welfare; Part 46, Protection of Human Subjects.

[10] Bayer, op. cit.

[11] IJsselmuiden, Carel B. and Ruth R. Faden. 1992. "Research and informed consent in Africa—Another look," *The New England Journal of Medicine* 326(12):830–834.

The authors found that the first of these arguments—that cultural differences mean that informed consent is inappropriate in Africa—is based on decades-old anthropological research. Drawing on studies of traditional societies, this rationale assumes that African culture is homogeneous and static, and it does not take into account urbanization, education, or the emergence of the modern nation-state. The authors then dismissed the notion that Africans cannot understand the concept of informed consent, which essentially equates the cognitive capacity of adults in Africa with that of children or the mentally ill. While communication across cultures is indeed challenging, it is hardly impossible. Finally, IJsselmuiden and Faden considered the urgency argument to be invalid given the slow pace of turning research findings into action in Africa.

Yet the challenge of implementing meaningful informed consent is undeniable. A study by Quarraisha and Salim Abdool Karim and colleagues, published in the *American Journal of Public Health*, evaluated the informed consent process for HIV testing in an antenatal clinic in South Africa.[12] Although consent was sought and women were consistently told that their participation was voluntary, 84 percent felt that it was "compulsory to participate." A large majority said they understood that they were "free to quit the study at any time," yet they also believed that the "hospital would not allow them to do so." And approximately one-third of the women thought that the care they would receive would be compromised if they quit the study. The researchers concluded that the consent was informed but not truly voluntary.

After a half-century's effort to define and realize the concept of informed consent, it is clear that historical, structural, and practical obstacles remain. Yet the impediments do not justify a slackening of effort or application. Those committed to the ethical conduct of research continue to seek ways to overcome these barriers, especially in research conducted with individuals who are vulnerable because they lack access to resources or services or face the possibility of a life-threatening disease.

RECENT DEVELOPMENTS AND CURRENT CONTEXT

While informed consent is a critical component of ethical research, it is only one of many challenging issues in research ethics. Recent trends have highlighted the need to continually assess the concepts behind and the implementation of research ethics, including informed consent. Increasingly, and especially in the United States, informed consent has become extremely legalistic, focused on preventing lawsuits against institutions rather than protecting the individuals participating in the research or therapy. Driven by a fear of litigation, researchers, manufacturers, and service providers have created mind-numbingly dense and legalistic forms, which are hardly conducive to meaningful comprehension and consent. What should be the real intent—aiding subjects in making informed decisions—is lost in a barrage of detailed information. Not surprisingly, many potential participants pay little attention to these forms, because they assume the purpose of the forms is to protect the institution. This has led some researchers and their institutions to review and revise the forms they use and to begin to question how they can support and assess comprehension. Internationally, informed consent has been affected by broader ethical debates spurred largely by the HIV/AIDS epidemic.

[12] Abdool Karim, Quarraisha, Salim S. Abdool Karim, Hoosen M. Coovadia, and Mervyn Susser. 1998. "Informed consent for HIV testing in a South African hospital: Is it truly informed and truly voluntary?" *American Journal of Public Health* 88(4):637–640.

Current Controversies in International Guidelines Concerning Research Ethics

Many people believe that the Declaration of Helsinki, originally promulgated in 1964, has lost much of its relevance. One of its flaws is that it creates an illogical distinction between therapeutic and non-therapeutic research.

Article II.6 governs therapeutic research, stating:

> *The doctor can combine medical research with professional care . . . only to the extent that . . . research is justified by its potential . . . therapeutic value for the patient.*

Article III.2 mandates that research subjects be volunteers who are either:

> *. . . healthy persons or patients for whom the experimental design is not related to [their] illness.*

These two articles, strictly applied, would prohibit research on the pathogenesis or epidemiology of a disease in a study population that has that disease. The research would have to be done with participants who are healthy or those who have an unrelated condition—an absurd notion in practical terms.

Another flaw in the Declaration of Helsinki is that it is increasingly out of touch with current ethical thinking on placebo trials, which has profound implications for research in developing countries. Article II.3 of the 1996 version of the declaration states:

> *. . . every patient—including those of a control group, if any—should be assured of the best proven . . . therapeutic method. This does not exclude . . . placebo where no proven method exists.*

In other words, all participants in research should be given the best-known therapy. This article creates significant barriers to developing new therapies for conditions for which there are already "proven" therapies, even when there is virtually no risk from withholding the "best proven therapy" (e.g., analgesics). It also prohibits research designed to develop relatively less costly alternatives to expensive therapies, for example, the trials for "short-course" zidovudine (AZT), described in Box 1.

Box 1: A Raging Debate—AZT Trials to Reduce Mother-to-Child Transmission of HIV

In the late 1990s, the debate around the ethics of trials in developing countries escalated, provoked by the controversial testing of AZT[13] to reduce mother-to-child transmission of HIV. A few years earlier, trials in developed countries showed that a regimen of AZT administered to pregnant women before, during, and immediately following birth cut vertical transmission by 60 percent. Because this proven regimen, called 076, was expensive and therefore difficult to implement in many developing countries, some researchers undertook placebo-controlled trials of a much cheaper "short course" of AZT.

These trials led to one of the most acrimonious debates that the medical research community had experienced in decades.[14-20] On one side of the debate were the "principlists" who thought that it was unethical to administer a placebo when a proven method was available. They felt that these trials exploited women in developing countries and employed a standard that would never be acceptable in developed countries. On the other side were the "pragmatists" who felt the trials were justified because 076 could not be used in many developing-country settings because of its expense (the drugs alone cost about $800 per woman in 1997)[21] and because it required that the health system have the capacity to administer intravenous AZT during labor and delivery and to provide systematic and early antenatal care. Many felt that the desperate and immediate need for therapies that could be used on a widespread basis in poorer countries justified the trials.

A new ethical standard for the conduct of international research has emerged, suggesting that the standard of care in a trial should be the "highest attainable and sustainable" in that setting.[22] "Highest attainable" means that researchers must provide the best care possible. At the same time, the sustainability stipulation means that researchers must consider the potential for services to be maintained and for any resulting product to be made available after the trial ends. This standard attempts to ensure responsiveness to the health needs and priorities of the host country and to address the issue of access to the product or procedure for trial participants and the broader community after the trial ends.

Determining the appropriate standard of care within a trial is one of the most difficult challenges that researchers face, especially in international trials. The provision of free medical services can be construed as an undue inducement to the host country and to trial participants who would

[13] Zidovudine, formerly called azidothymidine, is a drug that slows replication of some retroviruses, including HIV.
[14] Angell, Marcia. 1997. "The ethics of clinical research in the Third World," *The New England Journal of Medicine* 337(12):847–849.
[15] Varmus, Harold and David Satcher. 1997. "Ethical complexities of conducting research in developing countries," *The New England Journal of Medicine* 337(14):1003–1007.
[16] Angell, Marcia. 1997. "Tuskegee revisited," *Wall Street Journal*, 28 October.
[17] Bayer, Ronald. 1998. "The debate over maternal–fetal HIV transmission prevention trials in Africa, Asia, and the Caribbean: Racist exploitation or exploitation of racism?" *American Journal of Public Health* 88(4):567–570.
[18] Laurence, Jeffrey. 1997. "Ethical concerns in international HIV trials," *The AIDS Reader* 7(5):147–148, 154.
[19] Levine, Robert J. 1986. *Ethics of Regulation of Clinical Research,* ed. 2. Baltimore, Md.: Urban & Schwarzenberg.
[20] Lurie, Peter and Sidney M. Wolfe. 1997. "Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries," *The New England Journal of Medicine* 337(12):853–855.
[21] In that same year, many sub-Saharan African countries spent roughly $10 per capita on health annually, meaning that they would need to spend 80 times their per capita health budget to reduce mother-to-child transmission by some 60 percent, the rate shown in developed-country trials.
[22] Levine, Robert J. "Special populations," seminar presentation.

otherwise not have access to these services. Trial organizers should consult openly with host governments and local communities to determine the appropriate standard. They should also make every effort to ensure that the services set up for the trial are indeed sustainable and that products that result from the testing process will be available after the trial concludes.

HIV/AIDS Shifts the Debate

In the past, concern about abuse has shaped attention to ethical issues in research, especially informed consent. Today, it is a sense of urgency that drives developments in research ethics. The global HIV/AIDS crisis has caused a fundamental shift of focus in this area, from protection from abuse to access to the benefits of research. In the face of a life-threatening disease, "the right to be a research subject has displaced the right not to be" and the statement "research is treatment too" has become a rallying cry.[23]

This sense of urgency has led activists, especially in developed countries, to challenge the gold standard of the placebo-controlled trial and to question the role of medical "experts." The result of these changes has been a "democratic leveling" of research; human beings are not seen as subjects of research, but as participants in research.[24] Activists have called for access to the potential benefits of participating in research, including access to potential new and possibly life-saving drugs and treatments. While this shift has occurred mainly in the United States and Europe, it has major implications in a variety of other settings and situations.

Globally, the enormity of the HIV/AIDS epidemic, especially in Africa, has altered the discussion of research on human subjects in other ways. The crisis has highlighted the question of how global inequality should affect the ethics of international research. For example, how do standards for ethical research that have been largely generated in wealthy, industrialized nations apply to nations characterized by poverty and tremendous need? Do ethical standards applied in diverse contexts produce different conclusions about what is and is not acceptable?

In the late 1990s, the debate around the ethics of trials in developing countries escalated, provoked by the controversial testing of short-course AZT to reduce mother-to-child transmission of HIV. The acrimonious debate that ensued—the most public controversy about research ethics in more than 30 years—pitted "principlists" against "pragmatists"[25] and led to further reconsideration of ethical standards for research—a process that continues today.

[23] Bayer, op. cit.
[24] Bayer, op. cit.
[25] Caplan, Arthur L. "Informed consent: Miss or bust?" seminar presentation.

DEFINING INFORMED CONSENT

The goal of the informed consent process should be to increase potential participants' understanding of the study in order to better enable them to decide whether or not to enroll.

Meeting participants defined informed consent in different ways:

- An autonomous action by an individual that authorizes a professional to involve the individual in research.
- [A means] to assure that each individual who participates in biomedical or behavioral research does so willingly and with adequate understanding of the study in which he or she freely agrees to participate.
- How you make the principle of "respect for persons" happen [in research].
- A doctrine of informed decisionmaking that leads to informed consent or informed refusal.

The Elements of Informed Consent: Information, Comprehension, and Choice

Informed consent is often described as consisting of three components:

- Disclosure of information;
- Comprehension of that information; and
- Voluntary choice.

The Complexity of Disclosure: "Information Overload"

Disclosure of information is the most fully elaborated of the three components of informed consent. (See Box 2 for the categories of information that should be included in the informed consent document.) Indeed, the informed consent process as currently carried out often places too much emphasis on the written document. Long, detailed consent documents can be overwhelming, confusing, or intimidating for potential participants. A glut of complicated information rarely facilitates comprehension or informed decisionmaking.

To a large extent, this overemphasis on information disclosure can be explained by a fear of liability, especially in the United States. In addition, disclosure seems to be the easiest aspect of the informed consent process for researchers, their institutions, and Institutional Review Boards (IRBs) to understand and to address. Deciding how much information to present and how to present it, while complex, is within the researchers' control. Knowing how to foster understanding of that information, how to evaluate whether the information has been comprehended, or how to support a voluntary decisionmaking process is much more challenging.

At the same time, the disclosure component of informed consent has become increasingly complex, as the list of elements to be disclosed has grown. The requirement to disclose any

Box 2: Elements of Informed Consent Disclosure

The essential elements of informed consent disclosure are:

- The purposes or aims of the study
- Study procedures or interventions
- Reasonably expected benefits to the subject, the community or society, and/or scientific
- knowledge
- Risks, discomforts, and inconveniences
- Confidentiality of research records and information about individual subjects
- Right to refuse to participate and right to withdraw at any time without prejudice

Additional elements of informed consent disclosure include:

- Expected duration of the study
- Alternatives to study participation (i.e., treatment[s] available)
- Treatment and/or compensation that will be provided in the event of study-related injury
- The researcher's responsibility, if any, to provide *medical* care
- Name of person to contact regarding ethical concerns or study-related injury
- Conditions under which the investigator may ask the subject to leave the study
- Potential conflicts of interest
- Whether/how biological specimens will be stored
- Whether commercial products will be developed from stored specimens
- How study results will be published/communicated to subjects
- Whether/how an intervention demonstrated to be effective will be made available after the study

potential conflicts of interest has been added to the recently revised Declaration of Helsinki[26] and to the latest draft guidelines of the Council for International Organizations of Medical Sciences (CIOMS).[27] In the United States, this has become the latest "hot-button" issue, provoked by a case in Seattle in which investigators conducted research on products of a biotechnology company in which they had significant financial interest. The patients in the trial were not fully informed about the existence of reasonably effective standard therapies for their disease, nor were they told about the researchers' financial stake in the company, thus highlighting increasing concern in the United States about informed consent and conflict of interest.[28]

Another contentious issue related to informed consent relates to the storage of biological specimens gathered during research and their potential commercial use later. In a study at the University of California, for example, a spleen removed from an individual was later used to develop a cell line that was highly profitable. In a controversial ruling, a court decided that the patient had signed away his right to his biological specimens and their use when he signed the consent form.[29]

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[26] *World Medical Association Declaration of Helsinki*, op. cit.

[27] Council for International Organizations of Medical Sciences (CIOMS). 1991. *International Guidelines for Ethical Review of Epidemiological Studies*. Geneva: CIOMS.

[28] Wilson, Duff and David Heath. 2001. "Uninformed consent: What patients at 'The Hutch' weren't told about the experiments in which they died," http://seattletimes.nwsource.com/uninformed_consent/, accessed 30 May 2002.

[29] *Moore v. Regents of the University of California*, 51 Cal. 3d 479, 120 Cal. Rptr 146 (1990).

Despite the fact that much of the attention concerning disclosure is on risk, information is often presented in a way that does not address the magnitude and likelihood of particular risks in ways that prospective participants can understand (see "Understanding Risk," page 14). Disclosure must address not only physical risks, but also psychosocial risks (e.g., the potential for discrimination or mental anguish). Findings from research on genetics may affect entire ethnic groups or communities; for example, information about genetic predisposition to certain conditions or behaviors may lead to stereotyping. The principle of "respect for communities" has led some to suggest the controversial idea of community consent for some types of research. But this raises a set of tough questions about who defines a community and who speaks for it.

Finally, benefits of the research also must be presented in a more useful way, including information about the probability of each potential benefit and whether it is a direct or indirect benefit to the research participant or an "aspirational" benefit—to society, to medicine, or to future patients.

Informed Consent as a Process

Recognizing the limitations of information disclosure alone in facilitating truly informed consent, greater attention needs to be given to comprehension and decisionmaking. Research could help to determine the variables that affect understanding (e.g., time of day, language used, setting in which information is provided, state of mind of the potential participant) and decisionmaking (e.g., who influences the decision to consent, what matters most to the participants). Even if potential participants "understand" a particular research study, they may not fully grasp the implications of it for them. To aid in comprehension, information should be presented in a meaningful and culturally appropriate way.

Some experts in the field suggest that the informed consent process should be individualized, letting each potential participant determine what information he or she needs to make a decision. For example, a short consent form could be provided, with optional appendixes detailing all of the pertinent information. It would then be up to the individual to decide what to read in order to make his or her decision. While doing this would risk eroding some aspects of informed consent, it would recognize and address the fact that individuals have different information needs and make decisions in different ways.

Another vexing question concerns who defines and measures "adequate" understanding. Researchers have an obligation to strive for sufficient comprehension of the information to enable a potential participant to make an autonomous decision. Yet they should not set the threshold for understanding so high that it risks violating the principle of justice by denying participation to some people and not others. Who decides what is sufficient comprehension for an individual to make an informed choice? Should participation be denied to a person who does not seem to understand all of the information, yet expresses a strong desire to participate in the study? Is it not paternalistic for a researcher to decide that a potential participant does not understand the information well enough to decide whether or not her or she will participate in a trial? While there are no simple answers to these questions, most are clearly contextual: the higher the potential risks or costs of participation, the higher the threshold for comprehension

should be. Given the experimental nature of research, informed consent for participation in research should require a more rigorous measure of understanding than for therapy.

Decisionmaking, like comprehension, is poorly understood and has been inadequately studied. Striving to provide information in an understandable way to support decisionmaking, as described above, is primarily the researcher's responsibility. The researcher should be alert to coercive influences that interfere with autonomous decisionmaking. It is generally agreed that neither community nor partner consent should be required for an individual to participate in research, although the community should be brought into the process and consulted, often as a preliminary step (see "Consenting Partners," page 26). Researchers should guard against providing excessive incentives for participation and make it clear to potential participants that they will not be denied regular services if they decide not to join a study.

The Informed Consent Process: The Role of Institutional Review Boards

An important part of the informed consent process is the IRB. The IRB is the "institutional conscience" that is expected to safeguard the rights and well-being of human subjects in research. In the United States, the Common Rule requires IRB review of study protocols, including the informed consent document. If more than one institution is involved in a particular research project, each will require review by its own IRB. In the case of international research, reviews are done in the host country/countries and the sponsoring country. The differences in interpretation and priorities that emerge in IRB reviews within and between cultures underscore the fact that IRB review is a subjective process. While such differences in perspective can lead to confusion and conflict, they can also generate important discussion and debate on putting ethical principles into practice in the treatment of human subjects.

Given the complexity of IRB review across institutions and countries, international multi-center studies can benefit from the establishment of a central coordinating group. This group, or the lead IRB, can identify those elements of a trial that are "core"—that is, that require consistency in the informed consent form and process across sites—and where there is room for local variation. The central coordinating group or IRB can also resolve any important disagreements among IRBs. It is to be expected, however, that forms and processes will vary somewhat, reflecting local realities; indeed, IRBs have an obligation to change an informed consent form or process when local conditions dictate it.

IRBs face several constraints in their review process. The dearth of research on elements essential to informed consent comprehension and retention means that generally there is little information on optimal forms or processes upon which IRB members can draw in their deliberations. They may lack knowledge and information about the study population or research context and may be inconsistent or subjective in their views. IRBs are often expected to provide an ethical review of protocols that some members may not have the technical expertise to accurately judge. They may also be asked to review studies in which the quality or relevance of the science is weak. IRB members often find they must identify a balance among protecting individuals, exercising professional restraint, and allowing scientific progress to go forward.

Perhaps the most significant limitation of IRBs with respect to informed consent is that IRBs review and approve research protocols (including informed consent forms), but they do not play an active role in monitoring studies. IRBs do not conduct site visits, nor do they monitor the informed consent process on an ongoing basis. They do not witness how consent is obtained, review or approve the researchers' strategies for educating and informing potential study participants, or examine who is involved in the informed consent process (e.g., the researcher or an independent third party). Their focus is the review and approval of the informed consent form and any other study materials written for participants, which reinforces the tendency to view informed consent as written documents rather than an ongoing process.

Given that monitoring is beyond the purview of IRBs, other mechanisms could be established to ensure that every effort is made to inform potential study participants about the risks, benefits, and procedures involved in a study. These could include building more attention to the informed consent process into ongoing study monitoring or establishing independent monitoring by community advisory boards.

As currently conceived, IRBs are closed bodies that could benefit from increased transparency, especially at the local level. Ideally, IRBs would include representatives of study populations. As this is not always feasible, the interests and perspectives of study participants should be incorporated into the design and review of the research in other ways. Examples include community advisory boards, social science research in the study population, and community consultations.

A recent trend is to strengthen the capacity of IRBs through training of members (and researchers) to enhance their ability to focus on substantive issues in the informed consent process, rather than simply conduct a one-time paper review. Indeed, some effort is being made to develop an IRB certification process in the United States. Investing in training of IRB members and researchers should not be just another bureaucratic requirement, but rather should help to ingrain research ethics, including a commitment to informed consent, as integral to the research process.

As mentioned previously, while IRBs play a critical role in reviewing protocols, including informed consent materials, they are not charged with overseeing or monitoring research. IRB review is a critical component of conducting ethical research, but it does not in and of itself ensure that a study will be conducted in compliance with the highest ethical standards. Therefore, the ultimate responsibility for ensuring that ethical principles are adhered to lies with the researchers designing and conducting the study.

IMPLEMENTING INFORMED CONSENT

One of the principal challenges of implementing informed consent is to present information to potential study participants in ways that aid their understanding and support their decisionmaking. Practical efforts to improve the informed consent process have resulted in novel approaches to conveying information.

Efforts to Strengthen the Informed Consent Process

Improving the Informed Consent Document: The NCI Working Group

In the late 1990s, staff at the National Cancer Institute (NCI) of the United States became concerned about the state of informed consent in cancer treatment trials. They believed that informed consent had become a liability management tool for institutions and that the goal of providing information to help people make a decision had been lost. The informed consent documents were long, difficult, and complex. To address these concerns, NCI staff established a working group to review the informed consent process in cancer treatment trials.[30]

The working group—which consisted of 35 people, including patients, investigators, lawyers, and communications experts—worked together for two years. Members of the group reviewed the requirements under the Common Rule (see page 3) and drafted recommendations for the informed consent process, which included the following comments on the required elements of information disclosure:

- The description of the purpose of the study should include a statement on the limitations of potential benefits for the participant.
- The research regimen should be clearly distinguished from the existing standard of care, so that potential participants understand what is different about the research.
- Possible benefits should not be overstated.
- Possible side effects should be listed as a whole, not grouped by specific drug or procedure, and they should be categorized by probability and severity.
- Risks associated with usual medical care should not be included.
- Patients, both women and men, should be informed of reproductive risks.
- Patients should be informed of possible non-physical risks.

With the permission of researchers, the NCI working group rewrote informed consent documents for existing studies. The new forms were reviewed and critiqued in focus groups, after which further revisions were made. The final product, a two-page form with addendums, was used by the working group to develop a template.[31] The revised informed consent form:

- Uses the second person and is conversational in style;
- Employs a question-and-answer format; and
- Uses schemas or visual representations of the text.

Currently, other parts of the National Institutes of Health (NIH) are adopting similar forms, and some of the same revisions are being made in the United Kingdom and Germany. In addition, the

[30] McCabe, Mary. "Informed consent: Making it understandable—The recommendations of an NCI working group," seminar presentation.

[31] Comprehensive Working Group on Informed Consent in Cancer Clinical Trials. 1999. *Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials,* NIH Publication no. 99-4355. Bethesda, Md.: National Cancer Institute.

NIH is funding studies on research ethics, including informed consent. The NCI is also experimenting with the use of alternative means of conveying information (e.g., videos and pictures). It has found that using these tools results in only a small improvement in comprehension. Not surprisingly, the interaction between the health professional and the patient or participant often makes the most difference in the effectiveness of the informed consent process.

Finding Ways to Aid Understanding: The Flower Diagram

Researchers conducting a community development project among commercial sex workers in a Vietnamese community in Cambodia developed an innovative technique to improve the information disclosure process. Women in the community development project were young and had little money or education. Often they had been brought to Cambodia by relatives or "middlemen" who may have deceived them about the nature of the work in which they were engaged. Many of the women arrived in Cambodia already in debt and were forced to give 50 percent of their profits to brothel owners, in addition to paying for water, electricity, clothing, laundry, and police bribes and sending money to relatives at home. They faced harsh working conditions and suffered violence at the hands of clients and the police.

Many of the women in the project could read or write, but even those who were literate found the informed consent form boring and difficult to understand. Researchers responded by incorporating a visual image and exercise into the informed consent process to communicate to the women the risks and benefits of participation in the project and to stimulate their thinking about the implications of the project for their lives. First, researchers divided the women into three groups of eight to ten women. Using the image of a flower, the women were asked to create petals to represent the benefits of participation and thorns to represent the risks. The three groups then reunited and combined their petals and thorns into one flower (see Figure 1).

The researchers concluded that the flower exercise engaged the women's interest and aided their understanding. It was also an easier and quicker way to present relevant information. While this exercise has not been formally evaluated, it provides an example of adapting the informed consent process to different populations and local conditions.

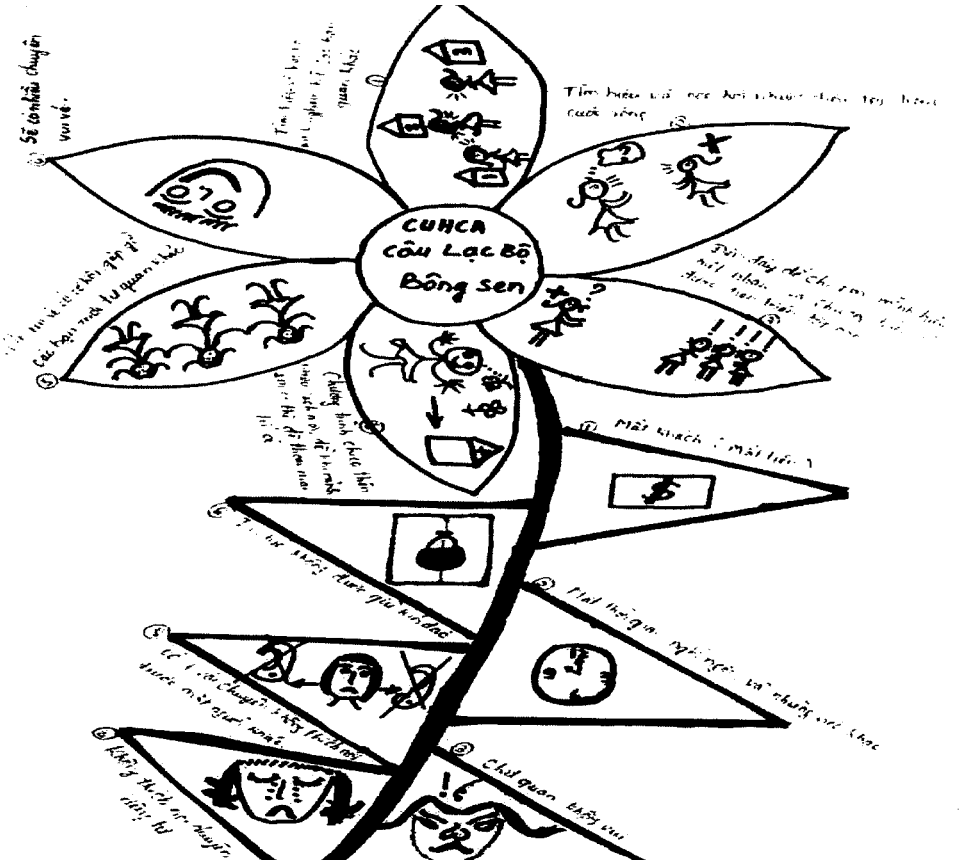
Understanding Risk

A significant part of the informed consent process is communicating and understanding the risks involved in participation in a study. The field of risk analysis offers some interesting and useful information about risk and the ways that people assess risk and apply risk assessment to their own lives.

People face many kinds of risk—financial and health risks, risks of natural disasters, and so forth. Risks to health occur at both the population and individual level. In assessing risk, three questions should be asked:

- What can go wrong?
- How likely is it that something will go wrong?
- If something goes wrong, what are the consequences?

Figure 1: The Flower Diagram[32]



Petals

- Learn more about women in other brothels.
- Get new information.
- You will learn more about us and life in Svay Pak.
- We will learn more about you.
- We can come here to "ease our mind" and talk to someone.
- Make new friends, have fun.

Thorns

- During the time spent participating, the opportunity to be with clients would be lost.
- Loss of leisure time usually spent napping, relaxing, socializing.
- Some (other) brothel managers might not be happy with sex workers who miss time with clients.
- Talking about some topics in front of other women can be dangerous. If managers or other sex workers heard some of the information that was supposed to be confidential, it could be damaging.

The informed consent process often focuses on the first of these questions—what can go wrong. For the purpose of avoiding liability, *all* the things that could possibly go wrong are listed. Less attention is given to weighing the probability of something happening or to evaluating the consequences for the individual.

[32] Da Ly, Saran. "Flower diagram consent form," seminar presentation.

The way that risk is presented and framed has a major effect on how it is understood and interpreted. Some of the factors that affect understanding are: quantitative or qualitative presentation, the numbers used (e.g., 2 in 10, 1 in 5, two-tenths, 20 percent, and so forth), and description of absolute versus relative risk. Not surprisingly, *who* delivers the information is important and influences comprehension and interpretation.

The field of risk assessment offers some interesting lessons about how people understand risk in the face of limited information:

- Generally, people exhibit an "optimism bias"; they feel "it won't happen to me." For example, one researcher asked a random sample of adults to rank their risk as below-average or above-average for 32 hazards, including asthma, drug addiction, food poisoning, and lung cancer. The study found a "significant optimism bias" for 25 of the 32 hazards.[33]
- People use "cognitive heuristics to make judgments about uncertain events."[34] One of these is "availability," or the ease with which an event can be imagined or recalled. Incidents that are widely reported in the media are perceived as more likely to occur than those that are not, making dramatic, "newsworthy" events seem disproportionately risky. The result is that rarer risks (e.g., airplane crashes) are overestimated and more common risks (e.g., traffic accidents) are underestimated. The Internet also influences risk perception, because information on the World Wide Web may seem authoritative, even if it is not. Immediacy and proximity of an incident also influence perception of risk. For example, seeing a burning house may increase the perceived risk of a fire in comparison to hearing about a fire on the radio. And, the more recent the experience, the more "available" it is and the more likely it will be viewed as a risk.
- Another factor is the "anchor," or starting point: the information people hear first influences their assessment. For example, on average, when asked to quickly estimate the product of $1\times2\times3\times4\times5\times6\times7\times8$, people will come up with a smaller number than if asked to estimate the product of $8\times7\times6\times5\times4\times3\times2\times1$. Unrelated information provided simultaneously may also change perception. For example, two groups of people were asked to estimate to themselves the percentage of countries in the United Nations that are in Africa. A roulette-type wheel was then spun in the background; participants believed it would stop on a random number between 0 and 100, but in fact it was fixed to stop either on 10 or 65. After the wheel was spun, people were asked whether their estimate was below or above the number showing on the wheel, and then they were asked to reveal their actual estimate. The group that saw 10 on the wheel gave an average of 25 percent as the percentage of African countries in the United Nations, while the group that saw 65 gave an average of 45 percent.[35]
- The way that a risk is framed also influences people's assessment of it. For example, using the terms "lives lost" or "lives saved" may impart a negative or positive association and influence the perception of risk.[36]

[33] Weinstein, Neil D. 1987. "Unrealistic optimism about susceptibility to health problems: Conclusions from a community-wide sample," *Journal of Behavioral Medicine* 10(5):481–500.
[34] Thompson, Kimberly. "What is it?: Understanding and communicating risk," seminar presentation.
[35] Ibid.
[36] Ibid.

Visual aids have been shown to be helpful in communicating risk and probability and to overcoming people's inability to understand numbers and even words. For example, "risk ladders" can help to convey where a risk falls in relation to other hazards. Showing people 100 dots on a piece of paper and indicating that a certain event would happen to two of those dots can effectively convey probability.[37]

In risk assessment, "perception equals reality," because people act on what they believe to be true, regardless of the facts. Hence the way that information about risks (and benefits) is provided greatly influences people's perception of risk and the decisions they make. More research about risk assessment is needed, especially on variability and uncertainty. Variability is the difference in real risk between individuals (e.g., how the use of air bags affects children differently than adults). Uncertainty is the lack of perfect knowledge about risk. Often little is known about research risks, especially in Phase 1 clinical trials. Nonetheless, it is important to talk through these uncertainties with potential participants and to communicate the possibilities of risk to them.

EVALUATING INFORMED CONSENT

Although informed consent is a part of virtually all research protocols, surprisingly little research exists on it. Evaluating informed consent presents a number of challenges. It is important to decide which aspects of informed consent are to be assessed: Is the goal to assess what the researcher or clinician told the participant, what that participant can remember, or what he or she actually understood? Interpretation of results also can be difficult. For example, if a participant says that she was not given a piece of information, was the information not provided, provided but not understood, or understood initially but now forgotten or confused? If the information was not understood, the reasons may vary: Too much information was given, it was not presented well, it was too technical, or it was perceived as having been given in order to protect the researcher. It may be that the person was given information, but did not want to know it. Even if a participant can recall information provided, it may not have been understood.

The methodology for studying informed consent also presents challenges. Researchers can review informed consent documents, listen to audiotapes of conversations, or question participants after the fact. Evaluating informed consent with people outside of a given trial is an alternative, but this has limitations, too: The emotions of the participants in an informed consent study are not likely to be the same as those of people who are truly considering participation in a trial. Finally, careful phrasing of evaluation questions is important so that the results of an informed consent assessment accurately reflect the understanding of participants.

A review of some of the existing research on informed consent and two examples of assessments that have been conducted provide some interesting lessons for those seeking to improve implementation and evaluation of the informed consent process.

[37] Ibid.

Review of Existing Research on Informed Consent

A review of research evaluating informed consent found four studies that assessed informed consent in research, ten studies that evaluated informed consent in clinical procedures, and 12 that focused on informed consent techniques.[38] Some of the findings of this research include:

- Most study participants think that they understand the information provided better than they actually do.
- The timing of both disclosing information and seeking consent matters. A few of the studies on informed consent found that it is better to provide participants with written information in advance and then go through the document orally at the time of the procedure. Other studies found that most people do not read such information.
- Possible side effects of treatments are remembered more easily than the burden of participation in research (e.g., the number and frequency of visits, tests, and so forth).
- In research, healthy people seem to understand the study better than those who are ill. Participants in cancer trials, for example, are often confused about the distinction between therapy and research. In general, the older or sicker the person, the less well he or she is likely to understand.
- People are less likely to remember "bad news," for example, a study of the informed consent process for a detached retina operation found that many participants did not remember being told that they might go blind.
- The more a participant understands about a study, the more likely he or she is to comply with the study requirements.

Informed consent in reproductive and sexual health research may differ from informed consent in medical treatment, because trial participants are usually healthy and thus have a broader range of genuine choices. Researchers at Family Health International conducted a study of the informed consent process and the understanding of risk in a contraceptive clinical trial in four sites.[39] At three of those sites, in Latin America and the United States, written forms were used and at the fourth, in Africa, they were not. The researchers found that:

- Participants without written materials recalled information as well as those who had received the information in writing.
- Altruism—the desire to help others—was given as an important motivation for participation.
- Recall was good, even when understanding was limited. For example, participants remembered the numerical assessments of pregnancy risk, but still thought that the risk of pregnancy was lower with a spermicide than with the pill or IUD.
- The longer the participants were in a study, the better they understood that they could leave it if they wished.

[38] Fortney, Judith A. "Assessing informed consent," seminar presentation.
[39] Fortney, Judith A. 1999. "Assessing recall and understanding of informed consent in a contraceptive clinical trial," *Studies in Family Planning* 30(4):339–346.

What should be done if it is clear that people do not fully understand the information that they have been given, but nonetheless choose to participate? Who decides what constitutes sufficient understanding? These questions have no simple answers, but clearly researchers need to ensure that the most important information is understood. As discussed in "Informed Consent as a Process" (page 10), the threshold of understanding for participation in research should be higher than that for treatment. In addition, the standards for comprehension must be related to the potential risk for participants: The higher the risk, the more rigorous the measure of comprehension.

Finally, the fact that clinical trials are research is often poorly understood and, indeed, may not be of importance to the participants. For researchers, answering the research questions is the focus, but the priority for participants may be the potential benefits to themselves, or, if they are motivated by a sense of altruism, to others. This creates a dilemma: If answering the research questions is not the main priority of the participants, how important is it that they comprehend the details related to them, let alone that they can recall them later? This underscores the point that participants may want and need different kinds of information in order to make their decisions (see "The Elements of Informed Consent," page 8).

Case Studies of Evaluation of Informed Consent

A Microbicide Safety and Acceptability Trial in South Africa

The Population Council is conducting clinical trials of its candidate microbicide Carraguard™, a product that potentially could be used topically to reduce infection from HIV/AIDS and other sexually transmitted infections. In an effort to ensure truly informed consent and voluntary participation in communities of people at high risk of HIV infection, the researchers assessed the informed consent process at several points before, during, and after a Phase 2 expanded safety trial of Carraguard in South Africa.

The design was a randomized, placebo-controlled, double-blind trial. Participants were instructed to insert Carraguard or its matching placebo vaginally every other day, and to use the gel and a condom every time they had sex. Monthly follow-up visits included safer sex counseling, a gynecological examination, and an interview.

Prior to beginning the trial, the informed consent form was pre-tested in the recruitment communities. The consent form, written at a U.S. eighth-grade reading level, had already been approved by the local ethical review committees at each of the study sites and by the Population Council's IRB. A lexicon was then developed to ensure clarity and consistency in translation, particularly for words and concepts (such as "placebo," "randomization," and "microbicide") that do not exist in Xhosa and Tswana, the local languages.

Local social science researchers conducted focus groups and in-depth interviews to assess women's understanding of the purpose of the trial and to solicit feedback on the readability and language used in the form. The results revealed that the women found the information overwhelming and the layout of the form difficult to follow. They did not fully comprehend the

research concepts and were confused by the primary and secondary purposes of the study (testing safety and testing preliminary effectiveness, respectively).

Based on these findings, the informed consent form was rewritten to clarify the main purpose of the study. The layout was also revised: Shorter sentences were used and lengthy paragraphs were replaced with bulleted lists. In addition, Population Council staff worked with local study staff to develop a recruitment script and flipchart to explain the trial to potential participants. Involving the staff who would do the recruitment and counseling in the process of reviewing and revising the informed consent materials also served an important training function.

Once the new informed consent form and procedures were implemented, interviews were conducted with the first 20 women actually enrolled in the Phase 2 trial. Based on the results of this evaluation, no major changes were made to the form itself. Instead, the researchers focused on improving the *process*. A series of questions was developed for use by study staff to probe for understanding during the consent process. To supplement the informed consent form, researchers created a booklet with illustrations and analogies to communicate difficult concepts.

The researchers made the following recommendations from the two assessments and their overall experience:

- Standardize the informed consent process for study staff (e.g., by developing scripts or lists of questions).
- Focus on the staff. Select personnel carefully; not everyone will be able to convey complex information. Provide education and training to increase staff commitment to informed consent and to give them the tools they need carry it out.
- Listen to staff feedback. Ask them to identify areas that participants have difficulty understanding. Get staff input on how to improve the documents and process.
- Use simple terms and find analogies that potential study participants can understand.
- Use various approaches to aid understanding that build on each other and work together, such as flipcharts, question-and-answer formats, visual aids, and analogies.

Perhaps the most important lesson the researchers learned was that developing and assessing a process for informed consent can be long, complex, and costly, and to do it effectively, resources and time must be dedicated to the process.

A Reproductive Morbidity Study in The Gambia

In 1981, the Medical Research Council of the United Kingdom conducted a reproductive morbidity survey in 20 villages in The Gambia. The researchers recruited 1,348 women 15–54 years old for the study, which involved an interview about their general, reproductive, and mental health; a gynecological examination at the village health post; and the taking of blood and urine samples.

The informed consent process was conducted at three levels. The researchers first met with village leaders, including religious leaders and traditional birth attendants, and told them about the nature and purpose of the study. Once the leaders had agreed, the researchers held meetings

with village residents to talk about the study. Finally, individuals who were interested in participating in the study went through a one-on-one informed consent process, after which they were asked to sign a consent form that had been translated into the three local languages.

Researchers then did a follow-up study of comprehension and acceptability of the original research project. They were interested in discovering whether informed consent had been meaningfully sought and granted in a context in which the study participants are poorly educated and have little access to health care. They also wanted to find out whether the women had learned anything about reproductive health. The methodology of the follow-up study was semi-structured interviews (Box 3 describes some of the findings and provides examples of the responses).

The researchers found that most of the women had understood that the purpose of the original study concerned health, without fully comprehending that it was a research project. The women's comprehension of the procedures was also limited, and they had a strong tendency to place their trust in the doctor. Eighty-seven percent of the women said they thought they had benefited from participating in the study, but many could not define how. Nearly one-third mentioned treatment as a benefit. The researchers also looked at the people involved in making the decision to consent to the study and found that two-thirds of the women had consulted someone.

Were the participants informed? Most had a basic understanding that reproductive health was the focus of the study, but they did not comprehend well that the study's purpose was research. Had they consented? Many had consulted with their husbands, and some felt that they could not participate without their husbands' permission. The opinions of others (e.g., mothers-in-law) were sometimes influential. The community perspective was important, but not determinant. A major incentive for participating was the availability of better services and treatment, which raises the question of whether availability of services and treatment served as too strong an incentive, thereby constituting "undue inducement."[40]

The researchers drew the following conclusions from the follow-up study:

- Staff play an important role and need to be provided with tools and training.
- The informed consent form should be standardized, but staff must have some flexibility. For example, in this situation, the field workers adapted some of the language to use with the older women.
- Information may need to be simplified and repeated. It may also be helpful to use alternative means to communicate information (e.g., videos).
- Participants should be told clearly what they should expect to hear back from the researchers about study results.
- Providing treatment can improve acceptability and may provide study participants with a strong incentive to consent to research.

[40] One suggestion for reducing the possibility that the provision of services may constitute "undue inducement," at least in some situations, is to organize a "health camp" for the entire community, during which treatment is provided to everyone. This also helps to maintain confidentiality of participants, since they are not the only ones getting treatment.

Box 3: An Evaluation of Informed Consent in The Gambia[41]

Did the women understand the purpose of the study?

They are checking to know whether we have diseases or not.
They came to give free treatment to us all.
The reason is just to take our blood and then go away.
I think they are doctors; that's why they came . . . because they know better than us.
I was examined but they did not tell us why.

Who gave the consent?

33 percent—mostly older women—had consulted nobody.
I did not discuss with anyone because I want to be healthy.

47 percent had consulted their husbands.
I discussed with my husband and he felt that they wanted to help us.
I did not discuss with my husband because he was not around, and when he came he said I should not have joined.

What did the women understand about the procedures?

I did not feel anything bad, but sometimes I felt shy.
I did not have any problem with it as the doctor is doing her work.
I did not know why the doctor examined inside my body.
I was not told my results but I was given medicine.
You don't understand anything about the work.

What did the women gain from the study?

31 percent mentioned the treatment.
I was tested and they found I was infected and I was treated.

9 percent said they had gained knowledge.
People were found infected without any symptoms, this made us surprised and we gained knowledge.

Final Reflections on Evaluating Informed Consent

While the seminar participants recognized the need to evaluate the informed consent process in order to find ways to improve it, they also identified several challenges:

- The informed consent evaluation may require IRB approval depending on its design. This could slow down the process of evaluating informed consent procedures.
- Independent review of the informed consent process helps to avoid possible conflicts of interest on the part of the researchers involved in the primary research. Even independent researchers are not immune to possible conflicts of interest, however, if they are paid by the sponsors of the original research project. The additional time and expense required for an independent review may also prolong and complicate the process to the point that it

[41] Paine, Katie. "Informed consent: What can it mean in rural Gambia?" seminar presentation.

becomes an undue encumbrance and a significant barrier to doing any evaluation at all. If measures are taken to avert conflicts of interest, an internal review process can be more manageable.

- Integrating the review of informed consent into the research process creates an important opportunity to train the field staff and to monitor and adjust the informed consent process on an ongoing basis.
- Monitoring and evaluation should focus on building the capacity of staff to communicate with participants and on improving implementation of the informed consent process, rather than enforcing overly rigid procedures.
- The need to monitor and evaluate informed consent should be kept in perspective. Not all research involves the same degree of risk or burden for the participants. The greater the potential risk or burden, the more essential it is to review and monitor the informed consent process rigorously.

INFORMED CONSENT IN SPECIAL POPULATIONS

Some study populations may be more vulnerable—due to age, gender, socio-economic status, or physical, mental, or emotional state—and thus require special consideration in the informed consent process. When working with people in these groups, researchers should seek ways to strengthen their autonomy and to support their ability to make informed decisions.

Adolescents: Balancing Autonomy, Protection, and Justice

In conducting research among adolescents, a potential conflict arises between the desire to honor the emerging autonomy of the individuals and the need to protect them. While adolescents are often inclined to be motivated by altruism, they are also particularly vulnerable regarding body image and the need for privacy and confidentiality. Specific guidelines have been developed to address some of the complexities concerning research with children and adolescents—providing an illustration of the kind of thinking needed to find practical ways to apply the principles of informed consent.

Laws regarding children have evolved over time. Under English Common Law, children were considered property. Over time, the law in the United States has recognized children's autonomy, including the right to treatment and the right to privacy, but it was not until 1967 that the U.S. Supreme Court classified children as persons with the right to due process. Despite this recognition, children are presumed incompetent, without legal capacity to give consent, and parents are viewed as the best protectors of a minor's interests. When a conflict of interest arises between the child and the parent(s) or guardian(s), however, the state may intervene on the side of the child.

In the United States, state laws vary. Many acknowledge the right to treatment, a sort of limited autonomy, for specific "medical conditions," such as STIs/HIV, pregnancy, and drug use. The ethical foundation for these laws is not belief in the capacity of adolescents, but rather a utilitarian view that the denial of such treatment could adversely affect their welfare by preventing them from seeking services.

Reflecting the broader debates around the principle of justice and participation in research, the understanding of the balance between protection from risks and access to benefits for adolescents has begun to shift. Children and adolescents cannot fully benefit from research unless they are allowed to participate in it. The lack of research involving young people has resulted in their exposure to unknown risk; for example, some 70 percent of medicines used in pediatrics have never been tested on children. A relatively new NIH policy states that "children" must be included in research, as follows:

> *. . . children (i.e., individuals under the age of 21) must be included in all human subjects research conducted or supported by the NIH, unless there are clear and compelling reasons not to include them.*[42]

The literature on the cognitive development of young people suggests that by the age of 12–13 years, they begin to understand abstract concepts, and that at approximately 14 years, their cognitive abilities roughly equal those of an adult. The term "assent" was developed to address the existence of a significant ability to make decisions in the absence of legal capacity. It is defined as:

> *. . . a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.*[43]

The assent process should be individualized, based on the ability of the young people involved:

> *. . . the IRB shall determine that adequate provisions for soliciting the assent of the children when in the judgment of the IRB the children are capable of assenting . . . the IRB shall take into account the ages, maturity, and psychological state of the children involved.*[44]

In addition to the assent of the child, parental "permission" is required.[45] Requiring parental permission, however, may cause some young people to be reluctant to reveal risky behavior or to seek services. In certain instances, such as child abuse, parental permission may be waived. In this case, alternative means are established to protect the young person, including:

- Court approval;
- Designation of a child advocate, who must have no connection to the research;
- Permission from a surrogate parent; and/or
- Community consultation.

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[42] National Institutes of Health (NIH). 1998. *NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects*, Section III: Policy. Bethesda, Md.: NIH.

[43] U.S. Department of Health and Human Services, Office for Protection from Research Risks, and National Institutes of Health. 1991. Code of Federal Regulations, Title 45, Part 46, Subpart D, Section 46.402(b).

[44] U.S. Department of Health and Human Services, Office for Protection from Research Risks, and National Institutes of Health. 1991. Code of Federal Regulations, Title 45, Part 46, Subpart D, Section 46.408(a).

[45] Because no one, including parents, may offer "consent" for another individual, the term "permission" is used to convey that the parent(s) or guardian(s) must agree to their child's or ward's participation in research.

In the mid-1990s, the Society for Adolescent Medicine developed new guidelines for adolescent health research, including the question of parental permission. Pointing to evidence of tremendous variation in IRB decisionmaking concerning research involving young people, society members believed that research was increasingly being restricted, with negative consequences for adolescents. They viewed the existing federal guidelines as inadequate and initiated a national consensus process to develop new ones, attempting to balance respect for parents as primary protectors of their children with the growing capacity and emerging autonomy of adolescents.[46] Using a typology of risk for health research with children[47] in the federal regulations (see Box 4), the guidelines recommend the following:

- In minimal risk situations, parental permission may be waived, as long as privacy and confidentiality are ensured, the adolescent provides informed consent, the adolescent is encouraged to consult with an adult prior to participation, and procedures are established for the adolescent to seek confidential assistance.
- For research that is of potential direct benefit to the participants, but of greater than minimal risk, more should be done to augment the adolescent's capacity to give consent and to find an adult who is committed to her or his welfare and willing to provide support. Furthermore, a professional unconnected to the research should assess the adolescent's capacity to give informed consent.

Despite the many barriers to conducting research with adolescents, the concrete guidelines referred to above can help to ensure the validity of the informed consent process, while enabling greater inclusion of adolescents in research.

Box 4: Typology of Risk in the Regulations for Research with Children

The range of risk involved in research varies tremendously, from simple survey research, where the risk is minimal as long as confidentiality is assured, to the administration of pharmaceuticals that could induce serious side effects or even death. A typology of risk has been developed within the regulations for research with children, as follows:

1. Minimal risk (e.g., surveys, drawing blood, and so forth) where the potential risk of harm or discomfort should not exceed that of "daily life," such as that encountered in a routine visit to the doctor's office.
2. Greater than minimal risk, but with direct benefit (e.g., therapeutic trials) where the potential risk is justified by the potential benefit.
3. Greater than minimal risk with no direct benefit (e.g., non-therapeutic research) where generalizable knowledge to be gained is of "vital importance."
4. Research requiring special approval (rarely used).

[46] Santelli, John S., Walter Rosenfeld, Robert H. Durant, Nancy Dubler, Madlyn Morreale, Abigail English, and Audrey Smith Rogers. 1995. "Guidelines for adolescent health research: A position paper for the Society of Adolescent Medicine," *Journal of Adolescent Health* 17(5):270–276.

[47] Risky, non-therapeutic research on children is prohibited.

Consenting Partners

Under what circumstances, if any, should the partners of study participants be asked for their consent? In the case of reproductive and sexual health research involving women, such as contraceptive trials, should men be asked to give their consent? The debate concerning the appropriateness of seeking male partners' consent for women's participation in research revolves around two issues:

- Sensitivity to cultural dynamics in which women are not recognized as autonomous beings and/or the community plays a key role in decisionmaking; and
- How women's participation in research may affect men, including the social, psychological, and biological effects.

It is argued that the concept of individual decisionmaking may violate some cultures' emphasis on the collective. This view was captured by an editorial in the *Journal of the American Medical Association* in 1995 that referred to a body of literature stressing that the individual is embedded in society and that family and community decisionmaking should be taken more seriously by researchers. The editorial states, "Autonomous decision making may counter family-centered values and the social meanings of competency and . . . obedience."[48]

Others challenge this view, which they say preserves existing power structures: "By appealing to a sense of cultural relativity or cultural respect, it is the male value systems that are given precedence. . . ."[49] In a recent article, bioethicist Ruth Macklin refers to unpublished guidelines of the Scientific and Ethical Review Group of the World Health Organization's Special Programme of Research, Development, and Research Training in Human Reproduction that state that partner agreement "violates the autonomy of research subjects and their right to confidentiality."[50] Nonetheless, Macklin points out, the guidelines also say that the prohibition against partner agreement may occasionally be outweighed if denying the eventual benefits of the research to the entire society would be "so great a drawback":[51]

> *However, because of existing cultural, religious, political or legal constraints it is sometimes impossible to achieve the ethical ideal and exceptions to this general principle may have to be accepted. . . . In rare circumstances it may be necessary for researchers to conform to local custom and request partner agreement.*[52]

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[48] Gostin, Lawrence O. 1995. "Informed consent, cultural sensitivity, and respect for persons," editorial, *Journal of the American Medical Association* 274(10):844–845.

[49] IJsselmuiden, Carel. 1997. "Some theoretical aspects of HIV/AIDS prevention trials: Protecting subjects against research risks and ensuring a fair distribution of potential research benefits," background paper prepared for the Symposium on Practical and Ethical Dilemmas in the Clinical Testing of Microbicides, Warrenton, Va., 26–30 April.

[50] Scientific and Ethical Review Group, World Health Organization (WHO) Special Programme of Research, Development, and Research Training in Human Reproduction. 2000. "Guidelines on reproductive health research and partners' agreement," in *Preparing a Research Project Proposal, Guidelines and Forms*, ed. 3. Geneva: WHO, pp. 28–31.

[51] Macklin, Ruth. 2000. "Informed consent for research: International perspectives," *Journal of the American Medical Women's Association* 55(5):290–293.

[52] Scientific and Ethical Review Group, op. cit.

In 2001, the U.S. National Bioethics Advisory Commission released a report on clinical trials in developing countries, which suggests that in some cases it may be necessary to seek the partner's permission, but only as a supplement to—never a substitute for—a trial participant's consent:

> *In none of these cases should permission from another person [e.g., husband] replace the requirement of the individual participant's [e.g., woman's] informed consent.*[53]

The most complex situation is one in which a product under investigation could have a biological or physical effect on the partner. This has been an issue in the context of microbicides trials. A report from a 1997 symposium on ethical considerations in the clinical testing of microbicides recommended that once safety has been established in early trials (e.g., male safety studies), researchers should not require partner consent.

> *Not only would [conditioning a woman's involvement in a clinical trial on the consent of her male partner] undermine women's autonomy, but it could put some women at risk of violence or abandonment. . . . It also raises questions about how to handle situations where women may have several partners. . . . Once safety ha[s] been established, trials should no longer require partner consent.*[54]

For example, in the Population Council's Phase 2 microbicide trial in South Africa, staff offer information and counseling for men, but it is the woman who decides whether to suggest to her partner that he make use of these services. In practice, women have often wanted their male partners to be involved. By encouraging women to make that decision, the researchers have sought to enhance, not diminish, their autonomy.

For researchers seeking to find the balance between respect for individual autonomy and cultural sensitivity, the compromise may be to create an informed consent process that enables the participants to consult and involve others without *requiring* them to do so. Ideally, such consultation can contribute to social change, by creating opportunities for learning, for communication, and for shared responsibility.[55]

Informed Consent and the Rights of Refugees

Refugees and displaced persons may live in circumstances and share characteristics that make them especially vulnerable, thus requiring special attention in the informed consent process. Most refugee situations stem from long-term conflicts, and the countries and people affected are among the world's poorest and have limited autonomy. An exploration of the conditions that

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[53] National Bioethics Advisory Commission. 2001. *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries, Volume 1: Report and Recommendations of the National Bioethics Advisory Commission*. Rockville, Md.: National Bioethics Advisory Commission.

[54] Heise, Lori L., C. Elizabeth McGrory, and Susan Y. Wood. 1998. *Practical and Ethical Dilemmas in the Clinical Testing of Microbicides: A Report of a Symposium.* New York: Center for Health and Gender Equity, International Women's Health Coalition, and Population Council.

[55] The same principle of consultation as a supplement to—never a substitute for—individual consent can be applied to the question of community consent.

affect informed consent among refugees offers a useful illustration of the factors that researchers should consider when doing research with any potentially vulnerable population.

Refugees[56] have the same rights in research settings as any other persons, although they are not named specifically in the international guidelines for research, such as those by CIOMS. In 1997, a WHO committee recommended that research in emergency situations should be of immediate and direct benefit to the affected population. Furthermore, it stated that the research should be done in any other, non-emergency setting, if at all possible. Since then, the discussion has shifted—along the lines that the general debate around the risks and benefits of research has moved—to emphasize the potential benefits of research to refugees.

Researchers working with individuals in forced migration settings should be guided by the same standards for informed consent as in any other situation, but they also need to take into account some factors specific to the population, including:

- Refugees often are dependent on others for food and other material needs. Given their dependency on others for survival, they may not feel that they are in a position to make choices about participation in research. They may believe that researchers control the resources and thus say whatever they think researchers want to hear in the informed consent process. In this situation, ensuring that consent is truly voluntary is a challenge.
- People who have been forced to migrate may be traumatized—by war, by physical violence, by being forced out of their homes—possibly affecting their ability to understand information and to make decisions regarding informed consent. Researchers must take special care to consider the participants' ability to comprehend and to decide freely.
- Refugee organizations often function in crisis mode, responding quickly in emergencies, that may not be consistent with the need for the long-term planning that research requires, including IRB review and careful implementation of a thorough informed consent process.

Good research that produces sound data can help to design better services for refugees. In doing that research, however, investigators need to recognize the special ethical and practical challenges inherent in emergency settings and pay close attention to how those challenges affect the informed consent process.

COSTS AND BENEFITS

Implementing and assessing informed consent, including providing adequate training for staff and thorough monitoring of the process, requires resources. Therefore, donors who support research should expect to designate funds for this purpose. Little is known about the actual costs of implementing informed consent in research, however, such costs are likely to be a very small part of the total research budget. Better cost analyses of informed consent could put those costs into perspective relative to other expenditures and help in the budget planning process.

[56] There are 14.5 million refugees and 20–24 million displaced persons in the world today. (U.S. Committee for Refugees, *World Refugee Survey 2001*). A legal distinction defines these two groups: Refugees have crossed national borders, and displaced persons remain within their own country. The latter status generally garners less international attention and protection. In this report, refugees is used as a general term to describe all people in situations of forced migration.

The cost of implementing and monitoring informed consent will depend on the guidelines and procedures established by the organizations sponsoring or conducting the research. These costs may even vary within one research project, as implementation of the informed consent process often happens at the local level, where guidelines can be interpreted very differently.

Frontiers, a health systems research project of the Population Council, is carrying out 61 studies in 25 countries, all of which include informed consent. In order to strengthen oversight of the informed consent process, project managers reviewed a sample of informed consent records and interviewed researchers, data collectors, and study managers about their views on the costs and benefits of the informed consent process. The review was completed in 19 of the 61 study sites. The following points were raised about the costs of informed consent:

- The cost of oversight is seen as potentially large. Research projects often have fixed-cost budgets, which may not allow for the expense of monitoring the informed consent process.
- Staff may see the informed consent process as "one more thing" to do—one of many "burdensome" bureaucratic obligations with which they must comply.
- Project staff are not always certain what they are expected to do. Guidelines can be helpful, but they often leave uncertainty about application and implementation in a particular study or setting.

The benefits of informed consent included:

- Participants appreciate information that gives them a better understanding of the study.
- Better-informed study participants are more committed to the research and are thus less likely to leave the study.
- Data quality may be improved because the participants understand the study better and are more likely to give thoughtful responses.
- Researchers and their institutions are protected from litigation.

The cost of oversight increases as activities are added to ensure that the informed consent process is carried out properly. Some of the determinants of marginal costs include:

- Complexity of the research project;
- Amount of training and supervision that may be required;
- Number and geographic dispersion of the study sites; and
- Level of documentation required.

The "cost"—monetary or otherwise—of implementing informed consent can vary depending on the perspective of who incurs the cost. The cost of the informed consent process for the study participant is likely to be relatively low, although the cost of actual participation in the study may be significantly higher. For study managers and researchers, the cost of informed consent may be relatively high. It can be time-consuming and, especially if on a fixed-cost contract, the costs incurred may not be adequately covered by the budget. For an institution, the cost is likely to be modest.

On the other hand, the cost of *not* implementing a comprehensive informed consent process to study participants can be quite high: They may be uninformed about the study, may potentially be exposed to risk without their knowledge or consent, and may not have the means to resolve complaints. For the institution, the costs of non-compliance can also be high: Research may be suspended or more closely scrutinized, the institution may be subject to financial and management audits, and research funds may be withdrawn.

In order to effectively monitor informed consent, standards must be established for different components of the process (e.g., informed consent forms, staff training, procedures to maintain data, and guaranteeing privacy). In addition, markers or clues must be identified that can highlight a need to initiate closer scrutiny and perhaps undertake an external review.

Any analysis of costs and benefits of the informed consent process should include some of the less obvious benefits of informed consent, such as the increased knowledge gained by the participants that may have significant benefits outside the study setting. It is also important to consider the sustainability of benefits beyond the research period. For example, the informed consent document might be adapted for use if a product or procedure is later introduced into the service-delivery setting, thus reducing the costs of materials development at that stage.

An assessment of costs should also take into account the availability of resources and the competing demands for their use. The poorer a country, the more burdensome the costs of research may seem. For example, for a country like Mozambique, which spends $75 million annually on health, a $3 million study would constitute 4 percent of its total health budget.[57] While the research may provide benefits to the study participants, the costs of doing the research are disproportionate to the resources available for health. This leads to questions about why research is conducted in a given setting: Is it to help the people in that country or because there is a high incidence of the condition being researched in that country, or is it simply cheaper to do research in that country? The issues around the costs of informed consent are part of a broader ethical debate regarding the appropriateness of conducting high-priced research in resource-poor settings.

CONCLUSION

The field of research on drugs, devices, and procedures is rapidly growing and diversifying. The challenge is to develop a process that includes the key actors—researchers, governments, nongovernmental organizations, funding agencies, sponsors, and diverse communities and constituencies—to ensure that research is conducted in a manner that is sound and ethical, with informed consent at its core.

[57] This raises the larger question of how resources are allocated and two related problems: the lack of consultation with civil society on determining spending priorities and the scant attention paid to research by many governments.

As the issues around doing ethical research in health will only grow in scope and complexity, the community of people and institutions concerned about informed consent and charged with protecting the rights of research participants should consider the following:

- As the conduct of medical research becomes increasingly globalized, it is important to look outside of the United States for examples of how to do ethical research, including informed consent. The laws and practices of France, Germany, India, Japan, and South Africa, for example, differ significantly from those of the United States. As both private industry and public research organizations in these countries increase both their investment in developing new pharmaceutical products and their participation in clinical research, their approaches will become more influential.
- The expansion and growing complexity of the field of medical research has increased the possibility of exploitation. Many researchers wrestle with the practical issues of implementing research in an ethically sound manner. However, the motivations for research are complex—among them profit, prestige, professional advancement, increased knowledge, and improved public health—making ethical guidelines difficult to implement and monitor. Given this, even the most comprehensive ethical guidelines or review processes cannot completely safeguard against unethical research.
- Recent developments in the pricing of AIDS drugs have increased awareness of the critical need to ensure that the benefits of drug development are shared by the people who participate in sometimes risky and burdensome research and the public, rather than going disproportionately to corporate stockholders or populations in wealthy countries or communities.
- The desire to speed up the development and approval processes for some products and procedures (e.g., AIDS drugs) needs to be tempered with the recognition that the current system, including requirements concerning informed consent, has evolved in response to past abuses. The imperative to protect potential research participants and future consumers of the products remains vitally important, even in the face of urgency. Indeed, current rigorous standards for the conduct of trials, including those for informed consent, should only be modified with great thought, consultation, and consideration of all of the possible implications.

This two-day seminar was an opportunity for representatives of research institutions, academic institutions, IRBs, governments, and funding agencies to discuss informed consent—from the philosophical foundations of ethical codes to the challenges of implementation. Sessions that explored the history and evolution of informed consent underscored its centrality to the conduct of ethical research. Sessions on the "nuts and bolts" of the informed consent process—developing the forms, undergoing IRB review, finding ways to convey risk and to assess participant comprehension—fostered discussion about practical ways to implement meaningful informed consent. Specific examples, such as the National Cancer Institute's initiative to involve patients and patient advocates in an effort to refine the informed consent process, provided promising indications of the willingness of institutions to focus resources specifically on improving informed consent.

Throughout the seminar, participants deliberated about the challenges and opportunities presented in translating good intentions into sound practices, echoing Henry Beecher's comments that "The reality is that informed consent is often exceedingly difficult or impossible to obtain in any complete sense. The difficulties inherent in this complex situation are no excuse for giving up the effort: informed consent is a goal toward which we strive."[58]

[58] Beecher, Henry K. 1966. "Consent in clinical experimentation: Myth and reality," *Journal of the American Medical Association* 195(1):124–125.

Appendix 1: Meeting Agenda

Thursday, 24 May

9:15–9:30 a.m. **Welcome**
Beverly Winikoff

9:30 a.m.–12:00 p.m. **Informed Consent: An Overview** Chair: Rachael Pine

Informed Consent: Lessons of the Past, a Guide to the Future?
Ronald Bayer
*International Guidelines and IRB*s
Bette-Jane Crigger
Discussant
Anrudh Jain
Commentary
Rachael Pine

- Informed consent in the context of research ethics
  – Key components of informed consent
- Institutional responsibility for informed consent
  – Role and function of Institutional Review Boards (IRBs)
  – Current international debates concerning research ethics
  – Applying standards and regulations to multi-country studies

Discussion

1:00–3:15 p.m. **Informed Consent in Varying Contexts** Chair: Purnima Mane

Informed Consent: Miss or Bust?
Arthur L. Caplan
Developed vs. Developing Countries
Suniti Solomon

- Developed and developing country/cultural contexts
- Research and services
- Trials for prevention and treatment

Discussion

3:30–5:00 p.m. **Understanding Risk and Its Implications for Decisionmaking** Chair: Sarah Hawkes

What Is It?: Understanding and Communicating Risk
Kimberly Thompson
Explaining Risk in Biomedical Research
Elof Johansson
Flower Diagram Consent Form
Saran Da Ly

- How are risks presented?
- How is risk perceived?
- How does risk perception affect decisions?

Discussion

Friday, 25 May

9:30 a.m.–12:30 p.m. **Informed Consent: Implementation and Evaluation** Chair: Barbara Friedland

Informed Consent: Making It Understandable—
The Recommendations of an NCI Working Group
Mary McCabe
Assessing Informed Consent
Judith A. Fortney
Evaluating the Informed Consent Process in a Phase 2
Microbicides Trial in Cape Town, South Africa
S'phindhile Magwaza
Informed Consent: What Can It Mean in Rural Gambia?
Katie Paine

- The informed consent process
  – Communicating information, and developing informed consent forms and supplementary materials
- Assessing informed consent
  – What do study participants understand?
  – What research methods have been used to assess their understanding?
  – How well do participants need to understand the study to make an "informed" decision? How should this be assessed and who should decide?
  – Examples from the field

Discussion

1:30–3:30 p.m. **Informed Consent in Special Populations/Situations** Chair: Robert J. Levine

Special Populations
Robert J. Levine
Including Adolescents in Reproductive Health Research: Informed Consent and Developmental Capacity
John Santelli
Consenting Male Partners of Women Involved in Reproductive Health Research: Rights, Realities, and Responses
Ellen Weiss
Informed?? Consent?? Considerations on Carrying Out Research in Forced Migration Settings
Therese McGinn

- What are the ethics of informed consent among legal "minors" in the United States and elsewhere?
- What are the rights of male partners of female reproductive health study participants if what is being studied also affects the male partners?
- What are the ethical informed consent concerns for reproductive health research with refugee populations and/or in emergency situations?

Discussion

3:45–4:45 p.m. **Cost/Benefits/Burdens of Informed Consent and Implications for Research** Chair: Shelley Clark

The Price and Value of Consent
John Townsend
International Finance and Informed Consent
Ok Pannenborg

- What are feasible/realistic/acceptable standards?
- Can informed consent be a barrier to research?
- Devising a cost/benefit analysis (or approach) to informed consent

4:45–5:00 p.m. **Closing Comments**
Beverly Winikoff

Appendix 2: Meeting Participants

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