BIOMEDICAL ETHICS, SEVENTH EDITION

Published by McGraw-Hill Higher Education, an imprint of The McGraw-Hill Companies, Inc., 1221 Avenue of the Americas, New York, NY 10020. Copyright © 2011 by The McGraw-Hill Companies, Inc. All rights reserved.

Previous editions © 2006, 2001 and 1996. No part of this publication may be reproduced or distributed in any form or by any means, or stored in a database or retrieval system, without the prior written consent of The McGraw-Hill Companies, Inc., including, but not limited to, in any network or other electronic storage or transmission, or broadcast for distance learning.

Some ancillaries, including electronic and print components, may not be available to customers outside the United States.

This book is printed on acid-free paper.

2 3 4 5 6 7 8 9 0 DOC/DOC 1 0 9 8 7 6 5 4 3 2 1

ISBN 978-0-07-340745-6
MHID 0-07-340745-3

Vice President & Editor-in-Chief: Michael Ryan
Vice President EDP/Central Publishing Services: Kimberly Meriwether David
Publisher: Beth Mejia
Sponsoring Editor: Mark Georgiev
Managing Editor: Nicole Bridge
Marketing Manager: Pamela S. Cooper
Senior Project Manager: Lisa A. Bruflodt
Buyer: Laura Fuller
Design Coordinator: Margarite Reynolds
Compositor: Aptara®, Inc.
Typeface: 10/12 Times Roman
Cover Image Photo Credit: C. Borland/PhotoLink/Getty Images
Cover Designer: Mary-Presley Adams

All credits appearing on page or at the end of the book are considered to be an extension of the copyright page.

Library of Congress Cataloging-in-Publication Data

p. cm.
Includes bibliographical references and index.
ISBN 978-0-07-340745-6 (alk. paper)
R724.B49 2010
174.2—dc22

2010011980

www.mhhe.com
25 Steinberg, supra note 6, at 27.
26 Scanlon, supra note 8, at 248–56.
27 Id. at 252.
28 Id. at 253.
29 So, for example, Rousseau argues that a choice to become a slave should not be respected precisely because it is irrational or unacceptably foolish:
    Now, since, in the relations between men, the worst that can happen to someone is for him to see himself at the discretion of someone else, would it not have been contrary to good sense to begin by surrendering into the hands of a leader the only things for whose preservation they needed his help? What equivalent could he have offered them for the concession of so fine a right?

Steinberg, in fact, makes this argument, stating that “no rational person would sign” a consent form that informed a potential subject that the ethics governing the protocol deviated from the ethics of medical care. Steinberg, supra note 6, at 27.
31 E. J. Emanuel and F. G. Miller, supra note 1; B. Freedman, K. C. Glass, C. Weijer, supra note 1.
34 World Medical Association, supra note 4.

The authors confront the issue of whether it can be acceptable for researchers in wealthy countries to enroll citizens of developing countries in clinical trials. Citing guidelines published by the Council for International Organizations of Medical Sciences, the authors argue that to justify such trials, the risks or burdens imposed on trial participants must be offset by the prospect of actual benefit to the inhabitants of the developing country. Thus, if the trial yields beneficial knowledge, benefits must actually reach individuals in the country in which the trial took place; otherwise, the subjects will have been exploited. A practical implication of this approach is that “an essential prerequisite to designing ethical research in underdeveloped countries is identifying the source and amount of funding for providing the fruits of the research to the people of the developing country”—a moral requirement that was not satisfied in recent African AZT studies. The authors then consider and reply to a wide range of objections to the ethical standard they propose.

An April 1998 New York Times Magazine article described Ronald Munger’s efforts to obtain blood samples from a group of extremely impoverished people in the Philippine Island of Cebu.1 Munger sought the blood to study whether there was a genetic cause for this group’s unusually high incidence of cleft lip and palate. One of many obstacles to the research project was the need to obtain the cooperation of the local health officer. It was not clear to

An April 1998 New York Times Magazine article described Ronald Munger’s efforts to obtain blood samples from a group of extremely impoverished people in the Philippine Island of Cebu.1 Munger sought the blood to study whether there was a genetic cause for this group’s unusually high incidence of cleft lip and palate. One of many obstacles to the research project was the need to obtain the cooperation of the local health officer. It was not clear to
Munger, or the reader, whether the health officer had a bona fide interest in protecting the populace or was looking for a bribe. The health officer asked Munger a few perfunctory questions about informed consent and the study's ethical review in the United States, which Munger answered. Munger also explained the benefits that mothers and children would derive from participating in the research. The mothers would learn their blood types (which they apparently desired) and whether they were anemic. If they were anemic, they would be given iron pills. Lunch would be served, and raffles arranged so that families could win simple toys and other small items.

Munger told the health officer that if his hypotheses were correct, the research would benefit the population of Cebu: if the research shows that increased folate and vitamin B6 reduces the risk of cleft lip and palate, families could reduce the risk of facial deformities in their future offspring. The reporter noted that the health officer “laughs aloud at the suggestion that much of what is being discovered in American laboratories will make it back to Cebu any time soon.” Reflecting on his experience with another simple intervention, iodized salt, the health officer said that when salt was iodized, the price rose threefold “so those who need it couldn’t afford it and those who didn’t need it are the only ones who could afford it.”

The simple blood collecting mission to Cebu illustrates almost all the issues presented by research in developing countries. First is the threshold question of the goal of the research and its importance to the population represented by the research subjects. Next is the quality of informed consent, including whether the potential subjects thought that participation in the research was related to free surgical care that was offered in the same facility (although it clearly was not) and whether one could adequately explain genetic hypotheses to an uneducated populace. Finally, there is the question whether the population from which subjects were drawn could benefit from the research. This research intervention is very low risk—the collection of 10 drops of blood from affected people and their family members. The risk of job or insurance discrimination that genetic research poses in this country did not exist for the Cebu population; ironically, they were protected from the risk of economic discrimination by the profound poverty in which they lived.

Even this simple study raises the most fundamental question: “Why is it acceptable for researchers in developed countries to use citizens of developing countries as research subjects?” A cautionary approach to permitting research with human subjects in underdeveloped countries has been recommended because of the risk of their inadvertent or deliberate exploitation by researchers from developed countries. This cautionary approach generally is invoked when researchers propose to use what are considered “vulnerable populations,” such as prisoners and children, as research subjects. Vulnerable populations are those that are less able to protect themselves, either because they are not capable of making their own decisions or because they are particularly susceptible to mistreatment. For example, children may be incapable of giving informed consent or of standing up to adult authority, while prisoners are especially vulnerable to being coerced into becoming subjects. Citizens of developing countries are often in vulnerable situations because of their lack of political power, lack of education, unfamiliarity with medical interventions, extreme poverty, or dire need for health care and nutrition. It is the dire need of these populations that may make them both appropriate subjects of research and especially vulnerable to exploitation. This combination of need and vulnerability has led to the development of guidelines for the use of citizens of developing countries as research subjects.

CIOMS GUIDELINES

In 1992, the Council for International Organizations of Medical Sciences (CIOMS), in collaboration with the World Health Organization, published guidelines for the appropriate use of research subjects from “underdeveloped communities.”

Like other human research codes, the CIOMS guidelines combine the protection of subjects' rights with protection of their welfare; as subjects become less able to protect their own rights (and therefore become more vulnerable), researchers and reviewers must increase their efforts to protect the welfare of subjects. Perhaps the most important statement in these guidelines is what appears to be the injunction
against using subjects in developing countries if the research could be carried out reasonably well in developed countries. Commentary to guideline 8 notes, for example, that there are diseases that rarely or never occur in economically developed countries, and that prevention and treatment research therefore needs to be conducted in the countries at risk for those diseases. The conclusion to be drawn from the substance of these guidelines is that in order for research to be ethically conducted, it must offer the potential of actual benefit to the inhabitants of that developing country.

In order for underdeveloped communities to derive potential benefit from research, they must have access to the fruits of such research. The CIOMS commentary to guideline 8 states that, “as a general rule, the sponsoring agency should ensure that, at the completion of successful testing, any product developed will be made reasonably available to inhabitants of the underdeveloped community in which the research was carried out: exceptions to this general requirement should be justified, and agreed to by all concerned parties before the research is begun.”

This statement is directed at minimizing exploitation of the underdeveloped community that provides the research subjects. If developed countries use inhabitants of underdeveloped countries to create new products that would be beneficial to both the developed and the underdeveloped country, but the underdeveloped country cannot gain access to the product because of expense, then the subjects in the underdeveloped countries have been grossly exploited. As written, however, this CIOMS guideline is not strong or specific enough to prevent exploitation. Exemplifying this problem are recent short course zidovudine (AZT) studies in Africa that were approved and conducted despite the existence of the CIOMS guidelines.

THE AFRICAN MATERNAL-FETAL HIV TRANSMISSION STUDIES

The goal of the short course AZT studies was to see if lower doses of the drug AZT than those used in the United States could reduce the rate of maternal-child transmission of HIV. It was well established that doses of AZT that cost $800 (not taking into account screening and other related costs) reduced maternal-fetal transmission of HIV by as much as two-thirds in the United States. If the developed countries had been willing to subsidize the cost of this regimen in Africa, no additional research would have been needed. But because many African countries could not afford this expense, the decision was made to attempt to see if lower (and therefore cheaper) doses would prevent maternal-fetal HIV transmission. Several impoverished countries were chosen as research sites. The justification for conducting research in those countries was that they suffered from a disease that did not affect people in developed countries, and not because no treatment existed, but because their impoverishment made an existing therapy unavailable to them (as long as developed countries refused to subsidize the costs).

The issue, as always, is to determine the ethical acceptability of the proposed research before it is conducted. In a case like this, where the researchable problem exists solely because of economic reasons, the research hypothesis must contain an economic component. The research question should be formulated as follows:

1. We know that a given regimen of AZT will reduce the rate of maternal-child transmission of HIV.

2. Maternal-child transmission of HIV in many African countries is a serious problem but the effective AZT regimen is not available because it is too expensive.

3. If an effective AZT regimen costs $X, then it will be made available in the country in which it is to be studied.

4. Therefore, we will conduct trials in certain African countries to see if $X worth of AZT will effectively reduce maternal-child transmission of HIV in those countries.

The most important part of the development of this research question is number 3. Without knowing what dollar amount $X actually represents, it is impossible to formulate a research question that can lead to any benefit to the citizens of the country in which the research is to be conducted. There is no way to determine what $X represents in the absence of committed funding. Therefore, an essential prerequisite to designing ethical research in underdeveloped countries is identifying the source and amount of funding for providing the fruits of the
HUMAN AND ANIMAL RESEARCH

research to the people of the developing country in which it is to be studied as a condition of the research being approved.

If a study found, for example, that $50 worth of AZT has the same effect as $800 worth of AZT, it would greatly benefit the developed world. Developed countries, which currently spend $800 per case on drugs alone, could pay substantially less for this preventive measure, and, because the research was conducted elsewhere, none of their citizens would have been put at any risk. At the same time, if the underdeveloped country could not afford to spend $50 any more than it could spend $800, then it could not possibly derive information that would be of any benefit to its population. This is the definition of exploitation.

It is only now that an effort is being made to determine how to raise the money to actually provide AZT to prevent maternal-child HIV transmission (as well as the other costly services that go with the appropriate administration of the drug) to the impoverished African countries that provided the human subjects. These efforts began after parallel studies conducted in Thailand reported that lower doses of AZT reduced maternal-fetal transmission of HIV. The Thai government had committed to providing the AZT before its trials began. In the African trials, however, no one "ensured" that at the completion of successful testing the product would be made reasonably available, thereby violating the CIOMS guidelines. The guidelines say that there can be exceptions to this general requirement, but that exceptions must be "justified" and "agreed to by all concerned parties." It is not clear to whom the exception must be "justified" or on what grounds. Moreover, if the "concerned parties" are the sponsor and/or the investigator and the host country, they may not adequately represent the interests of the research subjects. The fact that representatives of the research community and officials of the host countries agree to exploit the population does not make the research any less exploitive.

RULES FOR ETHICAL RESEARCH IN DEVELOPING COUNTRIES

We believe the standards for research in developing countries should include the following.

There should be a rebuttable presumption that researchers from developed countries will not conduct research in developing countries unless it can be shown that a direct benefit will be bestowed upon the residents of that country if the research proves to be successful. The person or entities proposing to conduct the study must demonstrate that there is a realistic plan, which includes identified funding, to provide the newly proven intervention to the population from which the potential pool of research subjects is to be recruited. In the absence of a realistic plan and identified funding, the population from which the research subjects will be drawn cannot derive benefit from the research. Therefore, the benefits cannot outweigh the risks, because there are, and will be, no benefits. Only by having committed funding and a plan to make a successful intervention available can it be determined that there will be sufficient benefit to justify conducting research on the target population. The distribution plan must be realistic. Where the health care infrastructure is so underdeveloped that it would be impossible to deliver the intervention even if it were free, research would be unjustified in the absence of a plan to improve that country's health care delivery capabilities.

Some might argue that this standard is too strict and that it would reduce the amount of research that could be conducted in certain countries. The answer, of course, is that if the benefits of the research are not made available to the inhabitants of that country, they have lost nothing by the lack of such research. Others might argue that research in underdeveloped countries is justified if it might benefit the individual research subjects, even if it will not benefit anyone else in the population. However, research is, by definition, designed to create generalizable knowledge, and is legitimate in a developing country only if its purpose is to create generalizable knowledge that will benefit the citizens of that country. If the research only has the potential to benefit the limited number of individuals who participate in the study, it cannot offer the benefit to the underdeveloped country that legitimizes the use of its citizens as research subjects. It should be emphasized that research whose goal is to prevent or treat large populations is fundamentally public health research, and public health research makes no sense (and thus
should not be done) if its benefits are limited to the small population of research subjects.

It might be argued that there is no requirement that such a plan be devised prior to conducting research in the United States, and, therefore, that by adopting such a requirement we would be imposing a higher standard for research conducted in developing countries than we do for research conducted in the United States.

This argument only further demonstrates the differences between wealthy and poor countries. The reality in the United States is that regardless of the very significant gaps in insurance and Medicaid coverage and the health care discrepancies between the rich and poor, medical interventions are relatively widely available, especially when compared to developing countries. Upon the successful completion of the research that demonstrated the effectiveness of the 076 regimen in reducing maternal-child transmission, the primary beneficiaries of this new preventive intervention in the United States were poor women and their newborns. Unlike the United States, absent a plan to pay for a new intervention and lacking the infrastructure to deliver an intervention, it is virtually guaranteed that the intervention will not be generally available in a developing country.

The more accurate analogy to the African AIDS trials would be if investigators proposed the 076 protocol in the United States knowing that only poor women would be recruited as research subjects and that, if successful, the intervention would not be made generally available to poor women. Such research would be clearly unethical. Not only would this be a gross violation of the ethical principle of distributive justice, it would be a violation of the regulatory obligation of the equitable selection of subjects.\(^{16}\)

A further objection is that one cannot always trust what a government or another potential funder promises. What is to prevent the promisor from reneging? The answer is, nothing. One can try to expose the funder to embarrassment and other pressures that might cause it to live up to the promise upon which researchers and subjects relied. However, the potential unethical behavior in the future by the funder is no excuse for not having a realistic plan at the outset. Furthermore, if we take this obligation seriously, this should only occur once per funder. After reneging once, they cannot be relied upon again to justify research in the future.

An additional objection to our position is that it will restrict access to new interventions because once a new intervention is developed, the price will come down and therefore the intervention will become available to the people of the impoverished country. The answer is to ask those who control the pricing of interventions if this will be the case in any particular instance. One could have asked Glaxo if it would reduce its price once it was shown that lower doses of AZT were effective. If the answer is yes, one can proceed. If the answer is no, or “we have not decided,” there seems to be no justification to proceed if the current price would significantly restrict availability. There is nothing magical about pricing. Pricing is in the absolute control of manufacturers and there is no need to guess or speculate about what will happen to price. Indeed, this objection to our argument would justify conducting the full 076 trial itself in developing countries. The price might come down enough so that determining the efficacy of short course AZT regimens might not be needed at all. Such speculation should not be sufficient to put subjects at risk.

Finally, it might be argued that there are diseases that only affect people in developing countries for which there are no effective treatments, but that the treatments that might be discovered could be expensive. The argument continues that it is not right to fail to develop treatments that could benefit some affected people because it will not be available to most affected people. This objection raises quite a different issue from the one addressed in this article. The impetus for such research is the absence of effective treatment and not the absence of economic resources. We have discussed research intended to determine whether effective but unaffordable interventions would work if used in lower, less expensive dosages. The researchable issue arises from an economic circumstance. The only way such research could offer any benefit is by “curing” the economic problem by establishing that the less expensive form of the intervention will be affordable and available. Absent knowledge of financial resources, one might well be creating a new unaffordable, and therefore
useless, intervention. In contrast, in the case in which one is developing a new intervention, not because of poverty, but because no known effective intervention exists, and the disease is prevalent in a particular geographic area, the issue is quite different. In such a case one is not conducting research to try to “cure” the effects of poverty but rather because of the need to create new knowledge to treat a currently untreatable disease. However, even this case may raise problems similar to the ones addressed here. If one were to try to develop an intervention for such a condition and chose research subjects from impoverished segments of a society, knowing that only the richest segment of that society could benefit from that intervention, such subject selection would be unethical for many of the reasons we have discussed.

Our proposal to require researchers and their funders to develop realistic plans to make their interventions available to the relevant population of the developing country in which the research is proposed should not be controversial. It is well accepted in principle not only by groups like CIOMS, but by the funders of many of the African HIV trials, including the Centers for Disease Control and Prevention and the National Institutes of Health. The principle is often honored in the breach, however. Research funders who hope that their studies will yield beneficial knowledge may neglect the steps necessary to ensure that the benefits will be made available. Ethical codes have not been sufficiently specific or enforceable to protect research subjects from exploitation. It is essential to replace vague promises with realistic plans that must be reviewed and approved before the research commences.

In at least one other instance it has been suggested that economic issues be addressed in the review of proposed research projects. The U.S. National Research Council’s Committee on Human Genome Diversity recommended that “Arrangements regarding financial interests in the products or outcomes of the research should be negotiated as part of the original project review and informed-consent process.”

It is essential that the wealthier countries of the world use their resources, both financial and technological, to help resolve the health problems that afflict the poor of the world. Doing so will undoubtedly require research. But research is a means to solving health problems, not an end in itself. The goal must be to create interventions that will benefit the people of the countries in which the research is conducted. They will benefit only if the knowledge gained produces interventions that are affordable and accessible. This needs to be determined as a condition of approval before research is conducted so that limited research funds are not wasted, and research subjects are not drawn from populations that will not be able to benefit from the research.

REFERENCES

ETHICAL ISSUES IN CLINICAL TRIALS IN DEVELOPING COUNTRIES

Baruch Brody

Brody addresses three moral criticisms of recent clinical trials in developing countries that tested the efficacy of short-course AZT regimens in reducing maternal-fetal transmission of HIV: (1) that subjects who received placebos were treated unjustly; (2) that subjects' dire circumstances coerced them into agreeing to participate in the trials; and (3) that the developing countries in question were exploited insofar as they would not have access to the AZT regimens under study even if they proved effective (as argued by Glantz et al.). In response to the first criticism, Brody argues that the trials probably met the following appropriate standard of justice: “all participants in the study, including those in the control group, should not be denied any treatment that should otherwise be available to [them] in light of the practical realities of health care resources available in the country in question.” He responds to the second criticism by analyzing the concept of coercion and arguing that subjects were not coerced on any reasonable construal of this concept. Regarding the third criticism, Brody suggests that legitimate concerns about exploitation will be met if the subjects themselves—not necessarily the broader local community—are provided access to effective treatment following the study.

Since the publication of the results of AIDS Clinical Trials Group (ACTG) 076, it has been known that an extensive regimen of Zidovudine provided to the mother and to the newborn can drastically reduce (25.5 to 8.3%) the vertical transmission of HIV.1 Unfortunately, the regimen in question is quite expensive and beyond the means of most developing countries, some of which are the countries most in need of effective techniques for reducing vertical transmission. This realization led to a series of important clinical trials designed to test the effectiveness of less extensive and less expensive regimens of antiretroviral drugs. These trials were conducted by researchers from developed countries in the developing countries which were in need of these less expensive regimens.

These new trials have been very successful. The Thai CDC trial showed a 50% reduction (18.9 to 9.4%) in transmission from a much shorter antepartum...