Ethical issues with health care research in developing countries

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In spite of the potential for ethical problems, health care research in developing countries has been expanding rapidly, and this trend is likely to continue in the years to come. An increasingly large proportion of research submitted to the Food and Drug Administration (FDA) is being conducted at foreign sites. It was in 1980 that the FDA first agreed to accept trials conducted outside the United States as part of the evidence of safety and effectiveness submitted in Investigational New Drug (IND) applications. Health care research has grown considerably. Although some of the reasons for this are acceptable, the economic disparities between the rich and the poor of the world make exploitation more likely, not less. The reasons for the move to developing countries are fairly obvious: It is usually cheaper, easier, and faster to carry trials out there compared to developed countries. Ethical regulations, approval, and oversight may be less rigorous and the processes faster. Participants are easier to recruit and will be unlikely to be taking other pharmaceuticals that might interact with the research drug (although the potential for other diseases or dietary factors interfering with the drug’s action must be taken into consideration). This article discusses the ethical issues involved with conducting trials in foreign countries.

Key words: clinical research, developing countries, foreign research

The Constant Gardener reveals a clandestine world of criminality surrounding health care research in developing countries. The 2005 movie, based on John le Carré’s novel, dramatizes the evils of corporate greed and international political corruption. The murder, intimidation, and bribery take the cover-up of bad research to a new level—that necessary for a thriller with mass appeal.

At the same time, the movie does an excellent job of placing this issue in context. Shot on location in Kenya, the movie makes the scenes of poverty and depravity even more stunning because they are real. The filmmakers did not create a Hollywood set; they shot in the midst of the dirt and filth that make up actual people’s homes. The people living without water, food, or basic health care portrayed themselves. Such scenes contrasted dramatically with the comfort and abundance of foreign researchers and diplomats, and the local politicians. That striking contrast sets the scene for the disparity that underlies the ethical issues facing those doing research in developing countries. The enormous differential in resources, knowledge, and opportunities creates such an imbalance in power that exploitation is possible, if not inevitable—even assuming the researchers and their companies had the best of intentions. Marcia Angell, former editor of the New England Journal of Medicine, claims that the only unrealistic aspect of The Constant Gardener is the company hiring hit-men to murder the whistle-blower. She maintains an unethical company would not be bothered enough to do so.1

In spite of the potential for problems, health care research in developing countries has been expanding rapidly. An increasingly large proportion of research submitted to the Food and Drug Administration (FDA) is being conducted at foreign sites. It was in 1980 that the FDA first agreed to accept trials conducted outside the United States as part of the evidence of safety and effectiveness submitted in Investigational New Drug (IND) applications.1 That year, 41 foreign clinical researchers were listed in IND applications; by 1990 this had increased to 271 and in 1999 it had reached 4,458.2 The number of trials being conducted in developing countries is not known, but estimates put it at about half of all clinical trials.1

The reasons for this move to developing countries are fairly obvious: It is usually cheaper, easier, and faster to carry them out there compared to developed countries. Ethical regulations, approval, and oversight may be less rigorous and the processes faster. Participants are easier to recruit and will be unlikely to be taking other pharmaceuticals that might interact with the research drug (although the potential for other diseases or dietary factors interfering with the drug’s action must be taken into consideration). The Vice President of Clinical Development Operations at Wyeth Research stated recently that “the U.S. and
Western Europe have not been good places to identify and recruit patients [into clinical trials] in the past several years…. Quite simply, we’re going where we can find patients.”

However, concerns about the ethics of this research initiated a significant amount of debate in the late 1990s that continues today. In December 2000, The Washington Post ran a series of articles under the title “The Body Hunters.” This series documented serious ethical (and legal) violations in health care research being conducted in several developing countries: in Africa, Asia, Latin America, and the former Soviet Union. One of the more highly publicized examples involved Pfizer’s trial of Trovan (trovafloxacin, a promising new antibiotic) during a 1996 meningitis outbreak in the city of Kano, Nigeria. Pfizer was trying to gain approval for the drug’s use in treating meningitis in children, but enrollment at U.S. clinical sites was very slow. The drug’s approval would have opened up a huge market. Learning of the Nigerian epidemic, a study was prepared within six weeks and a research team sent to Nigeria. After three weeks, with the epidemic continuing, the researchers left after involving about 200 children in their study. Trovan was approved in 1997 for use in adults, but not children. Its use was sharply restricted in 1999 after it was linked to liver failure. Debate has raged since about whether the research in Nigeria was ethical and conducted properly. Pfizer insists it did nothing wrong, but has been sued by a number of Nigerian families, so far unsuccessfully. However, in May 2006 a Nigerian government report criticized the research and concluded that Pfizer had acted improperly and broken international law.

Examples like this have led numerous organizations to examine the ethical issues underlying health care research in developing countries. Table 1 gives a list of some of the ethics guidelines available from different organizations. The Nuffield Council on Bioethics is an independent, interdisciplinary council in the United Kingdom (UK) set up to in 1991 to comment on ethical issues in biological and medical research. It carried out an innovative consultative process involving researchers from developing and developed countries that led to an influential 2002 report on ethical issues in health care research in developing countries. Noting the large number of new guidelines in the years immediately following its report, the Council convened another workshop involving researchers from 28 countries. The resulting 2005 follow-up report provided an organizational framework that was used in preparing this article. Page numbers given in the text refer to this 2005 Nuffield follow-up report.

Table 1: Ethics Guidelines for Health Care Research in Developing Countries

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<thead>
<tr>
<th>Organization</th>
<th>Document</th>
<th>Year</th>
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<tbody>
<tr>
<td>Council for International Organizations of Medical Sciences (CIOMS)</td>
<td>International Ethical Guidelines for Biomedical Research Involving Human Subjects</td>
<td>2002</td>
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<tr>
<td>Council of Europe</td>
<td>Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research</td>
<td>2005</td>
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<td>European Group on Ethics in Science and New Technologies to the European Commission</td>
<td>Ethical Aspects of Clinical Research in Developing Countries</td>
<td>2003</td>
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<td>Nuffield Council on Bioethics</td>
<td>The Ethics of Research Related to Healthcare in Developing Countries</td>
<td>2002</td>
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<td>Nuffield Council on Bioethics</td>
<td>The Ethics of Research Related to Healthcare in Developing Countries: A Follow-Up Discussion Paper</td>
<td>2005</td>
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<tr>
<td>US National Bioethics Advisory Commission</td>
<td>Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries</td>
<td>2001</td>
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<tr>
<td>Wellcome Trust</td>
<td>Research Involving People Living in Developing Countries</td>
<td>no date</td>
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<tr>
<td>World Medical Association</td>
<td>Declaration of Helsinki</td>
<td>2000, amended 2004</td>
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Informed consent

Informed consent has become one of the important ethical issues in all research involving human participants. When concerns about health care research in developing countries were raised in 1997, the editors of the *New England Journal of Medicine* pointed to problems with consent with another vulnerable population: poor, African-American farmers involved in the Tuskegee project. The Tuskegee Study of Untreated Syphilis lasted from 1932 to 1972, recruited 412 men with untreated syphilis and compared them to 204 others who did not have syphilis. The study began when there were no effective treatments for syphilis. When penicillin did become available as an effective treatment, the men were not offered it. Many ethical violations occurred during the study, including that the men were enrolled without them knowing what the “project” was about. The investigation into this project led, in part, to the current emphasis on informed consent in human research. Informed consent is seen as a fundamental moral duty arising out of the importance of respecting other persons. Researchers do this by not acting against the participant’s wishes, and by ensuring participants know what they are committing to.

Research in developing countries raises particular difficulties for informed consent. Apart from such obvious issues as language, concepts such as “randomization” or “placebo” may be difficult for people in these countries to grasp given their lack of familiarity with medical research. The amount of detail necessary for a true understanding of the research can be debated. For example, the Council for International Organizations of Medical Sciences (CIOMS) has developed very thorough guidelines for those conducting research in developing countries. This includes a list of 26 essential pieces of information that potential participants should understand. Those involved with the Nuffield report found it unrealistic to have this amount of detail in informed consent forms. They rearranged the 26 items into those which should be presented in the informed consent form, an accompanying participant information sheet, or the application to a local research ethics committee. This arrangement is presented in Table 2.

It is widely acknowledged that informed consent must go beyond presenting information to contribute to what has been called “genuine consent.” According to Nuffield, “Obtaining genuine consent requires medical practitioners to do their best to communicate accurately as much as patients, volunteers, or relatives can understand about procedures and risks, and to react to the limits of their understanding, and of their capacities to deal with difficult information” (p. 12). Genuine consent is more ethically significant than “complete consent,” if that is understood as giving potential participants as much information as possible. Sometimes concerns about legal liability are given higher priority than participant understanding. For example, the sponsors of a trial in Ghana insisted on using a 14-page informed consent form for legal reasons, in spite of numerous requests from the clinical site for a more simplified form (p. 15). In some cultures, presenting more information can lead to other problems. For example, in Vietnam it can be viewed as unacceptable for a physician to express uncertainty about the best treatment. This can create difficulties regarding the appropriateness of a range of options in informing patients about their treatment.

Informed consent in developed countries is highly individualized, which can be problematic in some developing countries. The notion of community consent has developed, although this must be balanced against concerns that influential community leaders may pressure individuals into participating in trials. Nuffield notes that “Such ‘community consent’ may be crucial in specific cases, although the guidance is unanimous that it must be in addition to, rather than instead of, properly informed individual consent” (p. 12).

Community consent should best be seen as a process of dialogue and partnership-building. It provides an opportunity for researchers to learn about what is important to the community and can help the community learn more about health care and the place of research. In this way, successful models of community consent in developing countries can teach important principles to the developed world. Such approaches not only contribute to genuine consent, but may also have a significant impact on retention rates. For example, a study in Zambia noted that female participants who enrolled when single, but married while in the study, came under pressure from their husbands to give up participation. Similarly, students who enrolled...
came under pressure from their parents to withdraw for the sake of their education. The researchers addressed these issues by conducting study information meetings with all members of the household, not just the potential participants. Dialogue with the community led the same researchers to discover that the researchers were rumored to be involved in Satanism. These arose from misperceptions about the purpose of

Table 2: Essential information for prospective research subjects (numbers in parentheses refer to the original CIOMS list of requirements)\(^7\)

The informed consent form should include:

that the individual is free to refuse to participate and will be free to withdraw from the research at any time without penalty or loss of benefits to which he or she would otherwise be entitled (2);

the purpose of the research, the procedures to be carried out by the investigator and the subject, and an explanation of how the research differs from routine medical care (3);

any foreseeable risks, pain or discomfort, or inconvenience to the individual (or others) associated with participation in the research, including risks to the health or well-being of a subject's spouse or partner (9);

the provisions that will be made to ensure respect for the privacy of subjects and for the confidentiality of records in which subjects are identified (14);

policy with regard to the use of results of genetic tests and familial genetic information, and the precautions in place to prevent disclosure of the results of a subject's genetic tests to immediate family relatives or to others (e.g., insurance companies or employers) without the consent of the subject (16);

the possible research uses, direct or secondary, of the subject's medical records and of biological specimens taken in the course of clinical care (18);

whether it is planned that biological specimens collected in the research will be destroyed at its conclusion, and, if not, details about their storage (where, how, for how long, and final disposition) and possible future use, and that subjects have the right to decide about such future use, to refuse storage, and to have the material destroyed (19);

that treatment will be provided free of charge for specified types of research-related injury or for complications associated with the research, the nature and duration of such care, the name of the organization or individual that will provide the treatment, and whether there is any uncertainty regarding funding of such treatment (23);

The participant information sheet should include:

for controlled trials, an explanation of features of the research design (e.g., randomization, double-blinding), and that the subject will not be told of the assigned treatment until the study has been completed and the blind has been broken (4);

the expected duration of the individual's participation (including number and duration of visits to the research centre and the total time involved) and the possibility of early termination of the trial or of the individual's participation in it (5);

whether money or other forms of material goods will be provided in return for the individual's participation and, if so, the kind and amount (6);

that, after the completion of the study, subjects will be informed of the findings of the research in general, and individual subjects will be informed of any finding that relates to their particular health status (7);

that subjects have the right of access to their data on demand, even if these data lack immediate clinical utility (unless the ethical review committee has approved temporary or permanent non-disclosure of data, in which case the subject should be informed of, and given, the reasons for such non-disclosure) (8);

the direct benefits, if any, expected to result to subjects from participating in the research (10);

the expected benefits of the research to the community or to society at large, or contributions to scientific knowledge (11);

whether, when and how any products or interventions proven by the research to be safe and effective will be made available to subjects after they have completed their participation in the research, and whether they will be expected to pay for them (12);

any currently available alternative interventions or courses of treatment (13);

the sponsors of the research, the institutional affiliation of the investigators, and the nature and sources of funding for the research (17);

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withdrawing blood from participants and led the researchers to hold further information meetings with the community.

Another problem with informed consent arises with severely ill children whose parents may be too distraught to comprehend large amounts of information. A study in Malawi investigated the effectiveness of rectal suppositories in children with moderately severe malaria.12 These children tended to arrive at the hospital semi-conscious. The original consent form had two pages of text and provided an unrealistic amount of information. In a number of cases, verbal consent was given on the day of enrollment with signed and witnessed consent given at a later follow-up visit.

The informed consent process is also complicated when incentives are offered by the researchers. Sometimes these incentives are implicit, especially if participants believe enrolling in the study is the only way they will be able to access any health care. The ethical concern here is that participants may take on greater risks than they would otherwise be willing to accept in order to receive the incentives. The broader issues of justice and fairness are involved here also. If the risks are such that a well-off person would not be willing to accept them, then poorer people will disproportionately take on those risks because of the incentives. Thus, the CIOMS guidelines state that incentives “should not be so large as to persuade them to take undue risks or volunteer against their better judgment. Payments or rewards that undermine a person’s capacity to exercise free choice invalidate consent.”10

Guidelines usually view it as acceptable to reimburse participants for direct expenses incurred, loss of earnings, or for health care needs arising from participation in the study. Local research ethics committees play an important role in determining what incentives are appropriate. For example, a payment of $50 in the United States to cover time and inconvenience would be the equivalent of several years’ earnings in rural Uganda.6 A particularly difficult situation arises when ill people seek to enroll in trials when they would otherwise have no access to health care. The pressure to obtain any medical care makes such patients particularly vulnerable to exploitation. They may be suitable participants for the study, but “someone without access to medical care may or may not be unduly influenced to participate in research simply to receive such care.”10 Such situations are often best examined by a local research ethics committee informed of all the benefits and risks of a particular study and the needs of the local community.

Standards of care

Over the last decade, this issue has been one of the most hotly debated ethical questions regarding
research in developing countries. The general question surrounds the sort of therapy that should be provided participants in the control group. One aspect is whether it is ethical to give the control group a placebo if another effective treatment exists, but is not usually available locally. A second dimension to the problem arises if the control group is given “standard care.” Should this be the best treatment currently available anywhere in the world (universal standard of care), or should it be the standard treatment available where the trial is conducted (local standard of care)?

The controversy initially arose in reaction to studies investigating the use of AZT to reduce mother-to-child transmission of HIV. In 1994, studies had shown that transmission was reduced from 25% to 8%. However, developing countries, where HIV was (and is) most prevalent, could not afford the $800 per pregnancy of the regimen tested. Government spending there is often less than $10 per person per year. Officials from the WHO, UNAIDS, the NIH and the CDC designed a number of placebo-controlled trials in which a short-course regimen of AZT (costing $80 per pregnancy) would be tested against standard care in developing countries—which was no treatment.

The studies were criticized on the claim that they violated the Declaration of Helsinki. The version current at the time read, “In any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method.” Critics said that the best treatment available was the long-course AZT that should have been compared with the short-course treatment under examination. They claimed that participants who ended up in the control arm were thereby harmed because they received less than current best standard of care. Supporters of the studies argued that participants in the control group were receiving the standard care that normally would have been available to them and thus were not being harmed by the trial.

Critics maintained that this argument went against another clause of the Declaration of Helsinki that reads, in its current version, “In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.” This raised memories of another infamous study in which participants received no treatment because the interests of science and society were put above those of the study participants. The Tuskegee Syphilis Study had been defended on the basis that, “These poor African-American men probably would not have been treated anyway, so the investigators were merely observing what would have happened if there were no study.”

The argument was put more callously in The Constant Gardener by a British diplomat who colluded with the research company: “We are not killing people who would not be dead otherwise. Look at the death rate, not that anybody’s counting.”

The critics interpreted the statement about best standard of care to mean the best available anywhere, what is now called the universal standard of care. However, the defenders of the studies claimed that the Declaration of Helsinki seeks to protect participants from harm caused by the study. Someone in the control group would have no greater risk of harm than someone not enrolling in the trial. The participants might even benefit from the counseling provided everyone in the trial and the community might benefit if the treatment turned out to be effective. Thus, enrolling in the trial placed a woman at no higher risk of harm and gave her a chance of benefit, when compared to the local standard of care. In addition, preventing the trials from proceeding could harm many people if important benefits were thereby not realized.

Given that the local standard of care appears to violate the Declaration of Helsinki, debate arose in 1999 and 2000 around amending the Declaration. A draft was circulated in which the local standard of care was used. This March 1999 version stated that no participants should be “denied access to the best proven diagnostic, prophylactic, or therapeutic method that would otherwise be available to him her [sic].” This version was not accepted, and in May 2000 another draft proposed that every participant “should be assured of proven effective prophylactic diagnostic and therapeutic methods.” By the time the new Declaration was ratified in October 2000, the wording was similar to what it had originally been, adopting a universal standard of care. “The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies
where no proven prophylactic, diagnostic or therapeutic method exists.”14 A note of clarification was added in 2002 stating that placebos could be used if there were compelling and scientifically sound methodological reasons or if those receiving the placebo would not be subject to any additional risk of serious or irreversible harm.

Somewhat differently, the 2002 CIOMS guidelines state that “As a general rule, research participants in the control group...should receive an established effective intervention.”10 They clarify that placebo or no treatment groups may be acceptable. They then describe at length an example of an acceptable placebo-controlled study that matches many of the features of the AZT short-course trial. Debate continues over which version of standard of care is ethically preferable. The Nuffield follow-up report found that ethics committees in developing countries increasingly favor a local standard of care, though determining that standard can be difficult in itself (p. 27).

Post-trial obligations

The 1996 meningitis trial in Nigeria was criticized for beginning in the middle of an epidemic and leaving three weeks later before the crisis was over. The researchers insist they left patients with medications and instructions for follow-up care.4 However, they would not have been able to monitor patients or evaluate long-term effects. Long-term follow-up is important to monitor for potential adverse side effects, especially since antibiotics like the one being tested were known to cause liver problems and arthritis. Other physicians in the area claimed they were unable to figure out which children had been in which group as they had no records and many children had no idea they were involved in a research study.

Such an approach to research in developing countries has been called “parachute research”15 or “safari research.”16 The researchers drop into the country for a short period, carry out their activities, and fly away again with whatever samples and data they wanted. Another approach has been called “postal research” where the researchers don’t even visit the developing country, but arrange to have someone there collect the samples and mail them overseas for analysis.15 Another approach uses “annexed sites,” where the researchers move to a developing country and set up and run a research facility. While such an approach predominates and has produced much good research, it often fails to develop an indigenous research infrastructure—and may even mitigate against one. Such an approach is also less likely to have its research findings translated into policy and practice in the developing country.

Hence, a process of developing research partnerships is being advocated as a way to develop internal research infrastructure. This is based on the belief that “funding agencies have a moral responsibility not to ignore the appalling problems facing national institutions in developing countries.”15 According to this model, researchers from the developed world serve more as consultants who visit regularly to guide local researchers in the projects they see as important and relevant. The visiting researchers mentor indigenous researchers who supervise and train others. This model is also more cost-effective as it avoids relocating researchers from developed countries who typically earn much higher salaries.

Such a model would provide a mechanism by which the long-term care of research participants could be provided. The Declaration of Helsinki states that “At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic, and therapeutic methods identified by the study.”14 This has been controversial over the past few years, with a proposed amendment leading to “sharp differences of opinion” (p. 39). A note of clarification was added to the Declaration in 2004 pointing out the importance of planning for such post-trial access prior to ethical approval of the study.

The European Group on Ethics is even more clear-cut. Noting that in developed countries “free supply of a proven beneficial new drug to all the participants of a trial after the trial is ended is the rule as long as it is not yet available through the normal health care system,” they insist on the same provision being made available in developing countries. This applies even if it involves “supplying the drug for a lifetime.”17

Concerns have been raised that such a requirement may deter some sponsors from carrying out certain types of research. Drug development for chronic
diseases prevalent in developing countries may be particularly vulnerable if successful treatments will need to be provided free-of-charge for many years. It may also be very difficult to predict the final costs of a treatment prior to conducting the research. Researchers at the Nuffield workshop recommended that this particular guideline lead to negotiations prior to trials beginning (p. 38). They cited an example from Uganda and Zimbabwe where the sponsors refused to pay for antiretroviral therapy beyond the four years of the research. The local ethics committee decided that this was still a significant benefit and agreed to the sponsor’s terms. Further negotiations led to a commitment from the Minister of Health in each country to provide treatment for participants after the trial finished.

Another dimension of this issue on which guidelines are unanimous is that research should only be conducted in developing countries for conditions that impact people in those countries. Yet even when drugs are tested for diseases inflicting developing countries, like HIV, it can take years before those countries can afford the drugs. As Angell notes,

In this sense, third-world countries are being used as laboratories for first-world needs. Relatively few studies are devoted to finding treatments for the diseases that plague poor countries, such as malaria, sleeping sickness, and schistosomiasis. The big companies are more interested in the usual first-world conditions, like high cholesterol, obesity, and arthritis.1

This issue in particular points to an area where practice falls short of ethical guidelines.

Ethical review

Local research ethics committees (REC) have been mentioned a number of times as playing an important role in evaluating health care research in developing countries. They bring a crucial element to the review process by having proposed research evaluated by those with appropriate cultural and scientific perspectives. However, they are also one of the resources that is lacking in many developing countries, and there are still some countries that do not have any research ethics committees (p. 47). Those which do exist are often short in funding, training, and support. However, a variety of initiatives, like one at the NIH, are in place to provide this training and support.18

There is some disagreement as to whether a REC should evaluate both the science and the ethics of a research proposal. Both guidelines and practice vary. It is accepted to include within ethical approval an assurance that the study is scientifically valid. Whether that is determined by the same committee or another one varies.

Guidelines also differ on whether ethical review should be conducted in the sponsor’s country or in the developing country. Some guidelines require both, which has raised concerns about bureaucratic delays in conducting research if it takes a long time for a number of committees to schedule discussion of a proposal. Many of the issues of concern mirror those faced by REC in developed countries. Some guidelines also require the REC to monitor the progress of approved studies.10 However, the resources for this are rarely available.

Conclusion

Health care research has grown considerably in developing countries. This trend is likely to continue in the years to come. While some of the reasons for this are acceptable, the economic disparities between the rich and the poor of the world make exploitation more likely, not less. The 10/90 gap refers to the estimate that about 10% of the world’s health resources are used to investigate the health problems that impact 90% of the world’s population. Since the term was coined in 1990, little progress has been made to overcome it.19 Yet it has been noted that the investment needed to develop a new anti-microbial agent is about one quarter that needed to develop a new Viagra-like drug.20 However, drugs like Viagra are the ones that become financial block-busters.

Meanwhile, much effort is being expended to address the sorts of unethical research practices portrayed in The Constant Gardener. Much progress has been made in improving the informed consent process, making it more genuine. Investment is continuing into building up the resources necessary for rigorous ethical review by local committees. Debate continues over the standard of care ethically required in research trials, and over the long-term obligations to research participants. That debate itself is important and represents...
progress. Only through such discussions will research remain firmly founded on the basic ethical principle of the Declaration of Helsinki: “to protect the life, health, privacy, and dignity of the human subject.”

References


