

EXECUTIVE SUMMARY

This report considers ethical dilemmas faced by U.S. physicians involved in international research, particularly in countries with developing economies and with healthcare infrastructures that are considered underdeveloped. This analysis traces some of the early historical development of ethics guidelines pertaining to research as well as some of the recent policy developments, from the Nuremberg Code to the latest revision to the World Medical Association's Declaration of Helsinki. These guidelines are examined in the context of the recent controversy spurred by clinical studies of HIV transmission from mother to infant, and also in relation to existing Opinions of the Code of Medical Ethics.

Overall, the report focuses on the need to foster trust as a necessary condition to the ethical advancement of science, and on the means to ensure the autonomy and protection of participants, as well as the need for meaningful collaboration between U.S. physicians and host countries. The report specifically considers the role of Institutional Review Boards (IRBs), the requirement of obtaining informed consent, and issues related to levels of care that can be offered in the context of clinical trials.

To guide the ethical conduct of international clinical research, the report recommends that international research proceed when studies are scientifically sound and answer a genuine question and after it has been approved by a U.S. Institutional Review Board. In turn, approval should be granted after careful review of risks and benefits, and a determination that a suitable informed consent process is in place. IRBs also should determine that the research corresponds to a medical need in the region where it is undertaken. Input must be provided by the host country and the research population. Finally, to ensure fairness in the conduct of international research, IRBs should foster research with potential lasting benefits and physicians should work to provide continuing beneficial study interventions to all study participants at the conclusion of the study.

REPORT OF THE COUNCIL ON ETHICAL AND JUDICIAL AFFAIRS*

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Subject: Ethical Considerations in International Research

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Presented to: Reference Committee on Amendments to Constitution and Bylaws
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1 INTRODUCTION

2
3 In this report, the Council on Ethical and Judicial Affairs undertakes the analysis of ethical
4 dilemmas faced by U.S. physicians either in their role as investigators conducting research in
5 other countries or as decision-makers involved in deliberations related to funding or in the review
6 of research to be conducted in other countries, in particular countries with developing economies
7 and with health care infrastructures that are considered underdeveloped. However, it is worth
8 noting that difficulties may arise any time research is conducted in a country with differing
9 cultural traditions, health care systems, ethical standards, and laws, and that in all such instances,
10 physicians will be called upon to recognize such differences and work to reconcile them in a
11 manner that is consistent with high ethical standards. Also, the Council recognizes that multiple
12 international entities already have promulgated guidelines on international research,^{1, 2, 3, 4} It is
13 not the intention of the Council to resolve the discrepancies that may exist among these
14 documents, nor to endorse any particular document or specific set of guidelines, but rather to
15 offer U.S. physicians ethical guidance that can assist them in evaluating the dilemmas inherent to
16 international research.

17
18 In essence, ethicists have debated whether U.S. standards and regulations ought to govern
19 research conducted in another country. Proponents of applying uniform standards have spoken of
20 “universal” standards, which they oppose to a more “pluralistic” or “relativistic” ethical stance
21 that would allow greater flexibility and arguably less stringent standards to govern research in
22 developing countries.^{5, 6, 7} Others have viewed this position as “imperialistic” and have argued
23 that local standards better reflect the cultural norms and economic resources that influence the
24 conduct of research in the country.⁸ However, all fundamentally seek to avoid the exploitation of
25 human subjects, even though they may argue over what constitutes exploitation and how best to
26 protect against it.

27
28 This report begins with a short overview of the historical developments of ethical standards in the
29 conduct of human experimentation before examining recent debates that erupted regarding the
30 appropriate application of U.S. research ethics standards. The report also reviews relevant AMA
31 policy. Building on this account of the development of international standards and the current
32 challenges faced in their application, the analysis focuses on a determination of the relevant
33 ethical considerations that should guide the ethical conduct of international research involving
34 U.S. researchers.

□ Reports of the Council on Ethical and Judicial Affairs are assigned to the Reference Committee on Constitution and Bylaws. They may be adopted, not adopted, or referred. A report may not be amended, except to clarify the meaning of the report and only with the concurrence of the Council.

1 *Historical development of research ethics guidelines*

2
3 In order to examine the merits of the various arguments being put forward regarding the most
4 appropriate standards for international research, it is important to be reminded, albeit briefly, of
5 the historical development of international guidelines and the ethical principles that they embody.
6 This exploration can begin with the Nuremberg Code,¹ which emerged out of experiments
7 conducted during the World War II. Specifically, the Nuremberg Code consists of 10 principles
8 that appeared as part of the written judgement in the *Trials of War Criminals Before the*
9 *Nuremberg Military Tribunals*. These judiciary proceedings were undertaken to investigate the
10 inhumane treatment research subjects – mostly prisoners detained in concentration camps – had
11 suffered at the hands of Nazi scientists.⁹

12
13 The provision of the Nuremberg Code that is most often referred to states in part: “The voluntary
14 consent of the human subject is absolutely essential.” This first provision also provided the
15 various elements that now comprise the requirements of informed consent in research, namely the
16 legal capacity to give consent; the ability to exercise free power of choice (voluntariness), and
17 knowledge and comprehension of the elements of the subject matter involved as to enable
18 participants to make a decision (disclosure). Other provisions addressed the nature and conduct
19 of the research, such that experiments should be purposeful rather than random and unnecessary,
20 and should be conducted in such a manner as to avoid all unnecessary suffering. Even if the
21 Nuremberg Code was not statutorily enacted in its entirety by any nation and did not have an
22 immediate impact on the way experiments were conducted in the U.S.,¹⁰ its basic requirement of
23 voluntary consent evolved into a cornerstone of ethics in human experimentation.

24
25 Within a decade, the World Medical Association identified the need for a document written by
26 physicians that also would address “therapeutic” experiments, in addition to the “non-therapeutic”
27 experiments performed by Nazi scientists, which were detached from any intent to provide a
28 therapeutic effect. The document that became known as the Declaration of Helsinki was issued in
29 1964 and has been revised sporadically. It recently underwent a fifth revision, discussed below.

30
31 Other than the two documents referred to above, there has been a proliferation of research
32 guidelines by international and national entities. Among them, the Council for International
33 Organizations of Medical Sciences (CIOMS) in collaboration with the World Health
34 Organization issued in 1993 the “International Ethical Guidelines for Biomedical research
35 Involving Human Subjects.”¹¹ Because it was developed more recently, this document benefited
36 from a considerable wealth of material on ethical issues in international research. The
37 development of the document also drew from a broad group that was culturally and professionally
38 diverse.⁸ A co-chair of the steering committee that drafted these guidelines has argued that
39 although they build on the legacy of the Nuremberg Code and the Declaration of Helsinki, they
40 have avoided many of the pitfalls that were identified in the other two documents, and therefore
41 should be considered as superseding them.⁸ The CIOMS guidelines specifically address the
42 situation where research is conducted in a host country that is different than the country which is
43 sponsoring, financing or carrying out the research, in part or in whole. Two ethical obligations are
44 set forth: (1) the research protocol should, at a minimum, meet the ethical standards that apply to
45 research conducted domestically; and (2) the proposed research should be submitted for ethical
46 review to appropriate authorities in the host country, so that they may determine whether it
47 conforms to their own ethical standards.¹¹

1 *Recent controversy in conducting international research*

2
3 As early as 1988, it was predicted that investigators conducting research in developing countries
4 would face considerable ethical challenges, particularly in regard to AIDS research.¹ Pointing out
5 that many researchers were unfamiliar with the cultures, customs and economic pressures faced
6 by those countries, one author emphasized that guidance already existed through the ethical
7 principles of autonomy, non-maleficence and beneficence, and justice.¹²

8
9 In an accompanying editorial,⁶ Marcia Angell asked the questions that would become the focus of
10 the debate that erupted almost ten years later: “Is it proper for Americans to insist that their
11 ethical standards be applied to clinical research performed in other countries? Should ethical
12 standards be substantially the same everywhere, or is it inevitable that they differ from region to
13 region, reflecting local beliefs and custom?” Angell favored the view that ethical standards are
14 not a matter of custom and that basic human rights must be honored universally, although some
15 accommodations could be necessary to respect local sensitivities.

16
17 In September 1997, two commentators reported in the *New England Journal of Medicine* that
18 studies on the reduction of maternal-fetal HIV infection being conducted in developing countries
19 and funded by the U.S. government were ethically at variance with similar studies conducted in
20 the U.S., in that participants in the control arm were given a placebo instead of zidovudine, which
21 was considered the standard of care in the U.S..¹³

22
23 In the ensuing debate as to the appropriate standards that should be applied in conducting
24 research in developing countries, both sides agreed that “identifying less expensive and similarly
25 effective interventions would be of enormous benefits, given the limited resources for medical
26 care in most developing countries.” Proponents of placebo-controlled studies believed that such a
27 design would be preferable to comparing shorter regimens to the standard one. They also
28 believed placebo-controlled trials were ethical since subjects receiving the placebo were receiving
29 the country’s standard care. Opponents of placebo trials counter-argued that the studies were not
30 undertaken in a state of equipoise. Furthermore, they argued that justifying the use of a placebo
31 in terms of a local standard fails to differentiate between a standard that is established among
32 known medical options and a standard that is the result of economic constraints.

33
34 Officials of the funding agencies that had made those trials possible responded to the criticisms
35 by explaining that interventions that could be conducted in the U.S. might well be beyond the
36 financial resources of developing countries or the capacity of their health care systems.¹⁴ Also,
37 some study could be more compelling in those countries because of the burden of disease. These
38 authors suggested that placebo-controlled trials could be justified on the basis that the assignment
39 to the placebo group carried no risk beyond that associated with standard practice, that such trials
40 provided a faster answer with fewer subjects, and that answers about safety and the value of the
41 intervention were definitive. Such answers could then allow a country to make a sound
42 judgement about the appropriateness and financial feasibility of the intervention.

43
44 *Revision of the Declaration of Helsinki*

45
46 It is against this backdrop that the World Medical Association recently undertook its 5th revision
47 of the Declaration of Helsinki. In particular, changes were favored by those who viewed the

ⁱ Much of the ethical debate regarding international research is centered on HIV/AIDS, which ranked fourth among the top 10 causes of the global burden of disease, 98% of which is borne by countries with low or middle incomes – check either WHO or World Bank, 1993, Investing in Health.

1 Declaration of Helsinki as defective in that it inappropriately maintained a distinction between
 2 therapeutic and non-therapeutic research and was out of touch with current ethical thinking, and
 3 therefore was violated frequently.¹⁵ In particular, some argued that the requirement that every
 4 participant, including those in a control group, receive the best proven intervention was outmoded
 5 since it resulted in limiting the use of placebos to instances where no proven intervention existed
 6 when in practice placebo were much more widely used.¹⁵ Other analysts, however, were
 7 concerned that such revisions could lead to an erosion of the protections offered to human
 8 subjects and that greater emphasis on utilitarian factors would dominate.¹⁶

9
 10 The revision adopted in October 2000 abandoned the long standing distinction between
 11 therapeutic and non-therapeutic research, but now refers to “basic principles for all medical
 12 research” and “additional principles for medical research combined with medical care.” It also
 13 emphasizes that a population can be chosen to participate in an experiment only if it is to benefit
 14 from the experiment. The World Medical Association maintained the requirement that new
 15 treatments be compared to the best existing methods, limiting the use of placebo to instances
 16 where the prevailing treatments are unproven. According to the leaders of the WMA, the
 17 protections of research participants had been strengthened through this round of deliberation,
 18 lasting 3 years.^{17, 18, 19} Such strengthening, however, may amount to an emphasis of the general
 19 nature of ethical standards as opposed to legal standards, namely that guidelines are normative
 20 and often aspirational.²⁰

21 *National Bioethics Advisory Commission*

22
 23
 24 American ethicists and researchers alike have recognized that much of the controversy that
 25 erupted over HIV research in developing countries stemmed from the application of the U.S.
 26 federal regulations, known as the Common Rule. In part, this led the National Bioethics
 27 Advisory Commission to investigate this debate and make recommendations regarding
 28 international research that could be implemented in the U.S. and govern investigators and
 29 sponsors conducting research abroad. A draft report was issued in the September 2000,²¹
 30 preceding by a week the revised Declaration of Helsinki. Although a final report is still pending,
 31 the extensive analysis of the Commission provides a valuable contribution to understanding the
 32 ethical issues at stake from a U.S. perspective. In particular, the Commission identifies two types
 33 of ethical requirements: substantial ones and procedural ones. This dichotomy also exists in
 34 relation to the substantial and the procedural requirements of informed consent.

35
 36 Overall, the National Commission emphasized that research conducted in developing countries
 37 should correspond to health needs of the host country; that participants in the control arm
 38 generally should receive established, effective treatments that exist at the time the research is
 39 undertaken; that there be meaningful community involvement in the design and implementation
 40 of the research; that the substantive requirement of informed consent be complied with, that there
 41 be post-trial benefits to the community, as required by the principle of justice as reciprocity, and
 42 that efforts be made to enhance international collaborative research.

43 *AMA Policy*

44
 45
 46 Principally, three existing Opinions of the *Code of Medical Ethics* address ethical issues related to
 47 the conduct of research. All were developed in the context of research performed in the U.S., but
 48 their framework may be applicable to research performed elsewhere.

49
 50 Opinion 2.07, “Clinical Investigation,” which first appeared in the 1969 edition of the *Code of*
 51 *Medical Ethics* and was substantially amended by addition in 1994 and 1998, builds on the

1 foundation of the Nuremberg Code by stating that “No person may be used as a subject in clinical
2 investigation against his or her will.” This Opinion also mirrors the distinction that formerly was
3 drawn in the Declaration of Helsinki regarding therapeutic and non-therapeutic research, referring
4 to “clinical investigation primarily for treatment” and “clinical investigation primarily for the
5 accumulation of scientific knowledge.” In the former case, the physician cannot abandon the role
6 of clinician and must exercise professional judgement and skill in the best interest of the patient,
7 whereas in the latter case, social policy dictates that concerns for the individual must be primary
8 and the advancement of scientific knowledge secondary. Also, in the context of clinical research
9 mixed with treatment, disclosure should include possible therapeutic benefits, as well as a
10 disclosure of alternative therapeutic options, two requirements that are not listed in the case of
11 purely experimental clinical investigation. Finally, the guidelines provide two additional
12 considerations in the context of clinical investigation mixed with treatment that are not discussed
13 in the context of clinical investigation for scientific advancement. First, when the experimental
14 treatment is the only potential treatment for the patient and full disclosure would pose such a
15 psychological threat of detriment to the patient, such information can be withheld, a doctrine
16 known as the “therapeutic privilege.” In addition, although consent should be written, in
17 circumstances where this is not feasible due to the physical or emotional state of the patient,
18 exceptions are permitted.

19
20 Opinion 2.075, “The Use of Placebo Controls in Clinical Trials,” issued in 1997, addresses the
21 circumstances when it may be permissible to use a placebo. The Opinion emphasizes informed
22 consent, and the role of Institutional Review Boards and investigators to ensure that each subject
23 has been adequately informed and has given voluntary consent. To that effect, the Opinion
24 requires that subjects be made aware that they can terminate their participation in a study at any
25 time. In addition, the Opinion lays out a gradation along which the use of placebo is permissible.
26 Specifically, it states that when research pertains to a condition that causes death or irreversible
27 damage, a placebo cannot be employed if an alternative treatment would prevent or slow the
28 progression of the illness. Where research is conducted on an illness that is characterized by
29 severe or painful symptoms, the use of placebo may be permissible. However, the more severe
30 the condition, the less justifiable would be the use of a placebo as a substitute for an existing
31 suitable therapy. A similar methodology was reiterated in Opinion 2.076, “Surgical Placebo
32 Controls,” issued in 2000.

33
34 Finally, in Opinion 2.071, “Subject Selection for Clinical Trials,” which was issued in 1998, the
35 Council on Ethical and Judicial Affairs specifically recognized the need to protect socio-
36 economically disadvantaged populations but also found that such populations should not be
37 categorically excluded or discouraged from participation in research. Also, the Opinion
38 emphasizes that when a subject has received a clear medical benefit from the experimental
39 intervention that is under consideration for market approval by the Food and Drug
40 Administration, the patient’s physician, the investigator, and the product sponsor, should seek to
41 provide access to the intervention, for example by having recourse to one of the FDA’s special
42 exception to final review and approval.

43 44 *International Research: Applicable Ethical Standards*

45
46 The fundamental question that is raised by international research is a matter of determining which
47 standards should be applied when those of the country of origin of the investigators or sponsors
48 differ from the standards that exist in the region where the research is to be conducted. In
49 practice, this question has arisen primarily when Western researchers have conducted research in
50 developing countries.

1 This single question, however, seems to be split into two lines of inquiry: first, whether the same
2 ethical standards apply regardless of the location where the research is conducted; second,
3 whether the standard of medical care that is offered in the control arm of the trial ought to be the
4 standard available in the country of origin of the investigators or sponsors, or whether the
5 experimental intervention can be measured against the local standard of care. It is important to
6 note that these two questions often have been confounded.

7 8 Uniform Ethical Standards: The Role of Informed Consent

9
10 As multinational research trials become more of a common occurrence, the question of whether
11 universal ethical standards govern the conduct of human subject research has become a
12 controversial topic. At the core of this question lie the notions of autonomy and informed
13 consent.

14
15 As briefly described above, informed consent emerged as a central requirement of human
16 experimentation through the Nuremberg Code. Until the adoption of these guidelines, the ethical
17 concern governing research had been one of beneficence: to control the risks presented to
18 subjects.²² The Code shifted the focus to include the distinct principle of respect for persons such
19 that participants exercised their autonomy in deciding whether or not to volunteer in research.
20 In the U.S., the Belmont Report, which was issued in 1979 by the National Commission for the
21 Protection of Human Subjects of Biomedical and Behavioral Research, identified informed
22 consent as one of the basic ethical principles that should underlie the conduct of biomedical
23 research on human subjects.²³

24
25 Since these developments, other ethical guidelines regarding research have been crafted around
26 values of individualism to emphasize individual rights, autonomy, and self-determination. Some
27 commentators, however, reject the idea that such standards cut across time, place, and culture. In
28 particular they question the relevance of the principle of informed consent in cultures that do not
29 promote individualism in the same manner that it is protected in Western countries. In this
30 regard, they point to non-Western countries where people have a more relational understanding of
31 personhood and place greater emphasis on collective rights to ask whether informed consent has
32 meaning where personal choice is limited in relation to community good. There is concern that
33 overriding the norms and values of a culture that grants decisional-making authority to the village
34 chief, the local leader, or the head of the family may be disrespectful. To insist on obtaining
35 consent from each potential research subject in these cultures may be morally incongruous.²⁴

36
37 Proponents of the universal moral status of individual informed consent contend that the
38 obligation to obtain consent transcends local custom or law, in that it is derived from a
39 fundamental human right, the right to self-determination.⁶ Some, in an effort to acknowledge and
40 respect the local sensitivities of certain cultural settings, suggest that consent be required from
41 community authorities, in addition to individual consent. Others simply propose that the local
42 authorities be informed of the research. They all agree, however, that community involvement
43 cannot override or substitute an individual's acceptance or refusal to participate. Indeed, such
44 substitution would fail to promote respect for the individual, and thereby deviate from the
45 substantive ethical standard of informed consent.

46
47 The fundamental concern of research ethics is to prevent the mistreatment of human subjects.
48 The principal safeguard, in the context of research, is to seek informed consent from each
49 potential subject. Regardless of whether the ethical standard of individual informed consent is
50 universal, it becomes necessary to obtain it when research is conducted and participants solicited.
51

1 Carrying out the process of informed consent in various cultural settings remains a challenge and
2 requires an understanding of the values from which community members derive meaning.
3 Therefore, research investigators will need to devote careful attention to the design of the
4 informed consent process, identifying sources of approval or authorization that are necessary, in
5 addition to the consent of the potential participant. Investigators also should seek to ascertain that
6 consent or refusal to participate is voluntary.

7 8 Standards of Care

9
10 The second component of the debate focuses on whether the best proven therapy must be used or
11 whether placebo-controlled trials are justifiable in the developing world when a proven treatment
12 already exists in developed countries. Fundamentally, this dilemma is one that translates into an
13 ethical issue of risks and benefits. It requires the same analysis that is required of all protocols,
14 namely a determination to be made by investigators and review boards as to whether the trial
15 design stems from a state of equipoise, such that there is genuine uncertainty among the clinical
16 community as to the comparative merits between the experimental intervention and the control
17 treatment.²⁵

18
19 From this perspective, researchers must use all the means at their disposal to review existing data,
20 and those in charge of reviewing research protocols must use their scientific judgement to
21 evaluate the hypothesis that is being studied. If the question is one that is scientifically
22 unanswered, then the study should be designed to minimize the risks in the face of uncertainty. If
23 a review board then determines that risks and benefits are favorably balanced, the research
24 usually is deemed ethical. Indeed, there are no substantive guidelines as to what constitute an
25 unacceptable risk or a significant benefit.

26
27 Clearly, difficulty remains in evaluating risks and benefits, including the risk of exploiting
28 participants. This concern is heightened in the context of unbridgeable disparities in health care
29 resources among countries,²⁶ whereby populations of developing countries may be used to
30 advance scientific knowledge that result in greater or more immediate benefit to the industrialized
31 world.²⁷

32
33 To ensure that international research does not result in an exploitative outcome, arguments have
34 been advanced that research should respond to needs of the local community and its research
35 participants and that measures should be negotiated at the outset to ensure the implementation of
36 a successful experiment among them. In this regard, some have called for “fairness as the
37 principal rule of engagement” and have invited the broad participation of all stakeholders.^{24, 29, 30}

38 39 CONCLUSION

40
41 Ethical research generally results from research designs that have been developed according to a
42 sound scientific inquiry. Review boards are then required to safeguard research participants
43 against coercion or abuse. Through the process of informing a potential participant of the nature
44 of the research endeavor, and by seeking the participant’s voluntary consent, the process of
45 informed consent is viewed as the principal ethical means to ensure the respect of individual
46 participants. Overall, respect for persons, through the informed consent process, fosters trust, a
47 necessary condition to the ethical advancement of science.

48
49 The protection of participants also requires review boards to determine that risks have been
50 minimized and that potential benefits are in a favorable ratio. In the context of international
51 research, the risk of exploitation warrants special attention and can best be attended to by

1 obtaining relevant input from the host country to ensure that the chosen population will not face
2 unjustifiable risks. Despair or dire need for basic medical care should not justify undue risk, just
3 as they cannot substitute for voluntary and informed consent.

4
5 RECOMMENDATIONS

6
7 The Council recommends that the following be adopted and the remainder of the report be filed:
8

9 Physicians, either in their role as investigators or as decision-makers involved in the
10 deliberations related to the funding or the review of research, hold an ethical obligation to
11 ensure the protection of research participants. When the research is to be conducted in
12 countries with differing cultural traditions, health care systems, and ethical standards, and in
13 particular in countries with developing economies and with limited health care resources,
14 U.S. physicians should respect the following guidelines:
15

- 16 (1) First and foremost, physicians involved in clinical research that will be carried out
17 internationally should be satisfied that a proposed research design has been developed
18 according to a sound scientific design. Therefore, investigators must ascertain that there
19 is genuine uncertainty within the clinical community about the comparative merits of the
20 experimental treatment and the one to be offered as a control in the population among
21 which the study is to be undertaken. In some instances, a three-pronged protocol, which
22 offers the standard treatment in use in the U.S., a treatment that meets a level of care that
23 is attainable and sustainable by the host country, and a placebo (see Opinion 2.075), may
24 be the best method to evaluate the safety and efficacy of a treatment in a given
25 population. When U.S. investigators participate in international research they must
26 obtain approval for such protocols from U.S. Institutional Review Boards (IRBs).
27
- 28 (2) IRBs, which are responsible for ensuring the protection of research participants, must
29 determine that risks have been minimized and that the protocol's ratio of risks to benefits
30 is favorable to participants. In evaluating the risks and benefits that a protocol presents to
31 a population, IRBs should obtain relevant input from representatives from the host
32 country and from the research population. It is also appropriate for IRBs to consider the
33 harm that is likely to result from forgoing the research."
34
- 35 (3) Also, IRBs are required to protect the welfare of individual participants. This can best be
36 achieved by assuring that a suitable informed consent process is in place. Therefore,
37 IRBs should ensure that individual potential participants will be informed of the nature of
38 the research endeavor and that their voluntary consent will be sought. IRBs should
39 recognize that, in some instances, information will be meaningful only if it is
40 communicated in ways that are consistent with local customs
41
- 42 (4) Overall, to ensure that the research does not exploit the population from which
43 participants are recruited, IRBs should ensure that the research corresponds to a medical
44 need in the region where it is undertaken. Furthermore, they should foster research with
45 the potential for lasting benefits, especially when it is undertaken among populations that
46 are severely deficient in healthcare resources. This can be achieved by facilitating the
47 development of a healthcare infrastructure that will be of use during and beyond the
48 conduct of the research. Additionally, physicians conducting studies must encourage
49 research sponsors to continue to provide beneficial study interventions to all study
50 participants at the conclusion of the study.

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