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ANNIVERSARY ESSAY: The Challenge of Assuring Continued Post-Trial Access to Beneficial Treatment

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Text

[*425]

Sam Jones has agreed to participate in a clinical trial testing an experimental drug as a possible treatment for his chronic disease. The primary outcome of effectiveness is a decrease in a specific disease marker after two months of taking the drug. Soon after Sam begins to take the drug, he reports feeling better and the level of disease marker in his blood is significantly lower at each study interval. The study reaches its predetermined endpoint, is stopped as planned, and the sponsor submits an application to a regulatory agency to license the drug for this indication. It is clear that Sam would clinically benefit from continuing to take the drug.

Is it the responsibility of the investigator or the research sponsor to ensure that Sam and other participants in this study continue to receive the drug or even to provide it to them after a study ends? This question is at the heart of recent controversy regarding post-trial benefits and may be one of the biggest ethical challenges facing clinical investigators, especially those involved in international research, over the next several years.

Post-trial Benefits

Until recently, regulations and codes of research ethics have been silent about what should happen at the conclusion of a clinical study. Regulations and codes have focused on protecting the rights and welfare of individuals in clinical research by requiring that the research design was appropriate, risks were minimized, research was reviewed by an independent body, and the participant's consent was adequately informed **[*426]** and voluntary. The Common Rule in the Code of Federal Regulations requires that investigators inform participants in advance of any interventions or compensation that will be provided if a research participant is injured during trial participation, ¹ but it offers no guidance regarding what should happen to a person like Sam. Even the forward-looking International Ethical Guidelines for Biomedical Research Involving Human Subjects, ² published by the

¹ [45 C.F.R. 46 \(2003\)](#).

² Council for Int'l Org. of Med. Sci., International Ethical Guidelines for Biomedical Research Involving Human Subjects (1993) (on file with author).

Council for International Organizations of Medical Sciences (CIOMS) in 1993, did not address the issue of what should happen at the end of a clinical study to participants who are receiving beneficial treatment. The CIOMS guidelines did address the issue of compensation for research injury and also introduced the idea that the sponsoring agency of externally sponsored research "should agree in advance of the research that any product developed through such research will be made reasonably available to the inhabitants of the host community or country at the completion of successful testing."³

Controversy in the late 1990s about the ethics of international HIV trials brought increased attention to the issue of post-trial benefits.⁴ Many agreed that in order to minimize the possibility of exploiting research participants in developing countries, a plan for how the benefits of research would be made reasonably available to the developing country or community was required.⁵ Most of the discussion focused on the requirement that products proven effective through research be made available to the wider community from which research participants were drawn. The question of continued treatment of participants like Sam has [*427] been less frequently attended to, with a few notable exceptions.⁶ The challenges of assuring that products proven effective during a trial are subsequently made reasonably available to the population in which the product was tested are formidable.⁷ Nonetheless, it is both practically and ethically a different challenge than that of assuring that individual research participants continue to receive beneficial treatments once the trial is over. Yet, the two issues are commonly conflated.⁸

Current Guidance

In the past few years, certain research ethics guidance documents,⁹ reports,¹⁰ and national guidelines¹¹ have begun to address the issue of continued post-trial treatment of participants like Sam who are receiving beneficial treatment. The Declaration of Helsinki, first published in 1964 by the World Medical Association (WMA), is internationally recognized as a major source of ethical guidance for the conduct of clinical research.¹² The WMA substantially revised the Declaration of Helsinki at its fifty-second assembly in 2000 due to intense public disagreement regarding the [*428] aforementioned international HIV trials. The extensive changes included the

³ Id. at 45.

⁴ See Marcia Angell, *The Ethics of Clinical Research in the Third World*, 337 *New Eng. J. Med.* 847 (1997); Peter Lurie & Sidney M. Wolfe, *Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries*, 337 *New Eng. J. Med.* 853 (1997); Harold Varmus & David Satcher, *Ethical Complexities of Conducting Research in Developing Countries*, 337 *New Eng. J. Med.* 1003 (1997).

⁵ See, e.g., Nat'l Bioethics Advisory Comm'n, *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries* (2001) [hereinafter NBAC]; Nuffield Council of Bioethics, *The Ethics of Research Related to Healthcare in Developing Countries* 11 (2002), <http://www.nuffieldbioethics.org/go/ourwork/developingcountries/publication> 309.html [hereinafter Nuffield]; Leonard H. Glantz et al., *Research in Developing Countries: Taking "Benefit" Seriously*, 28 *Hastings Center Rep.* 38 (1998); Eric M. Meslin & Harold T. Shapiro, *Ethical Issues in the Design and Conduct of Clinical Trials in Developing Countries*, 345 *New Eng. J. Med.* 139 (2001).

⁶ See NBAC, *supra* note 5, at 12-13; Council for Int'l Org. of Med. Sci., *International Ethical Guidelines for Biomedical Research Involving Human Subjects* cmt. on guideline 10 (2002) [hereinafter CIOMS 2002] ("If an investigational drug has been shown to be beneficial, the sponsor should continue to provide it to the subjects after the conclusion of the study, and pending its approval by a drug regulatory authority."); Joint United Nations Programme on HIV/AIDS, *Ethical Considerations in HIV Preventive vaccine research* 13 (2000) [hereinafter UNAIDS].

⁷ See *Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries*, *Moral Standards for Research in Developing Countries: From "Reasonable Availability" to "Fair Benefits"*, 34 *Hastings Center Rep.* 17 (2004).

⁸ See Editorial, *One Standard, Not Two*, 362 *The Lancet* 1005 (2003) [hereinafter *One Standard, Not Two*].

⁹ See, e.g., World Med. Ass'n, *Declaration of Helsinki* (2000), <http://www.wma.net/e/policy/pdf/17c.pdf> [hereinafter WMA] (clarified in 2002 and 2004); CIOMS 2002, *supra* note 6.

¹⁰ See, e.g., NBAC, *supra* note 5; Nuffield, *supra* note 5.

addition of several new ideas that had not appeared in previous versions of the Declaration.¹³ One addition to the 2000 version of Helsinki, Paragraph 30, directly speaks to what should happen to Sam: "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

Certain paragraphs in the 2000 version of the Declaration of Helsinki, particularly Paragraph 29 (regarding placebo-controlled trials) and Paragraph 30 (regarding post-trial treatment of participants), have continued to fuel considerable debate. A clarification to Paragraph 29, issued by the WMA in 2002, attempted (some would say unsuccessfully) to affirm a definitive stance about placebo-controlled trials.¹⁵ A call for clarification or an amendment to Paragraph 30 was also considered. The WMA voted early in 2004 not to amend Paragraph 30, but to consider issuing a clarification.¹⁶ In October 2004, a clarification of Paragraph 30 was issued by the WMA:

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.¹⁷

What Is the Issue?

At first glance, it may appear to be common sense that if someone is doing well on a medication or treatment, even if that treatment is [*429] investigational, it should be continued. Discontinuation of such a treatment may have poor health consequences for many research participants, and therefore should require compelling justification. Yet most research protocols do not include provisions to assure continued access to products that are providing clinical benefit to individual participants after the study concludes. Even for investigational drugs that eventually are approved, licensed, and made available through the health care system, there is usually a lag time during which a research participant could benefit from continued treatment. And in some cases, individual research participants will not be able to obtain such treatments even after approval.

Anecdotal evidence suggests that most investigators, at the very least, refer research participants to continued treatment through their regular health care providers when a trial is over. However, the realities of limited access to health care, primarily in the developing world, but also in many communities in the United States, suggest that referral to health care providers may often be inadequate. Research participants can also be referred to pharmaceutical company-sponsored patient assistance programs, which are designed to help patients obtain

¹¹ See, e.g., Clinical Trials Working Group of the S. African Dep't of Health, Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa P 9.3.5 (2000), at http://196.36.153.56/doh/docs/policy/trials/trials_contents.html; Indian Council of Med. Res., Ethical Guidelines for Biomedical Research on Human Subjects 27 (2000), <http://icmr.nic.in/ethical.pdf>; Nat'l Consensus Conf., Guidelines for the Conduct of Health Research Involving Human Subjects in Uganda (1997) (on file with author).

¹² WMA, supra note 9.

¹³ See Heidi P. Forster et al., The 2000 Revision of the Declaration of Helsinki: A Step Forward or More Confusion?, 358 The Lancet 1449 (2001).

¹⁴ WMA, supra note 9, P 30.

¹⁵ Douglas P. Lackey, Clinical Research in Developing Countries: Recent Moral Arguments, 18 Cadernos de Saude Publica 1455, 1457-58 (2002); Reidar K. Lie et al., The Standard of Care Debate: The Declaration of Helsinki Versus the International Consensus Opinion, 30 J. Med. Ethics 190, 190 (2004).

¹⁶ World Med. Ass'n, Workgroup Report on the Revision of Paragraph 30 of the Declaration of Helsinki (2004), http://www.wma.net/e/ethicsunit/pdf/wg_doh_jan2004.pdf [hereinafter WMA Workgroup Report].

¹⁷ WMA, supra note 9, at 5; see also Press Release, World Med. Assembly, Clarification on Declaration of Helsinki (Oct. 11, 2004), http://www.wma.net/e/press/2004_24.htm.

subsidized access to drugs they need that would otherwise be unavailable or unaffordable. Pharmaceutical companies sometimes pledge to continue to provide a drug that participants are receiving in a clinical trial for a predetermined period of time - often three to five years - and more rarely for the life of an individual participant.¹⁸ Investigators have been known to creatively seek out public assistance programs, social services, additional research protocols, and other sources of funds to be able to continue to provide beneficial drugs to research participants in the short term.¹⁹

Despite these efforts, there is no system in place for assuring continued treatment. And the question of whose responsibility or obligation it is to make sure a research participant continues to receive beneficial treatment remains unsettled, as noted by the editors of *The Lancet*:

The idea behind [the Declaration of Helsinki] language is straightforward: a person who participates in a trial should have a chance to benefit from what is learned from the trial - a principle that is particularly important for participants in the developing world. Trial [*430] participants in wealthy nations will usually be able to get the best available treatment after the trial is over. But in the developing world when the researchers pack up and go home, participants can be left with nothing.²⁰

As important as it is to recognize that research participants should have the chance to benefit from what is learned from a trial, it is also true that benefits can and probably should come in many other forms besides continued receipt of treatment. In addition, the Declaration of Helsinki is silent on who should assure continued treatment and assigning responsibility for assuring continued treatment is not straightforward.

Moral Reasons for Assuring Continued Treatment

If a participant is deriving clinical benefit from an investigational therapy, withdrawing that therapy can be harmful. For many diseases, especially those requiring chronic treatment, exacerbation of symptoms or disease can occur if treatment is stopped. In accord with principles of non-maleficence and beneficence, patients, including those who are being treated as participants in research, should continue to receive a treatment they need as long as they are benefiting from it.

Further, stopping a clinically beneficial treatment simply because a clinical trial ends seems unfair and might contravene ethical obligations created by enlisting people to participate in research.²¹ Because research participants accept some risk for the good of society and the advancement of science, certain things are owed to them in return. The U.S. National Bioethics Advisory Committee described this as "justice as reciprocity."²² Also, because research participants are asked to entrust certain aspects of their health to researchers, there is a corresponding responsibility of researchers to care for these aspects.²³ Although the basis for these obligations may seem indisputable, the extent of the obligation - or what exactly is owed to research participants and by whom - is at the center of the debate. Belsky and Richardson argue that the extent of researchers' obligation to care for participants is influenced by several factors, including the strength of the relationship and the vulnerability of the participants.²⁴ Participants who are ill and participate in research with the hope of deriving some therapeutic benefit put partial trust in investigators. [*431] Dropping them completely may be an abandonment of investigator

¹⁸ See Nancy Kass & Adnan A. Hyder, Attitudes and Experiences of U.S. and Developing Country Investigators Regarding U.S. Human Subjects Regulations, in NBAC, *supra* note 5, at B-1, B38-45.

¹⁹ *Id.*

²⁰ *One Standard, Not Two*, *supra* note 8, at 1005.

²¹ Forster et al., *supra* note 13, at 1451.

²² NBAC, *supra* note 5, at 59.

²³ See Leah Belsky & Henry S. Richardson, Medical Researchers' Ancillary Clinical Care Responsibilities, 328 *Brit. Med. J.* 1494 (2004).

²⁴ *Id.* at 1495-96.

responsibilities and trust. A physician's role, even as clinical investigator, includes that of advocating for the welfare of the research participant.

Exploitation is another worry in clinical research. In research, exploitation occurs when the participant is taken unfair advantage of for the investigator's or sponsor's benefit. Is the research participant who receives beneficial treatment for a limited period of time exploited? Receiving beneficial treatment through trial participation even for a finite period of time may be perceived by participants with limited access to health care as a good option, or at least as a better option than no treatment at all. I would argue that it is not necessarily exploitative to offer time-limited access to beneficial treatment through research for a willing and informed participant. Yet, there are other moral reasons why researchers should take steps to assure post-trial access to beneficial treatment.

The moral obligation to assure that beneficial treatment is continued might well be fulfilled by referring a research participant like Sam to a physician who can prescribe the drug and, when necessary, by making provisions through the sponsor or a pharmaceutical company to provide the drug in the interim. But what if the drug is unlikely to be licensed in the jurisdiction for the foreseeable future? And what if, even if the drug is licensed, Sam or someone like him will not be able to afford it? Growth in international collaborative research has called attention to this problem because of the reality of limited availability and access to medical treatment in many developing countries.²⁵ It is also an important issue in countries like the United States, where health care services are unevenly available.

Other Challenges to Providing Continued Treatment

Even if the rationale for assuring continued treatment is compelling, the question of who should be responsible for assuring this and how it should be accomplished remains. It has been argued that if pharmaceutical companies and sponsors are made solely responsible for assuring continued access to beneficial treatment, this requirement could serve as a major disincentive for companies to engage in certain kinds of research.²⁶ This could also jeopardize the future of research in places with limited health care access,²⁷ especially for diseases that might require **[*432]** chronic or expensive treatment.²⁸ Commentators worry about the possibility of dampening research in developing countries where new treatments are needed the most.²⁹

A recent and dramatic example of this tension unfolded in a planned study of tenofovir for possible prevention of HIV in Cambodia. The study called for the inclusion of almost one thousand sex workers. The study was halted when the Women's Network for Unity, a Cambodian sex workers union, demanded a guarantee that participants would receive health care for thirty years following conclusion of the trial. Ironically, the Asian Pacific Network of Sex Workers concurrently denounced the trial in a protest at the World AIDS Conference for offering participants access to better treatment than they would have otherwise received.³⁰

A separate question also arises about the limits of such responsibility if it is assumed by a sponsor. In other words, how should it be decided whether it is sufficient for a sponsor to agree to provide continued treatment to participants for three years, for thirty years, as the Cambodian sex workers wanted, or for participants' lifetimes? The recent WMA clarification suggests that the adequacy of arrangements for post-trial access to beneficial treatments should be decided by ethics review committees.³¹ Ethics review committees still need guidance to determine the

²⁵ NBAC, *supra* note 5, at 59.

²⁶ See P. G. De Roy, Helsinki and the Declaration of Helsinki, 50 *World Med. J.* 9 (2004).

²⁷ See Bernard Pecoul et al., Access to Essential Drugs in Poor Countries: A Lost Battle?, 281 *JAMA* 361 (1999).

²⁸ See Helen Frankish, WMA Postpones Decision to Amend Declaration of Helsinki, 362 *The Lancet* 963 (2003).

²⁹ See, e.g., Jintanat Ananworanich et al., Creation of a Drug Fund for Post-Clinical Trial Access to Antiretrovirals, 364 *The Lancet* 101 (2004).

³⁰ Jon Cohen, Cambodian Leader Throws Novel Prevention Trial into Limbo, 305 *Science* 1092 (2004); Marilyn Chase & Gautam Naik, Key AIDS Study in Cambodia Now in Jeopardy, *Wall St. J.*, Aug. 12, 2004, at B1.

³¹ WMA Workgroup Report, *supra* note 16.

adequacy of such arrangements for post-trial treatment in each case. This determination should also take into consideration the need for monitoring and administration of supplied treatments.

Previous arguments for modification or clarification of Paragraph 30 of the Declaration of Helsinki focused on the specifics of Paragraph 30.³² Some have debated the exact meaning of "best proven," and have pointed out that a single trial almost never proves the effectiveness of an intervention. Others have noted that an ethical requirement for assuring post-trial treatment could never be absolute, since many research studies [*433] are not treatment trials and it is far from clear what obligation would be due to participants who do not benefit from the trial. How would an obligation to assure "the best proven methods ... identified by the study"³³ be affected if it was known that a treatment not tested in the trial is more effective for the condition in question? All of these issues should be clarified in available guidance documents so that researchers and research sponsors know the extent of their obligations, and ethics review committees can determine whether proposed arrangements are acceptable. However, deliberations about particular details should occur against a background commitment to finding ways to assure continued access to beneficial treatment.

Certain commentators and reviewers have worried about the possibility of undue inducement from continued provision of treatment.³⁴ That is, if continued access to treatment is guaranteed, the treatment access may be so attractive that an individual might be unable to refuse participation even if he or she wanted to. For a study that is otherwise ethical, and from which the participant is deriving benefit and not subject to significant risk of harm, concerns about undue inducement from continuing beneficial treatment seem misplaced.³⁵

Possible Strategies

Despite the many problems and challenges in assuring continued treatment after a trial, there is basic agreement that this should be done. The real challenge is to specify how this obligation should be understood and discharged. With that in mind, I will suggest some possible strategies to help Sam and others like him.

First, the various partners to a research study - investigators, sponsors, communities, national health systems, international organizations - should assume responsibility for this problem together. Possible ways of addressing continued access for research participants who benefit from investigational treatments should be discussed and negotiated prior to beginning a study. Researchers and sponsors cannot ignore this issue, believing it is someone else's problem. At the same time, researchers and sponsors cannot be saddled with the sole responsibility of treating people [*434] who ought to be receiving treatment through the regular health care infrastructure. Expecting researchers and sponsors to fill that gap is not only an unrealistic expectation but would also act as a powerful negative disincentive. The aforementioned trial in Cambodia may be a good example. Involved parties should engage in good faith negotiations before a study begins to agree on how treatment will be assured after a study has concluded.

Those involved in research and health care delivery should be working together to come up with creative strategies to offer continued treatment to research participants who need it. One example of a creative strategy with multiple partners is the HIV Netherlands, Australia, Thailand Research Collaboration (HIV-NAT) co-payment and sliding scale drug fund program. HIV-NAT is a non-governmental, non-profit organization of three collaborators: the Thai Red Cross AIDS Research Center in Thailand, the National Centre in HIV Epidemiology and Clinical Research in

³² See World Med. Ass'n, WMA Secretariat Report on the Revision of Paragraph 30 of the Declaration of Helsinki (2003), <http://www.wma.net/e/ethicsunit/pdf/secretariat> report rev paragraph30.pdf; WMA Workgroup Report, supra note 16.

³³ WMA, supra note 9.

³⁴ See, e.g., Leah E. Hutt, Freebies for Subject 641: A Discussion of the Ethical Prospect of Providing Drug Trial Subjects with Post-Trial Access to the Drug Tested - A Canadian Perspective, 6 Health L.J. 169, 185 (1998).

³⁵ See Ezekiel J. Emanuel, Ending Concerns About Undue Inducement, 32 *J.L. Med. & Ethics* 100 (2004).

Sydney, and the International Antiviral Therapy Evaluation Centre in Amsterdam. ³⁶ Part of the motivation for creating the drug fund was eloquently described in a recent publication: "Although we stated clearly in consent forms that we could not promise post-trial drug supply, we were compelled to take action when faced with the tragic prospect of watching patients reversing their excellent quality of life gained while on antiretrovirals." ³⁷ In the HIV-NAT drug fund program, patients who apply are initially assessed and then re-assessed annually by experienced social workers to determine their ability to pay, and the case is then reviewed by the drug fund committee who decides on an amount to be subsidized. The committee works with prescribing physicians to consider possible ways to reduce costs without jeopardizing the patient and also oversees the bulk purchase of drugs to obtain low prices. Patient support may come in the form of cash or drugs or a combination of the two. ³⁸ Models such as this one can be adapted for other types of trials or other areas. In any case, it is clear that other approaches are sorely needed.

Second, the problem of post-trial access to beneficial treatments for participants should always be considered in the context of other considerations for ethical research. Continued treatment of research participants with medications they receive in a trial cannot make otherwise bad research ethical. Providing treatment to a small number of individuals during or after a trial does not eliminate or address concerns about [*435] exploitation. Negotiating fair benefits from research in order to minimize exploitation of participants and communities is a necessary part of collaborative research. ³⁹

Third, the world health community must remain committed to finding ways to promote better access to needed health care and treatment globally. This will require the energy and creativity of policymakers, scientists, clinical providers, politicians, and communities. If patients everywhere had better access to needed treatments, continued access to treatment at the end of a trial would be primarily a temporary issue. Research is only one way of contributing to improved access to health care. It does so through the application of rigorous methods to search for health care interventions that are appropriate, affordable, safe, effective, and easy to administer. Even those with creative strategies, like the HIV-NAT group, articulate this larger need. ⁴⁰

Fourth, sponsors and researchers should take responsibility for certain short-term solutions when appropriate. For example, sometimes it will be necessary to provide beneficial medications to participants while awaiting licensure, or to establish or support patient assistance programs for expensive treatments. Continued attention to reducing the costs of treatments for those who need them is also called for.

The goal of clinical research is to find new knowledge to improve health and health care. Participants in clinical research contribute invaluablely to this goal. Every effort should be made to find ways to assure that participants like Sam who are receiving beneficial treatments as part of their clinical trial continue to receive it after the trial ends.

³⁶ See Ananworanich et al., *supra* note 29.

³⁷ *Id.* at 101.

³⁸ *Id.*

³⁹ See Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries, Fair Benefits for Research in Developing Countries, 298 *Science* 2133 (2002).

⁴⁰ For any developing country, long-term drug supply for patients at the end of a trial can only realistically be sustained if the government provides it... . A drug fund should be a temporary solution until the ultimate goal of access for all is achieved." Ananworanich et al., *supra* note 29, at 102.