

Posttrial Access to Medical Interventions: Intricacies, Challenges, and Solutions

Abstract

With the recent increase in clinical trials, lower- and middle-income countries are preferred trial sites due to lower budgets and easy availability of potential participants. On trial completion, benefits to participants cease and it may affect their health adversely. Therefore, entitlement to posttrial access (PTA) of interventions is imperative. The Declaration of Helsinki and several other guidelines mandate that trial participants have access to experimentally proven efficacious drugs and that the research protocol should mention PTA provision mechanisms. A controversial question about PTA is whether, experimentally proven therapy should be made accessible to the control group as well as the community from which the participants were enrolled, especially if no satisfactory standard treatment exists. PTA has significant implications for various stakeholders – trial participants, investigators, sponsors, regulatory authorities, and governments and has been discussed and well addressed in recent guidelines issued by the Indian Council of Medical research. This article focuses on the PTA, guidelines related to PTA, disputes, different stakeholder perspectives, and practical difficulties in its implementation. It also looks at PTA from the Indian perspective and considers possible solutions to deal with the controversies.

Keywords: *Clinical research, clinical trial, Declaration of Helsinki, ethics, posttrial access*

Introduction

The field of biomedical research has witnessed an increase in number of clinical trials. To accomplish trial objectives, significant numbers of participants are required in most multicenter trials. Many pharmaceutical companies prefer to conduct trials in lower- and middle-income countries (LMICs) because this affords lower budgets and easy availability of potential participants. After approval, the new drug is generally made available in affluent countries, where greater sales and profits are guaranteed. Trial participants from LMICs are often needy and poor who lack adequate access to health care. Upon trial completion, benefits to participants cease, potentially having adverse health effects. In certain situations, extending therapy after trial completion may be required; therefore, the fundamental dilemma about whether the study participants should be given benefits beyond the trial period needs to be resolved in an ethical manner.^[1]

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Entitlement to posttrial access (PTA) to interventions is imperative to avoid exploitation and inculcate ethical practices. There are several pros and cons of permitting access to benefits after the research period and there are various reasons for providing or not providing PTA to a particular participant.^[2,3] The principles of bioethics include (1) autonomy, (2) beneficence (3), nonmaleficence, and (4) justice.^[4,5] They are widely used while forming guidelines for ethical conduct in clinical research. The increase in global research in medicine involving human beings has raised concerns about bioethics that need to be addressed in detail, and ethical guidelines regarding conduct, evaluation, and follow-up of clinical trials have accordingly been developed to avoid exploitation of trial participants.

As per the bioethical guidelines,^[4-6] necessary provisions for PTA for all participants need a drug/intervention identified as beneficial in a clinical trial should be predecided by the sponsors, researchers, and governments before the commencement of the trial; the trial protocol must also address the appropriate

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arrangements for PTA. If some molecule is doing well in a trial, it may be unfair to stop its access after the trial has been concluded. Ethical guideline documents,^[6,7] various reports,^[8,9] and national guidelines^[10] have raised issues for the continuation of PTA to trial participants. The Declaration of Helsinki (DoH)^[6] published in October 2013 has stressed on PTA provision in paragraph 34, and the Indian Council of Medical Research (ICMR) guidelines have also put forward the importance of PTA.^[10] A provision for PTA in the clinical research protocol fulfills these compliance requirements.

Posttrial Access: A Debatable Topic

PTA is a highly contentious topic as it involves bioethics, human rights, law, economics, and marketing concerns. The dispute mainly comprises two types of arguments as follows: one in its favor and another against it.

Based on the principle of nonmaleficence, inducing no harm, PTA appears to be useful and necessary, as withdrawal of therapy may be harmful to those drawing sustained benefit from it. When an investigational drug/intervention is identified as beneficial in a clinical trial, the participants should be considered for PTA. Terminally ill patients should also have the right to get the treatment to alleviate exaggerated suffering and improve their quality of life.^[11] Provision of PTA, if applicable, is an entitlement of study participants, and community from which the participants are drawn, may not get the same benefit. This may create disparity between the individuals who are enrolled in the clinical trial and those who are not. Researchers also do not have the authority or resources to provide treatment in a progressing trial.^[12] Few researchers suggest that “compensation” justifies the reciprocity principle,^[11] but how (mode of compensation), how much (quantum of compensation), and for how long it has to be given, is generally unclear.^[13]

A spectrum of views has been expressed on whether to provide PTA to trial participants or not. Dainesi and Goldbaum^[14] specified that PTA should be decided based on the efficacy and safety of the new investigational drug. Zong^[15] opined that PTA should be implemented when needed and not on a regular basis, which may create many obstacles in the treatment protocol.

Sofaer *et al.*^[16] conducted a systematic review and concluded against PTA in consideration with moral, legal, and practical aspects. They also listed 36 broad types of reasons why PTA to trial medication need not be ensured to participants. Usharani and Naqvi^[17] stressed that PTA must be in place and there should be no disparity between participants and nonparticipants as well as between rich and poor nations with respect to the provision of PTA. Furthermore, there should be an equal distribution of benefits of PTA among high-income and low-income countries.^[18,19]

Posttrial Access Guidelines

The primary concern of the DoH is to safeguard participants enrolled in investigational drug trials. This has expanded the scope of ethical practice in biomedical research. Revised guidelines stipulated that participants must be assured access to best proven prophylactic, diagnostic, and therapeutic interventions after trial conclusion.^[6]

The Council for International Organizations of Medical Sciences 2008 guidelines^[7] mention that the Ethical Review Committee should consider arrangements for PTA before approving clinical research protocols.

The WMA further made an attempt to strengthen the guidelines in the revision published in 2013^[6] with specific mention about appropriate arrangements for PTA in paragraph 22 and brief reference in paragraph 34. It stipulates that sponsors, researchers, and host country governments make PTA provisions in beneficial interventions, which must be disclosed at the time of obtaining informed consent.^[6]

The proceedings of the Multi-Regional Clinical Trials (MRCT) Center conference on posttrial responsibilities grade PTA regulations across various countries under five categories in terms of stringency as follows: “provide,” “ensure,” “refer,” “describe,” and “silent.”^[20] Brazil, Canada, Nepal, Japan, and Cameroon were placed in the “ensure” category, while the Philippines required researchers to “refer” participants for PTA. India, the Council of Europe, New Zealand, Nigeria, South Africa, and Australia have phrased provision of PTA in a manner that places them in the “describe” category, while the United States is silent on the issue.

The United States Food and Drug Administration (FDA) makes no special provision for PTA to an investigational product, even if it appears to be effective. In India, ICMR 2006 guidelines,^[10] in the principle of assuring maximum justice, call for PTA whenever research is proven beneficial, holding that research benefits should be provided to all participants without differentiating against socioeconomic or community background. The Prof. Ranjit Roy Chaudhury Expert Committee went one step ahead and outlined the provision of PTA of investigational product. The committee suggested that participants should have PTA when a new chemical entity is found to be beneficial in the clinical trial and that the sponsor/investigator must ensure its arrangement.^[21] PTA becomes very important for therapies showing outstanding benefits in the clinical trials and when denying such therapies could be detrimental to health of the participants.^[22]

Posttrial Access and Past Bitter Experiences

We have witnessed the poor ethical standards in the past and even in recent years, the ethical conduct has been diluted, especially in the field of drug trials.^[23,24]

A placebo-controlled trial in HIV patients evaluating the role of zidovudine in maternal–infant transmission showed 70% risk reduction. It was found later that trial participants in the US had access to zidovudine, while those from developing countries were not provided access.^[20] Tenofovir/emtricitabine was licensed in 2012 by the FDA for HIV preexposure prophylaxis due to high efficacy in reducing infection risk; however, the drug authority of South Africa did not license it, depriving the trial participants of the benefits.^[25]

In an imatinib trial, many patients died to whom PTA was not offered.^[26] In a breast cancer trial, many participants were denied PTA to lapatinib, though it was proven beneficial where other drugs had failed to prove effectiveness. With the provision of PTA in such trials, participants could have enjoyed longer lifespan or symptomfree survival.^[26]

Anticancer drug oxaliplatin (used for treatment of colorectal cancer) was rejected by the FDA despite approval in other countries. In January 2002, the FDA was requested for PTA to this drug, but approval was delayed until August 2002.^[27] Cetuximab, used to treat colorectal and head-and-neck cancers, was denied approval by the February 2004. Many patients were deprived of access to this drug and subsequently died.^[26] Similarly, FDA approval of pemetrexed for lung cancer treatment was held until February 2004. During this period, a number of lung cancer patients died. PTA to this drug could have extended their lifespan.^[26]

Lacunae and Challenges in Implementing Posttrial Access

PTA issues are certainly complex, as guidelines are inconsistent and unequivocal and it remains as one of the major unresolved issues in international research.^[28] There are many unresolved issues regarding PTA with no concrete answers. Some cardinal questions from the perspectives of participant, sponsor, and the community have been elaborated here.

Who should provide posttrial access – investigator or research sponsor or government authorities?

Even though guidelines compel continued access to the trial drug, the question of who should provide it must be resolved. It is generally believed that pharmaceutical companies and sponsors are held responsible for PTA. This finding could serve as a major hurdle for stakeholders to conduct clinical research.^[8] It has been suggested that all concerned parties – sponsors, investigators, communities, and the governments involved – accept PTA as a joint responsibility and decide on its provision before the trial begins.^[29,30]

If posttrial access is needed, for how long it has to be provided?

The most contentious issue around PTA is the duration for which it must be made available as it is not feasible to

provide PTA for an unlimited period. It is extremely difficult for the sponsor or the investigator to agree on how long to continue access – a specified number of years or lifelong.^[17]

Unresolved issues regarding duration of PTA may lead to the halting of a clinical trial. For example, a study on the use of tenofovir, for prevention of HIV in Cambodia to which about 1,000 sex workers were enrolled, was withheld when the Women’s Network for Unity, a Cambodian sex workers union, and demanded assurance of PTA for 30 years.^[31,32]

Is posttrial access to be given to all or to selected participants? What about the control group and the rest of the community?

It is not possible for the sponsor/investigator to provide PTA for a long time to trial participants as this may jeopardize the research atmosphere by raising costs and workforce requirements and deflecting from the main aim of the research. Posttrial responsibilities should be considered whenever needed and not as a blanket statement.^[33]

Another important aspect is whether the study drug/intervention should be provided to the control group if it is found to be effective. This is particularly relevant in situations where standard therapies are poor, and the new drug/intervention shows promising results. Providing PTA to the control group may help control the signs/symptoms of the underlying condition or halt its progression but adds to the burdening of sponsor/investigator. The situation may pose difficulty for clinical trial sponsors, especially in developing and resource-poor nations.^[17,20]

The government may intervene and provide a solution to this dilemma along with the study sponsor and investigator. Special tax and fee exemptions can be given to such therapies, and they can be made eligible for fast-track approval. However, once the new treatment is approved for marketing, what right does the patient have to PTA? Will it be provided at market price, a discounted price, cost of production, or no cost at all?^[20]

Uncertainty about continuous provision of posttrial access

Providing continued access to the study drug/intervention may be financially difficult for pharmaceutical companies. The participant may therefore perceive supply of the study drug as unreliable and doubt the pharmaceutical company’s commitment to providing benefit. Adding provision of PTA to trial requirements may significantly raise costs, possibly limiting the number of new clinical trials. Laying PTA obligations on trial sponsors/investigators may discourage them from initiating new research projects.^[22]

Posttrial access for chronic disorders

Access to intervention is justified until approval, but the duration of therapy cannot be determined beforehand. An

ethical issue may arise if the drug is not approved because the participants have been exposed to an ineffective drug that might induce harm rather than provide benefit.^[34]

Is posttrial access always desirable?

Offering PTA may attract more trial participants. The participant is an essential component of research, both for contributing to the research goal and acceptance of risk. PTA serves as a recognition of this contribution and is the obligation of the sponsor/investigator. The following points must be considered in this regard:

- i. Participants in developing countries may be unduly induced to participate^[34,35] to avail assured follow-up care
- ii. Unnecessary delays may occur due to additional documentation
- iii. PTA may reduce number of trials feasible to conduct, especially in developing countries,^[36] due to increased costs
- iv. PTA may be misused.^[37]

Key Stakeholder Perspectives

Although PTA has been described extensively in literature, it still merits a formal discussion regarding the commitment of sponsors, investigators, and organizations and implications for participants.

Posttrial access to the trial participant and the community

The participant is an integral part of clinical research. PTA becomes a fundamental right in studies with terminally ill patients or in places where medical care is lacking. Lack of treatment to such underprivileged populations would have no other outcome than death. To reduce the disparity between prosperous and poor nations, treatment proven to be beneficial should be made available at affordable costs,^[38] but such benefit should not lead to undue inducement.^[34,36] Once the trial is over, the drug safety monitoring may not be an active affair, so to prevent adverse effects from long-term use.^[17] Even though participants are compensated in case of injury, many gaps exist in the mechanism. An expended provision of the PTA to the community, from which the participants were drawn, remains an important issue. This becomes crucial when no standard of care exists for the disease in question.

Posttrial access to the sponsor/investigator

PTA crumbles trial budgets as this increased cost may not have been considered while planning the study.^[39] The reputation of the trial drug may increase and the concerned company's image may also improve with provision of PTA, but overall profit may be severely affected. The sponsor/investigator may want to offer access exclusively to terminally ill patients or in diseases without alternative medical care. This leads to improper and inefficient use of resources:^[33] "improper" in the sense that the sponsor's aim

should be to develop a new drug and "inefficient" because health-care providers offer medical care more efficiently than in a clinical trial.

In an MRCT conference,^[20] the concern was expressed by investigators that as they could not make provisions on their own, they might not be able to provide efficient PTA in larger groups.

Mandating PTA should not put strain on the government or researcher. Currently, study sponsors mention PTA in their protocol, which is specific and not for all. Sponsors and investigators must outline how and for how long PTA is to be given, which can be fixed in discussion with regulatory agencies and the local Ethics Review Board. Complete financial homework on PTA implications must be done before starting the research. Assurance from the host country that benefits will be provided after trial completion is essential to the sponsor, as the immense pressure for PTA, the international community puts on sponsors, and the cost constraints may result in incomplete trials. Pharmaceutical industries will also be reluctant to invest in trials in countries where the quality of health care is very poor. This is more prominent in LMICs, where access to health care is scarce.

In past instances, many participants have lost lives because of unavailability of, or delayed access to, beneficial therapy. PTA provision must therefore be encoded in national legislation/policy to prevent sponsors from evading responsibility. Currently, Brazil and Argentina have enforced PTA obligations in law,^[35] while other LMICs such as India and South Africa have formulated PTA guidelines.^[10,35]

The Indian Perspective and Indian Council of Medical Research 2017 Guidelines

The latest ICMR guidelines published in 2017 – the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants^[40] discuss the need and provision of PTA in multiple places (in clinical trials involving medicines, vaccines, devices, etc.) and calls for implementation of PTA wherever applicable. This document (page no. 13) terms PTA to trial participants and their communities as a "contemporary ethical issue" in biomedical and health research under debate. Section 2.11, devoted to PTA, stresses on the provision of its benefits to individuals, communities, and populations whenever relevant. It also calls for research teams to discuss benefits with trial participants, including those in the control group and for necessary arrangements to be described in the study protocol so that the Review Committee may examine them thoroughly and consider a prior agreement between the researchers and sponsors. The Review Committee should also carefully review and consider PTA to the medication when it has shown benefits to the trial participants. PTA has also been termed an "important recent initiative" by the

Central Drugs Standard Control Organization of India.^[41] Thus, PTA is definitely considered critical by the various authorities dealing with the regulatory and ethical aspects of clinical trials.

Possible Solutions to Posttrial Access Provision and Controversies

1. PTA must be supported by the host country government. Policies should be devised along with sponsors and investigators so that providing PTA does not add a significant burden to any one stakeholder. Special incentives, fee exemptions, or fast-track approval should be granted to useful new drugs/interventions
2. From the time of trial completion to regulatory approval of the new drug/intervention, special monitoring of its safety is required. This must be encouraged by the regulatory authorities of that country, and necessary steps should be taken to identify and address the safety issues, if any. This may necessitate the need for intensive pharmacovigilance practices
3. Special aids may be provided by governments and funding agencies to provide PTA in developing and resource-poor nations
4. Special research grants may be awarded to sponsors/investigators who have invented new drugs/interventions that were subjected to PTA. This will encourage further research activities, which may otherwise get diluted due to a larger focus on patient care than on hard-core research
5. Conferences/workshops on PTA and its requirements and implementation for Ethics Committee members, sponsors, and study investigators must be organized. Training pertinent to PTA must be provided to the different stakeholders, including potential study participants and their respective communities. Governments of hosting countries must encourage such events by providing funds to the organizing units.

Conclusion

PTA must be considered in beneficial trials and validated by weighing the advantages and disadvantages on a case-by-case basis without altering the core of bioethics as well as science. An unbiased approach toward PTA is must so that there is an equitable distribution of the benefits of the therapies proven to be useful. PTA is a collective responsibility of the sponsor/investigator and the host country government. All stakeholders must comply with the existing Ethical Guidelines and should have a clear and rational approach toward PTA. Government should also encourage PTA provisions by giving special benefits to the stakeholders willing to provide PTA. Due importance should also be given to the research components of the studies, so that it does not dilute with the provision of PTA rather there is a need to support and promote studies addressing the provision of PTA.

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Conflicts of interest

There are no conflicts of interest.

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