**Post Trial Access in Clinical Research: A Hallmark of Its Relevance To Bioethics and Current Clinical Research and Ethical Guidelines**

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**Abstract**

In recent years, number of clinical trials being conducted has increased in both developed as well as developing countries and several ethical issues linked with conduct of clinical trials have been witnessed . We have also observed the diluted standards of bioethics in developed as well as developing countries. Once the clinical trial is over, benefits of trial to the participants are brought to an end which may affect their health adversely. Entitlement to post trial access (PTA) is an imperative to avoid exploitation and inculcate ethical practices. As per the Declaration of Helsinki and several others guidelines, the participants enrolled in clinical trials must have access to experimentally proven efficacious drug and research protocol must mention the mechanism to provide PTA, if necessary. PTA is undoubtedly a contentious topic that has significant implications for various stakeholders i.e. trial participants, investigators, sponsors, regulatory authorities as well as the Government. PTA has been thoroughly discussed and well adapted in the recent guidelines issued by the Indian Council of Medical research (ICMR).

This review will focus on the PTA, PTA guidelines, disputes on PTA, PTA from different stakeholders’ perspectives, practical difficulties in its implementation and PTA from Indian perspective.

**Key words:** Clinical trial, Clinical Research, Declaration of Helsinki, Ethics

**Introduction**

Recent biomedical research scenario has witnessed increasing number of clinical trials that has diluted the standards of bioethics in developed as well as developing countries. For most multicenter clinical trials, a number of participants are required to accomplish the objectives of the trial. Many pharmaceutical industries prefer to conduct trials in lower and middle income countries (LMICs) because of the advantages like need for lower budgets and easy availability of potential clinical trial participants. After approval, the new drug will be generally made available to affluent countries where greater sales and profits are guaranteed. In a developing nation, participants are often needy, poor and do not have adequate access to health care. Once the clinical trial is over, benefits of trial to the participants are brought to an end which could possibly affect their health adversely. In certain situations, extension of therapy after completion of trial may be justifiable and this fundamental dilemma needs to be resolved in an ethical way that whether or not participants included in study should be given benefits beyond the trial period (1).

Entitlement to post trial access (PTA) is an imperative to avoid exploitation and inculcate ethical practices. There are several pros and cons of permitting access to benefit after the research period and there are various reasons for providing or not providing PTA to a particular participant (2,3).

As per the Declaration of Helsinki (DoH) and the European Group on Ethics in Science and New Technologies (4), participants enrolled in clinical trials must receive access to experimentally proven efficacious drug. In order to comply with commitment to participants or host country, provision of PTA in clinical research protocol fulfils the necessity. PTA is undoubtedly a controversial topic but considering its ethical and practical aspects, its understanding is critical for all stakeholders in clinical trial process.

Foundation of bioethics is based on four universal principles namely autonomy, beneficence, nonmaleficence and justice (5). These universal principles are widely used while forming guidelines for ethical conduct of clinical research. Increase in global research in medical fraternity involving human beings has raised concerns about bioethics that need to be addressed in detail. The trials are conducted in LMICs and the approved drugs thereafter, are generally made available in developed countries leaving lower income nation’s poor participants devoid of therapeutic benefits of such drugs. If some molecule is doing well in a trial, it is unfair to stop its access after the trial has been concluded. In order to achieve global justice; ethical guidelines regarding conduct, evaluation and follow up of clinical trials have been developed to avoid exploitation of participants enrolled in clinical trials.

In recent years various international and national councils have expressed their notion about after care access. Ethical guideline documents (6,7) various reports (8,9) and national guidelines (10) have raised issues for continuation of PTA to the trial participants. The DoH (6) published in October 2013 has stressed on PTA provision in paragraph 34. Indian Council of Medical Research (ICMR) guidelines have also put forward the importance of PTA (10).

**PTA: A Debatable Topic**

PTA is highly debatable topic due to involvement of bioethics, human rights, law, economics and marketing. PTA dispute is mainly based on two types of arguments, first in its favour and later against it.

Based on principles of nonmaleficence i.e. not to induce harm, PTA appears to be useful and necessary as withdrawal of the therapy may be harmful in those who are getting sustained benefit from it. When an investigational drug or intervention is identified as beneficial in a clinical trial, participants must receive PTA, as it’s denial in vulnerable subjects could be lethal. Terminally ill patients also should have right to alleviate exaggerated suffering and improve their quality of life. A common view is that if a participant enables beneﬁt for others in terms of improved healthcare then he/she should be reciprocated (11).Provision of PTA, if applicable, is entitled for those who participate in study and the benefit might not be extended to the community from where the participants are taken. This may create disparity between the individuals who are enrolled in the clinical trial and those who are not.

Academic investigators express their arguments against PTA because their research does not have any commercial basis. The aim of research is to acquire new knowledge. Researcher also does not have authority or resources to provide treatment in a progressing trial(12).Few researchers suggested that ‘compensation’ justify the reciprocity principles (11) but how, how much and how long PTA needs to be given, generally lacks clarity (13). A spectrum of views has been expressed by many authors whether to provide PTA to trial participants or not.

Dainesi and Goldman (14) specified that PTA decision should be taken based on the efficacy and safety of new investigational drug. Zong (15) opined that PTA should be implemented when needed and not on regular basis which may create many obstacles in the treatment protocol.

Sofaer et al (16) conducted a systematic review and concluded a remark against PTA in consideration with moral, legal, incentive and practical aspects. They also figured out 36 broad types of reasons why PTA to trial medication need not be ensured to the participants. Usharani and Naqvi (17) stressed that PTA must be in place and there should be no disparity between the participants and non- participants as well as between rich countries and poor nations with respect to provision of PTA.

Del-re et al (18) mentioned that sponsors and investigators from high income countries are likely to exploit participants in LMICs as the communities with limited access to essential healthcare may be more likely to accept the risk of trial participation. Mastroleo (19) criticized that the current DoH guidelines have to be revisited to assure justice, fairness to participants and LMIC’s in clinical trials.

**PTA guidelines**

Primary concern of the DoH is safeguard of participants enrolled in investigational drug trials. First mention about PTA came in the year 2000 in order to expand the scope of ethical practice in biomedical research. Revised guidelines in the same year mentioned about PTA in new Paragraph 30 which says that participants must be assured about access after conclusion of trial for best proven prophylactic, diagnostic and therapeutic interventions (6). This comment about PTA spread negative sentiments among pharmaceutical industries and led to further explanation by the WMA about the application and implications of PTA(20).

In CIOMS 2008 guidelines (7), it was mentioned that the ethical review committee can consider arrangements of PTA before approving the clinical research protocols*.* In 2008, DoH guidelines were re-revised where PTA provision was made less precise by stating that “participants of clinical trial are entitled to be informed about outcome of the study and share the benefit provided that trial is recognized as beneficial” (6).

WMA further made an attempt to strengthen the guidelines in the revision published in 2013 (10) with specific mention about appropriate arrangements for PTA in paragraph 22 and brief reference in paragraph 34 under the heading of “Post-Trial Provisions”. The sponsors, researchers and government of host country should make PTA provisions in beneficial interventions and the same may be disclosed at the time of obtaining informed consent (6). In the multi-regional clinical trials (MRCT) conference on post trial responsibilities, five categories of PTA regulations, from various countries of the globe grading them from more stringent to least stringent, as: “provide,” “ensure,” “refer,” “describe,” and “silent, were discussed (20) Here Brazil, Canada, Nepal, Japan, and Cameroon quoted “ensure” category while Philippines mentioned as “refer” for provision of PTA. The India, the Council of Europe, New Zealand, Nigeria, South Africa, and Australia have phrased provision of PTA as a “describe” category while the United States is silent on the issue.

As per the United States Food and Drug Administration (US-FDA), there is no special provision of PTA for an investigational product even if it appears to be effective. In India, ICMR 2006 guidelines(10) in the principle of assuring maximum justice, define about PTA as whenever research or experiment is conducted and proven beneficial, it’s benefit should be provided to all human kind without differentiating as socially better or poor and also participants as well as the community from which they are drawn. Prof. Ranjit Roy Chaudhury expert committee went one stage ahead and illuminated about the provision of PTA of investigational product. The committee suggested that participants should have PTA when a New Chemical Entity (NCE) is found to be beneficial in the clinical trial and sponsor/ investigator must assure about arrangement of necessary provisions in that concern (21).Currently Brazil and Argentina are the countries where PTA obligation has been enforced as a law(20) while other LMIC’s like India, South Africa etc. are also have also formulated guidelines for provision of PTA(10, 22).

**PTA and past bitter experiences**

Kottow (23) pointed out that in recent years, ethical standards of clinical research and medical practices are becoming less rigid especially in the field of drug trials. In 1932, U.S. Public Health Service began a study on effects of syphilis with the Tuskegee Institute where many black male volunteers participated and more than half of them were suffering from syphilis. Although, they were offered free of cost treatment and food but syphilitic patients were not given any standard therapy as investigators wanted to understand natural history and know effects of untreated syphilis (24). During the entire study period, participants were thinking that they are receiving the standard therapy. This trial remains a classical example of unethical practices exploiting vulnerable participants. A placebo controlled trial in HIV patients evaluating role of zidovudine in maternal-infant transmission, showed 70 % risk reduction. It was found later that trial patients in the US had access to zidovudine, while those from developing countries were not provided access (20). In another study, Tenofovir/ emtricitabine was licensed in 2012 by the US-FDA for HIV pre-exposure prophylaxis (PrEP) as study drug has shown clear efficacy in reducing infection risk by up to 92% but drug authority of South Africa did not license it, keeping trial participants away from benefits of this promising agent (2). PTA to Imatinib was also not offered to trial participants due to which many patients, to whom therapy was not offered after trial, died (26). In a breast cancer trial, many women participants were denied lapatinib therapy which was proved to be beneficial especially when other drugs had failed to prove effectiveness. With the provision of PTA in such trials, the trial participants could have enjoyed additional months of life span or symptom free survival (26). It has been mentioned that many American patients died due to unavailability of novel agent of that time, i.e. Oxaliplatin, used for treatment of colorectal cancer. Oxaliplatin was rejected by the US- FDA in spite of its approval in other countries. In January 2002, the FDA was requested for PTA to this drug but approval was delayed by the agency till August 2002 (27). Cetuximab, a drug for the treatment of colorectal and head and neck cancers whose approval was refused by the US-FDA in December 2001 Although, permission to allow access was asked to the US- FDA six months in advance, approval got delayed till February 2004. This also led to many patients devoid of this drug and subsequent mortality in many of them (26). Similarly, approval of pemetrexed for lung cancer patients from the US-FDA didn't succeed till February 2004. During this period a number of lung cancer patients were not having access to this drug and lead to mortality in these patients. PTA to this drug could have been helpful in extended their lifespan (26). In another case, refusal of PTA in clinical trial conducted in Kenya led to the disappointment in a participant who expressed his feelings in this regard as an unfair act (28).

**Lacunae and challenges in implementing PTA**

PTA issues are certainly complex as guidelines are inconsistent and equivocal with loop holes enabling avoidance of PTA responsibility. There are many unresolved issues regarding PTA with no concrete answer. Some cardinal questions from the perspectives of a participant, sponsor and the community have been elaborated here.

1. ***Who should provide PTA? An Investigator or Research sponsor or Government Authorities?***

Even though guidelines compel continued access to trial drug, the question that whether pharmaceutical companies and sponsors should provide it or not must be resolved. There is a conflict that if only the two are held responsible for provision of access to trial drug. This binding could serve as major hurdle for stakeholders to conduct clinical research **(**8, 20**).**It has been suggested that all concerned parties including sponsors, investigators, communities and involved organizations accept it as responsibility altogether and search for possible ways to resolve this issue before the trial begins (29, 30).

1. ***If provision of PTA is there, how long it has to be given?***
2. The most debatable issue in PTA is duration as it is not feasible to provide after care for unlimited period. It is an extremely difficult for the sponsor or the investigator to agree upon how long to continue access, specified years or lifelong (20).

The recent WMA clarification suggests that it should be decided by ethics review boards/committees. Unresolved issues regarding duration of PTA may lead to halting of a clinical trial. One such dramatic example was study conducted on tenofovir for prevention of HIV in Cambodia where about one thousand sex workers were enrolled. Study was withheld when the Women's Network for Unity, a Cambodian sex workers union, demanded assurance of thirty years of PTA (31, 32).

1. ***Is PTA to be given to all or to selective participants?***

It is not possible for the sponsor or the investigator to provide PTA all the time to trial participants as this may jeopardize research atmosphere by arising the need of more funds and manpower, and also deviating from the main aim of the research. Zong (15) stated that post trial responsibilities should be considered whenever needed and not as a blanket statement (33).

1. ***Uncertainty about continuous provision of PTA?***

Continued access to study drug or intervention may be financially difficult for pharmaceutical companies; this unreliability about sufficient supply of the study drug may raise doubts in the participant’s mind about their integrity to provide benefit. Another issue about uncertainty is migratory populations receiving trial drug in long term or lifelong therapy (20).

1. ***PTA arrangement for chronic disorders should be or should not be?***

Access to intervention is justified till the approval, but the duration of the therapy cannot be determined before (20).An ethical issue may arise if drug is not approved because the participants are exposed to ineffective drug that might induce harm rather than providing benefit. [34]

1. ***Is PTA always desirable?***

More subjects may get attracted by offering continued access. A participant is an essential component in research as he contributes to research goal and accepts the risk. PTA is recognition and obligation for his contribution without which study is not feasible. Following points are important in this context:

1. There may be undue inducement (34, 35) of participants in developing countries as people may believe to participate in the study with benefit of assured follow up care.
2. Unnecessary delay in clinical trial may occur due to additional documentation.
3. PTA may reduce number of trials especially in developing countries (36) due increased financial burden.
4. PTA may be misused (37).

**PTA: from key stakeholders’ perspective**

Although PTA has been described extensively in literature; its complexity still needs a formal discussion in relevance to commitment of sponsors, investigators and organizations.

***PTA and Trial Participant’s perspective:*** Participant is an integral part of the clinical research. PTA becomes a fundamental right in special situations like terminally ill patients or place where medical care is lacking. Lack of treatment to such underprivileged population would leave no other option than death. To reduce disparity among prosperous and poor nations, beneficial therapy can be made available at an affordable cost (38). Broadening the benefit of therapy should not lead to undue inducement (34, 36). Once drug trial is over, drug safety monitoring programme may not be active enough to avoid harmful effects of drug on long term use (17). Even though compensation to participant is allowed as result of injury, many gaps are present while allocating it.

***PTA from sponsor’s/investigator’s perspectives:*** Economical budget crumbles due to PTA as this increased cost may not have been considered in financial planning before the initiation of study (39). Trial drug’s reputation may increase and the concerned company’s image may also be improved by giving provision of PTA but overall profit may be severely cut down. Sponsor and investigator would like to offer access exclusively in terminally ill patients or diseases without alternative medical care. This leads to improper and inefficient use of resources (33), ‘improper’ in the sense as sponsor’s aim is to develop new drug and ‘inefficient’ in use because healthcare providers offer medical care more efficiently than by a clinical trial investigator or sponsor.

In an MRCT Conference (20), concern was expressed by investigators about PTA, as they could not make provisions on their own, hence, may not be able to provide efficient PTA in larger groups.

PTA binding should not impose strain on Government or researcher. Currently, study sponsors mention about PTA in their protocol which is specific and not for all. Sponsor and investigator should provide clear picture about how and how long PTA has to be given which may be obtained by discussion with regulatory agency and local ethics review board. Complete financial homework is necessary ensuring PTA before starting research activities to avoid confusion. From sponsor perspectives, assurance from host country is required to provide benefit after completion of trial but excess of pressure from international community demanding access to therapy from sponsors may result in incomplete trials. Pharmaceutical industries will also be reluctant to invest on such trials in countries where quality of health care is very poor. Such situations will be more prominently visible in LMIC’s where access to health care is scarce.

From past instances, it is understood that many participants have lost their lives because of unavailability or delayed access to beneficial therapy. This may lead to common agreement on the issue of PTA amendment as national legislation policy which may interrupt autonomy and freedom of sponsor on critical decisions.

**PTA : Indian Perspective with special reference to ICMR guidelines 2017**

We have already mentioned about the, ICMR 2006 guidelines (10) and Prof. Ranjit Roy Chaudhury expert committee (21) highlighting the importance of PTA.

Latest ICMR guidelines published in 2017 i.e. National Ethical Guidelines for Biomedical and Health Research Involving Human Participants (40) discuss the need and provision of the PTA at multiple places (in clinical trials involving medicines, vaccines, devices etc.) which points towards the importance and dire need of implementation of PTA wherever applicable. This document mentions PTA to trial participants and their communities as a ‘contemporary ethical issue’ in biomedical and health research under debate. A full topic of PTA has been added (section 2.11) stressing on the provision of benefits of PTA to individuals, communities and populations whenever relevant. It also mentions that research teams should discuss the benefits with the trial participants, including those in the control group and necessary arrangements must be described in the study protocol so that the EC may review it thoroughly and consider a priori agreement between the researchers and sponsors. The EC should also carefully review and consider PTA to the medication, when it has shown benefits to the trial participants. PTA has also been mentioned as an ‘important recent initiative’ by the CDSCO of India (41). Therefore, PTA is definitely considered critical by the various authorities dealing with the regulatory and ethical aspects of the clinical trials.

**Conclusion**

In brief, PTA must be considered in beneficial trials and validated by weighing advantages and disadvantages on a case to case basis without altering the core of bioethics, simultaneously keeping a vigilant eye to avoid unethical practices.

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