Review Article

Post-trial access

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INTRODUCTION

Globalization of clinical research introduced several new challenges to the major stakeholders. These emerging aspects are dealt by regulators by providing and updating guidelines, making recommendations, formulating and amending laws to safeguard the trial participant and assure the ethical conduct of clinical research. These issues do not end with the completion of the clinical trial as, the researchers and sponsors are facing another challenge of providing post-trial access (PTA) to the trial participants. There are several difficult questions for the health law and policy makers regarding providing access to investigational new drug. The first question raised in this regard is the legal or ethical validity of claim for post trial access, and other debatable aspects like giving priority over others, its description in consent process, and who will bear the responsibility associated with the access after the completion of trial. We require a firm consensus from all the stakeholders on best way to respond to such access demands. The Legislation and guidelines are inconsistent, ambiguous or silent about many of these aspects. The post-trial access is one of the issues which is still not been precisely analyzed and several aspect of it remain inconclusive. This article tries discussing the ethical issues, regulatory guidelines and perspective of major stakeholders on post trial access of the trial drug.

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The discourse on PTA begins with the evaluation of group entitled to claim the trial drug, the ones receiving trial drug, trial participants or the patient population. The trial subjects are a miniscule of the whole patient population from where they are derived and exposed to trial medicine. Providing PTA to those exposed to trial drug and denying others create disparity among patients. This is especially true in life threatening conditions where the trial drug is proven effective, as it seems to be inhumane depriving non-trial patients of the same benefit. Imatinib was approved by FDA in March 2003, although the drug was safe and highly efficacious in the trial patients, its post trial access was denied to 3,600 patients who died waiting for the wonder drug to cure them. Lapatinib also describes the similar story, where 28,000 women who were positive for the marker against which the drug works when other drugs fail, died waiting for the drug. They would, have each lived an average of eight months longer. *Long enough, perhaps, to see a child graduate from college or get married, or to meet a new grandchild.*[1]

According to Declaration of Helsinki "At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits."[2]

The claim for post trial access is defended to extend benefit to the trial participants, in such a case the participants of early phase II clinical trial are unarmed where the benefit of the trial drug is still at stake. The benefit is a relative term in many of the clinical trials and it is often difficult to quantify the benefit of the trial medicine compared to the standard treatment which forms the basis to advocate it during the post trial period.[3]

The phase I to III clinical trials provide preliminary evidence rather than proof of safety of the drug. Many a times, it is observed that after the drug is introduced in large general patient population, that the rare adverse effects are revealed. This explains the intense ADR reporting and long term pharmacovigilance studies conducted post approval of drug.[4] The withdrawal of cox-2 inhibitors after its approval and wide use exemplifies the situation. It is not justified to prolong exposure of investigational medicine to trial participant thus continuing to risk the participant, when a standard treatment with established safety is available. Various strategies are in place to monitor safety of trial participants during the conduct of a trial which is not possible once the study related activities cease. The delegation of safety monitoring is also a debatable issue, whether it lies on the investigator or to treating physician. The investigator is reluctant to monitor patients after completion of trial, where the duty of investigator also ends. There are still several lacunae in providing compensation for trial related injuries, and the validity of claims for any investigational drug related injury during post trial access adds to them.

The next important aspect to be debated in this regard is the duration for which the post trial access should be offered especially for the patients suffering from chronic diseases. It is not feasible for the sponsor to offer the investigational drug for unlimited period. It seems to be justified to some extent to provide access till the drug gets approval, but the duration for approval process cannot be pre determined and there should be gradual shift from test medicine to other standard of care. Some sponsors address this issue by extending the study into the continuation phase which is normally open label study and the subjects continue the treatment for a further period of about one to two years or so. But what if drug is not approved? The participants are exposed to ineffective drug for extended duration apart from that required for clinical trial. The legal implication of continuing the investigational drug beyond the duration of clinical trial should be considered and ethics committees may find it difficult to decide in such circumstances for granting approval and monitoring for extended periods.

However these issues should be predetermined and addressed in the protocol submitted for regulatory and institutional approvals, a haphazard decision during or after completion of trial to continue access to trial drug to its participants makes the situation complex.

Perspectives of major stakeholders regarding post-trial access

In the perspective of trial participant, the principle of beneficence as discussed above and non malfeasance where the loss of benefit derived during trial is equated to doing harm, support the claim for post trial access. Clinically the claim is more valid when no alternative effective treatment exists or when shifting patients to other therapies modify the outcome. The extension of benefit should not lead to undue inducement and participant joining the trial to obtain access to medication.[3]

Declaration of Helsinki states that 'Medical research involving an underprivileged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of that population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research'.[2]

Interestingly, developing countries have shown growing interest in joining this international effort and have indeed been taking part in many multinational trials. Of note, in at least two of the four clinical trials evaluating the role of trastuzumab in early breast cancer, a significant proportion of patients were from under developed countries. They have helped to boost recruitment and contributed to the swift results. Most of these costly drugs would never be used by the communities from where the experimental data are collected and create unprecedented difficulties for health economies in developing countries.[4] A subsidized access to interventions that have been proven successful might be the best alternative to extend benefit to the host communities and reduce inequalities between resource-rich and–poor countries and ensure fair division of benefits and burdens of research between countries that host and countries that sponsor the research. Sometimes more than the benefit to the participant, the community may be given benefit in an indirect way through improving their living conditions, establishing counselling centres, clinics or schools and giving education on maintaining good health practices.[5]

Sponsors perspective in providing access enables collection of data that lengthens product's market-life and improves company's public image but also reduces its share-holders' profits and funding of other projects. The commitment for post trial access reduces the incentives to conduct research due to financial constrains especially for academic projects. Sponsors lack power to make unilateral decisions about PTA, priorities of agencies providing health care in host country may differ from sponsor.[6]

Federal research regulations

The federal research regulations governing medical research say little regarding post trial obligations to subjects when the trial is terminated. The regulations do not discuss in any detail to what extent IRBs should consider post-trial access plans as part of their protocol review process or what

IRBs should ask and require of sponsor and investigator regarding post-trial access. Even if an IRB imposes post-trial access requirement as part of its condition for protocol approval, the requirement would be difficult to monitor and enforce. More importantly, IRBs simply have little authority or clear jurisdiction to compel a sponsor or investigator to offer post-trial access when the trial ends prematurely.[7]

Indian guidelines on the PTA

In the ICMR guidelines 2000, there is no separate mention of PTA. However, the principle of non-exploitation deals with the kind of remuneration, care and compensation in case of study related injury. In the revised guidelines issued in 2006 (Ethical guidelines For Biomedical research On Human participants: ICMR 2006) under the principle of maximization of public interest and distributive justice, states that: "Whereby the research or experiment and its subsequent applicative use are conducted and used to benefit all human kind and not just those who are socially better off but also the least advantaged, and in particular, the participants themselves and or the community from which they are drawn". It refers to the Helsinki Declaration and quotes the same (2004) on PTA.[8]

Points to ponder

Upfront disclosure should be made to IRBs about post-trial access plans before protocols are approved and subjects are enrolled thus favoring some form of time-limited, post-trial access as one year after the study which could be, waivable by an IRB for good cause.

Not all post-trial access claims will be equally valid, and the force of any right to post-trial access will likely vary depending on a number of context-specific factors.

Post trial access is not valid when the investigational treatment does not provide benefit over standard treatment.

The disparity produced by preferential access to participating subjects, can be reduced by considering request of other patients when there are limited alternatives.

The abandonment concerns can be minimized by giving proper notice to subjects regarding trial completion.

If subjects deserve greater post-trial access, it is important to impose acceptable boundaries till the drug gets regulatory approval, after which it is at the discretion of the sponsor to either continue or provide subsidy for subjects or community.

The cost of ensuring post-trial access need to be considered before embarking on projects, other potential research activities should not suffer at the cost of providing PTA.

Measures need to be taken so that promise of PTA does not interfere with the autonomy of participants in trials.

The Post-trial access should not hinder researchers and sponsors to conduct research in communities demanding it.

Subjects advocating early termination of trial to obtain access need to be checked.

Providing alternative benefit is more feasible for sponsors and can be applied uniformly to all subjects rather than promising post-trial access.

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