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RESEARCH ARTICLE

Evolution of post-trial access in India: An analysis of ethical and regulatory guidelines

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Abstract

Background: *Post-trial access (PTA) is an important element of any ethics or regulatory guidance document. It was first introduced in the Declaration of Helsinki (DoH) in the year 2000 but has only recently gained momentum. The objective of this narrative review was to examine the evolution of PTA in Indian bioethical and regulatory guidelines.*

Methods: *Websites of all Indian government agencies that issue ethics guidelines periodically as well as the website of the Indian regulator was searched by three authors and the guidelines downloaded. Identification of PTA in the guidelines was done by all authors and a consensus was reached. The Scale for the Assessment of Narrative Review Articles (SANRA) criteria were used as the reference framework.*

Results: *The Indian Council of Medical Research (ICMR) guidelines of 2000 and 2006 mention PTA, though the most comprehensive coverage can be seen in the 2017 ICMR guidelines. This was followed by a good coverage of PTA in the New Drugs and Clinical Trials (NDCT) rules of 2019. Other guidelines have also briefly alluded to PTA.*

Conclusion: *In the years to come, Indian guidelines must evolve beyond PTA towards post-trial provisions (as introduced in DoH, 2024) or post-trial care, which are broader in their vision and go beyond the individual participant in a clinical trial.*

Keywords: *benefit sharing, compassionate use, expanded access, long term extended studies, post-trial arrangement*

Introduction

The Declaration of Helsinki (DoH) is an ethics guidance document first released in 1964 by the 18th World Medical Assembly that lays down ethical principles that guide the conduct of research in human participants [1]. It has its origins in the Nuremberg Code and over the decades has been incorporated into laws and regulations of many countries around the world. For most medical journals, statements on ethics committee approval of the research, trial registration and informed consent are ethical obligations for authors, editors and publishers for the publication of research [2].

An important aspect of any ethics guideline is the principle of post-trial access (PTA). In the DoH, PTA found its first mention in the 2000 edition [3], followed by the 2008 [4], and 2013 [5] editions (Table 1). The 2013 edition lists it under a separate section called "Post Trial Provisions". The most recent version of the DoH clearly outlines stakeholder responsibilities in point 34 [6].

Table 1. Post-trial access/post-trial provisions in the Declaration of Helsinki

Year	Statement on post-trial access/post-trial provisions
October 2000	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. (point no 30)
October 2008	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. (point no 33)
October 2013	In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process. (point no 34, under the heading "Post Trial Provisions")
October 2024	In advance of a clinical trial, post-trial provisions must be arranged by sponsors and researchers to be provided by themselves, healthcare systems, or governments for all participants who still need an intervention identified as beneficial and reasonably safe in the trial. Exceptions to this requirement must be approved by a research ethics committee. Specific information about post-trial provisions must be disclosed to participants as part of informed consent. (point no 34, under the heading "Post Trial Provisions)

Given the significant globalisation of research and its spread to lower- and middle-income countries (LMICs), PTA becomes particularly important to the participants, community and country. India is home to approximately 3% of global clinical trials [7] and is also a LMIC. An analysis of ethics and regulatory guidelines from the country would give an indication of the extent to which they cover this topic, and this has formed the rationale for the narrative review.

Methods

The study protocol was granted a waiver by the Institutional Ethics Committee as the data was sourced from the public domain.

The study was designed as a narrative review with the overarching aim to provide a comprehensive yet critical summary and synthesis of Indian ethics guidelines, interpret them, identify lacunae and recommend the way forward [8]. The Scale for the Assessment of Narrative Review Articles (SANRA) criteria were used as the reference framework to ensure quality and comprehensive coverage of the narrative review methodology [9].

Scope of the review (with boundaries), inclusions, and exclusions

The scope of the present study was determined to be the evaluation of the historical evolution of post-trial access in guidelines in India, with a focus restricted to documents of Government agencies only. These included the Indian Council of Medical Research (ICMR), the apex organisation of the Government of India for the formulation, coordination and promotion of biomedical research and guidelines in the country and subsequently released by the other government bodies such as the Department of Biotechnology (Govt. of India) and the Central Standard Drugs Control Organization (CDSCO), the Indian regulator. Information on PTA from non-government sites such as NGOs and the pharmaceutical industry was excluded.

Definitions of PTA used for the narrative review

We used the Council for International Organization of Medical Sciences (CIOMS) definition of PTA for the study purposes: the obligation of sponsors and researchers in coordination with the host government and other relevant stakeholders including the community and the research ethics committees — "to make available as soon as possible any intervention or product developed, and knowledge generated, for the population or community in which the research is carried out, and to assist in building local research capacity." [10]

Data collection, synthesis and analysis

The data sources were primarily documents from the websites of the Government of India. Websites of the ICMR (https://www.icmr.nic.in/), the Department of Biotechnology (https://www.dbtindia.gov.in/), the Department of Science and Technology (https://dst.gov.in/) and the CDSCO (https://cdsco.gov.in/opencms/opencms/en/Home/) were searched by authors — VLC, PVB and NSS. All the guidance documents were then downloaded. Documents were collected sequentially as they had been published and the year of publication noted. Subsequently, the entire text of the document was both, hand searched and electronically searched. The relevant portion of PTA was searched using the following search terms — post-trial access, post research access, post-trial obligations, post-research benefit/s, long term extended studies, expanded access, benefit sharing, long term follow up benefit sharing, post-trial benefit, post-trial modalities, post- research plan, compassionate use, off label use, extended use and post-trial intervention/drug supply program. Results from each guidance document were verified by senior authors NJG and UMT and subsequently collated. We did not code or categorize the data but rather extracted the entire text. All authors then reached a consensus on the search and its outcome.

Results

The search yielded a total of eleven guidance documents with the key guidelines over the years coming from the ICMR.

PTA in guidance documents from the ICMR

The first ever reference to PTA access comes from the 2000 ICMR [11] guidelines which mention that the sponsoring agency must provide the drug until it is marketed in the country. Further in the ICMR 2006 guideline [12], there is a section of post-trial access in chapter III (General Ethical Issues) which mentions how the concept of PTA was introduced by the DoH in 2000, and again in 2004. The PTA specific for drug or vaccine trials, and DNA and cell-line banking/repository have been incorporated in respective chapters. The 2017 ICMR guidelines [13] talk about PTA in greater detail and has a separate section devoted to it (Supplementary Table, available online only). The section covers, in significant detail, benefit sharing with individuals, communities and populations, both direct and indirect. It also calls for inclusion of PTA in study protocols so that this may be discussed by ethics committees and the need for regulatory approvals for this as deemed necessary. In addition, it also covers benefits accrued from projects done by students where the onus rests with the institution to provide better care for participants, should an intervention be deemed beneficial. In addition, in the chapter on biological materials, biobanking and datasets (Section 11, Box 11.5), considerations for benefit sharing are described (Supplementary Table, available online only) [13].

The 2017 ICMR guidelines for research involving children [14] also refers to "benefit sharing". Here, there is a mention of benefit sharing with regards to data should it lead to commercialisation The ICMR guidelines provide clear instruction to ethics committees on reviewing Covid-19 protocols [15]. During the pandemic, PTA and benefit sharing were given a separate heading, and ethics committees were asked to consider an *a priori* agreement between investigators and sponsors on post-trial sharing of benefits with the community if relevant. The 2023 guidelines on the use of Artificial Intelligence (AI) do not directly refer to PTA [16]. They, however, discuss the fairness of distribution of AI technology by both the developers and concerned authorities. Also, they talk about establishing mechanisms to ensure delivery of information back to the patient/healthcare professional/health authority in case there are significant findings [16]. The ICMR guidelines of 2023 for conducting Controlled Human Infection Studies (CHIS) [17] covers PTA in depth and emphasizes that while research may not always yield clear benefits for participants, any benefits

that do arise should be made available to them. It does advise that ethics committees should consider PTA to treatment for placebo group participants; and that participants must receive comprehensive information about the study, including risks, benefits, treatment plans, and post-trial provisions. Additionally, informed consent forms should cover post-study plans, benefit sharing, dissemination of results, and long-term follow-up.

PTA in Indian regulatory documents

Since the 1940s, Schedule Y of the Drugs and Cosmetics Act governed the conduct of clinical trials in the country, and its 2016 amendment did not mention PTA [18]. In 2019, Schedule Y was replaced by the New Drugs and Clinical Trials Rules (NDCT) [19], which define PTA and outline the sponsor's responsibility to provide PTA free of cost for certain clinical conditions where no alternative therapy is available, and the investigational new drug has been found beneficial to the trial participant under rule 27.

PTA in Stem cell guidance from the Department of Biotechnology (Govt of India)

The 2017 ICMR guidelines on Stem Cell Research [20] mention PTA and state that if commercialisation of donated tissue or cells yield financial benefits, efforts should be made to share these benefits with the donor or the community. A portion of the benefits from commercial use should be returned to the community, which includes all potential beneficiaries, such as patients who have directly or indirectly contributed to the product, following established norms.

Discussion

The present study evaluated the evolution of PTA in Indian ethical guidelines and found that PTA was first addressed in the 2000 edition of the ICMR guidelines, and this was the same year in which it was addressed in the DoH [3]. The Indian regulator first addressed it only in 2017, but most Indian guidelines allude to it in depth, or in brief, indicating that the authorities are aware of its importance, and has introduced mechanisms to ensure its application.

The 2017 ICMR guidelines [13] represents as yet the most comprehensive coverage of PTA to date among all Government of India guidance documents, where the myriad aspects of PTA such as its philosophy, outlining of stakeholder responsibilities (sponsor, ethics committee, investigator and participant), approvals required for PTA, documentation, and PTA for clinical trials as applicable. The depth and extent of PTA coverage have considerably expanded from ICMR 2006 to the 2017 guidelines. The importance of PTA has also been emphasised in the 2023 ICMR CHIS guidelines. Given the importance of AI in today's context and the multiple clinical trials which use AI, the recent AI guidance does address it, albeit indirectly. We strongly recommend that the next version of ICMR's AI guidance directly use the term PTA and suggest mechanisms to ensure that it is put in place by stakeholders.

There is reasonable coverage of PTA in the NDCT 2019 rules [19] — relative to the old Schedule Y [19] — and this augurs well for the country. The rules in 2024 no longer remain "new" and any amendment or revisions should expand adequately on the existing PTA. The vast repertoire of PTA such as its duration, (especially for chronic diseases), safety monitoring, and its terms and stakeholder responsibility, can be made more comprehensive. This can be done through stakeholder engagement to address the diverse perspectives, ensure regular updates and due transparency in the processes.

It is also useful here to distinguish the narrow thought process in post-trial access — where the focus is on access to the intervention (found beneficial) and usually for the individual participant during a clinical trial — from the more broad based *post-trial care* (PTC) [21], which includes *responsible transition* to ensure continuity of care, future clinical care, another suitable trial or providing alternatives to the participant in the trial [22]. For LMICs, trials often remain a means of access to interventions otherwise beyond their means, and PTC then becomes even more relevant if PTA is not part of the trial. [22]. It is also important to ensure the barriers to PTA and PTC care are factored in by the stakeholders designing the access programmes. For example, in pre-exposure prophylaxis (Prep) trials in HIV for women, long queues and waiting times, inconvenient clinic visiting hours, and long distances to the clinic were identified as barriers for women seeking PTA [23].

In this narrative review, we specifically choose to include only the government guidance documents as these are used as a benchmark by researchers, ethics committees, policy makers, NGOs and the pharmaceutical industry. Researcher bias (reflexivity) was addressed by having objective search criteria, specific key words and a quality check of the culled data by senior authors. Both the strength and weakness of our review lie in the coverage of the government guidelines with them being both comprehensive (coverage from the inception to the present) and restrictive (only government websites searched).

In summary, our study has chronicled the evolution of PTA in Indian ethical and regulatory guidelines. The coverage of PTA while excellent today, can certainly evolve further. Aligning with the newly published Declaration of Helsinki (2024) [6], broader terms such as "post-trial arrangements" or "post-trial provisions" or "post-trial care" should be used rather than post-trial access alone [24]. Further evolution of Indian guidance documents will help future participants in clinical trials in the country, and this remains an ethical and moral obligation of all stakeholders in the country.

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