World Medical Association (WMA) Conference on

Declaration of Helsinki 1964-2024

Post-Trial Access and the Declaration of Helsinki (Part B)

Session 6: 11 am to 12.30 pm, 19 January 2024

Aula Vecchia del Sinodo, Vatican City

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Post-Trial Access
Research in Resource-Poor Settings

- **Symposium**
- **at St. Johns National Academy of Health Sciences, Bangalore**
- **Date**: 11th Dec 2023, 14:30 to 16:30.
- **Venue**: Video Conference Room, St. John's Research Institute, Bangalore
- **Chair**: Rev. Dr. Charles Davis
- **Speakers**: Dr. Prem Pais, Dr. Cecil Ross, Dr. G D Ravindran, Dr. Suman Rao, Dr. Hari Menon, Dr. Jayanthi Savio, Dr. Prashanth T
- **Moderator**: Dr. Tony D S Raj
- **Others**: Dr. Dhinagaran D, Dr. Abijeet Waghmare, Dr. Ryan Fernandez

acknowledgement

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Content of the Presentation

1. Clinical Trials and Post-Trial Access
2. Post-Trial Access and Bioethical Principles and Ethical Guidelines
3. Review of Post-Trial Access Case Studies and the Patient Experience
4. Ethical and Pragmatic Frameworks for Assessing the Costs and Benefits of Scientific Gains in LRSs

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Clinical Trials and Post Trial Access

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Clinical Trials are done to test safety and efficacy of new drugs to help improve public health.

Drug trials have different Phases-I, II, III and IV. Post Trial Access (PTA) generally refers to Phase-III drug trials.

- Current Protocol states that at trial completion if trial medication is to be stopped, trial participants are to be treated as usual at the physician's discretion.
- What if the New drug is effective but not available outside of a trial and/ or is very expensive, and current treatment methods are not satisfactory.
- Post-Trial Access is necessary -
  - For both **Intervention** and **Control** arms
  - For Participants who have shown benefit from treatment
  - If there is a potential negative consequence if treatment is stopped
- There is a lack of guidance and over-arching frameworks for PTA. While Clinical Trials are highly regulated, regulations for PTA are unclear.

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- In investigator Initiated Clinical Trials, usually the Drug molecule is already in the market and is being re-purposed for a new use, it is not very expensive and hence there is no need for PTA.
- In Sponsor-Driven Clinical Trials, Molecule is new, costly and not available in the market for patients, hence there is a need for PTA.
- Trial Insurance normally stops once the trial is over.
- Investigators must take a stand regarding toxicity/harmfulness.
- In case of hereditary defects or illnesses, trials need to be continued lifelong.
- In India, PTA was added to ICMR 2008 guidelines after people started demanding PTA.
- In PTA, apart from the actual drug, testing facilities and staff training need to be also considered.
- PTA is mandatory till the drug is approved by the Drug Controller/ regulator.
- Investigators need to advocate to make policy changes to fast-track drug/therapy towards the standard of treatment/care and the addition of drugs to the essential medications list (EML).

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Bioethical Principles and Ethical Guidelines to Regulate Post-Trial Access in LRSs

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The principle of **non-maleficence** demands continued access if withdrawal of an investigational medicine after the end of the trial would cause harm. Participants with chronic diseases who are benefiting from the research will be harmed if they are taken off treatment. This would violate the duty of non-maleficence.

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- **Autonomy** demands information to trial participants at the start of the trial whether there will be continued access to an investigational medicine and under what conditions. PTA should not become inducement to get informed consent.
- Distributive **justice** demands continued access not just to research participants but to the host population. In life threatening conditions, where the trial drug is proven effective, it might be inhumane to deprive non-trial patients of the same benefit.
- From the perspective of **beneficence,** sponsors and researchers have a duty to make efforts to safeguard the wellbeing of the research participants by maximizing the possible benefits and minimizing potential harm.
- Above all, the inviolable principle of human **dignity**, which is inseparable from the human condition, demands the continued intervention to avoid manipulation of vulnerable population and prevent harm to poor patients whom trial might have been the only hope. In other words, the trial participants are not mere means for research. Humanity precedes science, research and norms.

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Ethical Guidelines:

1. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH): **The ICH Good Clinical Practice** (GCP) Guidelines do not describe any responsibilities for continuing treatment after a trial.
2. **Declaration of Helsinki:** In advance of a clinical trial, sponsors, and governments should make provisions for PTA for all participants who still need an intervention identified as beneficial in the trial. This must be disclosed to participants during the informed consent process..
3. **CIOMS/WHO**: The Council for International Organizations of Medical Sciences (CIOMS), in collaboration with the World Health Organization (WHO), states in its *International Ethical Guidelines for Biomedical Research Involving Human Subjects* that companies should consider whether, when and how products proven by the research to be safe and effective will be made available to subjects after they have completed their participation in the research, and whether they will be expected to pay for them.

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4. ICMR guidelines: National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017

- **Where possible**, for example, if the drug is found useful and the standard of care is not available, the Institutional Ethics Committee should ensure post-trial access for the participants.

- Sponsors and researchers should strive to continue to provide beneficial interventions, which were part of the research initiative even after the completion of research **and till the local administrative and social support system is restored to provide regular services**.

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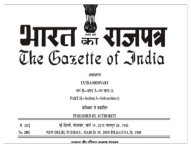
The New Drug and Clinical Trials (NDCT) rules 2019

MINISTRY OF HEALTH AND FAMILY WELFARE
(Department of Health and Family Welfare)


भारत का राजपत्र
The Gazette of India

- From page 157
- **27. Post-trial access of investigational new drug or new drug._**
- Where any investigator of a clinical trial of investigational new drug or new drug has recommended post-trial access of the said drug after completion of clinical trial to any trial subject and the same has been approved by the Ethics Committee for clinical trial, the post-trial access shall be provided by the sponsor of such clinical trial to the trial subject free of cost._
- (i) if the clinical trial is being conducted for an indication for which no alternative therapy is available and the investigational new drug or new drug has been found to be beneficial to the trial subject by the investigator; and
- (ii) the trial subject or legal heir of such subject, as the case may be, has consented

Drug Controller General of India (DCGI)
New Clinical Trials rules 2019, Part II Sec 3.1
#27: PTA is s legal requirement.

Where any investigator of a CT of an investigational new drug (IND) has recommended PTA after completion of trial and this is approved by Institutional Ethics Committee (IEC), PTA shall be provided by the sponsor trial subject **free of cost**.

- If a clinical trial is being conducted for a condition for which no alternative therapy is available
- Investigational New Drug is beneficial
- The participant has consented in writing to use post-trial use of the *investigational new drug* and that the sponsor shall have no liability for post-trial use.

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Review of Post-Trial Access Case Studies and the Patient Experience

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St John's Take on Clinical Trials

Comparative Effectiveness Research (CER)

Clinical Trials like Randomised Clinical Trials(RCT) determine Efficacy

(What can work)

RCTs may not determine Effectiveness

(What does work)

CER determines Effectiveness

Under controlled circumstances

Effect in the general population

Difference between Efficacy and Effectiveness

Sometimes operation is successful, but patient may die…

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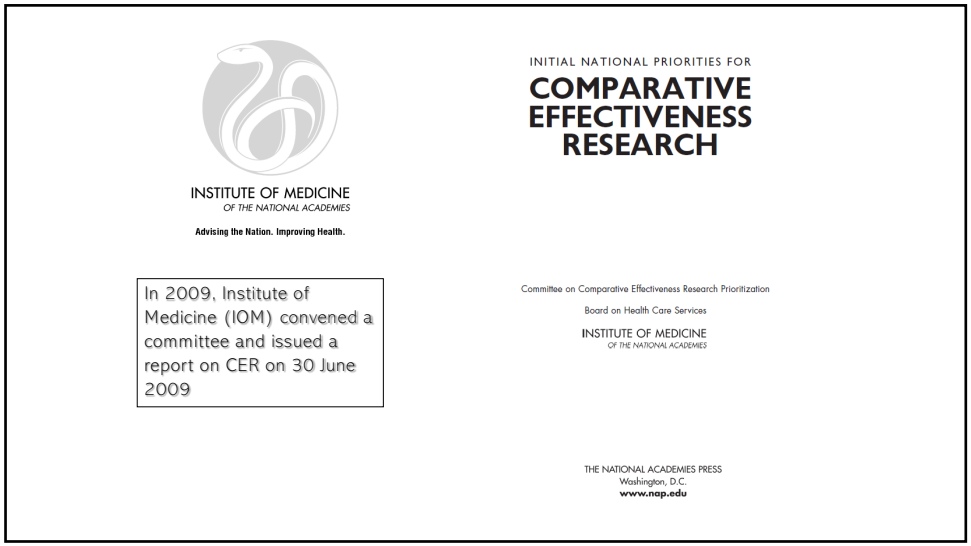

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Definition of CER:
Generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat and monitor a clinical condition or to improve delivery of care.

CER

"what works best for which patients under what circumstances"

Purpose

Inform consumers, clinicians, purchasers and policy makers to make informed decisions to improve health care

Real Life

Patients seek medical attention for subjective reasons like relief of pain, Regain of function or enjoy life.

Doctors use objective and easily measurable parameters like BP control, Patency of coronary, Size of mass....

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St. John's National Academy of Health Sciences
St. John's Medical College
St. John's Medical College Hospital
St. John's Research Institute, Bangalore, INDIA

Statistics of Clinical Trials from 2001 - 2023

Year	No of Clinical trials received	No of clinical Trials completed / closed	Ongoing Clincial Trials
2001-2023	1069	1045	23

CTRI: Clinical Trials Registry of India: 61,541 Trials in 2023

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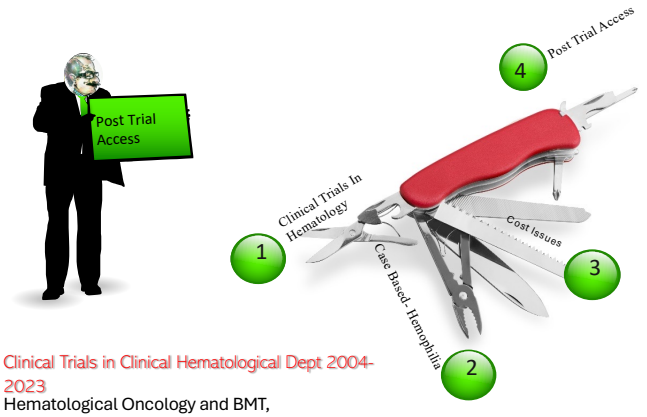

Clinical Trials in Clinical Hematological Dept 2004-2023

Hematological Oncology and BMT,
St John's Medical College Hospital Bangalore
Dr Cecil Ross
Professor and Head Clinical Hematology

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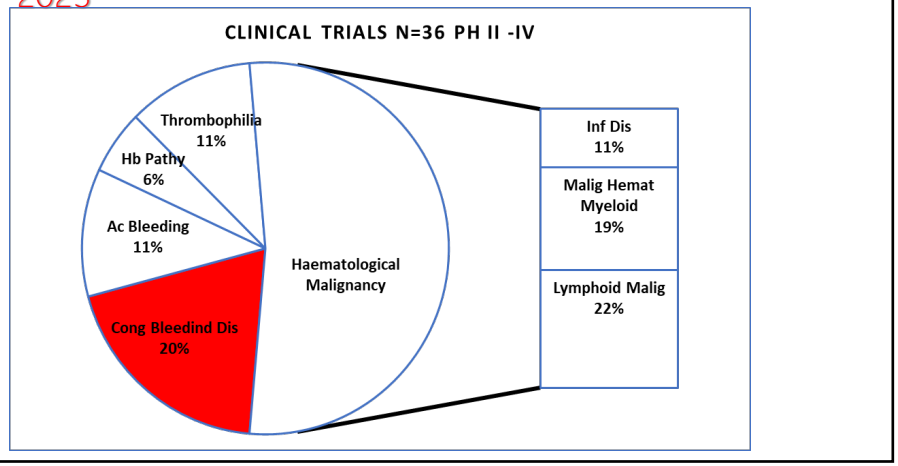
Clinical Trials in Clinical Hematological Dept 2004-2023



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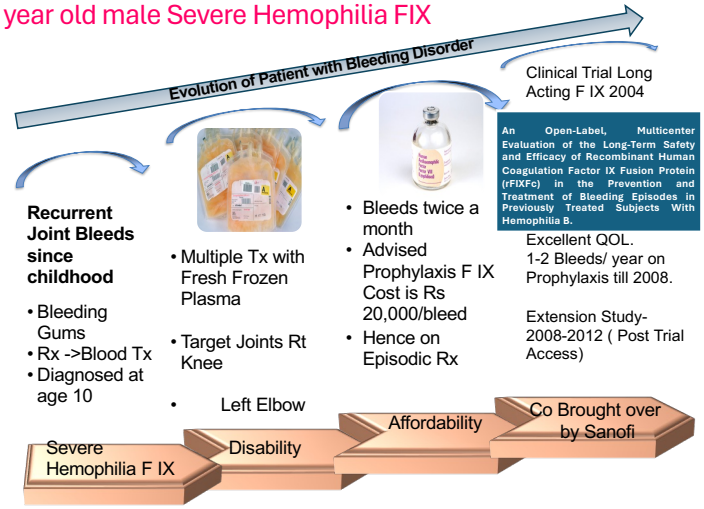
Pt PR 52 year old male Severe Hemophilia FIX



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Value of single bleed

Median life expectancy in Gen Population	• = 68 years
Expected median life expectancy Hemophilia	• = 45 years
No. of years of loss of life expectancy	• = 23 years
Average number of bleeds/patient/year	• = N= 12
Total expected bleed in a life span	• = 12×45 = 540

Value of a single bleed =

$$\left(\frac{\text{Loss of Life Expectancy} \times 365}{N \times \text{Median age of Hemophilia A Patient}}\right) \times N/12$$

$$\left(\frac{23 \times 365}{12 \times 45 \times 12/12}\right)$$

=15.54 days/bleed

A single bleed = Reduces life expectancy by 15.54 days
Cost of Rx of one Joint bleed is ~ Rs. 20,000. Cost of Brain Bleed is Rs 10 Lakhs

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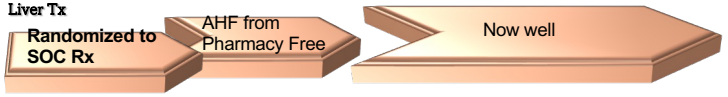
Pt PR 52 year old male Severe Hemophilia.
Factor IX

Pt got enrolled in a new study (company: Nord-Disc) – Explorer
Had hepatitis C virus (HCV) related chronic liver disease (CLD)
Covid Issues
PSE- Needed Liver Tx

• Pt was admitted and supportive care given

• Shifted to another hospital for Liver Tx
• ANTI-HEMOPHILIA (AHF) FACTOR 9
Alprolix provided by the previous PTA Rx
• Cured of Hemophilia



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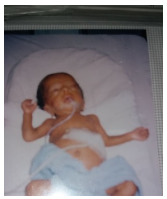
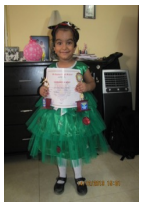
Trials in Mother and Child





- Pregnancy is transient, PTA - application to next pregnancy?
- Does PTA apply to siblings / next baby?
- How long to provide PTA?
- Changing physiology, monitoring?
- Role of clinicians?

Pregnancy is transient.

Is PTA - application to next pregnancy?

Does PTA apply to siblings / next baby?

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Post-trial Access in Maternal Vaccine Trials

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Am J Perinatol 2019;36(suppl S2):S41–S47.

- The above study identified that most researchers were not aware of the concept of PTA.
  - No impact on maternal vaccine trials.
  - 0/7 and 0/17 discussed in protocol
  - Half of researchers had no knowledge on PTA
- Even with the revised Declaration of Helsinki in 2013 and the CIOMS guidelines, there was no increase in provisions for maternal vaccine trials.
- **Inclusion of PTA provisions** in trial protocols and publications on trials in mother-child care is **essential** to increase transparency on the form and content of these provisions.

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Post Trial Access in Oncology:

- Oncology trials do not start **without a PTA clause** in the Clinical Trial Agreement
- For Oncology Clinical Trials in India, large number of participants are easily available. It costs less to conduct trials in India.
- Population-based intervention (Screening through a self-breast exam) reduced mortality for Cervical Cancer (by 35%) and breast cancer (by 15%). In such cases, intervention needs to be implemented for the entire population. PTA can be a challenge.
- Novartis ran an ambitious Patient Access project for LMICs
  - 65 thousand enrolled globally and 14 thousand patients benefited in India. It was not scalable or sustainable.

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• Negative results due to deprivation of PTA

(cf. Usharani P, Naqvi SM. Post-trial access. *Perspectives in Clinical Research*; Harmanjit Singh et.al. Posttrial Access to Medical Interventions, 9:1 (2019) 5)

- 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 patients in the US had access to zidovudine, while those from developing countries were not provided access.
- **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.
- **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.

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- *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.
- 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.
- Similarly, FDA approval of pemetrexed for lung cancer treatment was held until February 2004. During this period, several lung cancer patients died. PTA to this drug could have extended their lifespan.

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Ethical and Pragmatic Frameworks for Assessing the Costs and Benefits of Scientific Gains in LRSs

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From the perspective of conducting trials:

Pharmaceutical companies and sponsors prefer to have clinical trials in low resource settings due to low budgets and easy availability of large number of research participants.

From the perspective of scientific gains in low resource settings:

The primary goal of conducting clinical research in low resource settings should be to address the health needs of the host population.

Conducting clinical trials in good for low resource settings, and low-middle-income countries should encourage clinical trials to primarily to benefit their local population.

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Who will pay for access?

- Usually, the sponsor will pay for PTA.
  - If the cost is on patients and families, it will be a burden, but compliance would be great.
  - If PTA is given free, compliance would be poor. However, researchers would be able to do more research.
  - If PTA is fully sponsored, it raises costs and depending on financial returns research may not be encouraged.
- If the drug is not yet approved, PTA can be given after the trial is over by:
  - Regulatory approval for open-label trial extension studies, safety studies, or Extended Access Program (EAP)
  - Including a priori in protocols / separate protocols / protocol amendments.

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How long will you give the drug?

There is no clear answer on how long it can be provided. (e.g., cancer is in remission, but relapses if treatment is stopped)

- Not feasible to provide PTA for an unlimited period.
- ICMR guidelines state that PTA should be given 'where possible'.
- PTA to be given till the local administrative and social support system provides regular services. However, in LMICs, where basic services are a question, this could be Infinity.
- If PTA is provided to a baby with a rare disorder, it may be also required for the other siblings who might be at similar risk.

Lifelong drugs (heart disease, cancer, or drug for controlling cholesterol):

1) The industry has to determine if it can provide the drug *for a specific period.*
2) The industry will provide the drug *until* it is approved and locally available in the market.
3) The industry, before initiating the trial, should communicate through ***Informed Consent*** on how they are going to handle access
4) To avoid liability during PTA, the industry may need the participant/guardian to sign a waiver in case of any adverse event.

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In Oncological Trials How long: When to stop PTA in Clinical Trials with anti-cancer medication.

- Till improvement/ Till patient is in remission
- Some Cancer patients may have 5/10-year survival rates, hence sustaining PTA is a challenge.
- In LMICs, even when generic medicines are available in the market, patients may not be able to afford them.

- As newer/ better drugs become the **Standard of Treatment**, adapting patients to the next drug therapy/trial would help sustain PTA
- Keeping in mind the patient's well-being, one might have to balance and decide based on the benefits Vs risk of toxicity

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Long Term Support:

- Targeted therapies using Newer drugs for patients have improved their Median survivable duration.
- There is PTA in targeted therapies if the patient is progressing and deriving benefits from treatment.
- NGOs need to nudge the government to support the treatment of certain conditions.
- Research findings on PTA and care practices must be made public via publications.
- IEC Performa should request for details of PTA and management of patients at the end of Trial.
- Need to bring in Social teaching on the distributed care system. Distributive justice should be advocated.

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In the context of potential revision to the declaration of Helsinki in relation to research in resource-poor settings:

- PTA shouldn't be only for participants in the trial. It should be available for all those who need that drug, beyond the trial, through dissemination and scale-up.
- Post Trial Access could include 'Post Trial access to education' or 'Post Trial access to care' as well.
- When sponsors restrict PTA to study participants, advocacy must be done for benefits of the larger population
- The participant informed consent should disclose information regarding PTA at the start of the trials.

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- PTA must be for both arms: 'intervention' and 'control'.
- Monitoring is needed for new drugs against side effects
- If PTA is beneficial, it should be provided for everyone and not just those enrolled as Participants
- Need to disseminate information and scale up, reduce cost, and incorporate it into the 'Standard of Care'.
- To reduce the disparity between prosperous and poor nations, treatment proved to be beneficial should be made available at affordable costs or free of cost without inducing the vulnerable population to clinical trials.
- Post-trial responsibilities should not be restricted to drugs alone but include equipment, diagnostics, and care practices.

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- We also need to consider 'Specific Post-Trial access to care'.
- Researchers must stay connected with their patients to help them out when necessary.
- In studies done in low resource settings, the community needs to be made aware of Clinical Trial results.
- The community must have access post-trial benefits.
- Provisions for post trail access to non-drug trials must also be addressed.
- If the trial is found to be beneficial, the government must make efforts to implement it in a larger population and launch it as a National policy.

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- Upfront disclosure should be made to IRBs about PTA (some form of time-limited).
- Post-trial access is not valid when the investigational treatment does not provide benefit over standard treatment.
- 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.
- The promise of PTA should not interfere with the autonomy of participants in trials.
- Post-trial access should not hinder researchers and sponsors to conduct research in communities demanding it.
- Special aids may be provided by governments and funding agencies to provide PTA in developing and resource poor settings.
- Special research grants may be awarded to sponsors and investigators who have invented new drugs/interventions that were subjected to PTA to balance scientific research and patient care.

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Generics in India

India is known as the "**Pharmacy of the Developing world**"

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

Engineered in India — Patent Law 2.0

Amy Kapczynski, J.D.

India is known as the "pharmacy of the developing world," because it supplies much of the world's demand for affordable, generic drugs. So when the Supreme Court of India issued a landmark ruling

can create problems for innovation. Finally, patents cause especially acute problems for access to medicines in developing countries — not only because of low

Gleevec, which is used to treat chronic myeloid leukemia and other cancers, costs about $2600 (Rs140 000; £1710; €2000) a month. The generic equivalent is currently available in India for just $175.

'The Supreme Court decision will save a lot of lives in the coming decades.' —Leena Menghaney, Doctors Without Borders

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Generics in India

entary

tory for global public health in
eme Court

Hoen

y of Amsterdam, OZ Achterburgwal 185, Amsterdam,
lenthoen.ip@gmail.com

ct On 1 April of this year, the Indian Supreme Co
dian Patent Office to refuse the patent grant for Nov
. The patent application failed to meet the requirer
dian law. The global public health community follov
could affect the Indian generics industry – an imp
icines to the developing world.
f Public Health Policy (2013) 34, 370–374. doi:10.10
l online 16 May 2013

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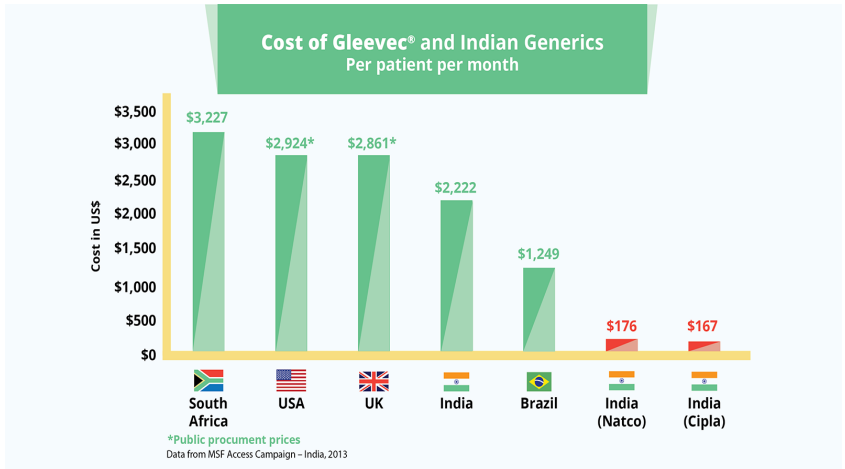

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Review Article

Health economics and cost-effectiveness research with special reference to hemato-oncology

*Rajat Kumar** MEDICAL JOURNAL ARMED FORCES INDIA 69 (2013) 273–277

Table 3 – Comparison of cost of drugs in Canada and India.

Drug	Cost of patent drug in Canada	Cost of generic brand in India (approximately)
Rituximab 500 mg vial	$2265	$1000
G-CSF 300 mcg vial	$181	$25
Bortezomib 3.5 mg vial	$1870	$200–250
Imatinib 400 mg/month	$3400	$100–250
Thalidomide 100 mg/month	$1700	$50
Lenalidomide 10 mg/month	$9600	$50–100

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Sponsors, investigators, communities, Institutional Review Boards and the governments – all concerned parties involved – must accept PTA as a joint responsibility and decide on its provision before the trial beings.

Post-Trial Access is an ethical imperative, particularly, in low resource settings.

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Thank you for your attention!

If we keep the patient at the center, we will be doing the right thing.

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