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ACCESS TO THE BENEFITS OF CLINICAL RESEARCH ON HUMAN SUBJECTS. VIRTUE ETHICS VS. NORMATIVE ETHICS

EL ACCESO A LOS BENEFICIOS DE LAS INVESTIGACIONES SOBRE SUJETOS HUMANOS. LA DIFERENTE APROXIMACIÓN DESDE LA ÉTICA DE LA VIRTUD Y LA ÉTICA NORMATIVA

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ABSTRACT:

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Post-trial access (PTA) for participants in clinical trials subsequent to research emerged as an important consideration during the work for the first antiretroviral drugs for AIDS. It evolved into a stringent ethical mandate in the 2000 iteration of the Declaration of Helsinki. The recent version of this Declaration (October 2024) places greater demands on this aspect of research, in part because over the past two decades tangible progress in actualizing PTA, particularly in developing nations, has been scant, notwithstanding the presence of PTA-related information on numerous pharmaceutical company websites. This article presents recent empirical data underscoring the limited availability of PTA in practice. It scrutinizes the guidelines put forth by prominent international benchmarks in clinical research. We highlight the intricacies associated with mandating universal compliance and advocate for an approach transcending mere normative ethics toward a virtuous ethics paradigm, one that fosters more equitable and supportive research endeavors.

RESUMEN:

Palabras clave:
Ensayos clínicos, Declaración de Helsinki, acceso beneficios, ética de la virtud

La cuestión sobre el acceso a los beneficios de un ensayo clínico por parte de los participantes una vez acabado el estudio (*post-trial access*: PTA) surgió como un tema ético importante en relación a la investigación con los primeros fármacos antirretrovirales para el sida. El concepto evolucionó hasta convertirse en un requisito ético estricto en la versión del año 2000 de la Declaración de Helsinki. La versión reciente de esta Declaración (octubre de 2024) impone mayores exigencias a este aspecto de la investigación, en parte porque en las dos últimas décadas los avances tangibles en la actualización de la PTA, sobre todo en los países en desarrollo, han sido escasos, a pesar de la presencia de información relacionada con la PTA en numerosos sitios web de empresas farmacéuticas. Este artículo presenta datos empíricos recientes que subrayan la limitada disponibilidad de la PTA en la práctica. En él se examinan las directrices establecidas por destacados referentes internacionales de la investigación clínica. Se ponen de relieve las complejidades asociadas a la imposición de un cumplimiento universal y se aboga por un enfoque que trascienda la mera ética normativa y adopte un paradigma ético virtuoso que fomente una investigación más equitativa y solidaria.

1. Introduction

The World Medical Association has just approved a new version of one of its seminal documents, the Declaration of Helsinki,[1] which delineates the ethical standards governing clinical experiments involving human subjects. Among the ethical considerations arising in the evaluation of research protocols concerning novel pharmaceuticals, the issue of post-trial access to the tested product has gained escalating significance over the years. While implicit within moral deliberations on human subject research, this concern was not expressly articulated until the latter part of the 20th century, particularly in the context of antiretroviral therapy for AIDS.[2] Recently, there has been renewed interest in neural implant research.[3] As early as the Belmont Report (1978), a document commissioned by the United States government to establish ethical guidelines for research funded by public resources, it was affirmed that justice suggests the exclusion of individuals unlikely to derive benefit from the investigational products upon conclusion of the clinical trial.[4]

The fundamental ethical inquiry of this paper can be articulated through the following query: What moral responsibilities do sponsors of research studies bear towards participants following the conclusion of experimentation? This question can be further delineated with the following questions: Is there an imperative to furnish the research product (be it a drug or diagnostic-therapeutic tool) in instances where it demonstrates efficacy for patients, or is such provision discretionary? Should such an ethical obligation be deemed existent, a subsequent query emerges: Who assumes the responsibility for ensuring compliance? Concurrently, another equally pertinent question arises: What is the duration for which this access must be guaranteed? These are inquiries that defy facile resolution. Indeed, some scholars, such as Doval, contend that there exists no compelling justification either for or against a universal mandate to furnish such a product.[5]

This article provides a comprehensive overview of the extensive literature pertaining to the subject matter, elucidating various formulations of the purported ethical obligation while adhering to established guidelines or pronouncements from national and international entities. It elucidates the rationales advocating for access to research benefits, alongside potential modalities for their realization. Furthermore, it critically evaluates raised objections and pragmatic challenges. Conclusively, the article proffers a plausible rationale for the persisting discord surrounding this issue, despite widespread acknowledgment among stakeholders regarding the imperative to confer benefits upon research participants. This discord is attributed not solely to the intricate nature of the subject, owing to the multifarious contexts in which the question is posited, but also to the normative ethical framework prevalent in the domain of bioethics. Such a framework, being inherently rigid, fails to furnish a versatile proposal that simultaneously upholds exacting standards. I think this moral problem is a good example to appreciate that virtue ethics would be better suited to find the best solutions in each case, which normative ethics is not able to achieve.

The primary corpus of literature concerning this subject is predominantly in English. The terminology employed to engage with the topic under examination exhibits variability, delineating diverse nuances of the underlying ethical quandary. The prevalent term utilized across this discourse is "post-trial access," (from now on PTA) which is often accompanied by adjunct nouns that either broaden or narrow the semantic scope. Additional terms include "post-trial benefits,"[6] "post-trial

1 Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Participants (October 2024): https://www.wma.net/policies-post/wma-declaration-of-helsinki/ (Access: 31-X-2024).

2 S. M. Dainesi and M. Goldbaum, "Provision of Investigational Drug after Clinical Research – Review of Literature, National and International Guidelines," *Revista Da Associação Médica Brasileira (English Edition)* 57, no. 6 (2011): 696–702.

3 J. J. Fins et al., "Identity Theft, Deep Brain Stimulation, and the Primacy of Post-Trial Obligations," *Hastings Center Report* 54, no. 1 (2024): 34–41.

4 National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, "The Belmont Report: Ethical Principles and Guidelines for the Commission for the Protection of Human Subjects of Biomedical and Behavioral Research," 1978, pt. at B, 3. Justice.

5 D. C. Doval, R. Shirali, and R. Sinha, "Post-Trial Access to Treatment for Patients Participating in Clinical Trials," *Perspectives in Clinical Research* 6, no. 2 (2015): 82–85.

6 C. Grady, "The Challenge of Assuring Continued Post-Trial Access to Beneficial Treatment," *Yale Journal of Health Policy, Law, and Ethics* 5, no. 1 (2005): 425–35.

provisions,"[7] "post-trial obligations,"[8] "post-trial responsibilities,"[9] and "post-trial healthcare."[10] The term 'benefits', which appears in the tittle of this paper and is also largely used in the literature, is certainly more general, and includes PTA alongside other measures which, as we shall see, have been proposed as a possible way of providing ethical experimentation.

2. Some numbers to start with

Prior to delving into the delineation of various formulations of the purported obligation to provide the investigational product to participants when the trial is over, it is pertinent to furnish some empirical insights from recent literature regarding how this issue has been addressed within research protocols. Notably, it is imperative to underscore the scarcity of scientific articles dedicated to addressing this inquiry. Few scholarly works have endeavored to explore the manifestation of these post-trial "obligations" within research protocols and their subsequent implementation upon the conclusion of the study.

One of the seminal studies in this field is the investigation conducted by Colona and Schipper in 2015, as documented in the SOMO Paper titled "Post-Trial Access to Treatment: Corporate Best Practices."[11] The authors undertook an inquiry wherein they engaged with major pharmaceutical companies to elucidate their approaches toward the issue of PTA. Their findings, while unequivocal, do not necessarily evoke optimism. They concluded that "The difficulty experienced by SOMO in collecting good examples of PTA from the companies in question and the absence of examples in the academic literature confirms the exceptional nature of PTA." A recurring theme discerned from the diverse responses received from pharmaceutical entities is the conception of PTA solely within circumscribed and extraordinary contexts, with an emphasis on case-by-case evaluation.

How many experimental protocols include estimates for post-trial access (PTA)? A study conducted by Da Silva's Brazilian team endeavors to address this question by analyzing data from 2014 obtained from the study of protocols registered in the EU Clinical Trials Register (EUCTR).[12] The analysis encompasses information from 1624 studies across 21 countries categorized into four income groups. The findings reveal that 54% of studies in high-income countries do not provide PTA predictions, whereas this figure decreases to 38% in countries classified within the "upper-middle" and "lower-middle" income brackets. Within the first group, among those protocols lacking PTA predictions, 55% are deemed to involve vulnerable populations, whereas in the other two income groups, this proportion rises to 71% and 76%, respectively.

A noteworthy insight, of considerable significance to our inquiry, is offered by a meta-analysis conducted by Van Roessel's team on PTA in vaccine trials involving pregnant women in clinical phases II and III.[13] The analysis revealed that the majority of principal investigators involved in these trials were unaware of the ethical obligation regarding PTA, although some had factored this aspect into their research planning. A temporal distinction is drawn between periods before and after 2000, as in that year, a revised edition of the Declaration of Helsinki was adopted, explicitly including the imperative to consider this ethical commitment. Interestingly, none of the studies examined (7 before 2000 and 17 after) mentioned post-trial access in their publication of results, although 35% of those conducted after 2000 asserted adherence to the Declaration guidelines. Nevertheless, according to these authors, 82% of studies published

7 Z. Zong, "Should Post-Trial Provision of Beneficial Experimental Interventions Be Mandatory in Developing Countries?," *Journal of Medical Ethics* 34, no. 3 (2008): 188–92.

8 E. R. m. Cohen et al., "Reporting of Informed Consent, Standard of Care and Post-Trial Obligations in Global Randomized Intervention Trials: A Systematic Survey of Registered Trials," *Developing World Bioethics* 9, no. 2 (2009): 74–80.

9 H. L. Cho, M. Danis, and C. Grady, "Post-Trial Responsibilities Beyond Post-Trial Access," *The Lancet* 391, no. 10129 (2018): 1478–79.

10 R. Iunes et al., "Who Should Pay for the Continuity of Post-Trial Health Care Treatments?," *International Journal for Equity in Health* 18, no. 1 (2019): 26.

11 I. Schipper and S. Colona, "Post-Trial Access to Treatment: Corporate Best Practices," 2015, at https://philpapers.org/rec/COLPAT-9 (Access: 31-X-2024).

12 R. E. da Silva et al., "The Patient's Safety and Access to Experimental Drugs after the Termination of Clinical Trials: Regulations and Trends," *European Journal of Clinical Pharmacology* 74, no. 8 (2018): 1001–10.

13 I. M. A. Van Roessel et al., "Post-Trial Access in Maternal Vaccine Trials," *American Journal of Perinatology* 36, no. S 02 (2019): S41–47.

after 2000 in some way considered PTA. However, a prevailing issue is that for many, PTA is conceptualized and potentially resolved through the dissemination of study information, rather than by providing the vaccine to study participants or their respective communities.

Homedes and Ugalde's (2015) article addresses the issue of access to pharmaceuticals tested in Latin American countries and approved by the FDA between 2011 and 2012, shedding light on the complexity of the matter.[14] The study scrutinized thirty-three newly introduced products in the U.S. market. Among these, only eight were registered and made available for sale in all Latin American countries where they underwent testing. Conversely, ten products were registered but remained unavailable for purchase in any of these nations, while fifteen were registered and marketed in select countries within the region. The investigation delves beyond mere commercialization statistics, examining the practical accessibility of these medications. It considers factors such as pricing, recognizing that in many Latin American countries, individuals must bear the full cost of medicines out-of-pocket. Notably, only one of the thirty-three new drugs was priced below the minimum monthly wage of the respective country. While the authors acknowledge the challenges inherent in obtaining precise data due to limited information access, the study offers valuable insights into the underlying barriers to medication access.

An illustrative case highlighting the practical efficacy of ethical guidelines advocating for PTA is evident in the research conducted by Jimenez's working group at the University of the Philippines.[15] Their examination focuses on the implementation of PTA within the 193 experimental protocols evaluated by the University of the Philippines Manila Research Ethics Board (UPMREB) during the period spanning 2012 to 2017. The findings from this inquiry reveal a disconcerting reality: "As of present, none of the clinical trial protocols scrutinized by UPMREB have achieved full compliance with the ethical imperatives governing PTA." The implications are unequivocal: " More work is needed if PTA, as stipulated in ethics guidelines, is to be reflected in reality." The authors of the study underscore that ethics committees predominantly prioritize PTA considerations when appraising protocols involving diseases of rare incidence or those lacking curative options, particularly when the proposed treatment entails significant cost, and when the drug's efficacy and safety profiles have been well-established.

Páez and García de Alba present a compelling perspective drawn from their extensive experience within Mexico's national Institutional Review Board (IRB). Their examination focuses on a spectrum of ethical dimensions across 34 research protocols scrutinized by the National Research Commission during the period spanning 2003 to 2004.[16] Notably, none of the studied cases entertain the prospect of PTA or inclusion of the drug within the essential medication lists of the National Institute of Social Security. In a prior investigation by the IRB, a mere 20% of protocols acknowledged the concept of PTA, signaling a deficiency in the committee's ability to discern ethical lapses concerning benefit sharing. Among the 193 protocols analyzed, 100 (51.81%) addressed PTA in some way, while the remaining 93 (48.19%) deemed PTA irrelevant. The delineation of eight distinct types of PTA within these protocols is noteworthy, with the authors highlighting five instances where the prescribed practices diverge from established ethical guidelines or even propose approaches antithetical to the principles underlying PTA. The authors delineate various types of PTA observed within the protocols, noting discrepancies between established bioethical standards and actual practices. These include: (1) the availability of standard care beyond the trial; (2) explicit denial of PTA for the investigational drug; (3) uncertainty regarding benefits due to the experimental nature of the study; (4) the commercial availability or future production of the drug; and (5) provision for access to the study drug during the

14 N. Homedes and A. Ugalde, "Availability and Affordability of New Medicines in Latin American Countries Where Pivotal Clinical Trials Were Conducted," *Bulletin of the World Health Organization* 93, no. 10 (2015): 674–83.

15 E. B. Jimenez et al., "Availability of Post-Trial Access in Clinical Trials: A Review of Clinical Trial Protocols Submitted to the Research Ethics Board of the University of the Philippines Manila," *Current Medical Research and Opinion* 35, no. 11 (2019): 1849–55.

16 R. Páez and J. E. Garcia De Alba, "International Research and Just Sharing of Benefits in Mexico," *Developing World Bioethics* 9, no. 2 (2009): 65–73.

trial. Furthermore, they identify additional forms of PTA consistent with prevailing bioethical literature, such as: (1) access to trial results or information; (2) PTA evaluation by the sponsor based on patient needs; and (3) the option to transition to an open-label follow-up study. Remarkably, among the 100 protocols acknowledging the relevance of PTA, none stipulate a concrete agreement on PTA prior to the commencement of experimentation. Of these, 40 protocols offer PTA-related information deemed pertinent for enrolled subjects, while 17 protocols indicate that the sponsor will assess suitable PTA arrangements at the conclusion of the study, potentially considering study extension options.

We conclude this section by highlighting the scarcity of scientific literature examining PTA provisions within research protocols. Among the limited studies available, the data underscore a significant disjunction between the recommendations outlined in ethical guidelines advocating for PTA and the actual incorporation of adequate measures within research protocols. This disparity underscores the pressing need for further investigation and attention to ensure alignment between ethical imperatives and practical implementation in research endeavors.

3. The PTA "obligation" in some international bodies

The imperative to share the advantages accrued from any clinical experimentation involving human subjects has historically manifested in various forms preceding its formal theorization and codification within ethical frameworks. A seminal contribution to this discourse predates contemporary conceptions of PTA can be attributed to Gustin's work in 1991. Although the explicit terminology of PTA may not have been employed, Gustin undertook a comprehensive examination of the ethical dimensions inherent in such endeavors. His scholarship aimed to provide, in his own words, an alternative perspective to the "Helsinki ethics," alluding to the renowned declaration of the World Medical Association.[17]

In fact, the Declaration of Helsinki does not mention this issue until its October 2000 version, which reads: "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" (n. 30). It is an indication that is perhaps too demanding, and in some cases too burdensome for clinical trial sponsors. The criticism it generated after its publication forced the World Medical Association to issue a Note of Clarification at the 2004 Tokyo General Assembly, which greatly diluted the ethical obligation of the PTA. This was the Note wording: "The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review".[18]

The transition was significant, passing from a stance that asserted the duty of providing PTA for prophylactic, diagnostic, and therapeutic interventions proven beneficial in the study, to emphasizing the necessity of delineating potential avenues for accessing such interventions or suitable alternatives in care. This revised formulation absolved study sponsors of the strict obligation for PTA provision.

In 2008, a revised version of the Declaration of Helsinki emerged, featuring two pertinent references to our subject matter. Firstly, in clause 14, it states: "The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits". And in n. 33 it said: "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

17 L. Gostin, "Ethical Principles for the Conduct of Human Subject Research: Population-Based Research and Ethics," *Law, Medicine & Health Care: A Publication of the American Society of Law & Medicine* 19, no. 3–4 (1991): 191–201.

18 J. Blackmer and H. Haddad, "The Declaration of Helsinki: An Update on Paragraph 30," *CMAJ : Canadian Medical Association Journal* 173, no. 9 (2005): 1052–53. In the same Canadian journal, a critical editorial had been published concerning the paradigm shift: Canadian Medical Association, "Dismantling the Helsinki Declaration," *CMAJ* 169, no. 10 (2003): 997–997.

example, access to interventions identified as beneficial in the study or to other appropriate care or benefits". Four years subsequent to the issuance of the Note for Clarification, the World Medical Association (WMA) underscores the imperative for subjects involved in the study to partake, to some extent, in the benefits arising from the research. Additionally, it emphasizes their entitlement to be apprised of the findings and reiterates the necessity of incorporating this matter within the research protocol.

The 2013 version mentions the issue of PTA in three numbers and creates a specific section of the document for this point ("Post-trial provision"). The first reference appears in n. 22: "In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions". The second is in the section on informed consent: "must be adequately informed of (…) post-study provisions". Number 34, the only one in the new section on forecasts at the end of the study, reads as follows: "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".

After the publication of the 2013 version some authors acknowledged the well-intentioned efforts of the World Medical Association to ensure post-trial access (PTA) but critiqued the final wording as somewhat awkward, suggesting that it may dilute these intentions.[19]

In the revised Declaration of Helsinki, approved in October 2024 in Helsinki, 60 years after the original declaration, the emphasis on ensuring access to post-trial treatments has been strengthened. A first reference still appears in n. 22, which states: "In clinical trials, the protocol must also describe any post-trial provisions." The second reference to this topic, previously located within the informed consent section, has been moved in this updated version to n. 34 which remains a single number in the section titled "Post-Trial Provisions." This number reads as follows: "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." Notably, this new n. 34 replaces the previous "should" [make provisions] with a mandatory "must," reinforcing the obligation to provide post-trial treatment. Additionally, it now requires ethics committee approval for any exceptions to this obligation, further underscoring the commitment to post-trial participant care.

In addition to the Declaration from the World Medical Association, since 2000, various organizations within the health and bioethics domain have provided commentary and ethical directives pertinent to our area of study. Notably, three examples include the guidelines from UNESCO, the CIOMS guidelines, and the insights offered by the *Nuffield Council on Bioethics*.

UNESCO issued its "Universal Declaration on Bioethics and Human Rights" in 2005. Among its 28 articles, Article 15 is specifically dedicated to "Benefit-sharing," outlining several avenues for realizing this principle while emphasizing that such benefits should not serve as undue inducements for study participation. The full text of the article is as follows:

"1. Benefits resulting from any scientific research and its applications should be shared with society as a whole and within the international community, in particular with developing countries. In giving effect to this principle, benefits may take any of the following forms:

(a) special and sustainable assistance to, and acknowledgment of, the persons and groups that have taken part in the research;

(b) access to quality health care;

(c) provision of new diagnostic and therapeutic modalities or products stemming from research;

(d) support for health services;

(e) access to scientific and technological knowledge;

19 A. Y. Malik and C. Foster, "The Revised Declaration of Helsinki: Cosmetic or Real Change?" *Journal of the Royal Society of Medicine* 109, no. 5 (2016): 184–89.

(f) capacity-building facilities for research purposes;

(g) other forms of benefit consistent with the principles set out in this Declaration.

2. Benefits should not constitute improper inducements to participate in research".

In its 1993 document on clinical research in resource-limited settings, the Council for International Organizations of Medical Sciences (CIOMS) had already underscored the necessity of equitable distribution of risks and benefits in the selection of potential experimental subjects. In the latest iteration of this document, "Clinical research in resource-limited settings" released in 2021, regarding the issue of PTA, CIOMS references the 2013 version of the Declaration of Helsinki, highlighting the shared responsibility of sponsors, researchers, and local governments. CIOMS asserts that it is not unreasonable to expect study sponsors to extend the benefits in low and middle-income countries by providing continued treatment proven to be effective. However, this obligation would cease once the drug is integrated into the public health system. Furthermore, CIOMS suggests that this obligation should only persist for a predetermined duration. Additionally, the CIOMS document discusses other potential benefits that could be extended to research participants.

In addition to the aforementioned guidelines from international organizations, it is pertinent to include the guidelines regarding PTA outlined in the document "Ethics of Health Care Research in Developing Countries," published in 2022 by the *Nuffield Council on Bioethics*. In the Executive Summary of this document, it states: "The Working Party concludes that it is unacceptable for research to begin without a decision having been made about whether or not participants in the control group will be offered an intervention shown to be successful on completion of the trial. Researchers should endeavor to secure post-trial access to effective interventions for all the participants in a trial who could benefit. In addition, the possibility of introducing and maintaining a successful treatment in the wider community should be considered before research is conducted. If it is thought that this will not be possible, researchers must justify to the relevant research ethics committee why the research should be carried out."

The working group posits that local governments bear the primary responsibility for ensuring the provision of drugs or procedures proven effective during experimentation, given that study sponsors and researchers frequently lack the resources to sustain such provisions. Nonetheless, sponsors and researchers can play a crucial role in expediting the commercialization of the products in question. Furthermore, this paper broadens the spectrum of potential beneficiaries by acknowledging various categories of subjects, including members of control groups in trials, all participants in the research project, and the wider community within which the research is conducted.

4. Reasons in favor of the PTA, objections and possible courses of action

More than twenty years prior to the initial World Medical Association (WMA) indication of Appropriate Access to Medicines (AWP), the renowned *Belmont Report* (1978) had underscored that "research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research" (Part B, 3. Justice). This directive conveys a moral obligation to ensure equitable distribution of benefits arising from clinical trials. Such a stance contrasts with prevailing practices in the corporate realm, where profit often supersedes considerations of solidarity—a term that many companies employ more for its superficial appeal in promotional campaigns rather than as a foundational principle of their corporate ethos. Conversely, within the domain of health research, distinct moral imperatives emerge, particularly concerning the ethical obligations owed to study participants given their assumed risks and vulnerability due to illness.

In their compelling article, Cook et al. (2016) undertake a comprehensive examination of academic literature, legislative frameworks, and international guidelines. Their meticulous review leads them to conclude that, amidst the increasing prevalence of clinical trials in developing nations, there is a pressing need for deep-

er exploration of the moral quandary surrounding PTA. Moreover, they highlight a robust consensus within the literature advocating for access to beneficial trial products, albeit acknowledging discrepancies among authors regarding the justification of such an obligation. Nevertheless, the pervasive challenge lies in the practical implementation of these principles. Consequently, scant attention is afforded to stringent regulatory measures essential for guiding these complex processes.[20]

In the realm of justifying PTA obligations, one of the most exhaustive studies to date is Sofaer and Stretch's.[21] These scholars have devoted their efforts to conducting systematic analyses of literature-based rationales guiding decision-making in medicine, medical research, and health policy. In 2011, they applied their analytical model to the pertinent subject of study: PTA. Their study draws upon data gleaned from the examination of 75 publications. Within their discourse, Sofaer and Stretch differentiate between "broad" and "narrow" types of justifications, identifying 36 instances of the former and 235 of the latter. These justifications are categorized into various thematic domains, including moral considerations, legal considerations, interests and incentives, practices, justice, and role-relationships among involved stakeholders (with occasional overlap between the latter two categories). Predominantly cited within the "broad" justifications is the notion of avoiding exploitation (cited 97 times), closely followed by considerations of stakeholder interests, which encompass participants, sponsors, governmental entities of the host country, and broader societal interests (cited 86 times). Conversely, examples of "narrow" justifications include assertions that research offers additional benefits beyond PTA (cited 6 times), reciprocity in response to risk undertaken by participants (cited 6 times), and reciprocal engagement with the host community by the sponsoring entity (cited 1 time). Among the corpus of analyzed publications, the prevailing ethical stance, as evidenced in 45 publications (60%), advocates for the provision of PTA under certain circumstances. Additionally, a minority position, comprising 13% (10 articles), maintains that PTA should be furnished unconditionally, while a solitary article posits the absence of such an obligation. In any case, the latter article could be included in the first group.

One commonly cited argument, particularly prevalent in early literature addressing PTA, revolves around the potential exploitation of research subjects. Notably, in the 2002 *Nuffield Council of Bioethics* document titled "The Ethics of Research Related to Healthcare in Developing Countries," the term "exploitation" is referenced 29 times. In the 2022 version, the concept of "real risk of exploitation" continues to be considered, albeit with reduced frequency, appearing only five times throughout the document. As a pivotal citation illustrating the nexus between the absence of PTA and exploitation, the document references a seminal 1998 article authored by Glantz et al. in the *Hastings Center Report*.[22] Within this article, mention is made of the 1993 guidelines issued by the CIOMS, which stipulated those sponsors ought to ensure reasonable access to investigational products, proven effective, for inhabitants of the developing regions where the study was conducted. However, Glantz and colleagues deemed this language insufficiently robust and specific to mitigate the risk of exploitation. Consequently, one of the key conclusions drawn from their analysis was: "It is essential to replace vague promises with realistic plans that must be reviewed and approved before the research commences".[23]

In the specialized literature addressing this topic, there has been a prevalent tendency to associate the absence of reasonable product availability with exploitation. However, Emmanuel's 2008 publication critiqued this standpoint and proposed the concept of "fair benefit" as a more apt approach to mitigating the risk of exploitation.[24] Subsequently, influenced by works such as

20 K. Cook, J. Snyder, and J. Calvert, "Attitudes toward Post-Trial Access to Medical Interventions: A Review of Academic Literature, Legislation, and International Guidelines," *Developing World Bioethics* 16, no. 2 (2016): 70–79.

21 N. Sofaer and D. Strech, "Reasons Why Post-Trial Access to Trial Drugs Should, or Need Not Be Ensured to Research Participants: A Systematic Review," *Public Health Ethics* 4, no. 2 (2011): 160–84.

22 L. H. Glantz et al., "Research in Developing Countries: Taking 'Benefit' Seriously," *The Hastings Center Report* 28, no. 6 (1998): 38–42.

23 Glantz et al., "Research in Developing Countries" 4.

24 E. J. Emanuel, "9. Addressing Exploitation: Reasonable Availability Versus Fair Benefits," in E. J. Emanuel and J. Hawkins,

Emmanuel's, recent scholarship has acknowledged that, although the exploitation of communities in developing countries should be rigorously guarded against, not every instance of insufficient PTA necessarily constitutes exploitation.[25]

On the other hand, human dignity serves as a significant category in the moral justification discourse surrounding PTA, as evidenced by its inclusion in the title of Andanda and Wathuta's article on the subject.[26] However, it is notable that despite its importance, the literature addressing PTA has not been extensively elaborated upon.

In his study conducted for the National Institutes of Health and published in 2011, Joseph Millium delineates several justifications for the obligation to provide PTA in the specific context of antiretroviral drugs. I cite this article because such extensive developments on our topic of study are not found in other areas. These are the justifications offered by Millium:[27]

1) Compensation for harm inflicted upon patients through study participation, warranting some form of reparation.
2) Preservation of the trust relationship between patients and researchers, which is essential for the integrity of medical research endeavors.
3) Reciprocity, wherein participants, who contribute significantly to the advancement of research, should also reap a portion of the benefits derived from it.
4) Ethical obligations rooted in principles of justice and beneficence, particularly in light of stark disparities in access to antiretrovirals between affluent and impoverished settings.
5) Ensuring access to antiretrovirals for patients, necessitating mechanisms to restore access post-study.
6) Ensuring equitable access to antiretrovirals across all settings, including those populations historically underserved in terms of healthcare access.

These reasons underscore the ethical imperative to provide PTA to essential medications, particularly within the realm of antiretroviral therapy, where access disparities are especially pronounced.

This author raises a crucial point regarding the determination of who should bear the obligation of providing PTA. Some potential candidates exist, including the trial sponsor, the researchers themselves, the local government of the trial site, or the national health system. Logically, it seems that the pharmaceutical company sponsoring the trial, which stands to profit from the drug's eventual commercialization, should assume responsibility for PTA. It would be impractical to burden the local government with this obligation, particularly if the drug is not yet available in the country's market while the sponsoring pharmaceutical company reaps profits elsewhere.

One could contemplate the case whether a pharmaceutical company might incur losses by guaranteeing PTA for an effective drug without available alternatives. While this scenario may seem improbable, as a highly effective drug with no alternatives would likely yield substantial profits upon market launch, there could be niche cases where the company's profit margins are not significant. However, such scenarios are less likely for drugs with viable alternatives or those targeting minor pathologies, which typically do not entail PTA obligations. In essence, while the responsibility for PTA may theoretically rest with various entities, the pharmaceutical company sponsoring the trial emerges as the most logical candidate, given its vested interest and potential for profit from the eventual commercialization of the drug.

For drugs with readily available alternatives or those targeting conditions that are considered less severe or impactful, the ethical imperative for PTA may be diminished. Consequently, the financial considerations for the pharmaceutical company in providing PTA may also be less significant. Overall, while there may be situations

Exploitation and Developing Countries. The Ethics of Clinical Research (Princeton University Press, 2008), 286–314.

25 Sofaer and Strech, "Reasons Why Post-Trial Access to Trial Drugs Should, or Need Not Be Ensured to Research Participants."

26 P. Andanda and J. Wathuta, "Human Dignity as a Basis for Providing Post-Trial Access to Healthcare for Research Participants: A South African Perspective," *Medicine, Health Care and Philosophy* 21, no. 1 (2018): 139–55.

27 J. Millum, "Post-Trial Access to Antiretrovirals: Who Owes What to Whom?" *Bioethics* 25, no. 3 (2011): 145–54.

where a pharmaceutical company's profit margins are not substantial due to market factors such as competition or the nature of the targeted condition, these scenarios may not typically entail significant PTA obligations. However, it remains essential for pharmaceutical companies and stakeholders to carefully consider the ethical implications and societal impact of their decisions regarding access to medications developed through clinical trials.

Transitioning to the critique of a stringent PTA mandate, it is pertinent to revisit the events surrounding the 2000 rendition of the Declaration of Helsinki, which mandated the provision of researched products in cases where their efficacy was demonstrated during experimentation. Following its promulgation, a chorus of dissent emerged, notably from major pharmaceutical entities in affluent nations. McMillan and Conlon adeptly encapsulate the crux of the opposition to an exacting PTA mandate: "The problem is that the Helsinki recommendation is strongly worded and if a treatment is for a chronic illness the cost of having to supply treatment to research participants on an indefinite basis may mean that valuable developing world research is not conducted".[28]

Roy's report on the meeting in Pretoria (2001), convened by the World Medical Association (WMA) itself, documented the participation of numerous pharmaceutical representatives, FDA delegates, and medical associations from affluent nations.[29] One of the primary contentions raised against a universal PTA mandate was the assertion that pharmaceutical companies operate primarily for profit rather than philanthropic endeavors. Additionally, it was argued that the absence of guaranteed PTA in less developed countries did not exacerbate the existing situation, as these regions would have been devoid of access to such drugs even if they had not been tested there. The health policy milieu surrounding the Pretoria gathering was grave, given the FDA's ultimatum to cease enforcing the Declaration of Helsinki as the ethical standards for trials conducted outside the United States.[30] This ultimatum heavily influenced the 2004 WMA Clarification Note, significantly watering down this requirement.

In the early stages of the PTA debate, a prominent argument aimed at undermining the PTA obligation was the concern over "undue inducement." This argument posited that offering experimental subjects access to a drug they could not otherwise obtain might unduly influence their decision-making capacity and could potentially compromise the validity of informed consent. Emanuel, Currie, and Herman's 2005 article in *The Lancet* adeptly debunked this line of reasoning by highlighting the inherent benefits to patients in most cases where PTA was offered. Moreover, they astutely noted that it is the responsibility of the ethics committee approving the research protocol to assess whether there are any ethical concerns regarding the recruitment of research subjects. Furthermore, the article provides a comprehensive examination of not only undue inducement but also other potential moral dilemmas that may arise in research conducted in underdeveloped areas, including coercion, exploitation, injustice, deception, inadequate information provision, and misunderstanding. This comprehensive analysis underscores the complexity of ethical considerations inherent in conducting research in such contexts.[31]

When delineating the moral imperative to share the findings of an experiment, the specialized literature presents various options, some of which have been previously referenced, drawing from the UNESCO Universal Declaration on Bioethics (2005).

In their 2012 article, Wang and Ferraz propose several potential avenues: (1) referral of participants to continue treatment through their usual public or private healthcare provider; (2) enrolment in other research studies; (3) subsidized purchase; (4) provision of treat-

28 J. R. McMillan, C. Conlon, and Nuffield Council on Bioethics, "The Ethics of Research Related to Health Care in Developing Countries," *Journal of Medical Ethics* 30, no. 2 (2004): 204–6, at 206.

29 P. G. De Roy, "Helsinki and the Declaration of Helsinki," *World Medical Journal* 50 (2004): 9–11.

30 F. Hellmann, R. de L. C. Bernabe, and N. Homedes, "Post-Trial Provisions in the Declaration of Helsinki: A Watered-Down Principle That Needs to Be Strengthened," *Journal of the Royal Society of Medicine* 115, no. 11 (2022): 420–23.

31 E. J. Emanuel, "Undue Inducement: Nonsense on Stilts?" *The American Journal of Bioethics* 5, no. 5 (2005): 9–13.

ment free of charge by the sponsor for a short period; (5) provision of unused drugs; (6) creation of a fund for the treatment of participants through donations from non-governmental organizations, developed countries and the pharmaceutical industry; (7) creative strategies such as the sale of artwork from the host country of the research; (8) collaboration with local governments and other organizations; or (9) a mix of two or more of these mechanisms.[32]

Numerous authors, such as Schipper and Colona, highlight the "open-label extension study" as the most pragmatic approach to guarantee PTA. This methodology entails providing the investigational drug (assuming its efficacy and safety have been established) following the completion of Phase III trials until the product obtains marketing authorization.[33] However, a significant challenge arises, particularly in less developed countries, as the likelihood of securing market approval for the product is often low, and the time to market can be prolonged. Consequently, the "open-label extension" strategy may not be a viable long-term solution in such contexts.[34]

Before coming to the conclusions of this article, I think it is important to underline the work of Zong in his 2008 article. He proposes a nuanced approach, advocating for a case-by-case determination of provision, and suggests that PTA should be obligatory in situations where research participants stand to benefit from the intervention under investigation and lack alternative means of access.

5. Conclusion: moral obligation and impossibility of formulating a single rule

Reviewing the guidelines of numerous national and international institutions engaged in biomedical research reveals a spectrum of perspectives concerning PTA. While some assert a definite obligation, many others emphasize the importance of exerting every feasible and rational effort to maintain access to research products post-study.[35]

It becomes evident that a universal standard for PTA cannot adequately address the complexities of all potential cases. However, it is increasingly apparent that if a pharmaceutical company anticipates its inability to provide an effective drug necessary to treat a significant pathology after the research is over, without a viable alternative available in the intended research location, it would be prudent to exclude that specific site from the protocol. Moreover, it is the responsibility of the research ethics committee tasked with protocol approval to ascertain the appropriate form of PTA required for each unique case, as outlined in the UNESCO Universal Declaration on Bioethics and Human Rights of 2005 and in the latest version of the Declaration of Helsinki. The absence of sufficient PTA provisions should serve as grounds for the non-approval of a protocol. By adhering to such ethical principles and practices, we can strive to uphold the welfare and rights of research participants while advancing biomedical research responsibly.

We can conclude with a last theoretical point which should be developed in another article. The concept of differentiated provision highlighted by Zong prompts us to reflect on a fundamental aspect of the issue under examination and many others within the realm of bioethics and clinical ethics: the underlying moral reasoning. The prevalence of principle-based bioethics has often predisposed us to an ethics grounded in norms, seeking precise formulations capable of encompassing all, or most, scenarios. However, in scenarios such as the one concerning the moral obligation of study sponsors to provide the experimental product post-trial if proven effective, we recognize the impracticality of prescribing a singular solution. Instead, the "optimal" course of action is contingent upon numerous circumstances specific to each individual experiment. This realization underscores why virtue ethics, rather than norm-based

32 D. W. L. Wang and O. L. M. Ferraz, "Pharmaceutical Companies vs. the State: Who Is Responsible for Post-Trial Provision of Drugs in Brazil?" *Journal of Law, Medicine & Ethics* 40, no. 2 (2012): 188–96.

33 Schipper and Colona, "Post-Trial Access to Treatment."

34 P. Naidoo et al., "Mechanisms for Sustainable Post-Trial Access: A Perspective," *South African Journal of Bioethics and Law* 14, no. 3 (2021): 77–78.

35 Zong, "Should Post-Trial Provision of Beneficial Experimental Interventions Be Mandatory in Developing Countries?"

ethics, is preferable in such contexts. While virtue ethics acknowledges the importance of rules, it endeavors to discern the most appropriate course of action within the unique circumstances of a given situation, time, and place. This course of action may diverge from what is deemed optimal in alternative contexts. The determination of these actions is influenced by the virtuous aims set forth by individuals and organizations. It is evident that a company driven primarily by profit maximization will often seek to evade its obligations to research subjects whenever possible. Conversely, a more solidary company, while still taking into account profits essential to its sustainability, will prioritize the welfare of individuals involved in research, particularly the subjects, placing them at the forefront of its concerns.

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References

P. Andanda and J. Wathuta, "Human Dignity as a Basis for Providing Post-Trial Access to Healthcare for Research Participants: A South African Perspective," *Medicine, Health Care and Philosophy* 21, no. 1 (2018): 139–55

J. Blackmer and H. Haddad, "The Declaration of Helsinki: An Update on Paragraph 30," *CMAJ : Canadian Medical Association Journal* 173, no. 9 (2005): 1052–53

E. R. Cohen et al., "Reporting of Informed Consent, Standard of Care and Post-Trial Obligations in Global Randomized Intervention Trials: A Systematic Survey of Registered Trials," *Developing World Bioethics* 9, no. 2 (2009): 74–80

K. Cook, J. Snyder, and J. Calvert, "Attitudes toward Post-Trial Access to Medical Interventions: A Review of Academic Literature, Legislation, and International Guidelines," *Developing World Bioethics* 16, no. 2 (2016): 70–79

H. L. Cho, M. Danis, and C. Grady, "Post-Trial Responsibilities Beyond Post-Trial Access," *The Lancet* 391, no. 10129 (2018): 1478–79

R. E. da Silva et al., "The Patient's Safety and Access to Experimental Drugs after the Termination of Clinical Trials: Regulations and Trends," *European Journal of Clinical Pharmacology* 74, no. 8 (2018): 1001–10

S. M. Dainesi and M. Goldbaum, "Provision of Investigational Drug after Clinical Research – Review of Literature, National and International Guidelines," *Revista Da Associação Médica Brasileira (English Edition)* 57, no. 6 (2011): 696–702.

P. G. De Roy, "Helsinki and the Declaration of Helsinki," *World Medical Journal* 50 (2004): 9–11

D.C. Doval, R. Shirali, and R. Sinha, "Post-Trial Access to Treatment for Patients Participating in Clinical Trials," *Perspectives in Clinical Research* 6, no. 2 (2015): 82–85

E. J. Emanuel, "9. Addressing Exploitation: Reasonable Availability Versus Fair Benefits," in E. J. Emanuel and J. Hawkins, *Exploitation and Developing Countries. The Ethics of Clinical Research* (Princeton University Press, 2008, 286-314

E. J. Emanuel, "Undue Inducement: Nonsense on Stilts?" *The American Journal of Bioethics* 5, no. 5 (2005): 9–13

J. J. Fins et al., "Identity Theft, Deep Brain Stimulation, and the Primacy of Post-Trial Obligations," *Hastings Center Report* 54, no. 1 (2024): 34–41

L. H. Glantz et al., "Research in Developing Countries: Taking 'Benefit' Seriously," *The Hastings Center Report* 28, no. 6 (1998): 38–42

C. Grady, "The Challenge of Assuring Continued Post-Trial Access to Beneficial Treatment," *Yale Journal of Health Policy, Law, and Ethics* 5, no. 1 (2005): 425–35

L. Gostin, "Ethical Principles for the Conduct of Human Subject Research: Population-Based Research and Ethics," *Law, Medicine & Health Care: A Publication of the American Society of Law & Medicine* 19, no. 3–4 (1991): 191–201

F. Hellmann, R. de L. C. Bernabe, and N. Homedes, "Post-Trial Provisions in the Declaration of Helsinki: A Watered-Down Principle That Needs to Be Strength-

ened," *Journal of the Royal Society of Medicine* 115, no. 11 (2022): 420–23

N. Homedes and A. Ugalde, "Availability and Affordability of New Medicines in Latin American Countries Where Pivotal Clinical Trials Were Conducted," *Bulletin of the World Health Organization* 93, no. 10 (2015): 674–83

R. Iunes et al., "Who Should Pay for the Continuity of Post-Trial Health Care Treatments?" *International Journal for Equity in Health* 18, no. 1 (2019): 26

E. B. Jimenez et al., "Availability of Post-Trial Access in Clinical Trials: A Review of Clinical Trial Protocols Submitted to the Research Ethics Board of the University of the Philippines Manila," *Current Medical Research and Opinion* 35, no. 11 (2019): 1849–55

A. Y. Malik and C. Foster, "The Revised Declaration of Helsinki: Cosmetic or Real Change?" *Journal of the Royal Society of Medicine* 109, no. 5 (2016): 184–89

J. R. McMillan, C. Conlon, and Nuffield Council on Bioethics, "The Ethics of Research Related to Health Care in Developing Countries," *Journal of Medical Ethics* 30, no. 2 (2004): 204–6

J. Millum, "Post-Trial Access to Antiretrovirals: Who Owes What to Whom?" *Bioethics* 25, no. 3 (2011): 145–54

P. Naidoo et al., "Mechanisms for Sustainable Post-Trial Access: A Perspective," *South African Journal of Bioethics and Law* 14, no. 3 (2021): 77–78

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, "The Belmont Report: Ethical Principles and Guidelines for the Commission for the Protection of Human Subjects of Biomedical and Behavioral Research," 1978

R. Páez and J. E. Garcia De Alba, "International Research and Just Sharing of Benefits in Mexico," *Developing World Bioethics* 9, no. 2 (2009): 65–73

I. Schipper and S. Colona, "Post-Trial Access to Treatment: Corporate Best Practices," 2015, at https://philpapers.org/rec/COLPAT-9 (Access: 31-X-2024)

N. Sofaer and D. Strech, "Reasons Why Post-Trial Access to Trial Drugs Should, or Need Not Be Ensured to Research Participants: A Systematic Review," *Public Health Ethics* 4, no. 2 (2011): 160–84

I. M. A. Van Roessel et al., "Post-Trial Access in Maternal Vaccine Trials," *American Journal of Perinatology* 36, no. S 02 (2019): S41–47

D. W. L. Wang and O. L. M. Ferraz, "Pharmaceutical Companies vs. the State: Who Is Responsible for Post-Trial Provision of Drugs in Brazil?," *Journal of Law, Medicine & Ethics* 40, no. 2 (2012): 188–96

Z. Zong, "Should Post-Trial Provision of Beneficial Experimental Interventions Be Mandatory in Developing Countries?," *Journal of Medical Ethics* 34, no. 3 (2008): 188–92.