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# ARTICLE

## Exportation of unethical practices to low and middle income countries in biomedical research

## Exportación de prácticas éticas deficientes de investigación biomédica hacia países con menor grado de desarrollo

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## Abstract

Substandard ethical practices in biomedical research have been exported from more developed countries to less developed countries worldwide. The term for this practice is called ethics dumping, which can be described as exporting, in clinical research, sensitive ethical practices from more developed to less developed countries, with subpar requirements and other economic or operational advantages that would be inadmissible in developed countries. Examples for this practice are described, as well as its origin, receptivity, and perpetuation, together with some preliminary guidance and advice in order to work towards possible solutions for this ethically sensitive issue in the future.

**Keywords**: clinical research; ethics; ethics dumping; research ethics; research bioethics.

## Resumen

En la investigación biomédica se han exportado prácticas éticas deficientes desde los países con mayor grado de desarrollo hacia países con menor grado de desarrollo a nivel mundial. El término para esta práctica es el de deposición de prácticas éticas ("Ethics Dumping"), que puede describirse como el hecho de exportar, en la realización de investigación clínica, prácticas éticas sensibles del tipo de exigencia disminuida y otras ventajas de índole operativa y económica no aceptables en países desarrollados, hacia países no desarrollados. Se describen ejemplos de esta práctica, así como su origen, receptividad, y perpetuación, junto con algunas guías preliminares y recomendaciones, con el fin de trabajar hacia el futuro en busca de posibles soluciones para este asunto éticamente sensible.

**Palabras clave**: investigación clínica; ética; deposición ética; ética de la investigación; bioética de la investigación.

# 1. Introduction

## Exporting substandard ethics to developing countries

That substandard ethical practices in biomedical research are continuously exported to the developing world have been the topic of discussion in the research ethics literature for some time now.[1, 2, 3, 4, 5] It is only recently, however, that the concept of "ethics dumping" has received regulatory attention.[6] The term "dumping" seems to have been borrowed from the realm of commerce and economics referring to the practice of exporting goods at prices lower than the home-market prices. It is used in the context of international commerce law where a company fixes for its export goods a price lower than the cost of producing them in the importing country, thus driving local competitors out of business.[7] Even though the term has negative connotations, free-market supporters consider the practice beneficial for consumers.

In clinical research, "ethics dumping" designates the risk of sensitive ethical issues being exported from more developed countries (MDCs) to less developed countries (LDCs) in pursuit of potential economic and operational advantages under conditions deemed unacceptable in MDCs. The European Commission defines it as "the exportation of research practices that would not be accepted in Europe on ethical grounds".[6] For more than two decades, some research organizations have been seeking to conduct their work in LDCs, regardless of whether the drugs tested can be marketed under local economic and organizational conditions.[8, 10] One of the advantages researchers see in these countries, precisely, are large numbers of patients who are completely new to treatment and significantly easier to recruit.[11]

A clearer definition is needed in order to understand what we mean by "ethics dumping". We can begin by expanding the definition "exporting ethically unacceptable practices to developing countries": in clinical research, this refers to the practice of exporting to developing countries research practices that may be ethically unacceptable in developed countries. The motivation for this exportation are usually economic and/or operational advantages.[12, 13]

What would constitute examples of unethical practices being exported by countries who commission clinical research abroad? Relatively well-known instances of this would be exerting undue pressure by offering researchers incentives to recruit patients faster, or individual cases in which legal, economic, operational or competitive standards are lowered to the advantage of MDC organizations dominant in LDCs. Another example would be working with payment rates that fail to match first-world rates or compensate for the cost of operation for LDC researchers and facilities. Yet another instance of these practices is the adoption of double standards, as discussed by Macklin, for

example.[14] What the term implies here is that, with the intention of avoiding the pitfalls associated with the differences in clinical research between MDCs and LDCs, certain practice standards are applied in the former, while entirely different standards are applied in the latter. Table 1 shows some examples of ethics dumping and its consequences. Note that we are not claiming that all practices are "unethical". To do so, we would need to make a case for each of these examples. In the table below, we simply wish to demonstrate the undesirable consequences of the various ethics dumping practices.

| Ethics dumping practice | Examples (ethical and unethical) | Undesirable consequences |
|---|---|---|
| 1. Patient recruitment issues | Recruiting babies for epilepsy studies and taking advantage of mothers' commitment to watch over their children for the 24 to 48 hours needed to complete the study. | Abusing parents' and guardians' availability, good faith and mistaken beliefs about potential treatment benefits. |
| 2. Methodological issues | Using placebos in cases where lower treatment standards in LDCs seem to justify it. The argument is that patients are not being exploited: since their condition does not actually worsen, it is not necessary to administer active medication. (8)*) | Abusing the good faith of patients; denying patient -participants of a proven intervention even when such exists. |
| 3. Advantages in dealing with authorities and Research and Ethics Committees (RECs) | Studies with varying degrees of risk can be difficult to carry out in MDCs due to tighter restrictions. RECs in LDCs might be less rigorous. | This practice entails increased risk to participants from LDCs. |
| 4. Recruitment advantages | Studies deemed burdensome or problematic in other countries because of increased patient discomfort/burden (e.g. complex laboratory testing or use of IV markers). | Abusing patients who often are unaware of the absence of benefits and the increase in risks. |
| 5. Advantages due to increased prevalence of certain diseases | Studies of the antibiotic treatment of diarrhea conducted in the North of Mexico. (e.g. Studies in the 90s). | Some diseases are more prevalent in LDCs. The availability of subjects is abused, with little compensation or for LDCs. |
| 6. Economic advantages | Studies are less costly in LDCs, though the burden of work is the same. | Taking advantage of the lack of negotiating power and the availability of local research teams. |
| 7. Logistical advantages (e.g. implementation times) | Shorter implementation times, accelerated patient recruitment achieved by offering questionable incentives to researchers, which may be unacceptable in MDCs. | Inadequate compensation, unethical in MDCs. |

Table 1. Ethics dumping practices and examples of practices.

* The use of placebos has to do with using or not the best methods available worldwide as control treatment. In the Nevirapine controversy it is shown that the rule of best methods available worldwide and, as a result, the limitation of using placebos to conditions in which there is no medical alternative under no circumstances are good rules, but there are some exceptions in which research may be carried out while at the same time participants are not exposed to exploitation" (15).

An additional manifestation of ethics dumping emerges as a more subtle issue when it comes to recruiting patients for research. In MDCs, participating in research may be seen as a moral obligation, a commitment by subjects to help find more and better treatments.[16] In the less developed world, by contrast, the agreement to take part in a study is often predicated on patients' hope of solving their medical problems or improving their health. This issue has been detailed in a very comprehensive study[17] (See also: International Conference on Harmonization, ICH-E6, specifically the definition in 1.61: Vulnerable subjects).[18] Clinical studies thus make "therapeutic promises" they may not actually fulfill, but participants may not be fully aware of this when they sign the informed consent.[19] It is the nature of clinical research to not claim expected therapeutic benefits for the present or future health of patients, with the exception of phase IV clinical trials.[20] The phenomenon wherein therapeutic benefit is expected in clinical trials has been described in the medical literature as "therapeutic misconception": study participants believe that their individual therapeutic needs will be considered during clinical trials, a faulty understanding of the nature of clinical trials coupled with the unreasonable expectation of receiving medical benefits.[21] It is worth noting that the many unsolved issues in clinical research (such as the use of placebos, or justifications unconvincingly rooted in the principle of equipoise)[22] only add to the problems raised by the exportation of substandard ethical practices. This in turn only deepens rifts of misunderstanding and abuse.

The moral obligation to take part in a trial, as may be understood in MDCs (i.e. the importance of contributing in the search for more and better treatments[23] is invalidated by the fact that these new therapies might not be available, at least in the short term, to LDCs population. When they do become available, it is likely that their market price will continue to make them unavailable for as long as patents are valid. Generic versions, though less expensive, will still be unaffordable for some. Informed consent requirements and therapeutic promises are thus unequal, insufficient and surely unjust.

## 2. Origins of ethics dumping

With the aim of arriving at a viable solution, we must first investigate the causes of ethics dumping. The answer is many-sided. First, there is an increased demand for clinical services in MDCs. This puts pressure on existing research capacities to grow, in a context of research saturation and patient shortage.[23] Second, strict requirements and regulations in MDCs are subject to additional pressure from other, equally urgent factors as are economic and marketing factors. There follows pressure to conduct research with simpler regulatory requirements and at lower cost.[24]

Next, we should consider the effects of a certain automaticity in southbound exportation. Together with the exported research, countries where requirements tend to be more flexible and authorities more lenient also receive the pressure and demands typical of MDCs if LDCs wish to be competitive hosts of clinical trials.[25] The demand for research services in LDCs are increased, along with the possibility that sponsors or their intermediaries may act unfairly characterized by uneven commercial interactions between countries and unequal negotiations. The risk is that this kind of interaction will result in exploitation, i.e.

> *…when wealthy or powerful individuals or agencies take advantage of the poverty, powerlessness, or dependency of others by using the latter to serve their own ends (those of the wealthy and the powerful) without adequate compensating benefits for the less powerful or disadvantaged individuals or groups.*[26]

To sum up, the context of research is subject to pressure from authorities and corporations. Many of these demands can be traced back to economic interests, as the term "time-to-market" denotes. Such pressure can move international clinical researchers to apply double standards (moral and otherwise) and resort to ethics dumping, a phenomenon in which unequal ethical practices inadmissible in MDCs are offshored to the developing world. The consequences include a sense of disappointment, frustration and lack of empathy, and misunderstandings in transnational clinical research, with a loss of prestige and moral credibility for both sides of the equation.

Also at the root of ethics dumping are faulty negotiations. LDCs might not be familiar with the standard of rights and obligations to be observed in specialized transnational research negotiations. Other issues which perpetuate the exportation of substandard ethical practices will be discussed in the following sections.

Finally, an allegory extracted from family dynamics might help explain the "natural" course MDCs follow in the attempt to deal with increased pressure. In some families, one parent is less strict than the other when it comes to demands like pressure to succeed in school and restrictions placed on the children's behavior. The natural course of action for a child seeking to obtain special permissions or approval will thus be to appeal to the parent that offers less resistance. Though both parents are equivalent as authority figures, their authority is exercised differently, with one of them offering less resistance. It can be understood in this same sense that the search for new research territory "naturally" (also) looks to developing countries.

## 3. Receptivity of LDCs to ethics dumping

LDCs become receptive to ethics dumping for a number of reasons. Some of the most widely acknowledged include the need for growth and international recognition, economic needs, the quest for scientific and technological development, and a duty to stay in line with parent corporations. Other less studied motivations have to do with cultural nuances, such as the perception of flattery combined with feelings of inferiority, and the resulting pressure to demonstrate ability, worth and equality.

Receptivity in LDC regions is reinforced by the relaxed regulations we have mentioned, plus some operational advantages. An undeniable fact is that patient availability is greater in these regions, together with accommodating management, reduced costs, and qualified, efficient personnel with unmet economic needs.

We can group all these factors under "LDC receptivity". Together with "reduced regulatory and economic demands," this preserves a relationship that can lead to the exportation of unacceptable ethical practices. In summary, the pursuit of clinical research shifts from its origins in the direction of LDCs seeking increased speed, reduced costs and advantages in implementing and carrying out studies as far as ability (and goodwill) will allow it.

## 4. Perpetuation of ethics dumping

We will now attempt to surmise on the possible contributing factors to the long-term prevalence of these practices. Note that a systematic approach to look into the causes for the perpetuation of ethics dumping would have yet to be done in future research.

Ethics dumping subsists and even change shape over time mainly because the ethics that MDCs apply outwardly are seldom revised by LDCs. This depends on the perception that practices of varying acceptability on both sides should be geared towards fulfilling the demands and priorities of the sponsoring agents. In other words, the idea is to solve a host of different and varying problems of conducting clinical research. An additional complication is that LDCs often approach negotiations with little knowledge of accepted and acceptable practices, guidelines and valid premises in MDCs. Also, there is much to be desired with regard to community engagement or participant consultation[27] in global research. LDCs are thus unable to identify ethics dumping, its origins and its forms. LDCs place a blind trust on MDCs and adapt to their precepts easily.

## 5. Working out our differences

We have seen that there are various issues related to the installment by receptivity of LDCs and how this leads further to the perpetuation of ethics dumping.

We think that there is a need to intervene on existing norms, both in procedural and tangible matters (the former being conflict resolution, changes in terms, etc., and the latter compensations, duties, and performance). Requirements should be regulated to harmonize with the developing world, encouraging openness and transparency in negotiations, and eliminating the unfair exportation of ethical practices such as double standards.

We could start by harmonizing our understanding of patient involvement, supporting the conditions of moral obligation to participate in studies. Though it seems complicated, this is not impossible. The search for homogenous visions and regulations (as part of a proposed harmonization conference) could include negotiating the terms of participation by LDCs, as well as establishing clear guidelines for solving issues of ethics dumping. Additionally, we should commit to sharing study results and benefits more equitably, so as to ensure fair conditions for LDCs.

In the recent CIOMS Guidelines[28] of mid-2016, in GUIDELINE 2: "Research conducted in low-resource settings", there are recommendations in order to tackle different issues partially discussed already; for instance, the use of comparators provided in our table. In the comments section "Responsiveness of research to health needs or priorities", it states: "a question about responsiveness might arise if a study of a new intervention is planned for a community in which established effective interventions for a health condition are not locally available and the new

Intervention has features that would make it difficult to implement in that community. In such cases, researchers and sponsors must consider whether the study could be made more relevant to local health needs." It further states: "If the knowledge to be gained from the research is intended for use primarily for the benefit of populations other than those involved in the research, the responsiveness requirement is violated". Further, this last sentence would address the compliance that is necessary with community interests, brought about in general form originally by the Declaration of Helsinki. In general, the valuable recommendations brought about by this last review should help to tackle ethics dumping further in some of its most salient features. Other recommendations in Guideline 2, as is the building of local research capacity or to ensure an overall fair distribution of the benefits and burdens of the research, should well serve the purpose of preventing this phenomenon.

The issue of informed consent should also be on our agenda. Informed consent needs to be justified and culturally sensitive to the conditions of LDCs. A "showtime" approach, in which patients are called upon and dismissed as needed, leaves a community's real needs unaddressed when the study concludes. In LDCs, this might be interpreted as abandonment, creating a sense of emptiness or alienation, with no perceived gain. Such issues could be eliminated with clear guidelines as to personal and community benefits, in accordance with the latest version of the Declaration of Helsinki.[29]

Most importantly, we should endeavor to eradicate ethics dumping to the best of our ability, through a clear discussion and understanding of existing differences. Practices such as offering payments to expedite recruitment, for example, might prove too complex to solve in the short term, but we could outline feasible solutions to correct imbalances wherever possible, without resorting to unacceptable practices, always seeking to eliminate abusive, unfair or exploitative behavior.

Technical and methodological aspects should also be on our agenda. In a provocative review, Contopoulos-Ioannidis[30] examines the differences between MDCs and LDCs in relation to the over or underestimation of risks. The study concludes that there is a need to prioritize and standardize the documentation and reporting of harms in all randomized trials, both in MDCs and LDCs.

Our first priority should be instituting a negotiating table guided by a bilaterally established agenda, with the goal of harmonizing differences. We must keep in mind the need for open, honest and transparent discussion of the existing differences that have so far been the cause of many misunderstandings and obstacles (or even disrepute). Such difficulties, however, can and should be overcome. The ongoing practice of ethics dumping is, undoubtedly, in need of being addressed and solved as soon as possible. The advice and rules expressed in many ways through different channels at present should make it more difficult in the future to trespass the desired limits, getting closer to the ideal of complying with what is feasible, and at the same time what is decent, fair and just in biomedical research as it is practiced in developing countries.

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