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Critical analysis of the principle of benefit and harm

Flávio Rocha Lima Paranhos¹, Volnei Garrafa², Rosana Leite de Melo³

Abstract

Benefit and harm are essential elements in any consideration of bioethical nature. Preventing harm is already present in the Hippocratic Oath as a central concern. The purpose of this article is to critically analyze the principle of maximizing benefit and minimizing harm. It takes as its starting point the article of the *Universal Declaration on Bioethics and Human Rights* (UDBHR) dedicated to this principle. First we propose a more general, philosophical approach grounded in classical authors such as Kant and Mill, but also contemporaries such as Ruwen Ogien and Edgar Morin, among others. We then present several approaches to bioethics in the Brazilian and international literature. At that point we were able to observe a clearly misconceived bias, in that a rather limited concept of benefit is proposed by certain American authors. Using arguments from principlism to defend their positions, these authors (unintentionally) reinforce the need for another standard for bioethical evaluation, the UDBHR.

Keywords: Bioethics. Beneficence. Risk-benefit assessment. Critical path method.

Resumo

Estudo crítico do princípio de benefício e dano

Benefício e dano são elementos essenciais em toda ponderação de natureza bioética. A prevenção de danos está presente no juramento de Hipócrates como preocupação central. O objetivo deste artigo é analisar criticamente o princípio de maximizar benefício e minimizar dano, tendo como ponto de partida o artigo da *Declaração Universal sobre Bioética e Direitos Humanos* (DUBDH) que trata do tema. Propomos, primeiramente, uma abordagem geral, filosófica, a partir de autores clássicos, como Kant e Mill, mas também contemporâneos, como Ruwen Ogien e Edgar Morin, entre outros. Seguimos com algumas abordagens da literatura bioética brasileira e internacional. Nesse ponto, pudemos observar um viés claramente equivocado, na medida em que é proposto um conceito bastante limitado de benefício, por parte de alguns autores norte-americanos. Ao valer-se de argumentos tradicionalmente principlistas para defender suas posições, tais autores reforçam (involuntariamente) a necessidade de outra via de ponderação bioética, a DUBDH.

Palavras-chave: Bioética. Beneficência. Avaliação do benefício-risco. Método do caminho crítico.

Resumen

Estudio crítico del principio de beneficio y daño

Beneficios y daños son elementos esenciales de cualquier ponderación de carácter bioético. La prevención de daños ya está presente en el juramento hipocrático como una preocupación central. El propósito de este artículo es analizar críticamente el principio de maximizar el beneficio y minimizar el daño, tomando como punto de partida el artículo de la *Declaración Universal sobre Bioética y Derechos Humanos* (DUBDH) que se ocupa de la temática. En primer lugar se propone un carácter más general, filosófico, de los autores clásicos, como Kant y Mill, así también como los contemporáneos como Ruwen Ogien y Edgar Morin, entre otros. Seguimos algunos enfoques de la bioética brasileña y la literatura internacional. En este punto se observa un sesgo claramente equivocado, ya que propone un concepto más limitado de beneficio por parte de algunos autores estadounidenses. Al hacer uso de los argumentos tradicionalmente principlistas para defender sus posiciones, estos autores destacan (involuntariamente) la necesidad de otro camino de ponderación bioética, la DUBDH.

Palabras-clave: Bioética. Beneficencia. Medición de riesgo. Método de la ruta crítica.

1. **Doutor** flavioparanhos@uol.com.br 2. **Pós-doutor** garrafavolnei@gmail.com 3. **Doutoranda** rosanaleitemelo@gmail.com – Universidade de Brasília, Brasília/DF, Brasil.

Correspondência

Flávio Rocha Lima Paranhos – Rua 38, nº 300, Marista CEP 74150-250. Goiânia/GO, Brasil.

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In applying and advancing scientific knowledge, medical practice and associated technologies, direct and indirect benefits to patients, research participants and other affected individuals should be maximized and any possible harm to such individuals should be minimized^{1,2}.

Concerns regarding the minimizing of possible harm and the maximizing of potential benefits to patients are not a recent development, with the issue mentioned in the following extracts from the Hippocratic Oath:

*With regard to healing the sick, I will devise and order for them the best diet [treatment], according to my judgment and means; and I will take care that they suffer no hurt or damage. (...) Nor shall any man's entreaty prevail upon me to administer poison to anyone; neither will I counsel any man to do so*³.

However, it can be argued that the necessity of an ethical approach truly gained strength in the 20th century, following the atrocities of WWII, revealed at the Nuremberg Trial in 1945. From this moment on it was no longer enough to deal only with patients in general, but a specific type of patient, namely medical research volunteers, had to be considered. This was because one of the atrocities that surfaced in the period was the fact that during the war, research had been carried out on extremely vulnerable individuals, without such individuals giving their consent.

The discussions that surrounded the trials, and the conclusions drawn from them, led to the creation of the Nuremberg Code in 1947. This document, in turn, served as an inspiration for the publication of the Belmont Report in the late 1970s, produced by the then recently created National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, in the USA. Published in 1979, the basic principles of the Belmont Report were as follows:

- Respect for persons – Respect for persons incorporates at least two basic ethical convictions: firstly, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy;
- Beneficence – The term “beneficence” is often understood to cover acts of kindness or charity that go beyond strict obligation. In the Belmont Report, beneficence is understood in a stronger

sense, as a requirement. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm and (2) maximize possible benefits and minimize risk;

- Justice – There are several widely accepted formulations of just ways to distribute benefits and harm. These are (1) to each person, an equal share, (2) to each person, according to his or her individual need, (3) to each person, according to individual effort, (4) to each person, according to societal contribution, and (5) to each person according to merit⁴.

Such principles were redefined, in the same period, by Beauchamp and Childress in their book “Principles of Biomedical Ethics”, the 7th English edition of which was published in 2013. This includes four principles, which became known as the “Georgetown Mantra”, namely: *beneficence, non-maleficence, respect for autonomy and justice*. Principlism, as the concept became known, eventually became one of the most common approaches to the issue of bioethics – understandable, given its practical nature.

It was not long, however, before questions concerning such principles arose, casting doubts over their central role in ethical questions, some of which will be discussed herein. In the context of a negative reaction to the failure of the principles to respond to the scope and plurality of bioethics, the Universal Declaration on Bioethics and Human Rights (UDBHR)¹ was created by UNESCO in 2005. Article 4 of the declaration deals with benefit and harm, and will be discussed here in greater depth.

Philosophical Approaches

It is assumed that ethics can be divided into descriptive ethics and normative ethics, with the first representing an attempt to understand the moral nature of actions and judgments, and the second going further by proposing rules of conduct. In suggesting such rules, the consequences of the act may or may not be considered, resulting, in turn, in consequentialist and non-consequentialist rules. The so-called utilitarian philosophers are representatives of the first approach, with the German philosopher Immanuel Kant a figurehead for the second.

When reading Article 4 of the UDBHR, it is soon apparent that the utilitarian ethic applies, as the text deals with maximizing benefits and minimizing harm. In fact, the formula for attempting to max-

imize benefit for the greatest number of people is typical of utilitarianism: *Ethical universalism, or what is usually called utilitarianism, takes the position that the ultimate end is the greatest general good - that an act or rule of action is right if and only if it is, or probably is, conducive to at least as great a balance of good over evil in the universe as a whole*⁵.

It would be wrong, however, to consider that the principle of maximizing benefits and minimizing harm applies only to the utilitarians. The non-consequentialist philosophy of Kant can also be invoked to defend a patient, particularly if based on one of his categorical imperatives: *Act in such a way that you treat humanity, whether in your own person or in the person of any other, never merely as a means to an end, but always at the same time as an end*⁶.

Ruwen Ogien⁷, inspired by John Stuart Mill⁸, took utilitarianism to its logical conclusion, asking: *Why should we be concerned with victimless moral crimes? And what are such crimes?*” Such crimes are those where there is no harm to others, that is, that are of concern only to the person that commits the crime, or persons in agreement (masochism, sadomasochism), or abstract concepts (such as “homeland”, “nature”, “God” “society” and “man”). They also include drug and alcohol use and even suicide.

Edgar Morin, in turn, warns of the dangers of the blindness of science for subjectivity, for itself and for ethics. For Morin, *barbarism lies within in us. Our civilization rests on a base of barbarism (...). Resistance to the cruelty of the world and resistance to human barbarity are two sides of ethics. The first requirement of ethics is not to be cruel or barbaric. It makes us call for tolerance, compassion, gentleness, mercy*⁹.

A moral obligation towards others, which may include maximizing benefits and minimizing harms, is taken still further by Levinas: *One of the key themes of Totality and Infinity is that the intersubjective relationship is an asymmetrical relationship. In this sense, I am responsible for another, without expecting reciprocity, even if it costs me my life. Reciprocity [or the lack of reciprocity] is not the responsibility of another. It is precisely when the relationship between another and myself is not reciprocal that I become subjugated to another; and I am a ‘subject’, especially in this sense. I am responsible for everything*¹⁰.

However, when considering philosophical premises, there is one major danger of which researchers and members of an ethics review committee (ERC) should be aware: non-compliance with Article 4 of the UDBHR based on the transfer of re-

sponsibilities. By this reasoning, a researcher would be justified in delegating responsibility to a superior (the party funding the research, for example) for an act which is harmful to the subject of research (or withholds a benefit). In this case, we can turn to Hannah Arendt, who, when analyzing the trial of the Nazi Eichmann, *argued that being just a cog in the machine is not a valid excuse, because, as the judges explicitly pointed out, in the courtroom it is not a system, a history, a historical trend, or an ism, such as anti-Semitism, that is on trial, but a person, and if the defendant is by chance an official, he is accused exactly because even an official is still a human being, and it is for this quality that he is on trial*¹¹. In the same way, a researcher cannot invoke the obligations imposed by a sponsor, or a health professional use the orders of the director of a hospital, as justification for harm caused or a benefit withheld.

Bioethical approaches

The importance of clearly defining what “minimize risks” means is made evident in an article by Miguel Kottow: *Minimizing risks. There are at least three rhetorical strategies proposed, which are preferably used to soften the severity of potential risks when recruiting research subjects: a) inadequate information; b) comparison with risks of activities outside the research; c) classification of the risk as minimum*¹². The author is concerned with the rhetoric used when presenting risks, either orally or in writing, in free and informed consent forms (FICF). The concern also extends to the possibility of “maximizing” the possible benefits when inviting a volunteer to participate in a research project, including implying benefits not covered by the study.

At the conclusion of his article, Kottow expresses his concerns about the direction taken by medical research, citing the greed that determines the unjust 90:10 formula (90% of resources are used to investigate and solve only 10% of the medical problems of richer nations). This was also the concern of Lorenzo et al¹³ and Garrafa et al¹⁴ when criticizing the Declaration of Helsinki (DH)¹⁵, following the significant changes that have been made since 2008, and of reports of clinical trials conducted in “peripheral countries” that may have caused harm to the volunteers involved, revealing a dangerous loosening of ethical research standards in poorer countries.

The authors argue that particular protection should be given to the especially vulnerable, a

classification which is defined by a lack of income, information, knowledge and technology; a lack of access to public bodies and other social representation; a limited network of social relations; a diversity of beliefs and practices in relation to the society around one; old age and physical disabilities. Given the ineffectiveness of the latest versions of the DH to protect research subjects, the authors suggest the adoption of the UDBHR as a general framework document, recommending that each country creates, alone or with the support of trusted partners, its own resolutions and legislation.

One of the most controversial and heavily criticized points of the 2008 version of the DH refers to the use of placebos (paragraph 32): *The benefits, risks, burdens and effectiveness of an intervention must be tested against the best proven intervention, except in the following circumstances: 1) The use of a placebo or no treatment is acceptable in studies where there is no proven intervention. 2) When, for scientifically strong methodological reasons, the use of placebo is necessary to determine the efficacy or safety of an intervention, and patients do not become subject to any serious risk or irreversible damage from either placebo or no treatment. Extreme care must be taken to avoid abuse of this option*¹⁵. It may be noted from the wording of the passage quoted that the authors of this version of the DH realized that the text was open to abuse through a potentially “loose” interpretation of the paragraph.

The following paragraph (33) is also problematic: *At the conclusion of a study, patients who took part in the study have the right to be informed of the results and to share in any benefit arising from the study, or other appropriate care or benefits*¹⁵. Article 15 of the UDBHR is much more assertive and comprehensive in dealing with the sharing of benefits, being not only specifically aimed towards such an end, but also including the following language:

- a) The benefits resulting from any scientific study and its applications should be shared with society as a whole and throughout the international community, particularly in developing countries. For this principle to be fulfilled, benefits can assume one of the following forms:
 - (i) special and sustainable assistance and recognition of the groups and individuals that participate in a research study;
 - (ii) access to quality health care;
 - (iii) the offer of new diagnostic and therapeutic modalities or the products of the research;

- (iv) the support of healthcare services;
- (v) access to scientific and technological knowledge;
- (vi) access to research training facilities;
- (vii) other types of benefits arising from the principles contained in the present Declaration.

- b) The benefits should not constitute improper inducement to encourage participation in the study¹.

Evaluation of the possible risks involved in a study, Van Ness believes, *is of fundamental importance when conducting an ethical review of a clinical trial. However, in clinical research, particularly international trials, risk is not the only form of uncertainty at stake, nor is it an absolute factor; the expected benefits, just as with the risks involved in everyday activities or standard therapies, are defined by the concept of minimum risk*¹⁶.

Lorenzo and Garrafa questioned whether *international clinical studies are truly beneficial to peripheral countries, noting that the production of medicine is historically connected with the capitalist production system, and disregards the primordial interests of populations, especially poorer citizens. These authors also criticize more recent versions of the DH, which leave a space for methodological justifications, which, in turn, follow winding roads, seeking, in truth, to maximize private interests, allowing the production and marketing of 70% or 80% of similar medications for chronic conditions or pre-morbid states*¹⁷.

A proper characterization of “benefits” and “harm” is crucial and has direct consequences, both for the patient and especially for research study volunteers. The concerns of a number of Latin American authors, therefore, are both pertinent and urgent.

Discussion

The preceding literature review shows that a number of factors have contributed to the need for an international declaration of principles that are more in tune with global reality, particularly in more vulnerable countries. As well as principlism having been proven to be epistemologically insufficient, traditional protection mechanisms, such as the DH, have in practice been adapted to accommodate para-ethical and even, in a way, parascientific interests. Such interests follow the same paths as ethics and science, but such paths do not truly cross. While

they may draw closer to one other from time to time, they will never meet, as such interests are ultimately focused solely on profit.

The danger in relying solely on the Georgetown Principles for decision making, or even to justify decisions made, can be seen clearly in an article in the International Association of Bioethics magazine by Benjamin Sachs¹⁸. Sachs' aim was to *demonstrate (...) that several rules [of conduct in research] are not supported in the principles [canonical]*. The author goes on to attack the guidelines set out in different declarations, including the Belmont Report and the DH. In the case of the section of the Belmont Report that advises minimizing risk, Sachs refers to the principle of non-maleficence, arguing that this rule should not apply: *Suppose a researcher proposes expose a subject to unnecessary risk, and the subject agrees [for example, because he was well paid for it]. What would justify saying, as the rule of minimizing risk demands, that the researcher is doing something wrong?*¹⁸

Regarding the access of the patient to the medication in question following the end of the study (quoting the Declaration of Helsinki), Sachs¹⁸ draws on two principles, that of non-maleficence and of justice, again questioning the validity of both. The manner in which he rejects the principle of justice is revealing of his thinking and the moral blindness of a number of bioethics scholars in the United States, the cradle of principlism. According to this line of thinking, the "benefits" propitiated by the participation of a subject in a study would, in themselves, be sufficient to repay him or her for such participation.

An example of this would be the case of an individual who took part in a study of glaucoma medication: the simple fact of having access to diagnostic tests and consultations with experts through participating in the study should be considered sufficient as a "benefit". In other words, the subject should be satisfied with this "handout". Sachs does not mention that more tests than necessary are often performed, turning the "handout" into a headache for the participant (some individuals even abandon studies as a result). Even where a study is theoretically streamlined and incorporates only essential tests, such tests would still not "benefit" the participant, but would instead be obligated by the researcher. The "benefit" will be the outcome of the research, directly or indirectly. If, to minimize harm, it is necessary to provide treatment for adverse effects, either directly or indirectly related to the research, this is still not a benefit, but merely a reduction of harm.

An analysis of the case of AIDS vaccines further explains this thinking. In 2010, a number of articles were published in the publication *Developing World Bioethics*¹⁹⁻²¹, revealing a serious ethical problem: the treatment of individuals participating in an anti-HIV vaccine study who became infected even after having taken part in the study. As the drug was tested on subjects with both a high and low risk of becoming infected, and as its effectiveness was not 100% (and certainly not 100% proven), a number of individuals would inevitably become infected, even among those who received the vaccine.

However, the public health system of the African countries involved in the study could not meet demand for medication, as the disease had reached epidemic proportions, leaving patients without expensive antiretroviral treatment. Such cases clearly characterize an investigative double standard – much criticized by many Latin American authors – as such methodologies would never be approved by ethics committees in developed nations.

This "epistemological inadequacy" is again seen in the attempt to solve the problem by using the principle of beneficence, described in one of the articles cited²⁰. While the principle of beneficence still applies in this situation, it is clearly insufficient. In this sense, the so-called bioethics of protection, as conceived by Schramm, offers a more comprehensive and therefore more effective approach:

*The bioethics of protection chooses as its primary mission the support of those excluded from public health policies, and to ensure a reasonable quality of life for one and all. Due to the difficulties of coordination between the descriptive and normative levels, the bioethics of protection adds another level, namely the protective level. But this is not exactly a third level, and, is in fact in all probability is the most basic level, the first level, as it refers to suffering that is avoidable, and therefore should be avoided, as this level can be considered one in which pleasure and pain are confused, intuitively, with good and bad*²².

It is, as we see, the complete reversal of the obligation and right to benefit, all too present in the cited clinical trials conducted in Africa; the preponderance of the "needy" over "greedy"¹⁴.

The position of Edwards²³ reflects such misguided thinking, being based on scientific arguments yet focusing on profit. Believing that the absence of obligation of a participant in a study results in damage to research in cases where individuals choose to

leave the study, the author proposes the creation of a regulatory agreement which provides for penalties to be applied to research participants who leave before the end of testing. It is based on the notions of causing “harm to science”, “harm to other patients” and “harm to oneself”.

The last of these “harms” occurs because, when leaving a study, the participant is put at risk of potential harm that may yet occur as a result of his or her participation in the study. Such notions of harm are certainly conceptually idiosyncratic, and their analysis deserves attention. *Harm to oneself* as the result of departure from a study falls within the scope of minimizing risk by simply ensuring, before participation begins, that the necessary precautions are put in place to protect against adverse events occurring as a result of the study, both during and after participation, which may be terminated either by the withdrawal of the subject or by the end of the study. After all, it is more than reasonable to ensure the protection of the subject from events connected (directly or indirectly) with participation in the study, regardless of when any harm arising from these event may occur. It is noted, however, that Edwards’ text, a “target article” was not accepted without protest, and received some editorial opposition²⁴.

The maximizing of benefits and the minimizing of risk of harm to the research subject is interpreted by Rosamond Rhodes as limitation and interference in scientific progress: *To find treatments that can be made widely available and to quickly find reliable answers to research questions can be good reasons for performing studies that disrespect* [the principle of beneficence]²⁵. This vision of beneficence as a maximizer of benefits, without losing sight of the need to minimize risks – while closer to that of UD-BHR –, is perfunctory and inappropriate.

Just as Lorenzo et al¹³ proposed that clinical trials which are not related to the health priorities of the country in which they are performed should be charged a fee, so Ballantyne²⁶ proposed the creation of a global research tax. The money generated from this tax would not be distributed equally, but instead would be shared according to a principle called “*maximin*”, where the benefits are maximized for those who are worse off, or the most vulnerable. In a way, however, this is a somewhat Anglo-Saxon version of bioethical protection.

A rather unusual and counterintuitive method of maximizing benefits for a patient (note the use of the term patient, rather than research subject) was proposed by Tavaglione and Hurst²⁷: lie. This argu-

ment is based on rejecting the non-consequentialist argument that telling the truth is a duty, by using the opposing consequentialist argument of the obligation to lie for the good of the patient. In this case, it might mean lying to the organization responsible for paying for treatment (a health plan or the government) to ensure coverage and continuity of care. Of course, this proposal has not been comfortably accepted.

The problem raised by Garrafa et al¹⁴, regarding the double standards applied to the use of placebos in vulnerable populations, was also considered by Haire, Kaldor and Jordens²⁸, who asked, “How good is “good enough”?”, in reference to two large studies conducted in African countries that achieved positive results for the prevention of HIV infection: CAPRISA 004 and iPrEx. Both strategies included the use of antiretroviral drugs administered locally/vaginally (CAPRISA) and orally (iPrEx).

The question of the authors is based on the fact that while the two studies returned clinically and statistically significant results, the drugs involved have not replaced placebos as standard treatment in subsequent trials. The justification for this is the requirement that at least two large clinical trials with significant positive results must be carried out before a drug can be used in this way. However, the authors note that the drugs used in the tests are already commercially available in countries outside Africa, and that the populations of non-African countries, which have better access to information, can even use them. But the most serious problem is the continued use of a placebo while waiting for another study to confirm the effectiveness of the drug, which indicates that the lack of more efficient testing of other new HIV prevention drugs among populations with a high incidence of AIDS determines continued placebo use – a fact that raises important ethical questions.

Final considerations

The drawing up of the *Universal Declaration on Bioethics and Human Rights*, which featured a significant Brazilian contribution²⁹, was a historic moment in the development of global bioethics, as important as the Nuremburg Code, the Helsinki Declaration and the Belmont Report. However, in contrast with such other demonstrations of the importance of ethical issues, the UD-BHR is wider ranging, more democratic, in the global sense of the word, and more concerned with the needs of the

most vulnerable, even covering issues such as the social responsibility of governments³⁰.

It can be seen from this literature review, however, that there are still many situations in which the most vulnerable are at risk. It is no coincidence that these situations occur in the poorest countries. Efforts must be made to reduce the vulnerability of such populations, thus enhancing the benefits due to them and the minimizing the risk of harm to which they are potentially exposed.

It is also noted, both in terms of threats to vulnerability and the defense against such threats, that the traditional principles of the Belmont Report are insufficient. In this regard, however, Article 4 of the UDBHR leaves no doubt. It speaks, effectively and without subterfuge, of the need to maximize direct and indirect benefits to patients, research subjects or other affected individuals, as well as minimizing the possible risk of harm to patients and research subjects.

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Participation of the authors

Flávio Rocha Lima Paranhos participated in the literature review, the writing of the first versions of the text and the final review. Volnei Garrafa was responsible for the study design, participated in the literature research and the final review. Rosana Leite de Melo participated in the literature research and the writing of the first versions.



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