Biomedical research on human subjects from the perspective of public ethics: the social value of research

La investigación biomédica en seres humanos desde la ética pública: el valor social de la investigación

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Abstract

Biomedical research on human subjects in Middle-Low and Low Income Countries (LMICs or LICs) has aroused the interest of bioethics in how to achieve an equitable distribution of benefits. Questions of justice have been addressed under the concept of «reasonable availability» or «fair benefit sharing». However, the inadequacy of this approach lies in the fact that public issues have been addressed from the bioethical principles of beneficence, non-maleficence and justice. Recently, the subject has been approached from the standpoint of social justice, but the approach of ethics referring to populations or public ethics is a pending subject to be studied in greater depth. This paper aims to point out the importance of this complementary approach. It is intended, from public ethics, to see the need to focus on the social value of the knowledge generated, and to offer some guiding criteria to be detected by Research Ethics Committees.

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1. Introduction

Biomedical research on human subjects in Lower Middle-Income or Low-Income Countries (LMICs or LICs)[1] has raised interest in bioethics on how to achieve an equitable distribution of benefits, with the interaction of several agents with very different power, interests and needs: on the one hand there is the pharmaceutical industry, which sponsors much of the research in LMICs, seeking knowledge to improve therapeutics, but clouded by large commercial interests and, on the other, the reality of the localities where such research is carried out, generally conducted in public medicine, with a low research budget, with their health research programs and priorities that often do not coincide with those of industry, with a good research staff but with insufficient facilities and equipment, and with a large demand of patients in need of diagnosis and treatment.

The conflict of interest that exists in this briefly described reality has been characterized as a primary scientific interest, which is clouded by another commercial or secondary interest. The issues of justice inherent in such a conflict of interest have been addressed in bioethics under the concept of «reasonable availability» or «fair distribution of benefits», emphasizing a fair distribution of the benefits generated by the research among the participants (1). However, the inadequacy of this approach lies in the fact that questions of a public nature have been dealt with from the standpoint of the ethics of the doctor-patient relationship –beneficence and non-maleficence–, or involving third parties –particularly distributive justice–. The subject has been dealt with from the point of view of social justice, but the approach to ethics referring to populations, or public ethics, is a pending subject for further exploration (2). An example of this is the use of data obtained in research, which has traditionally been limited to the personal sphere, as stated in the document of the World Medical Assembly in Taipei in 2016 (3). Today, it is requested that the data obtained be studied from the perspective of public ethics or, at least, from the collective, as indicated by the latest LMICs standards (4).

Research ethics has focused on informed consent and the protection of personal data, but public ethics is now questioning whether collective data can be disseminated because of a need so great as to justify making the data public (5). Consider the case of data that can be shared for the development of vaccines against SARS-CoV-2, as well as mechanisms to take vaccines off patent for the duration of the emergency. Or to generate collateral research to help mitigate the effects of the pandemic (6).

Outside the field of public ethics, another related aspect that has been worked on is to evaluate the social value of the research; that is, whether it generates knowledge that avoids harm (7) and has an impact in favor of the local community (8). This is knowledge oriented to banish those injustices that make the population sick; for example, the social determinants of health that make the health burden of certain diseases much greater for LMICs. It has to do with what kind of knowledge will be generated and for whose benefit (5).

Finally, although there is some awareness of the duty to ensure social value, in the practice of Research Ethics Committees (RECs) it is not known what this is or how to measure it. Moreover, issues of justice are often far from the experience of IRBs, which are limited to aspects of informed consent or the risk-benefit balance (9).

This paper aims to highlight the importance of a complementary approach to the reasonable availability and fair benefit-sharing approaches, given that the issue of fair benefit-sharing in biomedical research has been widely addressed in the bioethics literature (1, 9-13). The aim, from the perspective of public ethics, is to highlight the need to focus on the social value of the knowledge generated, and to offer some guiding criteria to be detected by RECs.

2. Social value of research

The term social value is very plural and ambiguous. In research ethics, it has been conceived as generating knowledge that leads to improvements in health. For E. Emmanuel, knowledge and social value are indistinguishable. Emmanuel, as well as the improvement it produces in health as the instrumental value of research (13).

The Declaration of Helsinki affirms the need to generate benefits in every research: *The primary purpose of medical research on human subjects is to understand the causes, evolution and effects of diseases and to improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments)* (14). And the World Medical Association's Manual of Medical Ethics devotes a subheading to the need to incorporate social value assessment into the ethical review process of human research protocols. It states that:

> One of the most controversial requirements of a medical research project is that it contribute to the welfare of society at large. It was widely accepted that advances in scientific knowledge were of intrinsic value and needed no further justification. However, since the resources available for medical research are increasingly inappropriate, social value has emerged as an important criterion for deciding whether a project should be funded...The social value of a research project is more difficult to determine than its scientific merit, but it is not a good reason to ignore it (15).

The 2016 LMICs standards say of the social value of research:

> The scientific and social value of research can be difficult to quantify, but is generally founded on three factors: the quality of the information produced, its relevance to significant health problems, and its contribution to the creation or evaluation of interventions, policies, or practices that promote individual or public health (4).

Some say that the social value of research lies in the knowledge generated or in the type of information produced, which can be of various forms; for example, progressive, translational (16), humanitarian, clinical, present or future information, and so on. It must benefit local populations, and not only those who resemble the clinical trial participants. However, what they all mean is that social value has to do with values shared by a set of individuals or held by a society, in contrast to individual conceptions. It gives the concept of benefit the notion of appreciation, esteem or importance. While confusing, it offers more than the concept of benefit. It presupposes that the IRB questions the research question of the clinical trial in the sense of whether it will benefit the population involved, or whether it subjects the research subjects to unacceptable risks or harms (7, 17, 18).

Other authors conceive it as the knowledge valued by a society, and for which research subjects may submit to certain risks of harm in scientific experiments. This eliminates ill-considered research or research that seeks superfluous or redundant knowledge. For knowledge to have social value, it must include an instrumental or applicable component, which will depend on the context of each place; for example, prevalence of a disease, public resources for health, local infrastructure, etcetera (19).

The social value has to operate on the basis of the intended or expected output of a clinical trial, and the anticipated value that can be placed on the knowledge that will be generated. Although there is no access to the knowledge that will be produced, it is possible to know what type of knowledge will be created and how robust the findings will be, which diseases are investigated and how relevant the results are for a given population, as well as how to obtain them (20).

Offering immediate therapeutic benefits from a clinical trial is difficult to guarantee because of the uncertainty of obtaining them. A Phase I trial will take many years to progress to new stages, and may not reach completion, let alone success. But what can be asked of research in advance is that the social value generated be significant for the society in which it will be carried out.

For the same reason, in some cases, rather than evaluating the risk/benefit ratio, the risk/social value ratio must be considered, given that the damage to which the research subjects may be exposed must be offset by the value of the research in terms of its nature or significance; that is, by the knowledge generated for a given place, beyond the direct benefits.

This is evaluated in advance. It requires not only methodological rigor in the design, but also to see how the population will benefit. It also assumes that the research can evolve towards generating knowledge that translates into concrete clinical or therapeutic improvements for the people in the place where the research is being conducted or transferred. And, finally, the validity of a trial is evaluated by experts (17).

More recently, D. Wenner has argued that social value lies in subjecting research to the principles of social justice and going beyond the transaction between researchers, industry, health authorities and research subjects. Social value implies that the research has a clinical impact on the research community and, therefore, that the sponsors are in some way responsible for the health of the research community (20). Other authors criticize this view for having unclear theoretical foundations, or because it is publicly funded research and because it has a minimal risk for withholding consent from participants. In other words, the social value is justified from a soft rationale, but not from a strong one (21, 22). The issue needs more debate and a better social justice rationale. In Latin American countries it will have to do with the responsible use of limited resources and the avoidance of exploitation (23).

When research is carried out in places where epistemic injustice is the main feature (24),[2] the benefits must be designed not to reinforce the established order, for example, the creation of drugs as an extension of patents, but which are not an improvement over the *gold standard* and which will be marketed at prices inaccessible to the majority (1), but to generate knowledge aimed at banishing those injustices that make the population sick. Therefore, it will have to do with existing resources, with health priorities, with the prevalence of diseases, with what type of knowledge will be generated and for the benefit of whom, etcetera.

Collaboration between researchers and community builds the principle of collaborative research, which assumes that the community where the research is conducted should favor and participate in the research effort. Collaborative research indicates to the community whether the scientific effort will help to solve their problems and to define whether it is acceptable to develop the research in their own environment (25). It is clear, therefore, that this problem escapes from the field of research ethics to become part of the ethics of public health, health policies and health systems (8).

3. Some causes of the forgetting of social value in an investigation

a) Explanatory individualism (26)

Disease and its treatment are often considered from the individual point of view, i.e. as a condition precipitated by isolated factors, which have to do with each person, his biography, his genes, and his behavior. The disease is due to definite entities independent of the subject who will suffer from them, generally from specific pathogenic organisms and, therefore, the cause is of natural origin. But it is not related to the society in which one lives and to the social factors that determine its possibilities of action, such as, for example, the social class to which one belongs. Specifically, the poor have less access to prevention because they devote most of their salary to meeting their basic needs, without the capacity to invest in better quality food.

The biomedical model operates on the basis of a single level, the individual, and expresses a form of individualism in its explanation. It studies short pathways confined to the human body, without recognizing any supra-individual level or social process as part of the long causal chain in the production of disease. As a result, this model studies the individual in a vacuum, disconnected from others; it focuses only on what happens in and within each individual. Populations are understood only as a collection of individuals without emergent properties. Public health is only the sum of the health of each individual, without recognizing the causal factors of the distribution of a disease in the population.

b) Forgetfulness of causal or explanatory factors of the disease (26)

Another reason for the neglect of social value in research is the neglect of «the causes behind the causes» or the so-called social determinants of health; that is, those causes that make a population vulnerable: income inequality, lack of access to education, health care, etc. In middle or low-income countries, and particularly in Latin American bioethics, the social vulnerability of many populations that participate in research, for example, motivated by the need for medical care or the belief that they will be treated for their condition, has been pointed out. These situations are little recognized by medical personnel or researchers due to the predominant biomedical model in which they have been trained.

The biomedical model only recognizes certain patterns of distribution of disease and mortality in humans, outside of biological, behavioral causes or those due to certain exposures to external factors. Social factors are outside its scope of understanding, and taking them into account is considered an unscientific or political practice. Social classes are considered only insofar as they have some particular disease that characterizes that entity; for example, hunger as a disease of poverty, but it does not analyze inequality in the distribution of wealth as the predominant cause. It is interested in the biological, behavioral or external cause of hunger, but not in the cause of unfair distributive patterns. For the same reason, it does not consider the cause of why there are different health outcomes according to social class.

It is therefore a model with a restricted explanatory capacity and with little capacity to recognize distributive patterns and, therefore, it will prescribe partial health policies.

From the ethical point of view, the above limitations will mean that these types of conditions will be seen as tragic situations, proper to the action of charity, but not as something to be prevented or a motive for action from the social point of view (27).[3] Therefore, they would not fall within the realm of social justice, since they are not situations in which action should be taken to prevent disabilities or mortality. From the ethical point of view, the crisis of the biomedical model concerns social justice, insofar as it prevents consideration of the action of primary agents that can help to prevent diseases, the burden of which is much greater in certain social conditions.

c) A conflict of interest that is not very evident

Conflict of interest is in fact the tip of the iceberg of a discussion that fails to acquire the dimension it deserves, between the private and the public. It is an issue related to the social value of research, since it is not enough to limit conflicts of interest to the use of private capital in research, but also to their impact on the detection of the social value of research, i.e. their repercussions on the public sphere.

An individual conflict of interest is understood as a situation in which the judgment of a physician, academic, teacher or researcher regarding his or her primary professional interest tends to be unduly influenced by a secondary interest, such as financial gain (28).

Conflicts of interest in research bioethics have been defined as: *a situation in which a professional's judgment concerning his or her primary interest, e.g., the health of patients or the integrity of research, tends to be unduly influenced by a secondary interest, such as financial or personal gain* (29). The Universal Declaration on Bioethics and Human Rights, in Article 15.2, states: *Profits should not constitute undue inducements to participate in research activities* (30).

In this type of definitions, conflicts of interest are limited to the field of conflict between a primary and a secondary interest, such as the pursuit of the researcher's own good over that of the scientist, or the taking of undue economic or other advantage through research. But they do not question other hidden aspects of the established order that place research participants in serious situations of injustice due to their vulnerability, especially when the protocols are carried out in LMICs, in public health institutions or in vulnerable populations due to their ethnic origin, gender or belonging to marginalized groups. These aspects have to do with the non-maleficence that can be generated by taking undue risks, the responsibility to look after social value in advance and with beneficence seen from the perspective of social value.

The primary interest represents adherence to a set of values, among which is the commitment to respect the rights of individuals and, in particular, of the subjects involved in experimentation; it has to do with the private. The secondary interest represents the desire for prominence, power, or simply money, which ends up by obscuring or bracketing a series of values clearly identifiable by all the actors involved in biomedical research and experimentation; it has to do with the public sphere.

If the «primary interest» is simply examined from the harsh demands of the labor market, it is necessary to immediately recognize the fragility and orphan hood of the researcher's conscience, in order to adequately solve the equation posed by the conflict between a primary and a secondary interest.

d) Privatization of knowledge

This theme begins to be made explicit in the discussion on the knowledge economy. What the progress ordered and energized by the knowledge economy disturbs, in a context where privatization takes away from the community the ownership of fundamental means of subsistence, such as water, electricity, agricultural production, etc., is the production of a collective intelligence. «Cognitive capitalism does not seize what is inappropriate, but destroys what the community produces» (8, p. 32), the knowledge that every community is necessarily called upon to produce.

Research robs public medicine of its resources by making use of ongoing research and then privatizing and profiting from it. It uses public medicine's own facilities, patients and researchers (31). Other neglected aspects are the privatization of acquired knowledge that destroys the common ground on which the possibility for knowledge to progress is built. Under this tenor is the common practice of industry to keep secret the knowledge acquired in its research, or the very restricted management of patents.

Research is at the service of a market system that functions on the basis of the dependence it creates between producers and consumers. It dilutes and fragments the community, which is turned into a passive spectator, consumer and client of innovations that determine its present and future life. Much could be said here about the practice of the industry, which is caught between science and the market (1).

Modern biomedical research, given its complexity, can only be carried out «thanks to the involvement of capital (public and private) of enormous dimensions». The involvement of this capital obviously creates a dependent relationship between the physician or researcher who conducts research and the industry that conceives, programs, organizes, finances and ultimately publishes it (8, p. 30).

The conflict is the result of the growing individual interests and private capitals of the industry that privilege unmeasured enrichment over the scientific interest and the common welfare. They use research centers all over the world to carry out research in the shortest possible time and recruit as many patients as possible in order to obtain a patent for a successful drug. As this research is sponsored by the FI, a relationship of dependence is created between industry and local research centers that is difficult to break.

4. A view from the perspective of public ethics

Public health ethics identifies, analyzes and resolves the ethical problems inherent to public health, beyond the individual. It is concerned with populations (race, gender, age, locality, etc.), governmental action, public or collective goods, prevention, and is intrinsically results-oriented. It is related to an essential dimension of well-being, health, to the avoidance of harm that threatens it and to those strategic determinants for its preservation, including those that belong to other non-health fields (2, 6).

Public ethics is concerned with preventing or avoiding harm and promoting well-being. It is also concerned with social responsibility. Such ethical categories, when viewed from the social lens, are not considered from the individual but from the collective, and are therefore relational in nature. Non-maleficence, beneficence and responsibility have to do with concrete relationships of dependence that are not chosen, established between moral agents, individual or collective, but always with public repercussions. Also with the inequitable or repressive modes that are structured in a given society, causing groups of people or social sectors to be harmed or not to be granted the benefits to which they are entitled. For example, it is a matter of considering that research in a population that is vulnerable due to its poverty is much more likely to incur in therapeutic confusion, as the subjects believe that they are receiving treatment and are unable to assess the social benefit, given the magnitude of their need, as their right to health care is not

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satisfied; in other words, it is research under conditions of epistemic injustice.

Specifically, and analogous to the reasons for the crisis of the biomedical model, it is first and foremost a public ethics that focuses its attention not on individuals but on populations, with all that this implies. If populations with unmet primary needs are recruited, it will be very difficult for them to understand the meaning of the procedure to which they will be subjected, i.e. everything related to informed consent. Similarly, populations subjected to conditions with a greater burden of disease should see the knowledge generated reflected in a social benefit that others subjected to the same burden will possibly obtain (32); for example, research on measures for the detection of pre-diabetes, before having already developed symptoms of the disease.

Secondly, public ethics is related not only to the immediate factors that impact the health of a population, but also to the prevention and removal of damage, as well as to the social determinants of health and to those factors that define the society in which one lives (33).[4] Such influences on health are best described in terms of probabilities and risks, and public ethics is thus motivated by a concern for uncertainty and precaution. Thus, in a population where diabetes is endemic, such as Mexico, research protocols should not be based on the search for the «best» therapeutic molecule, but on the probability of efficacy of preventive measures, or on the limitation of risk factors in society. Or based on cost/benefit studies of already marketed treatments that are cheaper and, therefore, more accessible.

In the light of public ethics, biomedical research must take into account the great variability of factors that can make a population dependent; for example, the economic situation, the purchasing power of wages, gender, race, social class, and so on. It must also be in tune with that which goes beyond the aggregate or distributive dimensions, such as the social or environmental determinants of health: the causes that are shared by many and the degree to which these causes are contained, controlled or excluded from a population. For example, investigating the social impact of advertising campaigns for various foods and how they do or do not affect diabetes prevention. Similarly, to study the beneficial impact of advertising campaigns in favor of healthier lifestyles and lower sugar consumption.

Thirdly, public ethics requires collective action, often undertaken by the State; for example, prevention and health care, inasmuch as many ends are impossible to achieve by individuals in isolation. It goes hand in hand with factors related to the lack of prevention or removal of harm, or with the absence of due health protection by the State (34).

Health research is one of the most important inputs to forge a rational and fair response to the problems of backwardness and, above all, to the emerging challenges, which are more complex and more costly to address. Its contribution to the reduction of the burden of disease in our country can, moreover, be improved if it is directed at solving priority problems... (35).

This is health research organized in a strategic, interdisciplinary and interinstitutional manner, beyond the individual, which is what characterizes our country, with the consequent dispersion of the objectives of such studies *...focused on the 21st century, we have in our country as many health research topics as active researchers* (36).

In the bioethics literature, not only in Latin America, but also in the literature with a social perspective, vulnerable populations are those who suffer a greater burden of disease and, therefore, require extra attention or protection. They are identified as social groups that have a relative risk of susceptibility to adverse health outcomes (37). Social vulnerability is the product of conditions of special fragility, in which certain environments or socio-economic situations place the people who suffer from them (38).

The following Table 1 shows in a synoptic way some criteria to assess the adequacy between research and public ethics, and to determine their respective social value (5, 35, 39).

Table 1. Criteria to evaluate the adequacy between scientific research and public ethics and their social value.

	Public Ethics	Social Value
Public benefit	Scientific integrity and social value	Type of knowledge generated: to whom and how the results will be disseminated.
Proportionality	Necessity and the least infringement	That responds to the major health needs.
Equity	Solidarity and reciprocity	Human resources for health research and health risk regulation: improving current health policies, programs and interventions.
Trust	Commitment	Research aimed at the control, prevention and surveillance of risks and diseases.
Accountability	Public justification and transparency	Evaluation of interventions, programs and public policies in all health fields: how the local community will benefit, usefulness and accessibility of the successful drug.

Source: Own elaboration.

Thus, for example, in the case of research on non-communicable diseases:

1. To discover the causes of late diagnosis in priority diseases in Mexico: diabetes mellitus, systemic arterial hypertension, senile dementia, cancer, etcetera.
2. To detect the cost/benefit/effectiveness ratio of the various interventions aimed at improving the quality of medical care.
3. To measure the genetic predisposition to develop them.

4. To study the mechanisms of carcinogenesis and other processes in their development, for early diagnosis and effective treatment.

5. To promote the development of biotechnology for early detection, diagnosis and treatment.

6. Strengthen research in the training of human resources for its study and control (35).

5. Conclusion

International collaborative biomedical research needs to be thought out and regulated from the perspective of public ethics, so that the knowledge generated has an impact in favor of local communities. The classical approaches based on principles read from research bioethics are insufficient, such as reasonable availability or fair distribution of benefits. The public ethics approach focuses on the benefit generated or not for a given population, and not only for specific individuals, so it seems to be a complementary approach in multinational research.

The social value of research has been defined in several ways. One of its main characteristics is that it can be foreseen prior to the research, and that it can be seen in what way the population will benefit from the line of knowledge in order to translate it into concrete clinical or therapeutic improvements.

The social value of research has been forgotten for various reasons, such as explanatory individualism, the neglect of causal factors of the disease, the existing conflict of interest that is little evidenced, and the privatization of knowledge. Public ethics rescues the social value, focusing attention not on individuals but on populations in a given context. The explanatory factors are analyzed from the prevention and removal of harm, as well as the social determinants of health, and the causes that make a certain population dependent or exploited. And it places the State as a central agent in arbitrating the existing conflicts of interest between the public and private spheres.

Finally, the social value of research can be detected on the basis of guiding criteria that help RECs; for example, in the generation of knowledge that includes epidemiological aspects that apply the trial to the community or the relationship of the protocol with the major local health research priorities.

Bibliographic notes

[1] The 2019 World Bank classification of Lower Middle Income or Low Income Countries (LMICs or LICs) is used, since it is universally recognized to conceptualize countries formerly called underdeveloped or developing. This last way of naming them is avoided because it implies a theory of the underlying dependency on the developed, as if the latter were the model to follow, and the underdeveloped need to make a path to be like the former.

[2] Epistemic injustice is one that results from the deficit of education and information. This causes a fundamental disadvantage for people: they lack the necessary resources to understand their social experiences and their exchanges with others. Thus, information and education are epistemic goods. Essential to act in the world.

[3] An example is the population of Tlaxcala, Mexico, which has shown a large increase in the rates of chronic kidney failure. Health authorities encourage kidney transplantation. But it does not allude to the root cause of kidney disease: the contamination of the water in the Atoyac-Zahuapan basin, due to the installation of thousands of industrial companies in the basin together with the labor and environmental deregulation applied by the State. See: National Commission for Human Rights. Recommendation No. 10/2017. Mexico, CNDH. (Accessed on May 8, 2019). Available at: http://www.cndh.org.mx/sites/all/doc/Recomendaciones/2017/Rec_2017_010.pdf

[4] The social determinants of health can affect some areas of well-being, for example, the lack of health care results in the poor health of certain groups; but when there are several determinants, the areas of well-being affected are multiple and do not act individually but rather synergize with each other, causing very complex and difficult to change pictures. The vulnerability of these cadres is structural, that is, it is related to social, economic or political factors that cause large groups to live under situations of domination from which it is only possible to escape.

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