Presidenza del Consiglio dei Ministri

Pharmacological trials in developing countries

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Presentation

As part of the clinical trials being conducted in developing countries, in the context of increasing globalization of research, it is necessary to pay specific attention to the ethical reference criteria in order to safeguard basic human goods and values.

What emerges - even at an international level – is the concern that the "relocation" of the experimentation is activated to reduce costs and simplify paperwork, to facilitate the rapidity and finding of "bodies" to be used to penetrate new markets. The risk is that commercial interests could hide behind scientific interests resulting in forms of bioethical “colonialism”, unfair exploitation due to the differences in scientific-technological knowledge and socio-economic and cultural inequalities.

The NBC Document, starting with an analysis of documents and international guidelines, highlights some elements of ethical importance. The NBC recommends that research should be oriented according to a single ethical standard, an indispensible prerequisite to avoid any form of discrimination in order to ensure health and global justice, and reduce inequality. It stresses, in addition, how international experimentation should constitute a specific sphere within the context of a broader promotion of the defense of fundamental human rights as a whole, with particular attention to the specific needs of populations in particularly vulnerable conditions. For this purpose, the NBC considers it necessary that research should have adequate justification as regards the clinical importance to the country in which the trials are conducted, that there should be a consultation process with the community, the establishment of appropriate procedures for informed consent and that the safety and health of participants should be protected. The Committee believes that research should avoid hidden forms of involvement that take “advantage” of a lack of awareness or state of need and should take into account the health requirements of the population, with solidarity, ensuring to the research participants and, hopefully, to the population as a whole, appropriate assistance even after the trial. Particular attention is placed on the use of placebo which as a rule is considered unjustifiable when treatment is available and on the creation of local ethics Committees.

The opinion was drafted by the coordinators of the working group Profs. Salvatore Amato, Silvio Garattini and Laura Palazzani, and contributions made by Profs. Adriano Bompiani, Lorenzo d’Avack, Antonio Da Re, Marianna Gensabella, Laura Guidoni, Demetrio Neri and the participants of the group, Profs. Luisella Battaglia, Assunta Morresi, Monica Toraldo di Francia.

Valuable contributions to the discussion were proposed by the hearings of Profs. Zeno Bisoffi, Director of the Institute of Tropical Diseases of the Hospital "Sacro Cuore - Don Calabria" Negrar (Verona) and Antonio Gioacchino Spagnolo, Director of the Institute of Bioethics, Faculty of Medicine of the Catholic University of the Sacred Heart in Rome.

The document discussed in the plenary session of the 27th May 2011, was approved unanimously by those present: Profs. Amato, Bompiani, Canestrari, Dallapiccola, Da Re, d’Avack, Di Pietro, Fattorini, Flamigni, Forleo, Garattini,

Gensabella, Guidoni, Mancina, Neri, Nicolussi, Palazzani, Possenti, Proietti, Scaraffia, Toraldo di Francia. Dr. Di Segni and Profs. Luisella Battaglia, Assunta Morresi, and Giancarlo Umani Ronchi, absent at the meeting, have expressed their approval.

The President
Prof. Francesco Paolo Casavola

1. Premise

The NBC considers it important to focus, within the growing process of globalization, on the ethical principles of transnational or international multicenter clinical studies involving the relationship between so-called "developed countries" and "developing countries".

International documents use the terms "developing countries" or "countries of the South" opposed respectively to the "economically developed countries" or "countries of the North". This general and imprecise terminology embraces very different realities which are not simplistically linked to a unique category[1]. However, these expressions have now entered the common lexicon[2] and it is clear to all that the reference is to those countries or to those populations that are particularly "vulnerable"[3] for several reasons: cultural, social, political, legal, religious, etc., mainly attributable to economic underdevelopment that slows down the progress of science and technology and / or broadly configures a different approach towards scientific knowledge, research and the applications of medicine. This condition can be experienced by some populations in different areas on a regular basis, and by others contingently (due to epidemics, natural disasters, famine). Vulnerability also affects those countries which are certainly not under-developed economically, but they are not accustomed to testing and unaware of the ethical and legal rules that govern it. This condition exposes some populations, in the context of drug testing, to a substantial risk of exploitation in terms of people, resources and results.

Effective globalization of research would provide a clear quantitative and qualitative improvement of the clinical horizon of reference and would increase the conditions of justice and equality in the distribution of drugs. Unfortunately what has emerged with increasing frequency at an international level is the concern that the globalization of clinical studies hides only a "relocation" or "outsourcing" of the experimentation, to reduce costs and simplify paperwork, to facilitate the rapidity and finding of "bodies" to be used to penetrate new markets. About ten years ago (December 2000), "The Washington Post" published a six-part investigation on *The Body Hunters* (Angell, 2005) denouncing the serious ethical shortcomings of some forms of experimentation that would never have been allowed in the United

[1]There are countries, which, despite their falling into the category of "developing" countries, have started internal testing programmes with scientific and ethical standards of “good clinical practice”comparable to those of "developed countries". See, as an example, the extensive and demanding experimentation involving the health facilities of various African nations reported in the journal "Lancet" 2010, vol. 376, November 13th *(Artesunate versus Quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomized trial)*. In contrast, there are "countries of the North" which on these issues are still "developing" (eg, countries of Eastern Europe and the Russian Federation).

[2] Cf. Final bibliography.

[3] There is no reference to 'vulnerability' as an ontological condition or personal situation, but to vulnerability as a particular condition experienced by some populations which, for various reasons, may be exposed to undue manipulation of their autonomy through participation in the trials.

States[4] firstly because of the danger involved, and secondly because of the lack of information: patients were not aware of being treated as "*Guinea pigs*". This expression has now become part of bioethical jargon to indicate, in its crudity, the emergence of a situation of vulnerability (not limited, however, to developing countries), which leaves, because of regulatory gaps or institutional contradictions, unprotected the poorest of the poor and the weakest of the weak[5].

This leads to the fear, interpreted by the NBC, that commercial interests could hide behind scientific interests and may take precedence over respect for fundamental human rights, resulting in forms of bioethical “colonialism” and “imperialism”, unfair exploitation and manipulation due to the differences in scientific-technological knowledge and socio-economic and cultural inequalities.

1.1. Bioethical and regulatory references

For a proper evaluation of the issue the following documents are to be considered.

In the context of international documents of the United Nations, the *Universal Declaration of Human Rights* (1948) Articles 1 and 2 refer to human dignity regardless of race and the *International Covenant on Civil and Political Rights* (1966) Art. 7 refers to informed consent in medical treatment. In addition, in the

[4] The articles were inspired by a serious case which occurred in Nigeria in 1996. Taking advantage of the emergence of an epidemic of bacterial meningitis, Trovan, a new, not yet approved antibiotic to be taken orally was used, which deprived the young patients of the standard intravenous therapy whose effectiveness was certain. A similar exploitation of emergency conditions and poverty had been exposed during the Chernobyl disaster.

[5] It is noted that in recent years the number of countries involved in the 'outsourcing' of clinical trials has increased more than tenfold. It is estimated, to give an idea of the phenomenon that more than one third of the drugs placed on the U.S. market have been tested totally outside the United States (Glickman et al. 2009). UNESCO has also denounced the tendency in Europe to recruit *healthy volunteers* from other countries, such as tourists for limited periods of time (Report of the International Bioethics Committee on Consent, May 19, 2007, § 43). Appropriate international organizations have emerged, including several *Contract Research Organizations* (CROs), specializing in organizing, on commission, the trial and its recruitment of patients in all parts of the world (Petryna, 2005) within a sort of "economic viability" (Rose, 2008, p. 54), which includes scientific research and marketing, involves multinational pharmaceutical companies, and individual nations, leading to a unique blend of international and national regulations, universal ethical models and local traditions. The phenomenon of relocation of trials is not new. At the beginning of the twentieth century, Europeans used it the natives of the colonies to perform experiments that would not have been permitted in their own country, while the United States resorted to Cuba (Chamayou, 2008). Even in 1956, to hasten the time of marketing, testing of oral contraception was conducted in Puerto Rico, Haiti and Mexico City. In recent years, there have been increasing reports of undisciplined recruitment of 'bodies', in very poor countries, albeit due to a positive increase in cultural sensitivity, or even to a negative intensification of the phenomena of exploitation, caused by a significant increase in the economic interests of all that concerns 'biocapital', 'genetic piracy' for purposes of patent to collect genetic material for biobanks, the search for organs, the search for `bodies` on which to perform experiments with fictitious or extorted consent due to ignorance or poverty. Recently, experimentation has been carried out mainly in Eastern Europe, Latin America and in Asia.

Universal Declaration on Bioethics and Human Rights UNESCO (2005) there are references to human dignity (Article 3), the direct and indirect benefits for patients participating in the research (Article 4), informed consent (Article 6), respect for human vulnerability and personal integrity (Article 8), equality, justice and equity (Article 10), non-discrimination (Article 11), respect for cultural diversity (Article 12), Solidarity and cooperation (Article 13), social responsibility and health as a fundamental human right (Article 14), international cooperation (Article 24), promoting the international dissemination of scientific information, freedom of movement and sharing of scientific and technological knowledge.

As to European documents one should mention the European *Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine* of the Steering Committee on Bioethics of the Council of Europe (1997) that emphasizes human dignity (Article 1), and the primacy of human well-being over the sole interest of science and society (Article 2), equity of access to healthcare (Article 3), free and informed consent (Article 5), the protection of the people that lend themselves to research (Articles 16-17) and the *Barcelona Declaration on Policy Proposals to the European Commission on Basic Ethical Principles in Bioethics and Biolaw,* 1998) which proposes four fundamental principles of bioethics and the European biolaw: autonomy, dignity, integrity and vulnerability.

The *Charter of Fundamental Rights* of the European Union (2000) appeals to human dignity (Article 1), the right to personal integrity, the respect of free consent, the prohibition of exploitation of the body (Article 3). The standards of "good clinical practice" that regulate drug testing in the world[6] and represent a scientific and ethical quality standard that ensures the acceptability of the data by regulatory authorities, even with the aim of reducing duplication of experimentation, with the understanding that these involve unavoidable risks for the participants, regulations which have given rise to a specific Directive 2001/20/EC of the European Parliament and of the Council of the 4th of April 2001 on the Approximation of the Laws, Regulations and Administrative Provisions of the Member States Relating to the Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use[7], incorporated under Italian law with the Decree of the 24th of June 2003, No. 211 and No. 184[8]. The Additional Protocol

[6] These regulations have been implemented in Australia, Canada, European Union, Japan, in Northern Europe and the United States; in 1995 they were gathered together in a WHO guideline (World Health Organization WHO Technical Report Series, No . 850, 1995, Annex 3 Guidelines for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products).

[7] L. 121/34 Official Journal of the European Communities 1.5.2001.

[8] Cf. also *Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, as amended*; *Directive 2003/94/EC of the European Commission of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use*; *Regulation (EC) No 726/2004 of the European Parliament and of the Council laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency; Directive 2005/28/EC of the European Commission of 8 April 2005 laying down*

Concerning Biomedical Research (2005) of the Convention on Human Rights and Biomedicine (Article 29) refers to the multi-center research and the duty to apply one standard of ethical evaluation.

In the context of international guidelines the ethical criteria of experimentation with particular reference to developing countries have been developed (*International Ethical Guidelines for Biomedical Research Involving Human Subjects* 2002, which updated the 1993 guidelines of the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO); *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects,* in its most recently developed form by the World Medical Association (adopted in 1964, revised in 1975, 1983, 1989, 1996, 2000 and 2008)[9], Working Party for the Elaboration of *Guides for Research Ethics Committee Members* (CDBI, 2010, Rev. 1. 2*); Barcelona Declaration on Policy Proposals to the European Commission on Basic Ethical Principles in Bioethics and Biolaw,* 1998).

The Reports and Opinions of national bodies that must be reported include: the Report of the Department of Health and Human Services, Food and Drug Administration, *Human Subject Protection; Foreign Clinical Studies not Conducted Under an Investigational New Drug Application*, Federal Register, Vol. 73, No 82,

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principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products; *Regulation (EC) No 1901/2006 of the European Parliament and the Council, as amended, on medicinal products for paediatric use*. Cf. also *Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use (revision 2) as required by Article 18 of Directive 2001/20/EC*; *Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions* (EudraVigilance – Clinical Trial Module) (revision 1) as required by Article 11, Article 17 and Article 18 of Directive 2001/20/EC; *Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use* (revision 1) as required by Article 8 of Directive 2001/20/EC*; Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial* (revision 2), as required by Article 9 (8) of Directive 2001/20/EC; *Detailed guidance on the European clinical trials database* (EUDRACT Database) as required by Article 11 and Article 17 of Directive 2001/20/EC, CT 5.1 Amendment describing the development of EudraCT Lot 1 for 1 May 2004 and CT 5.2 EudraCT core dataset.

[9] In 2005 the two organizations created a study group to implement the 'good clinical practice' in drug research being conducted in countries with limited resources Joint CIOMS/WHO Drug Development Research in Resource-limited countries: How to succeed in the implementation of Good Clinical Practice Guidelines, Draft CIOMS found on htp:// www.cioms.ch/activities/frame_drugdeveloprpt14dec2005.htm. See also the European Medicines Agency (EMEA) Committee for Medicinal Products for Human Use (CHMP), Guideline on Clinical Trials in Small Populations, CHMP/EWP/83561/2005; Guideline on Conduct of Pharmacovigilance for Medicines Used by the Paediatric Population (June 2006) and World Health Organization, Operational Guidelines for Ethics Committees That Review Biomedical Research (Geneva, 2000) and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

April 28 (2008); opinion expressed in ethical lines *Ethical Aspects of Clinical Research in Developing Countries* of the European Group of Ethics in Science and New Technologies, European Commission (2003); the ethical concepts outlined in the views expressed by national ethics committees (National Bioethics Advisory Commission, *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries*, Report and Recommendations, Bethesda, Maryland, vol. I, 2001, Nuffield Council on Bioethics, *The Ethics of Research Related to Healthcare in Developing Countries*, 2002 and the Comité Consultatif National d'Etique pour les Sciences de la Vie et de la Santé, *La coopération dans le domaine de la recherche et équipes françaises biomedical entre équipes de pays en voie de développement économique. Rapport* 1993).

In light of these indications, the NBC expresses some ethical considerations and recommendations.

2. The bioethical problem of International experimentation: from general principles to specific criteria

The phenomenon of relocation of trials is not new. In recent years, there have been increasing reports of undisciplined recruitment of "bodies", in very poor countries, albeit due to a positive increase in cultural sensitivity, or even to a negative intensification of the phenomena of exploitation, caused by a significant increase in the economic interests of all that concerns "biocapital", "genetic piracy" for purposes of patent to collect genetic material for biobanks, the search for organs[10], the search for "bodies" on which to perform experiments with fictitious or extorted consent due to ignorance or poverty. Much experimentation, as has been said, is conducted in the most backward countries in order to reduce costs and shorten the length of the research, given the greater ease in recruiting volunteers, reduced burocracy and different regulations for the approval of research protocols. Recently, experimentation has been carried out mainly in Eastern Europe, Latin America and in Asia.

The subjective condition therefore must be that experimentation on human beings in these countries, as well as in the countries of the North, can be justified in the first place, if it results in real progress in the cognitive ability to cure human beings and, secondly, and simultaneously, if such progress is achieved through a genuine ethical process that minimizes the increased risk of biomedical and pharmacological trials in developing countries being conditioned by economic policies, related to the market and the profit criterion.

The NBC believes that the general ethical principles of experimentation on human subjects[11] - recognized in international documents - should be applicable everywhere, without making a distinction between more or less developed areas, to avoid unequal treatment, considered ethically unacceptable as detrimental to universal justice. Trials in developing countries must meet the same scientific and ethical standards of developed countries: no deviation or modification is justified in terms of principles.

[10] Cf. NBC, *Motion on the sale of organs for transplantation*, 18th of June 2004.
[11] Cf. NBC, *The experimentation of drugs*, 17th of November 1992.

The necessity for the application of general principles to be adapted to the needs of different contexts, should however be highlighted, on the basis that the universally shared principle that experimentation in developing countries should be primarily oriented to meet the real health needs of the communities or populations on which it is carried out. In the field of experimentation, as, indeed, in that of health, one needs to know how to relate to “the other” and ensure cultural identity when this contributes to social balance and the personal development of that country. In reality, it is a question of facing the problems of research as well as those related to access to the protection of health, starting from the real needs of vulnerable populations, clearly more affected by certain diseases and therefore with specific health requirements. In some countries, poverty makes people so vulnerable that often they find it difficult to express their needs, or they do so with resignation, and even humiliation.

In these populations, it is a case of following the “spirit” of general ethical principles, as it is actually practically impossible to follow them “literally”. This does not mean accepting a “double standard” of ethics: on the contrary, it means reiterating that the ethical standard should be “unique” as concerns principles. What is evident in ethical terms, is, that the contextualization and specific interpretation of general principles should not determine a reduction of the fundamental requirements for protection of the human being. This “additional” ethical reflection is necessary in countries where objective living conditions, such as poverty, lack of access to basic services for survival and health, also influence the field of development of intellectual capacity, forcing populations into situations of illiteracy, poor education, poor level of scientific-technological knowledge and ethical development.

2.1. Justification for the clinical relevance of research for the country where the experimentation is conducted

Each drug trial requires scientific justification, as the expected benefits to be gained must outweigh the risks to which the individuals subjected to experimentation are exposed. In the sphere of international experimentation, in addition to the medical and scientific relevance in general, a further criterion must be added, because of the particular vulnerability of the population.

Ethically, the programming of research by a researcher, team of researchers, or research organizations, is fully justified if they cover diseases present only in the population on which experimentation is being carried out, or when these diseases are present in both the promoting country and the host country, and in the latter it is generally more widespread, with higher morbidity, mortality and disabling outcomes.

Regulatory powers should not allow experimentation for diseases that are prevalent in other countries and not in the country where the testing is being conducted: international testing should be considered as a priority in relation to the specific interests and priorities of the health of the populations of the host country. A preliminary assessment of the impact of the trial in the host country is indispensible, as is the direct relevance of experimentation for the acquisition of knowledge that can improve conditions and the specific health needs in the short

term or future, or those subjected to it, but also as regards the population in general.

Pharmaceutical companies must first of all carry out trials “for” the populations, which have the right to participate in the experimentation in order to obtain drugs to treat diseases for which they have a direct interest. We can say, together with Kant, that populations whatever their social-economic-cultural condition should be considered "always as an end" and never "just as a means" for experimentation. In this sense, the right to health care as protection of the objective good of a person must be considered a fundamental international right.

2.2. *Community consultation*

It is essential to establish a dialogue between investigators and participants in the experimentation through “community consultation” with the representatives of the local culture. This allows the acquisition of adequate information on the traditions, cultural customs and habits, the understanding of health and disease, moral values and religious beliefs, the level of scientific knowledge and the social-economic context. This information is necessary in the development and application of the research project.

In this context, the role of the cultural mediator is important. It is hoped that the mediator may be a person from the country in which the trials are being carried out (or someone with an in-depth knowledge of the culture) and with adequate training according to international standards. This person’s task is to mediate the general ethical requirements of the experimentation and the local issues, and avoid the unification of Western culture recognizing the value of local needs and traditions.

Support can also come from voluntary associations, especially those operating in the sphere of community health, that have lived the reality of the country for years and know the needs, habits, and customs of life there, and above all the level of information regarding health care.

2.3. *Informed consent*

As regards the recruitment and selection of participants in the trial, thorough verification of the actual voluntariness and awareness of the participation is essential. With regard to voluntariness and lack of preconditioning, it should be noted that in developing countries participation in a trial could be an advantage for those who have difficulty in obtaining food and basic health care: the social and economic conditions could push the “volunteers” naively and without adequate awareness of the risks to participate in research. Even due to the fact that often in these populations the concept of research is not clear, and tends to be confusing - but this phenomenon is not unknown also in populations of developed countries - with care and assistance (therapeutic misconception). In all international documents and guidelines great attention is paid to the search for ways to avoid (in consideration of what will be said in § 2.8) that the choice of taking part in research is determined solely by the ability to access treatment or basic

sustenance that otherwise would be inaccessible, constituting "undue inducement" that would undermine the actual voluntariness of participation.

One must keep in mind that an appropriate level of information and comprehension / understanding of that information is a basic requirement in any trial. The particular difficulty at this level that can be detected in populations living in economic poverty and / or lack of culture and scientific knowledge should not be a reason to exclude them from the trial and the benefits that it can bring: it would be a kind of acceptance and amplification of a disadvantaged condition. The objective difficulties regarding information must be a stimulus to support the activity of experimentation with a contemporaneous intensification of the activities of information and formation (from the fight against illiteracy to health education campaigns as far as the disclosure of scientific and ethical base). Alongside these long-term commitments, it is essential to identify, without delay, suitable methods (however innovative compared to the usual ones) in order to provide appropriate information, apposite to the understanding of individuals, fitted to their educational level and the type of culture. It is never acceptable in any situation, for information to be hasty, ambiguous and unclear, or that it does not take into consideration essential cultural specificities. The ascertainment of informed consent must ensure understanding of the information and responsibility of choice, taking into account local traditions and customs[12].

Forms of verbal consent or consent expressed by others (the community leader or a family member) are highly questionable. The choice of methods of expression of consent must verify the actual voluntariness and awareness of individual participation (as well as the opportunity to refuse or withdraw participation at any time), the absence of coercion or indirect external pressure on the subject entering the trial. The involvement of other figures in the procedure of obtaining informed consent is acceptable and understandable, but they can never replace free personal expression. Oral consent is acceptable only for the illiterate in the presence of a witness. In some cultures where the role of women is subject to various forms of family and / or social[13] authority, third party involvement can be accepted as 'additional assent' in as much as it is essential to the cultural context. The important thing is that research, to the extent that it needs women[14], should

[12] The problem of verification of the real understanding of the information received from participants in research is particularly pressing in the case of some experimentation in developing countries, but it is not a solved problem in trials in developed countries. In order to verify the actual understanding of information, it is from some time that many international documents call for a more active involvement of the ethics committees in the stage of recruitment of participants, and the next stage of monitoring the conduct of research (Cf. specifically the Italian National Bioethics Committee , Guidelines for Ethics Committees in Italy, 13th of July, 2001).

[13] The same is true for men in matriarchal cultures.

[14] On the issue of experimentation on women see NBC, *Drug testing on women* (2008). It should be noted that as regards experimentation on women special attention should be paid to women who are pregnant or breastfeeding. It is to be reiterated that within the *Additional Protocol to the Convention on Human Rights and Biomedicine*, *Concerning Medical Research*, Italy expressed the following position: "The government of Italy will not allow that a research which does not produce direct benefits to the health of the research participants be carried out on persons not able to give their consent and on a pregnant or breastfeeding woman".

protect - in every way possible – a woman's autonomy. In this context, the intervention of international organizations, devoted to the protection of women, is hoped for.

2.4. Confidentiality

A further issue that emerges contemporaneously to that of consent is confidentiality. Confidentiality is inevitably weakened (if not obliterated) given the family's possible permission to research, as well as the fact that in some cultures there is a lack of the very concept of "privacy". This raises an ethical problem because the mere act of participating in research for vulnerable populations means risking the stigma of being sick. It is hoped that cultural associations may play a supportive role to those who undergo experimentation, helping the patient to be seen as a person and not to be ghettoized. This, in the context of experimentation, highlights the importance also of solid culturally formative intervention in this direction.

2.5*. Protection of the health and safety of participants*

The balancing of risks / benefits, a preliminary for access to experimentation, should be commensurate with the basic conditions of the population (including nutritional, epidemiological and health conditions), in reference to each individual, but also to the community, i.e. the population of the host country as a whole. Commensuration of risk for the individual and the population in relation to the benefits for "third parties" (with reference to the countries performing the trials) is ethically unacceptable. Research is ethically justified if it provides reasonably direct benefits to participants and indirect benefits for the overall population, and minimization of risks to people participating in the research, but also for the vulnerable population as a whole.

Consideration and management of risk should be commensurate with local conditions and in relation to the selection of individuals (also considering the difficulty in knowing medical history), both for clinical monitoring (given the inadequateness of medical facilities) and the problems in the relationship between participants and research group (there being, at times, difficulties in transport and communications. The compensation of direct and indirect damage to health should be assessed with particular attention in relation to local conditions and the weak (children, women, and the elderly). Appropriate treatment is to be ensured during the trial, with attention to the guaranteeing of emergency services.

With regard to the risks that the individual runs concerning current and future physical integrity, a system of "liability without fault" should be established: so-called responsibilities of an objective nature, which exempts the injured party from the need to prove that the investigator departed from the model of diligent service. A solution that shifts, on the one hand, from the assumption that the danger is not applicable to the conduct of that individual nor to the structure holder of the activity of experimentation, but rather that it is immanent in the activity of research, and on

the other hand from the need to ensure full protection to patients during and after the experimentation.

It is a system that would avoid forms of neglect once the trial is over and can ensure the individual has effective social care facilities, able to provide care even in the long-term regarding the possible negative consequences of the experimentation. Protection should be provided through arrangements for automatic mandatory insurance in view of the payment of possible damages, where the premium is assessed in relation to the local economic state. It therefore seems natural that the same research group agrees to bear the economic consequences and the risks inevitably associated with such testing. It would probably be beneficial to establish independent organizations that are non-profit and internationally accredited to monitor the implementation of international multi-centre trials, and in particular those carried out in developing countries (Kelleher, 2004)[15].

2.6. *Communicable and non-communicable diseases*

The evaluation of the scientific relevance of research in developing countries must take into account the differences between communicable diseases and non-communicable diseases in relation to the various stages of experimentation.

Communicable diseases include all types of bacterial, viral, fungal and parasitic diseases; non-communicable diseases include acute and chronic non-infectious diseases. In the past, the attention to developing countries was addressed primarily to the first category, but in more recent times, since the increase in life expectancy is a global phenomenon, the second category is becoming important.

It should be noted, in general, that the clinical trial is divided into four phases, which are in continuity and are distinguished as follows: Phase I is represented by the first administration of the drug in humans based on adequate documentation of pre-clinical investigation on animals in order to ascertain the tolerability of the product (most often performed on healthy volunteers, except for toxic drugs, such as anti-cancer chemotherapies, which are assessed directly on the sick); Phase II covers the effectiveness and serves mainly to assess in advance whether the product carries the desired pharmacological effects; Phase III compares the drug with other products of reference or, failing this, to placebo in a randomized manner, and if possible, double-blind (this is a comparative study in which you define the benefit-risk ratio and determines the position in the arsenal of drug treatment available); Phase IV is to control, even after the marketing of the new drug, the side effects and / or possible problems that have escaped the previous clinical trials, because they occur very rarely or in the long / very long term, or only under specific conditions.

In the context of communicable diseases, the initial testing of all four phases must be done on site for obvious reasons, since it is difficult to find a sufficient

[15] Currently in the United States two such institutions are already operating: the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP) and the Partnership for Human Research Protection (PHRP).

number of persons who live outside the countries in the developing world. It should also be borne in mind that the testing could involve people with severe nutritional imbalances and comorbidities. The ethical problem in phase III is very delicate because if there are other effective treatments, these should be provided free by the sponsor[16]. There is also a school of thought that believes it is important that the control group receives the treatment that is used locally, even if lacking in scientific evidence.

In the context of non-communicable diseases, the initial testing, seeing as it regards diseases that are widespread in industrialized countries should not only be carried out in developing countries. This may suggest that the various stages will be carried out even in countries that promote experimentation, but only subsequently, after receiving information on the tolerability of the drug. In any case, before entering Phase III, there should be at least one study for "dose-finding" to take account of any high frequency polymorphisms that affect the metabolism or the target of the drug evaluation.

2.7. *The use of placebo*

One of the most delicate ethical issues concerning experimentation in developing countries concerns the use of placebo[17] that is generally opposed to the assessment of "best current therapeutic methods"[18].

In fact, the term "best current therapeutic methods", easily applicable to developed countries, has sparked a heated debate in relation to developing countries, because it can be understood both in the sense of the best treatments available in the world or best existing standard, and also in the more restrictive and less guaranteed sense of known and normally applied treatments at the local level (Errico, 2004, 2007)[19].

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[16] Cf.§ below.

[17] NBC, *The improper use of placebo* (29th of October 2010) and *Bioethical problems in clinical trials with non-inferiority design* (24th of April 2009).

[18] Cf. the Declaration of Helsinki (2000): "The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods. This does not exclude the use of placebo or no treatment in studies where no proven prophylactic, diagnostic or therapeutic methods exist".

[19] The discussion on the issue of the use of placebo in developing countries has become particularly evident since 1997 because of testing on pregnant women with HIV of a new method to prevent HIV transmission from mother to child, already approved by the Food and Drug Administration (FDA) and used in developed countries. The first trials conducted in the U.S. (also not without controversy) had actually proved that the drug (known by the abbreviation AZT) could reduce HIV transmission from mother to child by two thirds, but the high cost and the methods of administration made it prohibitive to use this medicine in developing countries. Subsequent trials conducted in several African countries, South-East Asia and the Caribbean, under the sponsorship of the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) were designed to evaluate the effectiveness of reduced doses of the drug and using application methods best suited to local conditions. The study design included a placebo control arm, the justification given being the consideration that high costs would have prevented, in any case, the administration of these therapies, which cost around one thousand U.S. dollars, the

Some believe, in the context of a pragmatic view inspired by the idea of satisfying the real needs of local health, that the use of placebo may be legitimized under certain conditions by the balance between costs and benefits: seeing as locally, because of the differences in economy and health, these alternative treatments of proven efficacy that are found in other parts of the world are never available, the deviation from the requirement of "best current therapeutic methods" could be offset by the fact that at least half of the study population obtains the drug the other half is still subject to health surveillance. To the general advantage of more rapid testing is, on a local level, greater availability of care and treatment. To prevent experimentation, because there is no guarantee of the best therapy in the world for everyone, would mean to reduce even this small opportunity to enjoy a much better form of care than the one that is in point of fact practiced, even if this is not optimal at all.

This argument is rejected by others, according to which, in any form of experimentation, the aspect of solidarity must prevail over every other consideration, in order to prevent that economic and social inferiority may justify exploitation, creating irreversible situations of vulnerability. For these reasons, when there is a best proven treatment that is effective and efficient, it must be made available to the population by those conducting the experimentation, considered that the use of placebo is always unjustified. The prospect of possible future benefit to others does not justify the rejection of an effective treatment to research participants, whose dignity must be at the center of ethical reflection. The use of placebo is subject to the same ethical standards of developed countries: placebo can not be used in view of speeding up the length of the experimentation or for the reduction of costs. The admission of the use of placebo would legitimize a “double standard” of experimentation with a difference between rich and poor countries, resulting in discrimination.

The range of positions on this matter, and arguments in support, is much larger than it is possible to give an account of here and this is reflected in the different positions expressed papers by international documents and guidelines[20]

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average income in these countries amounted to few dollars, and just as low was government expenditures for the protection of health. A criticism of the trial emerged from those who drew attention to the fact that testing should be done first in developed countries (where the disease was widespread) with a study based on the comparison between taking the full dose and half dose, and not half-dose and placebo.

[20] During the discussion on the revision of the *Declaration of Helsinki* (version 2000), the World Medical Association refused to change Art. 29 in order to make it more permissive, as some demanded. Instead, in 2002, the position of the CIOMS was less steadfast against the possible use, in some cases, of placebo and the following year this position was endorsed by a large majority, by the EGE, in an Opinion in which, in reaffirming that the use of placebo in trials in developing countries should be regulated, in principle, but the same regulations in force in European countries, provides the possibility to derogate from the rule of "best proven treatment" "when the primary purpose of the clinical trial is the attempt to simplify or reduce the cost of treatment in countries where the standard treatment is not available for logistic reasons or is inaccessible because of the cost"(§ 2.10). It should also be noted that the latest version of the *Declaration of Helsinki* (2008). Art. 32 affirms that "The benefits, risks, burdens and effectiveness of a new method should be tested by comparing the best proven intervention in use, with the

The NBC believes that the general ethical principle must always apply which states that placebo is usually unjustified as part of experimentation when there is already available treatment, therefore, even in trials in developing countries. Where, for exceptional reasons, the use of placebo is deemed necessary, it is essential that the reasonableness of this is scientifically demonstrated, and never due to economic and / or organizational reasons and it should always take into account the primary health needs of the local population.

Specific attention should be placed on providing exhaustive information to individuals and the obtaining of their consent, and on the reasonable expectation that the temporary suspension of an active treatment does not have serious and irreversible clinical consequences and also to the balance between exposure to minimum damage and consistent future benefit for the individual.

This reasonable scientific justification should be expressed in the research protocol and evaluated by the Ethics Committee of Research and the local Ethics Committee. It calls for a unified regulation that is also harmonized between the different countries involved in the experimentation and research, since - as mentioned - the strict application of general ethical principles in different contexts may hinder development in countries that are already disadvantaged.

2.8. *The duty of solidarity during and after experimentation*

The countries that carry out experiments in developing countries should avoid increasing inequalities and contribute to the reduction of inequalities. It is within this perspective that assistance should be guaranteed to developing countries during the experimentation without inflicting on them the burden of the “indirect costs” of the trial (on an already precarious local health system) and helping them to become full partners in international research, stimulating the improvement of the local health system and transferring technical and scientific skills, involving also doctors and representatives of the host country, to monitor compliance with ethical standards and avoid abuse. As a result there should also be specific training for doctors and the medical staff conducting this experimentation as well as formation of the local doctors and health personnel, often in particularly fragile conditions, so that the care becomes a “*collaborative partnership*” and consents to develop in the host country the skills to be able to independently conduct clinical trials and ethical assessments.

It is an ethical requirement of experimentation that the investigators assume responsibility and solidarity - in the framework of international cooperation - which continues even after the trial, so that research participants do not feel abandoned.

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exception of the following circumstances: the use of placebo, or no treatment, it is acceptable in studies where no proven intervention exists in use or where compelling reasons and scientific methodological reasons for the use of placebo is necessary to determine the efficacy and safety of an intervention and the patient who is receiving the placebo or no treatment is not subject to any serious or irreversible risk. Extreme care must be taken to prevent abuses in this area". The danger is that this opening up in more permissive terms to experimentation and the use of a lower standard of care or placebo may be introduced for economic and not scientific reasons only in order to exploit the state of vulnerability of those countries. The ethical 'double standard' denies the equal dignity of human beings by increasing the gap between developed and developing countries.

In this sense, experimentation is considered justified to the extent that the product - if it proves effective - can be made available to the entire population. There is considerable international debate, even as regards the ways in which this ethical requirement can in actual fact be accomplished.

The NBC considers it a duty to guarantee access to new treatment – should it be necessary - and privileged assistance to volunteers, taking into account the risk to which they are subjected during experimentation. It is certainly possible that the "post-trial benefits" - which especially in the case of certain diseases may be continued indefinitely - constitute improper incentives to participation in research, but the alternative would be that, due to the cost of the drugs, those who have actually contributed to their experimentation would be excluded from treatment.

More controversial is the question on how to access the new drug by the population. The NBC considers it worthwhile to ensure access to the drug for the entire population, although in view of the complexity of the problem, many international documents suggest dealing with this through the preliminary negotiations between the sponsors and representatives of the community, in order to find a balance between economic sustainability and respect for local needs. It is hoped that pharmaceutical companies may concede the experimented drug to the entire population at affordable prices. It is not possible to provide general rules and proof of this comes from the language, marked by caution, used in international documents on the subject, even those from developing countries.

The inequalities in wealth and resources on a global level and inequality among men in accessing treatment and health care are of such magnitude that it would be unrealistic to expect that those who want to conduct experimentation in developing countries should shoulder the burden of resolving them alone. However having stated this, it should not be overlooked that experimentation is part of a general political context regarding the environment (health, nutrition, education, the fight against illiteracy).

2.9. *"Social ecology"*

A balanced development of research and experimentation, a development that does not create conditions of vulnerability and exploitation, determines an improvement of the overall epidemiological picture. A factor that is not to be underestimated is, in fact, the correct assessment of the influence on the results of the research both of the different genetic profiles and the economic and social diversity. Regarding the former, there is an ever increasing number of studies that highlight the impact of genetic profiles in response to drugs therefore one can not disregard consideration of the ancestry (African, Asian, European ancestry) of the individuals subjected to experimentation (Glickman et al. 2009). Similarly, as regards the second aspect, one can not ignore that there is a profound difference in the clinical assessment of the individuals subjected from birth to multiple drug regimens and those who have never or almost never had access to systematic and constant therapies. In addition, a correct study can not even ignore, cultural differences, education levels, the relationship with disease and suffering, and social expectations.

All these elements help to understand how operating in unilateral conditions, which do not take into account the "specificity" of the populations tested, may, in addition to often bringing about serious damage to these very populations, may also provide unreliable results, which could lead to new and unexpected situations of risk. The immediate utility in terms of cost saving and rapid results is often only apparent when one considers the elements of uncertainty that in the long run, could emerge. Only a balanced social relationship can provide optimum conditions for the correct assessment of the possible advantages of a trial. From this point of view, the issue of vulnerability[21] assumes particular ethical importance and plays an increasingly central role in the protection not only of those who are particularly weak, but as regards the international community as a whole, directing it towards policies that take into account the different weights of vulnerability and power, in a view that emphasizes the ties of interdependence not only between individuals but also between communities and peoples. In this perspective it becomes clear that the perpetuation of situations of marginalization and exploitation of some individuals or some populations may not reflect on us all. Morally "suspicious" situations that occur in many clinical trials conducted in populations that are particularly vulnerable (Hawkins, Emanuel 2008) are not only unacceptable in themselves from the ethical point of view, but they reflect negatively both on the relations between populations and on the 'scientific reliability of the data to be analyzed. It is common interest of all countries to develop an ethic based on the awareness of the mutual bonds of interdependence, an ethic of solidarity, which ensures not only the respect of fundamental human rights, but which also preserves the particularity of individual social contexts.

2.10. *The role of Ethics Committees*

Research must be approved by the Ethics Committee of the health facility of the country or countries that undertake experimentation. If a trial is undertaken by a pharmaceutical company, it must refer to an ethics committee that consists of medical and bioethical experts with appropriate formation, who are independent from the promoters of the research.

[21] In the Barcelona Declaration (1998) vulnerability, included in the four fundamental principles of bioethics and the European Biolaw (autonomy, dignity, integrity and vulnerability), is defined as follows: “Vulnerability expresses two basic ideas. (a) It expresses the finitude and fragility of life which, in those capable of autonomy, grounds the possibility and necessity for all morality. (b) Vulnerability is the object of a moral principle requiring care for the vulnerable. The vulnerable are those whose autonomy or dignity or integrity are capable of being threatened. As such all beings who have dignity are protected by this principle. But the principle also specifically requires not merely non interference with the autonomy, dignity or integrity of beings, but also that they receive assistance to enable them to realise their potential. From this premises it follows that there are positive rights to integrity and autonomy which grounds the ideas of solidarity, non-discrimination and community” (*The Barcelona Declaration on Policy Proposals to the European Commission on Basic Ethical Principles in Bioethics and Biolaw,* adopted in November 1998 by Partners in the BIOMED II Project, reprinted in the *Final Project Report* - two volumes - *on Basic Ethical Principles in European Bioethics and Biolaw*, Institut Borja de Bioètica, Barcelona & Centre for Ethics and Law, Copenhagen, 2000).

The experimentation project must also be approved by the ethics committee of the host country of the reference health care facilities. In the absence of an ethics committee, it is possible to refer to the WHO regional committees for research on medicines, present in many regions of the world. If the host country has not yet established an ethics committee, it is important that its establishment is prompted, by stimulating also appropriate training for this purpose. The establishment of a "Joint Ethics Committee" composed of doctors, independent bioethical experts and local representatives, is foreseeable. It is hoped that in the local committee or joint committee a representative of the local associations and a cultural mediator will be present. Currently, the subordination of the authorization to the introduction of the tested drug to the registration of the trial is mandatory (e.g. on the database of the WHO Register WHO International Clinical Trials Registry Platform), as a guarantee of visibility, transparency and controls[22].

The primary goal is to guarantee a "double check" (ethical review) on the ethicality of the research, both by the country carrying out experimentation and also by the country hosting the trial. A double check that fosters communication and integration between the different needs of countries[23].

3. Recommendations

1. Research in developing countries should not be discouraged, on the contrary it should be encouraged, but oriented according to ethical criteria considered essential to avoid all forms of exploitation and discrimination in order to ensure health and global justice, and reduce inequality. Different standards of ethical assessment can not be applied in other countries: ethical criteria must be unique, common and shared.

2. International trials must constitute a specific area in the context of a more extensive promotion of the protection of fundamental human rights. In this sense, experimentation can be an opportunity for development if properly supported by suitable campaigns regarding information and scientific and ethical training.

3. Special protection should be ensured as to the specific needs of developing countries because of the socio-economic-cultural context in order to contribute to the improvement of their conditions and prevent that needs constitute an undue influence on the choice of participation and ways of participating in the research.

4. The direct scientific importance of the experimentation for the country in which it is conducted should be determined in advance (both for communicable and non-communicable diseases), the balance of risks and benefits for

[22] ICTRP www.who.int/ictrp.

[23] In the field of experimentation on communicable diseases, especially AIDS, the experience of UNAIDS is to be recalled, from which a very detailed document originates, proposed as a guideline for the development of HIV vaccine. The document examines the main aspects of development and testing of this type of medicine in populations with different exposure to infection and poor access to care, taking into account the unique aspects of local cultures and scientific infrastructures. Cf. *Ethical considerations in HIV preventive vaccine research,* UNAIDS guidance document - May 2000 available on the website http://data.unaids.org/publications/.

participants, the obtaining of consent, avoiding hidden forms of involvement in research which `takes advantage` of the lack of awareness or the condition or need.

5. The experimentation must take into account in a supportive manner the health needs of the population as part of international cooperation, providing the research participants and hopefully the population as a whole with adequate assistance even after the trial, with reference to the availability of drugs which have proved effective.

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