

Sources of post-study medication in cases of rare disease: ethical conflict

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Abstract

Taking off from a definition and comprehension of concepts related to medication, rare diseases and ethics, as well as the interface of these concepts in the core of reflection on sanitary law, the details and exceptionalities of the orphan drugs, designed to treat rare diseases, defined by domestic and international epidemiological standards as those that proportionally affect few individuals. Below, we examine the international debate concerning the supply of medication post-study, to conclude by evoking the required ethical commitment.

Keywords: Ethics, research. Rare diseases-Orphan drug production. Drugs from the specialized component of pharmaceutical care.

Resumo

Fornecimento do medicamento pós-estudo em caso de doenças raras: conflito ético

Partindo da definição e compreensão dos conceitos relacionados ao medicamento, às doenças raras e à ética, bem como à interface entre esses conceitos no bojo da reflexão do direito sanitário, são detalhadas e discutidas as excepcionalidades das drogas, destinadas a tratar doenças raras, definidas por padrões epidemiológicos nacionais e internacionais, como aquelas que afetam poucos indivíduos, proporcionalmente. Em seguida, examina-se o debate internacional acerca do fornecimento de medicamento pós-estudo, para concluir com a evocação do necessário compromisso ético.

Palavras-chave: Ética em pesquisa. Doenças raras-Produção de droga sem interesse comercial. Medicamentos do componente especializado da assistência farmacêutica.

Resumen

Provisión del medicamento post-estudio en el caso de enfermedades raras: conflicto ético

Partiendo de la definición y la comprensión de los conceptos relacionados al medicamento, a las enfermedades raras y a la ética, así como a la interfaz entre estos conceptos en el nudo de la reflexión del Derecho Sanitario, son detalladas y discutidas las excepcionalidades de las drogas, destinadas a tratar enfermedades raras, definidas por patrones epidemiológicos nacionales e internacionales como aquellas que afectan a pocos individuos, proporcionalmente. Posteriormente, se examina el debate internacional a propósito de la provisión de medicamentos post-estudio, para concluir con la evocación del requerido compromiso ético.

Palabras-clave: Ethics, research. Rare diseases-Orphan drug production. Drugs from the specialized component of pharmaceutical care.

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Declara não haver conflito de interesse.

Medicine, rare diseases and ethics

The obligation to provide the medicine that proved most advantageous in a clinical study to all those who participated in the study - as long as they need it and free of charge - is today one of the themes that provoke major discussion among those who are interested in the matter. Perhaps the most controversial aspect of the issue is the one related to ethics.

Some argue that participants of the study have already benefited from the special care provided during the study but others argue that it is not fair to "use" those participants to develop a medicine and then make them buy the drug which would not have been developed without the contribution of each one of the participants. And the argument intensifies when the drug in question is an orphan drug developed for the treatment of a rare disease.

To try to find the appropriate ethical response, we should first examine the terms of the problem. There is no internationally standardised concept about which are rare diseases or orphan drugs. In general, there are two criteria used to determine whether a drug is an orphan drug: a) epidemiological - prevalence or incidence of the disease in a population; b) economic - presumption of non-profitability of the drug used for the treatment due to its low demand¹.

The US legislation in 1983 defined rare disease as one *which affects less than 200,000 persons in the United States, or affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug*².

Now, the Committee for Orphan Medicinal Products (COMP) of the European Medicines Agency (EMA), created in 2000, defines "orphan drug" as a drug developed to treat serious diseases that affect fewer than 5 in 10,000 people across the European Union³ And, in Brazil, both the National Policy on Comprehensive Care for People with Rare Diseases, established by the Ministry of Health by Ordinance 199/2014, and the Bill 530/2013 of the Federal Senate, aimed to establish the National Policy for rare diseases in the public health system, consider rare disease the one which prevalence does not exceed 65 cases per 100,000 inhabitants⁴ and orphan drug, *medicine or immunobiological designed specifically to treat rare disease that, for the*

*purposes of this law, is the one which prevalence does not exceed sixty-five cases per hundred thousand inhabitants*⁵.

Considering the epidemiological criteria set out above it should be noted that, in this article, rare diseases are not understood as neglected diseases, or even as neglected tropical diseases, which, according to the World Health Organisation (WHO), cited by Oliveira et al, correspond to a *diverse group of diseases with distinct characteristics that thrive mainly among the poorest populations: malaria, leishmaniasis, schistosomiasis, onchocerciasis, lymphatic filariasis, Chagas disease, African trypanosomiasis, leprosy, dengue fever, Buruli ulcer, cysticercosis, echinococcosis, yaws, rabies, trachoma and some soil-transmitted helminths (Ascaris lumbricoides, Trichuris trichiura and hookworms)*⁶. Despite affecting large population groups, neglected diseases are not seen as profitable by the pharmaceutical industry and, consequently, do not arouse their interest as those diseases are not considered profitable because they are prevalent in poor nations⁷.

Proceeding on the understanding of the terms used here it should be noted, in addition to the specific health aspect, social, economic and technological factors are also associated with the drug. That's because the drug should be understood as basic raw material and essential to health action plans⁸, and precisely because *it is a critical raw material used for the prevention, diagnosis or treatment of diseases, the access to it should be guaranteed universally. Ensuring the equity of access to medicines is the State's role, considering its impact on health*⁹.

In the same line of thought, Professor Celso Fernandes Campilongo stresses that drugs are an important element of the state health policy. *Being a basic necessity, medicines transcend civil rights and achieve the level of public good. There is, as a result, need for greater control, care and attention, by the State, in pricing policies, distribution and supervision, among other factors that interfere or may interfere with the access to medicines. Thus, encompassed by the right to health, the policies adopted in the pharmaceutical market have not only economic importance but also social importance*¹⁰.

There is no doubt, consequently, that this "hybrid object", as it is placed between therapeutics and consumer goods, requires that the action of the State in this area consider, among other factors, aspects of the nature of the market. An effective State intervention in the field of medicine thus requires the analysis of the pharmaceutical market in order to know the influence of the pharmaceutical in-

dustry and its market strategies, without forgetting other variables and actors in this scenario, so that a policy aimed at the interests of the population can be effectively formalised and, at the same time, will not harm economic investments of the pharmaceutical industry.

Still, for the purpose of uniformity of understanding, it should be remembered that ethics, as Aristotle teaches¹¹, consists in reflecting about the conduct of man in the *polis*, that is, the conduct of the citizen. This reflection include, at the same time, the practical and the theoretical plan, somewhat indistinct from each other. It exists in theory only if it can coexist in practice, as it allows to define a course of action that can lead people to happiness, in the fairest way possible.

The same Aristotle also explains: *let it be understood, before we go on, that all reasoning on matters of practice must be in outline merely, and not scientifically exact: for, as we said at starting, the kind of reasoning to be demanded varies with the subject in hand; and in practical matters and questions of expediency there are no invariable laws, any more than in questions of health*¹². In short, ethics is a reflection, a thought about the ethos, not the establishment of rules. Therefore, to apply ethics is not properly possible.

It's possible, however, to identify certain rules of conduct that can and should be followed in order to reach that ideal end: the happiness, in the fairest way possible. To establish standards is not, therefore, to establish what is ethics. Standards should have ethics as their foundation, but ethics are just ways to operationalise the behaviour of people in cities. These standards, called "ethical", can not therefore be neutral, as they always aim at the improvement of the human being. Thus, rules of conduct based on ethics should always have as paramount objective to add knowledge to the care of the human being.

Aristotle goes further by teaching that *he who wishes to make men better by training (whether many or few) should try to acquire the art or science of legislation, supposing that men may be made good by the agency of law*¹³. The philosopher warns, however, that *for the same degree of accuracy is no more to be expected in all kinds of reasoning than in all kinds of handicraft (...)* The reader, on his part, should take each of my statements in the same spirit; for it is the mark of an educated man to require, in each kind of inquiry, just so much exactness as the subject admits of: it is equally absurd to accept probable reasoning from a mathematician, and to demand scientific proof from an orator¹⁴.

It can be concluded, absorbing the teachings of Aristotle, that the regulatory power of "ethical" standards on research with human beings makes coincide its limit with that one imposed by *each kind of enquiry*. It is very pretentious to say that an "ethical" norm can ensure the safety of the subjects of a research. Certainly, a norm of this kind should be able, however, to find the *mean amount* which, still according to the philosopher's lesson, should be praised at all times¹⁵. It is essential, however, to be clear that the regulatory power of "ethical" standards on research involving human beings is limited precisely because of its ethical character.

The exceptionality of orphan drugs

To better circumscribe the problem, it's convenient to examine how the academic world, and also the political world, has been reacting to rare diseases. Initially, one realizes that the issue has attracted wider interest, having, for example, the United Nations Educational, Scientific and Cultural Organisation (UNESCO) stated that countries *should foster, inter alia, research on the identification, prevention and treatment of genetically based and genetically influenced diseases, in particular rare as well as endemic diseases*¹⁶. It is an extremely important issue. Indeed, the entire universe of clinical trials and, therefore, the protection of persons involved in them, is being revolutionised with the development of drugs for the treatment of rare diseases.

Since the first movements in Europe and the United States, it is possible to see the preoccupation with clinical trials in the area of rare diseases aimed at the development of the "orphan drugs". In a recent study¹⁷, developed by the Center for Research in Health Law at the University of São Paulo (USP), which I am honoured to coordinate, we affirm that the literature presents as main obstacles to the development of medical products for the treatment of rare diseases: difficulty in finding patients for trials for development of clinical studies due to the rarities of the diseases; difficulty to reach clinical and cost-effectiveness relevance, making it difficult to perform medical studies based on evidence, due to the low number of subjects, being the majority of studies in experimental phase; high cost of medicine development affecting the budget of public health systems; and low market perspective, requiring public subsidies for the development¹⁸.

No one doubts that to develop safe products to treat rare diseases is a challenge, especially because

the number of patients affected by the disease is so small that it makes it very difficult to conduct clinical studies with that population. And also because, given its rarity, the clinical picture of these diseases is often little known, creating difficulties in the design and conduct of clinical studies, such as the identification and selection of significant “clinical outcomes”, biomarkers or measures from clinical results to evaluate the effects of the intervention. For these reasons, both in the United States and the European Union, the legislation has offered incentives, including tax credits to offset the cost of clinical trials and the potential eligibility to obtain seven years of marketing exclusivity after approval of the drug^{19,20}.

Researchers, in turn, claim that the development of orphan drugs will still need many financial incentives in the next years²¹. In addition, medicine regulatory agencies have established various mechanisms to make therapies available as quickly as possible, because they are usually the first treatment for these serious and rare diseases. Thus, the US Food and Drug Administration (FDA) *recognises that certain aspects of drug development that are feasible for common diseases may not be feasible for rare diseases and that development challenges are often greater with increasing rarity of the disease*.²²

Due to the specifics of these diseases, the FDA established, for example, a *fast track* mechanism, whereby the granting of marketing approval takes place on the basis of *adequate and well-controlled clinical trials establishing that the drug product has an effect on an surrogate endpoint that is reasonably likely to predict clinical benefit or an endpoint other than mortality or irreversible morbidity*²³. This procedure requires that the drug should be further studied in the post market period to verify and describe its clinical benefits or their effect on irreversible mortality or morbidity. The European Medicines Agency (EMA), in turn, included among the priorities of its work programme *a review of the aspects of good clinical practices relating to clinical trials*²⁴.

Important meetings have been organised to discuss rare diseases and orphan drugs. In July 2012 a meeting took place in Europe²⁵ and in July 2014, to fulfil a legal requirement^{26,27}, another meeting was convened, at the FDA, to discuss *complex issues developing drugs and biological products for rare diseases*²⁸. In the latter case, just to give an idea of the complexity of this theme in clinical research, two out of four sessions of the meeting were designed solely to discuss it.

It was recommended caution in the development of programs for rare diseases in which participants of intervention trials differ from participants in natural history studies. To this end, the elimination of phase 2 in order to shorten the development period and go directly to the studies from phase 3, without the sufficient characterisation of the “outcome”, can undermine the ability to conduct efficient studies. It was also noted that the FDA is not averse to risk when it comes to drug studies which have the potential to treat a rare disease. Because of the severity of rare diseases, often fatal, there is a general recognition that both the FDA and patients as well as doctors are willing to accept greater risks or side effects of drugs that treat rare and serious diseases than of drugs for not serious diseases. This implies, however, a higher demand concerning the informed consent to participate in the study and a clear labelling of the drug, which reflects its effects and its safety profile.

It appears, therefore, that clinical researches aimed at the development of drugs to combat rare diseases - drugs known as “orphan drugs” - experience a differentiated legal treatment in relation to other clinical researches. Moreover, it seems important to note that the differentiated treatment depends exclusively on the characteristics of these diseases, which ultimately change even the registration system of drugs for their treatment. In this case, it is no small matter the express recognition that everyone involved in the process - from patients to regulators - are willing to accept greater risks or side effects.

From this unique circumstance also arises the creation of different registration mechanisms and commercialisation of drugs for the treatment of rare and serious diseases and, above all, the use of different measures of effectiveness, which break away from traditional patterns, for the approval of studies. Moreover, It should be noted that the legal treatment given to the development of drugs for these diseases is also different in terms of legal incentives offered to companies interested in this market. Such stimuli have ranged from tax credits to offset the cost of clinical trials to the potential granting, as it turned out, of seven years of marketing exclusivity following approval of the drug.

Internacional debate on the supply of post-study drug

It completes the picture of the basic information necessary to understand the problem of

the treatment that has been given, in the most important documents of health care ethics, to the obligation to provide - free of charge and as they need - the drug that was more advantageous to all those who participated in its clinical trial.

Ethical aspects of research involving human beings have been standardised by documents with international relevance, since the promulgation of the Nuremberg Code in 1947²⁹. Initially it seems that a professional self-regulation appears to occur, that is, a voluntary adoption of declarations of principles by the community of doctors or researchers, such as the Declaration of Helsinki from 1964³⁰, which was widely supported and adopted by those communities around the world, and which effectuation depends exclusively on individual respect. Then the Council for International Organisations of Medical Sciences (CIOMS), in collaboration with the WHO (World Health Organisation), elaborated the *International Guidelines for Ethical Review of Epidemiological Studies*³¹, in 1991 and, since 1982, various revisions of the *International Guidelines for Biomedical Research Involving Human beings*^{32,33}.

These documents have been widely publicised and have become, in many countries - including Brazil - important references for the development of national guidelines on ethics in research with human beings. Another relevant international document is the Belmont Report, published in 1979³⁴. It is the result of the work of the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research, created by the US government. This report presents the ethical principles to be observed in these studies, and has been the reference for the elaboration of various normative documents.

From the 1980s, it is sought to expand the comprehensiveness of ethical response to the control of scientific development, with the creation of ethics committees in charge of discussing their social repercussions. They are the national committees of bioethics or ethics for the life sciences, crossing the border of classes, being composed of representative figures of great evaluative options present initially in the US and later in Europe, extending then to the international community. They consist, for example, of the Comité Consultatif National D'éthique pour les Sciences de la Vie et de la Santé in France in 1983; the Comitato Nazionale per la Bioetica in Italy in 1990; the European Group on Ethics in Science and New Technologies in 1991, and the International Bioethics Committee in 1993.

The economic and social importance of the biotechnology sector in fostering this process is par-

ticularly evident in the case of the establishment, by the European Commission, of the Working Group on Ethical Issues Related to Biotechnology, because of the pressures from this industrial sector in favour of the systematic treatment of the ethical implications associated with the drug's development. In 1997, the 29th UNESCO General Conference adopted the *Universal Declaration on the Human Genome and Human Rights*¹⁶, and in 2004, in the 32nd General Conference the *International Declaration on Human Genetic Data* was approved³⁵. Finally, in 2005, UNESCO adopts the *Universal Declaration on Bioethics and Human Rights*.³⁶

Examining carefully all these important documents produced by several forums of the international community with regard to the obligation to provide, free of charge, medicines for clinical research's participants after the end of the trial, the progress of the treatment of the matter can be verified. Initially, however, we must emphasise that from the first one of them - the Nuremberg Code - a different role is recognised to the research participant, because it is admitted that it is not just a patient submitted to therapeutic decisions laid down by the doctor who treats a patient, but an autonomous subject, who is free to decide whether or not to participate in a survey conducted by medical researcher²⁹.

It is assumed, therefore, that more general humanitarian considerations (to allow the advance of science and social well-being, for example), or even private reasons (increasing their likelihood of cure or improvement of symptoms, for example), could lead the subject to want to freely participate in a survey. The judges of the Nuremberg Tribunal judged suitable to also ensure that research would be carried out with people only after it was realised with animals and the desired knowledge could not be obtained otherwise.

The recommendations set from that mentioned court, moreover, consisted of avoiding all damage and balance the risk with the desired benefit, making sure that participants would be guaranteed the possibility to withdraw their consent at any stage of the research and to require interruption from the researcher whenever the continuation of the experiment results in probable damage. These were the concerns about the protection of research participants present in the *Nuremberg Code*, where - under no circumstances - it was cogitated to institute the obligation to provide drugs free of charge to participants in clinical research after its end, since its goal was restricted to safeguard the lives and autonomy of research subjects.

The *Declaration of Helsinki* is constantly reviewed with the intention to adapt it to scientific development and underlying social aspects. It was in force, in the beginning of the twenty-first century, the version adopted in Edinburgh, at the 52nd General Assembly of the World Medical Association, with the alterations introduced in 2002 and 2004, which added notes, respectively, to articles 29 and 30 of the document. In 2008, it adopted a new redaction, in accord with the review drafted and approved at the 59th General Assembly held in Seoul. This wording remained until 2013, when it was adopted the current text, at the meeting of the organisation held in Fortaleza, Brazil.

The version elaborated in 2000³⁷ was much discussed by the scientific community, who was divided: many believed that the 1996 text, adopted in Somerset-West, South Africa, should not be changed, whilst others judged necessary to adapt it to the great development of biomedical research, especially occurred since 1975. Surely the point of greatest debate, which resulted in a significant change in the text, was the conviction of the need to benefit the communities in which research is conducted. In short, for the first time it was considered that people who did not directly benefit from the research - the community, especially in developing countries - should be considered for ethical protection.

As a result, the article 19 warns that clinical research is only justified *if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research*. In addition, the article 27 requires the publication of negative results and of any possible conflicts of interest (source of funding, institutional affiliations). A new concept was also introduced, related to the participant access, after the study, to the best proven therapy, that is, the need that, *at the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study*.(art. 30).

The debate regarding this article is perhaps the most telling point of contention between the values of the most developed countries and those of other countries. An attempt was also made in the following meetings (2002 and 2004), to clarify the understanding of this article through the adoption of explanatory notes, without there being any consensus reached. Indeed, the "clarification note" to Article 30, adopted in 2004, only intensified the debate, saying to *benecessary to identify when planning trials of ways to access the volunteers of*

prophylactic procedures, diagnostic and therapeutic methods identified as beneficial in the study or access to other appropriate care. The mechanisms for the post-trial access or other care must be described in the study protocol, so that the Ethics Committee may consider these mechanisms during the review of the Protocol.

Then comes up, the sixth review, which involved more widely the medical profession, including the representations of Brazil and South Africa in the working group responsible to present the suggestions received. And in October 2008, in Seoul, the new version³⁸ was adopted. The new version reaffirms that *the well-being of the individual research subject must take precedence over all other interests* (art 6.); that *No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects* (art. 10); that *reasonable likelihood that this population or community stands to benefit from the results of the research*. (art.17), and *Authors have a duty to make publicly available the results of their research on human subjects*(art. 30).

As for the controversial issue dealt with in Article 30, there was the prevalence, now in Article 33, of the following wording: *At the conclusion of the study, patients entered into the study are entitled to be informed about the endpoint of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits*³⁸. In short, there has been no substantial change of what was foreseen in the 2000 version.

The controversies and divisions about the text continued, because at that time an important group of panelists believed that a clarification should be added to Article 32, stating that *before the start of the trial, all those responsible for the research must agree through participatory processes and the mechanisms to provide and maintain such care and treatment*. This only occurred, then, with the adoption of the new text of the Declaration of Helsinki in October 2013³⁸. Indeed, the Article 34 of the revised text says: *In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process*.

The Belmont Report³⁴, in turn, is organised into three parts, dedicated to examining the boundaries between practice and research, and fundamental

ethical principles and their applications. Especially with regard to these three principles (respect for persons, beneficence and justice), the document recognises that in most cases of research involving human beings, the respect for persons requires that the participation of individuals in a research should be voluntary and based on appropriate information; beneficence requires that in addition to protect the participants from damage, efforts should be made to ensure the greatest possible benefit, with minimal losses, and the justice principle recalls that, *whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.* Here too, as it can be seen, the concern for the fair distribution of burdens and benefits of a research did not actually consider the hypothesis of requiring, from the sponsor of a clinical research developed by private laboratory, the provision of drugs free of charge to clinical research participants after the end of the study.

*The International Ethical Guidelines for Biomedical Research Involving Human Subjects*³², prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with WHO, as adopted in 1993, requires that the researcher makes certain that *persons in underdeveloped communities will not ordinarily be involved in research that could be carried out reasonably well in developed communities; the research is responsive to the health needs and the priorities of the community in which it is to be carried out* (guideline 8).

The review of these guidelines in 2002³³, clarifies that before initiating the study, the researcher must ensure that the research *is responsive to the health needs and the priorities of the population or community in which it is to be carried out; and any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.* (now in guideline 10).

For the understanding of what is “reasonable availability” it is argued that it should be considered, on a case-by-case basis, *the severity of a subject’s medical condition; the effect of withdrawing the study drug (e.g., death of a subject); the cost to the subject or health service; and the question of undue inducement if an intervention is provided free of charge.* In addition, the guideline 21, states that

the sponsors are required to ensure the availability of *services that are a necessary part of the commitment of a sponsor to make a beneficial intervention or product developed as a result of the research reasonably available to the population or community concerned.* At that point, the guideline states that *The sponsors’ obligations in particular studies should be clarified before the research is begun. The research protocol should specify what health-care services will be made available, during and after the research, to the subjects themselves, to the community from which the subjects are drawn, or to the host country, and for how long.*

The International Declaration on Human Genetic Data 35, adopted at the 32nd UNESCO General Conference in 2004, suggests that benefits of the use of human genetic data for medical and scientific research, to be shared with the international community, could take the following forms, *in accordance with domestic law or policy and international agreement* : *special assistance to the persons and groups that have taken part in the research; access to medical care; provision of new diagnostics, facilities for new treatments or drugs stemming from the research; support for health services; capacity-building facilities for research purposes; development and strengthening of the capacity of developing countries to collect and process human genetic data, taking into consideration their specific problems; any other form consistent with the principles set out in this Declaration.* (art. 19).

Now, the *Universal Declaration on Bioethics and Human Rights*³⁶, adopted in 2005 by the 33rd General Conference of UNESCO, reflects, in a way, the consolidated ethical thought until that time. Thus, it states its aims as:

- *to promote equitable access to medical, scientific and technological developments as well as the greatest possible flow and the rapid sharing of knowledge concerning those developments and the sharing of benefits, with particular attention to the needs of developing countries; (article 2, paragraph f);*
- *The interests and welfare of the individual should have priority over the sole interest of science or society. (Article 3);*
- *The fundamental equality of all human beings in dignity and rights is to be respected so that they are treated justly and equitably. (art. 10);*
- *Solidarity among human beings and international cooperation towards that end are to be encouraged. (art. 13).*

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

(a) special and sustainable assistance to, and acknowledgement of, the persons and groups that have taken part in the research; (b) access to quality health care; (c) provision of new diagnostic and therapeutic modalities or products stemming from research; (d) support for health services; (e) access to scientific and technological knowledge; (f) capacity-building facilities for research purposes; (g) other forms of benefit consistent with the principles set out in this Declaration. (art. 15).

Still on the topic, the document provides that *when negotiating a research agreement, terms for collaboration and agreement on the benefits of research should be established with equal participation by those party to the negotiation.* (art. 21, item 4) .

In short, *the International Declaration on Human Genetic Data*³⁵ as well as *the Universal Declaration on Bioethics and Human Rights*³⁶, , both adopted by UNESCO with only one year apart between them (2004 and 2005 respectively), indicate the need for prior arrangements to research regarding the benefits arising from it, strengthening measures to promote social justice and suggesting - as an example - some forms of social return, including the provision of medicines resulting from the research. It is important to note, however, that in both documents is determined that this sharing of benefits should have been agreed previously, being in the research protocol. And such understanding is also marked in the 2013 revision of the *Declaration of Helsinki*³⁹.

The evolution of the theme in the Brazilian standardisation was no different. In fact, the Resolution 196/1996⁴⁰ of the Conselho Nacional de Saude (National Health Council), founded in statements and other international standards, considers ethical the research that ensures the free and informed consent of participants; commits to the maximum benefits and minimal damage and risks; ensures that foreseeable damages are avoided, and which is socially relevant, with significant benefits for the research subjects (guideline III.1, item d). It required, too, that it should be guaranteed to the research subjects: access to procedures, products or research agents (guideline III.3, item p) and that the research protocol explicitly points out the responsibilities of

the researcher, institution, promoter, and Sponsor (guideline VI.2 , item f).

To discipline specifically the field of research with new drugs, medicines, vaccines and diagnostic tests, the resolution 251/1997⁴¹ of the Conselho Nacional de Saude (National Health Council) was edited, reinforcing the need to include in the research protocol the guarantee that the sponsor, or failing that, the institution, researcher or promoter will ensure access to the medicine being tested, if their superiority to conventional treatment is show (norm IV.1, item m).

It also went into force, as of August 2008, the resolution 404/2008⁴² of the National Health Council, which insists on the theme: *at the end of the study, all participants must have guaranteed access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study* (item a) and clarifies, in one of the annotations, that the access should be extended to all who can benefit from the progress provided by clinical research, stating that it should include, for example, the industry's commitment to market the medicine *in the country where the method was tested on the population.*

Already in 2013, with the Resolution 466/2012⁴³ of the Conselho Nacional de Saude (National Health Council), there was no significant change concerning the provision of post-study medicines because *researches using experimental methodologies in the biomedical area involving humans (...) should also ensure (...) to all participants at the end of the study, by the sponsor, free of charge and indefinitely, the best proven prophylactic, diagnostic and therapeutic methods that had been demonstrated effective* (III. 3 guideline, item d).

Ethical commitment necessary

Some points should guide ethical reflection regarding the requirement to give the orphan drug, that has proved to be the most advantageous, to any of the participants in the clinical trial - free of charge and as needed. Perhaps the most important is to remember that, given the severity of rare diseases, all - the regulator institution, patients and doctors - must be willing to accept greater risks or side effects in the case of drugs that treat these diseases than in the case of drugs for diseases not so serious. Thus, it requires more of the participant, who is submitted to greater risks and discomforts, but at the same time offers more in terms of actual care and future prospects.

The analysis of the behaviour of the drug producer shows that the economic risk assumed by the sponsor, in the face of the relatively small market of orphan drugs, tends to be offset by financial incentives such as tax credits and eligibility for obtaining seven years of market exclusivity after approval of the drug, as seen in the United States and the European Union. Another important point seems to be the current understanding of the human community, Brazilian and international, that the benefits of scientific research are shared with society, especially since new products and therapeutic means or diagnostic resulting from the research are provided free of charge to participants, further reducing the small market of orphan drugs.

Nevertheless, the response most common seems to echo the wise lessons of the Greek philosopher. Indeed, it is indispensable to search a prior consensus on how to find the fairest possible way, that *mean amount* which, as Aristotle says, must be praised in all circumstances⁴¹ And this is just what those legal standards are showing: *In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an interven-*

tion identified as beneficial in the trial. (Declaration of Helsinki; 2013, art. 34)³⁹ The sponsors' obligations in particular studies should be clarified before the research is begun (International Ethical Guidelines for Biomedical Research Involving Human Subjects, 2002, guideline 21³³; when negotiating a research agreement, terms for collaboration and agreement on the benefits of research should be established with equal participation by those party to the negotiation. (Universal Declaration on Bioethics and Human Rights, 2005, art. 21, item 4³⁶.

It is necessary that all actors involved in the process, whose interests may converge but not necessarily match up, be able to find the optimal balance between risks and benefits assumed individually. Participants in clinical trials, pharmaceutical companies and public authorities, both as regulators and health care providers, take risks and can receive benefits that, in the case of rare diseases, for which orphan drugs are in general developed - are essentially different from those obtained with the development of other medicines. It is essential to consider each of one of these actors to elaborate - in an open debate - the ethical response.

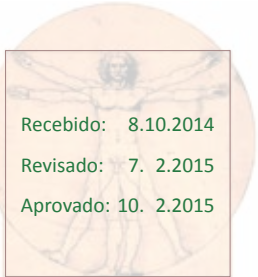
Work produced under the Centre for Studies and Health Law Research (Cepedisa / Center for Research in Health Law), University of São Paulo (USP).

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