Provision of investigational drug after clinical research – Review of literature, national and international guidelines

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Summary

The post-trial access to investigational drugs has been the object of discussion since the late 1980s at least, initially linked to trials carried out in acquired immunodeficiency syndrome and, particularly, in developing countries, where the concern with patient vulnerability is more important. National and international guidelines do mention the subject; however, the complexity of the issue is not easily addressed and usually requires additional and specific discussions. The decision on providing the investigational drug after the trial shall rest on at least two dimensions: efficacy and safety assessments, as the new drug is still on the experimental phase. Each clinical trial shall have its own assessment, taking into account the disease being studied, as well as the study population and their specific needs. Therefore, the nature of post-trial obligations cannot be considered the same in all situations and contexts; nevertheless, it should be assured that the relationship developed between investigators and patients during the study must be always terminated with respect and responsibility.

Keywords: Continuity of patient care; drugs, investigational; clinical research; bioethics; ethics committees, research; vulnerability.

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Conflict of interest:
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The globalization of clinical trials, observed in recent years, brought up new issues and the continuity of treatment that includes the drug under investigation, after research completion, is one of them. The subject can be seen on the pages of scientific journals since the late 1980s, particularly associated with continuing treatment in patients who participated in studies on HIV (human immunodeficiency virus) and/or AIDS (acquired immunodeficiency syndrome). The continuity of medical care, including treatment, is based on the ethical responsibility to compensate individuals who voluntarily agreed to participate in the research for the development of science, and were exposed to unknown risks, additional invasive procedures, questions about their habits and personal life, among others.

Additionally, the research participants may not have, after the study conclusion, access to the drug in the healthcare service of their country or even the medical care they need[1]. This concern is certainly greater in developing countries, as the research participants (and the population itself) are particularly vulnerable as a result of poverty, illiteracy, limited resources, insufficient access to healthcare, and lack of familiarity with clinical research[2].

International guidelines

National and international documents refer to the subject of post-trial access to the investigational drug. The Declaration of Helsinki, accepted and recognized worldwide as a reference document on biomedical ethics (World Medical Association, WMA, 1964), incorporated the subject related to post-research obligations[3] only in the review carried out in 2000, stating that "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". A note of clarification issued by the WMA in 2004, added: "it is necessary, during the study planning, to identify ways to ensure the procedures identified as beneficial in the study or access to other appropriate care."

In the sixth review of the Declaration (Korea, 2008), the issue was revisited and, since then, the new text include, in paragraphs 14 and 33, respectively: "the protocol must describe post-study agreements so that the research subjects have access to interventions identified as beneficial in the study or access to other appropriate care or benefits" and "at the study conclusion, patients included in it have the right to be informed about the results and share the benefits of the study, for instance, access to interventions identified in the study as beneficial or other appropriate care"[4].

Another important international guideline is the Council for International Organizations of Medical Sciences (CIOMS), a non-governmental, non-profit organization created in 1949 by the World Health Organization (WHO) and the United Nations Educational, Scientific and Cultural Organization (UNESCO)[5]. In its 1993 publication, it mentions that the product under study should be "reasonably available" to the country or the inhabitants of the community that hosted the study and that exceptions should be justified and agreed by all concerned before the start of the study. This text was also reviewed in 2002: "the sponsor and the investigator shall make every effort to ensure that any intervention or product developed or knowledge generated, is made reasonably available for the benefit of the population or community"[5,6]. The Declaration points out that the post-trial access is a benefit only to the research subjects, while the CIOMS extends this group to also include the community or population. In dealing with the documentation on post-trial availability, the Declaration proposes that the preparations for post-trial access should be documented in the research protocol, while the CIOMS demands that they be incorporated into the Free and Informed Consent Form[3].

The WHO published, in 2000, the "Operational Guidelines for Ethics Committees that Review Biomedical Research". When dealing with recruitment of patients in clinical studies (item 6.2.6.6), the need for "a description of the availability and affordability of any successful study product to the concerned communities, following the research" is mentioned[5].

Other commonly cited guidelines are those of the Nuffield Council on Bioethics[7] and the National Bioethics Advisory Commission (NBAC)[8] of 2001 and 2003, respectively. In dealing with the sponsors' responsibility, the first document emphasizes that researchers must commit, before starting a trial, to ensure that upon completion, participants will have access to effective interventions. However, it also recognizes that access provision will depend on several factors, such as availability of alternatives, the threat that the disease brings and the cost of providing the drug(s) and that the responsibility of making a successful intervention available is, primarily, of governments[7]. The NBAC recommends that research projects must include an explanation on how new interventions will be made available to some or all the populations of the countries that are hosting the research, in addition to the study volunteers themselves, when they are proven to be effective, after the research[8].

Finally, the Universal Declaration on Bioethics and Human Rights (UNESCO, 2005), signed by 191 countries, including Brazil, quotes (Art. 15): "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". The "benefits", however, can take many forms, consistent with the principles of the Declaration, not necessarily continuity of treatment[9].

National guidelines

In Brazil, the reference document in biomedical research is Resolution 196, published by the Conselho Nacional de Saúde – National Health Council (CNS), in 1996[10]. It depicts, in several paragraphs, quotes that make direct or indirect reference to the issue of post-trial drug access (III.3m): "ensure that research carried out in communities, wherever possible, will translate into benefits of which effects will continue to be felt after its completion"; (III.3n) "ensure the return of benefits gained through researches to individuals and the communities in which they are carried out"; (III.3p) "to ensure the research subjects will receive the benefits resulting from the project, either in terms of social return, access to procedures, products or investigation agents"; (V.3) "as soon as the superiority of one method undergoing investigation over another is established, the project should be suspended, and all subjects must be offered the benefits of the best regimen"; (VI.3h) "present estimates of reimbursements to research subjects; the amount cannot be such that it may interfere with the autonomy of the individual's or the person in charge of this decision on whether or not participate in the research".

Resolution 251 of the CNS, 1997, quotes the subject more explicitly (IV.m): "it shall be ensured by the sponsor or, if it does not exist, by the institution, investigator or promoter, access to drug under test, should it be proven to be superior over the conventional treatment"[11].

Considering that the Declaration of Helsinki was under review, the CNS published Resolution 404 in September 2008: "considering the responsibility of the CNS to protect the integrity of research subjects and the several existing national and international guidelines, all participating patients must have guaranteed access to the best methods identified by the study, preserving the 2000 version of the Declaration of Helsinki"[12].

Available literature: original articles and reviews

There are few published studies on post-trial drug access and the existing ones are mostly on HIV/AIDS, where the subject was born.

A survey carried out in developing countries, with researchers in the HIV/AIDS field, concluded that the patient population of the studies should benefit from the study, and more than half of the professionals surveyed said that the interventions (HIV drugs) should be provided to the research population after the study, for a year or more[13].

A study carried out through interviews with presidents and members of research ethics comittees (RECs), as well as researchers and research participants, evaluated the ethical aspects related to conducting clinical trials outside the United States. Sixty-five of 94 questionnaires sent to members of RECs returned, as well as 117 of 159 sent to researchers and 359 of 510 sent to research participants. Eighty-three percent of research participants (of which 43% were from Latin America, Brazil included), 29% of RECs members and 42% of researchers said the drugs should be provided for all infected people worldwide, if proven beneficial. Most research participants from Europe and Latin America said that the drug should be continued, while those from North America, Australia and Thailand said that the drug should be made available at a price that a middle-class individual could buy[14].

A qualitative study, carried out through focal groups in Kenya, with 89 subjects (potential patients for HIV/AIDS studies, researchers and administrators) has brought, as conclusion, that it would not be reasonable to discontinue therapy after studies in HIV/AIDS patients, except in fully justified cases[15].

A systematic review of clinical studies enrolled in international registries, from 2004 to 2007, was carried out by Cohen et al.[16] involving HIV/AIDS, malaria and tuberculosis. Of the 312 studies that were included, the majority in developed countries (56%), with 28% being sponsored by pharmaceutical companies, only 4 (1.3%) mentioned post-study provisions: one mentioned the post-study drug would be provided by the governments of the respective countries; another, that the participants who became infected with HIV during the study would receive counseling and education about the infection/disease and access to necessary healthcare, including free-of-charge antiretroviral drugs, if indicated.

In 2008, Zong[17] published an article discussing the issue of post-trial continuity of care, citing the main international guidelines and recommendations about the subject, including Resolution 196/96 of the CNS. After careful reflection, the author suggests collaborative partnership between the various participants in the research scenario: the REC (by approving the conditions of drug provision after the research), the sponsor (by organizing the drug provision), the local health system (by distributing and monitoring patients), researchers, and finally, the patients, by following the appropriate rules of provision, regular attendance at follow-up visits and adequate reporting of possible adverse events.

Ciaranello et al.[18] published in 2009, a systematic review of protocols and informed consents for phase III and IV clinical trials with ART, carried out between 1987 and 2006. Studies were selected from www.clinicaltrials.gov and from the AIDS Clinical Trials Group (ACTG) registry, with the purpose of analyzing the reference to post-trial services. Thirty-one studies met the inclusion criteria: 14 (45%) trials mentioned some post-trial service: 12 (39%) mentioned the study drugs (10 of them offered the test drug) and 5 (16%) mentioned healthcare services. Of the 10 studies that offered the medication after the study, 8 did so with sponsorship from industry; 6 offered

the drug to all study participants until it became available commercially, or for a defined period, and 2 of them only to patients who completed the study in the experimental arm. This diversity of actions reflects the differences in interpretation of the current guidelines.

Sofaer et al.[19] described the opinion of 93 individuals who participated in clinical trials in chronic diseases in the United States. In this study, patients were divided into 10 focal groups. Many participants felt that researchers, sponsors and insurance companies should share the post-trial obligations. Others commented that no care or drug should be necessary after the research, but there was an almost general agreement that patients should receive information about the study and its results. The authors conclude by suggesting that the debate on post-trial obligations must go beyond the issue of the test drug.

Barsdof et al.[20], in a study published in 2010, assessed the viewpoints of a community in South Africa regarding the provision of HIV vaccines, after participating in research on contamination prevention: 29 adults participated in depth interviews. According to them, researchers should help patients have access to treatments and healthcare because "they are in a position to do that" and because "they have a relationship with the research participants".

A study published by Shah et al.[21], in 2009, assessed whether the NIH guidelines have been established in studies sponsored by it in developing countries. The 18 studies identified in the database of the Division of AIDS (DAIDS) contained access plans after the research: more than 70% (13 of 18) had specific mechanisms for that, but none of them guaranteed long-term access. All but one study discussed the post-study topic in the protocol or informed consent. The study that did not do it, addressed the issue in letters sent to the DAIDS. Half of the included studies contained descriptions of post-study access that included collaboration with outside sources or national access programs, created by the governments of the countries hosting the researches. None of the studies stated that the research participants would receive priority access in relation to other patients in the country. The authors conclude that the strength and shape of the NIH guidelines encourage researchers to seek alternatives and collaboration to facilitate access to the required treatment. At the same time, the flexibility of the guidelines facilitates and encourages the learning of practical difficulties, a more effective strategy than imposing requirements that researchers may be unable to meet[21].

The NIH has enlightening guidelines on various aspects of this theme. For instance, one of the questions covered by the Questions and Answers (Q&A) session is why the NIH itself does not provide antiretroviral treatment after completion of the study carried out by themselves[22]. The answer is the justification that the NIH is statutorily authorized to conduct and support biomedical research. In this context, it cannot give support or provide medicinal products outside the research situation. Still, it acknowledges the need to assess alternatives for continuing treatment after the study. It also explains why the policy applies only to the area of HIV/AIDS, and only for developing countries, where the discontinuity of treatment could have tragic consequences, including increased risk of mortality. When the study includes research centers inside and outside the United States, the guideline applies only to those outside the country.

Thus, it can be observed an additional concern with patients from other countries, unlike what is usually seen when criticisms are made to the "unethical" conduct of international multicenter studies in countries of lower income. The answer to the question: "Does the treatment after the study have to be the same regimen used during the research?" clarifies that the purpose of the guideline is to ensure that patients continue to receive effective treatment after the study, but not specifically a particular type of treatment. Treatment should be determined based on individual medical needs, on what is available in the country, and the scientific progress in the study field.

In Brazil, Cabral et al.[23] address the issue of post-trial provision also with predominant focus on studies in the area of HIV/AIDS. In the article, the authors comment that making the research product reasonably accessible is not enough to prevent the exploitation of the participant, in most cases. According to them, when the research is of high risk for the individual, this principle is not sufficient to ensure non-exploitation.

One usually speaks only of benefits to patients, putting aside the important concern that must be considered regarding the potential risks of a product not yet fully studied[24]. Falit & Gross[25] discuss the question of the risks involved and of patient protection, in an article from 2008 about terminally ill patients' access to experimental drugs, highlighting the importance of minimizing damage, seeking balance in the selection of appropriate treatment for these patients.

Lacativa et al.[26] published in 2008, the result of a cross-sectional study in an outpatient research center, in Rio de Janeiro, in which a questionnaire was used to assess how patients perceived their participation in research at that center, and what motivated them to participate. One of the questions specifically investigated why patients agreed to participate. Fifty-nine percent answered that the main motive was to learn more about their own health and 47% said it was for the benefit of others in the future. Lack of or difficulty to obtain medical care in their city was mentioned by 21% of respondents; to receive free medication and examinations was mentioned by only 16% of interviewees.

In 2007 and 2008, three review articles on the subject were published in Brazil on the themes presented here, proposing some solutions and at the same time, stimulating debate and acknowledging this discussion as new and still controversial, within the environment of the national and international ethics[3,27,28].

A recent work carried out as a doctoral thesis evaluated the views of the key stakeholders on the continuing provision of drugs after the completion of clinical trials (clinical researchers, REC members, sponsors and patients) through an internet survey. Questionnaires and the respective Informed Consent Forms were sent by e-mail, between October 2009 and January 2010, to REC members (all RECs registered with CONEP by that date), researchers (in two therapeutic areas, HIV/AIDS and *diabetes mellitus*) and sponsors. Researchers were asked to apply the questionnaire to their research patients. The response rate of RECs was 20.7% (124 responses of 599 questionnaires), 20% for the researchers (58 of 290) and 45.3% for the sponsors (24 of 53). Fifty-four patients invited by their doctors answered it. With respect to information contained in the consent form, the item that contained the least information was how to obtain the drug after the study, for all groups surveyed.

When asked about who should receive the test drug after the study, patients and the RECs answered that everyone should receive the drug after the study (respectively 60.4 and 35.3%); among researchers, most (43.1%) answered that the drug should be provided to people participating in the study and 39.7% of them answered that the drug should be given to people who would benefit from the study medication. The sponsors felt that the study drug should be given to research participants who would benefit from it (50%).

There was a consensus among groups regarding that, with continuing treatment, this should be provided by the sponsor and for free. When answering the question of for how long the drug should be provided, researchers and sponsors considered that the drug should be provided until it would be available to the public, while REC members stated that provision should continue while there were benefits to the patient. The patients responded that the benefit should be maintained for life. Due to the limitations of this study (sample representativeness, population restricted to internet users), its results cannot be generalized, but contribute to the views of various participants in the national clinical research scenario[29].

A Master's Degree dissertation submitted in 2009 also assessed the issue of drug provision after research, interviewing 25 professionals from the pharmaceutical industry and Clinical Research Organizations (CROs). It was observed that patients with severe and life-threatening illnesses are not neglected and always receive the medication after the end of the study. The author comments that the existing legislation in Brazil was not sufficiently comprehensive for all situations and that CONEP kept an uncompromising stance against the request of post-study drug provision, regardless of the type of research and patients' needs[30].

A work published by researchers in the field of oncology at Duke University in 2010, assessed the implications of "off-protocol" treatments in relation to patient safety, access to healthcare and inclusion in clinical trials[31]. In this work, 172 phase-III studies were selected according to criteria defined by the authors. Although 47% of the experimental interventions proved to be superior in at least one major clinical outcome, only 27% of them showed improvement in relation to survival. In about two thirds of randomized clinical trials, at least a greater toxicity was observed in the experimental arm when compared to standard therapy. Additionally, although in most clinical studies the outcomes were at least comparable between the two groups, in 11 randomized trials, patients in the experimental arm got worse. These are potential consequences of experimental treatments outside the research protocols.

A meeting promoted by CONEP in 2009 led to the discussion of post-trial access issue, with the contribution of various participants in the clinical research scenario[32]. It was clear, for instance, that effectiveness cannot always be ensured immediately after study completion and, in phase-III double-blind studies, at the end of the study, it is yet unknown which medication each patient is receiving and to break the randomization code implies in protocol violation. At this time, ANVISA reaffirmed that the drug provision as an extension of the study would be the ideal process, as the patient would receive follow-up according to the protocol, in a (still) controlled research environment. CONEP did not agree with changing the text regarding the norms, suggesting the maintenance of the access request as a general rule, while there is benefit to the patient.

At the start of a clinical trial, the physician becomes the investigator, the patient, formerly treated in care, becomes the research subject and treatment becomes an investigational drug, according to the research protocol. In this context, the research protocol is simply part of the formation of scientific evidence, and thus differs from the final evidence, consisting of a set of studies and publications that can be transformed into guidelines and consensuses. Additionally, the patient is the focus of treatment in medical assistance and in clinical research, it is the drug[29].

Conflicting legislation points

The analysis of post-trial access issue, from the legal point of view, shows difficulties and even prohibitions, when attempting to enable medication donation. Article 12 of Law 6360, of 1976, for instance, cites: "none of the products mentioned in this Law, including imported ones, can

be industrialized, exposed for sale or delivered to the consumer before it is registered with the Ministry of Health"[33]. The only exception to this rule is the use of experimental drugs in clinical trials, controlled by the physician in charge and approved by ANVISA, limited to three years, after which the drug will be subject to confiscation, in accordance with Article 24 of Law 6360[33].

Interestingly, although addressing the same theme – experimental drug use – the Collegiate Board Resolutions (RDCs) of ANVISA and the CNS do not mention the same decrees and laws in their initial "considerations". Law 6360, for instance, which deals with health surveillance to which drugs, pharmaceutical raw materials, etc. are subject, is cited in all RDCs of ANVISA, but in none of CNS resolutions. As for the CNS resolutions, they usually cite Decree #99438 of 1990 (organization and competences of the National Health Council), the Organic Health Law 8080 of 1990 (on the conditions of healthcare, organization and operation of services), Law 8142 of 1990 (on the participation of the community regarding the management of the Brazilian Public Health System - SUS) and Decree 5839 of 2006 (on the organization, competences and election processes of the National Health Council)[34].

In general, the laws mentioned in the resolutions, decrees or legislative acts are those that empower the authorities to regulate on the subject or deal with the matter to be regulated. Thus, the laws that created and established the powers of the CNS and ANVISA are distinct: the CNS has an advisory nature only and should work with public health policies, only. ANVISA deals with product registration and sanitary surveillance. Although both protect the same asset (health), one agency might eventually recommend something that is practically impossible for the other.

Conclusion

The investigational drug continuity after the clinical research is necessary in some situations, but may not be appropriate in others. The decision must be submitted to at least two assessments: efficacy and safety of the new experimental drug. And possibly, the solution is not going to be either sole or simple; each clinical study must have its own assessment, with its specificities, as every disease has its own characteristics and each population has specific needs. The nature of post-trial obligations, therefore, can not be considered the same in all situations and contexts; however, the relationship created between researchers and patients during a clinical trial should always be terminated with responsibility and respect.

First, one should consider and reflect upon the differences between the locations where the research is carried out and the available health area resources. Instead of denying or limiting the participation of patients and communities that can benefit from the research, the interaction between the various participants and sectors is strongly recommended. Second, to require agreements made prior to the start of the research, one is encouraged to build collaborative partnerships between sponsors, whether they are public or private, researchers, the government and other organizations. And, while allowing flexibility, to enable the development of proposals so that access can be guaranteed in the long term, after the research has ended and not only in the period immediately following its conclusion. Third, to extrapolate results and experiences from one therapeutic area to another may not be so simple.

The primary goal of clinical research is to contribute to scientific knowledge and, if properly designed and conducted, it is the most ethical and methodologically appropriate way to attain new therapeutic options. The benefits resulting from clinical research are, therefore, extended to all people, not only to the research participants.

It is also noteworthy the fact that legislation on these issues (RDC 26/99 on Expanded Access) is being timely reviewed by ANVISA, with the active participation of the government, sponsors (industry and CROs), researchers and CONEP, in order to incorporate aspects related to the compassionate use of experimental drugs and drug provision after the research, in addition to reviewing processes as a whole.

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