Guarantee of Access to Post-Clinical Trial Drugs

ABRACRO – Associação Brasileira de Organizações Representativas de Pesquisa Clínica [Brazilian Association of Clinical Research Organizations]
São Paulo, 2011
Table of Contents

Introduction ....................................................................................................................................... 3
ABRACRO - Vitor Harada .................................................................................................................... 4
Dr. Freddy Goldberg Eliaschewitz - Endocrinologist ................................................................. 7
Dr. Luis Augusto Tavares Russo - Endocrinologist ....................................................................... 10
Dr. Sonia Dainesi - Endocrinologist ............................................................................................... 13
Dr. Nelson Keiske Ono - Traumatologist ......................................................................................... 17
Paula Goldenstein Strassmann and Maristela Precivale - Statistics ........................................ 19
Dr. Angela Fan Chi Kung - Lawyer ................................................................................................ 22
ANVISA - Patrícia Ferrari Andreotti and Fanny Nascimento Moura Viana ................................ 25
Instituto Nacional de Salud Publica [National Institute of Public Health] (Mexico) - Dr. Julieta Ivone Castro Romero ................................................................. 28
Introduction

GUARANTEE OF ACCESS TO POST-CLINICAL TRIALS DRUGS

The provision of post-study medication is a highly important issue and requires further discussions in order to achieve an understanding between the various parts dealing with the issue in the country.

One has to weigh the clinical, ethical and legal aspects in this discussion, as well as to consider the point of view of CROs, investigators, industry experts, lawyers, ANVISA and CONEP, considering the Sistema Único de Saúde (SUS) [Unified Health System] scenario.

In order to present to the parties interested and to the society the points and counterpoints of the discussion, ABRACRO has organized this publication, which contains the opinions of several health professionals, a lawyer specialized in Health Law, a statistician specialized in Clinical Research, as well as the point view of ANVISA, Agência Nacional de Vigilância Sanitária [National Agency for Health Surveillance]. Unfortunately CONEP (Comissão Nacional de Ética em Pesquisa), the National Research Ethics Committee, has declined the invitation to participate in this publication and state its arguments regarding the issue to the interested parties.

By the end of the publication, the wording of the Chairman of the Bioethics Committee from the National Institute of Public Health of Mexico, one of the leading countries in clinical trials in Latin America is presented.
ABRACRO - Vitor Harada

INTRODUCTION

Ensuring access to investigational products after the study is necessary in certain situations, but may not be suitable for all indications. Our regulations need to foresee this type of provision and authorize it only in some specific cases.

Currently, CONEP regulates the approval of clinical trials through means of the sponsor’s guarantee to provide free and unrestricted access to the investigational product, should the Principal Investigator prescribe it by the end of the treatment. The rule is unique and it applies to any kind of clinical trial conducted in Brazil, even for vaccine studies, prophylactic trials with cessation of risk factor, or acute indications, in which there is need for further continued.

THE ANALYSIS

In clinical research, as well as in medical practice, most interventions involve risks. For the treatment of each patient, a risk management that assesses two distinct dimensions is performed: efficacy or benefits of the treatment and the safety and possible adverse reactions from the treatment. It is the balance between these two variables that define the therapeutic value of a treatment and whether it is suitable for a particular indication.

At the end of a single clinical study, either phase II or III, we may have a good idea regarding the efficacy of the product, but generally, we do not know for sure about its safety. During the study, all adverse events that have no known definite causal relationship with the drug are captured, and it is through the statistics of many studies that the possible related risks are discovered.

In cases of serious diseases with no proven alternative treatment, or in cases in which there is immediate life-threatening risk, there is no discussion about the need of post-study access. In these cases, the efficacy and possibility to save a life overlap the risks, regardless of any safety issues.

In other cases, even when the efficacy is clear, we do not know all the statistics regarding the safety of the product under study. In the absence of the possibility of assessing this balance between efficacy and safety and having known and proven alternative treatments, the more conservative decision would be to not continue the use of a product that is still in its experimental phase.

---

1 Paragraph 8 of Declaration of Helsinki.
ACCESS TO THE CLINICAL TRIAL VERSUS POST-CLINICAL TRIAL ACCESS

Apparently, there is consensus on the fact that it is not appropriate to provide the post-study investigational product in every case, but there is still a problem.

The need to possibly provide a product that it is still under tests and without record of its long-term use can be potentially harmful to the subject and has dubious legal basis. Although CONEP see the provision decision as a sole responsibility of the Investigator, in reality it is a responsibility shared by the investigator, sponsor and the institution in which the subject is receiving care for.

In some cases, the actual supply would be ethically dubious and that causes fear and shy away sponsors from clinical trials, whether they are from private, public, academic, national or international sources.

In addition to the abovementioned case, the very possibility of providing the drug where it makes no sense (vaccines, prophylactic, etc...), prevents many sponsors from performing clinical trials in Brazil.

There is much discussion regarding the post-study access, but the access to the clinical trial itself is not discussed. Adding this complication to our long regulatory timeframes and double ethical approval, many patients end up being deprived of the opportunity to participate in studies that are their only hope for treatment. One example is the case of our former Republican Vice-President, who is known to have gone to the United States in order to participate in a clinical trial that could have been conducted in Brazil.

THE USUAL COUNTERPOINT

The Declaration of Helsinki, in its paragraph 33, states that the research subject should be given information regarding the study outcome and sharing the benefits deriving there from. Our Brazilian regulations also provide that return.

Facing this point, I point out that, at the same time, the item 6 says that the welfare of the subject should prevail over any other interest.

As explained before, by opening up the possibility of providing an unproven substance, except in the cases already mentioned, we are not taking the most conservative measure for the patient’s safety.

There are other indirect benefits, such as the level of attention and care given to a subject, knowledge generation and discovery of new treatments.

The patents of innovative drugs expire, but the knowledge and therapeutic alternatives are common, universal and long-lasting.
ABRACRO – Guarantee of Access to Post-Clinical Trial Drugs

Speaking about this matter, we are reminded of the bioequivalence studies. These studies are necessary to the approval of generic drugs, and it is undeniable that these medications are a truly important component of the public health system. These studies are done with healthy volunteers and it is impossible that they benefit directly from the object of study, reinforcing the point that the collective benefit can add up to the direct individual benefit.

THE PATIENT’S FREE WILL

Our legislation does not allow the payment of research subjects so there is no economic influence on the decision to participate in the study, but the promise of a possible unrestricted and permanent supply of the investigational product is an attraction strong enough to influence the patient’s decision. Stronger than a monetary payment.

CONCLUSION

The balance between allowing the guarantee of the subject’s well-being and the access to studies would be set by previously defining that only cases which are life-threatening or serious diseases with no alternative treatment are valid for the supply of the investigational product after the clinical trial.

In these cases, there is no doubt about the balance between efficacy and safety of research subjects and the suggestion is that only these studies require the phrasing regarding post-study guarantee in the free and informed consent forms, aiming for the safety of the patient himself/herself.

The indications in which there are proven and known treatments would be left out, and if there are situations that diverge from the main rule, this requirement could be made individually to the clinical trial in question, at the time of their evaluation by the Ethics Committee, on a case by case basis.

Vitor Harada
President Director – ABRACRO
Clinical Operations Director of ICON Clinical Research in Brazil
ACCESS TO THE POST-CLINICAL TRIAL MEDICATION

The issue of access to experimental drugs after completing a clinical trial is a complex subject involving ethical, moral, humanitarian, economic, legal and especially medical. For these reasons it is not possible to adopt a reductionist approach, like for or against, without carefully examining each case in its circumstances and peculiarities.

In clinical research, the medication is used strictly according to a protocol, and it is in this circumstance that the ethical and regulatory authorities allowed its use within well-defined criteria for inclusion, exclusion and discontinuation. Approval was granted because the risk/benefit ratio, in these circumstances and for a limited time, has been evaluated as favorable, considering that the goal of any research is to generate knowledge. Thus, even if a research volunteer has obtained benefit during the study, it does not mean that this would be the most appropriate treatment to be prescribed. Outside the clinical trial scenario, the physician must decide which is the best treatment available, based on risk/benefit and cost/effectiveness assessment, knowledge generated not by a single research, but by a series of studies involving hundreds or thousands of people, and whose results were scrutinized by regulatory authorities during the approval process.

To assume that, just because one patient had therapeutic benefit over a comparator in a clinical trial, this is the best treatment is a serious mistake that can yield disastrous consequences.

Take an example from real life that my experience as an investigator allowed me to observe: Some years ago we conducted a study in type 2 diabetes that compared the metabolic control achieved with an experimental drug called rogaglitazar compared to treatment with a sulfonylurea, which is widely used up to this date. The study was 24 weeks long and the primary endpoint was the change in glycated hemoglobin levels between baseline and end of the study visit. Suppose that a particular patient (as it happened with several) has reached, with rogaglitazar, normalization of glycated hemoglobin without presenting hypoglycemic episodes, which are common with sulfonylureas. This was the greatest benefit to be gained from this study. Imagine that depending on the outcome, the investigator continued to supply the experimental drug to the former volunteer, now patient. After some time, the drug development was discontinued for causing bladder cancer, and all patients exposed to the drug had to undergo years of tests by cystoscopy and urine cytology tests. On the other hand, the patient in question could, at the end of the study, be re-treated with metformin (free in the popular pharmacy), which is as potent as rogaglitazar and does not cause hypoglycemia, but this drug was not part of the clinical trial protocol.

From this example it is clear that the fact that the drug was demonstrated to be superior in one parameter over a certain comparator used in a clinical trial does not mean it should be prescribed as a treatment.
This is one of the reasons for which the Declaration of Helsinki, in its paragraph 30, states that all participants must be assured access to the PROVEN best therapeutic methods. While the resolution of our CNS 251/97 refer to PROVEN SUPERIORITY (item m) and the BEST TREATMENT REGIME (item v-3). The text of the statement refers only to those clinical trials comparing two treatment options that have already been approved, whose safety profile is known, in order to establish the superiority of one or the other treatment.

In addition, the dispensing of drugs that are not yet licensed and outside of clinical trials may configure the crime of illegal medical practice or lack of ethics. The legal and ethical authorities have established these safeguards to prevent a non-approved medication from being used as a treatment.

Therefore, an initial and necessary step before establishing the requirement to provide post-study experimental medication would be to modify the current legal framework which turns the doctor who provides the drug into a criminal and induces criminal behavior by CONEP.

The responsibility of the industry in this case is limited, because outside of a clinical trial, it is only responsible for what happens with the use of its medication if the treatment is conducted according to the label approved in the country, so the responsibility lies entirely on the physician.

It is expected that no doctor wants to indicate an experimental treatment without legal protection to do so. Thus, the indiscriminate requirement of post-study medication supplies ends up being inefficient and generates insecurity by the investigators, sponsors and medical class.

However, the end of the study brings, without a doubt, an ethical dilemma that is the suspension of a treatment that may have been effective.

For situations involving serious, life-threatening or limiting diseases without an equivalent alternative medication, or when there is excessive risk in the substitution of medication, it can be maintained and is provided without any costs by the sponsor within the legal framework of a protocol extension for the patient who had benefited from it. In this case the expanded access is being duly justified before ANVISA or before the donation of regulated medicines.

In such circumstances, the free access to the post-study experimental medication has always existed and shall continue to exist.

In principle, no doctor should use an experimental drug as a treatment if there is an equivalent approved medication. Especially in a country like ours, in which the right to healthcare is universal and guaranteed by the constitution.

If in practice this constitutional right is not fulfilled, this is the problem to be solved rather than throw it on the back of the medical class.
The responsibility to alleviate the difficulty of access to treatment is a task of the government and the society as a whole and cannot be solved in a way that physicians have a professionally irresponsible attitude or by inducing patients to demand treatments whose safety has not been proven yet.

Dr. Freddy Goldberg Eliaschewitz
Master in Endocrinology by Universidade de São Paulo [University of São Paulo]
Clinical Director – CPCLin Centro de Pesquisas Clinicas – [CPCLin Clinical Research Center]
APCB Director – Associação de Pesquisa Clinica do Brasil [Brazilian Clinical Research Association]
**POST-STUDY ACCESS: SEARCHING FOR A SOLUTION**

The long debate about the responsibility of sponsors to provide treatment after the clinical trials requires rationalization and a solution within a spirit of intellectual honesty and scientific clarity. After years of discussion, it is time to find, within the ethical principles and health safety, a reasonable and rational solution, set apart from emotions and justicialism.

Within the scope of WMA\(^1\) (World Medical Organization) and reviews of the Declaration of Helsinki, a just and reasonable “way out” to the post-study situation has always been sought after. The latest amendments ended up suffering double interpretation: by the authorities of developed countries in a more flexible way and in poor and developing countries in another way, more intransigent and comprehensive.

In Brazil, the requirement that “providing ample and unrestricted access to the research subject in case it shows superiority or current treatment” has been conditioned for ethical approval in the scope of the central committee on studies involving foreign participation. It is unclear whether the provision is *sine di*, and at what time this drug superiority has to be demonstrated and achieved (sometimes it lacks time and further analysis), without forgetting something important, who would be responsible for also monitoring these patients *sine di* (since they are followed up in a controlled and especial way during the research)? Furthermore: who will be responsible should health damage occur after the studies?

The document of “access to post-study experimental drug” has passed the *sine qua non* condition for approval, which ultimately becomes, without a doubt, one of the multiple barriers (in addition to the bureaucracy and double ethical review in the country for studies with foreign participation) and leads many sponsors to stray away from conducting studies in the country, which is known by the clear decline in number of projects\(^2\).

**THE MYTH OF FREE SUPPLY**

The break of some paradigms and myths like the real motivation for participation by the population in clinical studies is remarkably noted. The literature clearly demonstrates that the search “free medication and treatment” is not the main motivation of volunteers. Other more important and enlightening factors such as *pure altruism for the good of mankind, and clear determination of volunteers to learn more about their own health condition*, are reasons that are repeated in analyses, standing in front of “access to drugs” as main determinant factors for voluntary participation in studies. In a work performed in a research site\(^3\), not only these data have been clearly demonstrated, as was also noted that the social, economic, and cultural level of voluntary participants resembled the profile of the average population of the city of Rio de Janeiro, where the study was conducted, not consisting of a fragile population\(^3\) (another myth in relation to research subjects in our country).
Similarly, this issue of access to investigational drugs was also discussed in other countries, not only from the perspective of the subjects’ opinions, but also from investigators and members of Ethics Review Boards in multinational studies with HIV/AIDS. Although the volunteers favor that the “majority” of project participants and the entire population that needs the medication worldwide should be given the medication, both members of IRBs/REC (Independent Review Board/Research Ethics Committee) and the investigators were far more conservative and less expansive regarding “for whom and how” the medication should be guaranteed.

**SYSTEMATIZATION**

Thus, it is necessary to observe some rules for conditions that may determine advantages and outweigh the risks of post-study access of a new experimental drug for our population.

A systematization for the country (which no doubt is not a country of extreme poverty anymore, increasingly assuming a leadership role in all sectors in the scientific field), with defined rules as recently occurred in a comprehensive debate in American society in the document “Final Rules for Expanded Access to Investigational Drugs for Investigational Treatment for Drugs and Changing” published by the FDA in 2009 is needed. In the search of a straightforward and rational solution for standardization, based on scientific evidence, the whole society and the parties involved have taken part, from the patients’ associations to the lawyer’s associations in the country, which could widely provide their opinion in this document. Standards were created to know under what circumstances the experimental drug should be demanded, to establish criteria for different types of access expansion and the costs to be covered for different groups and populations. As a key factor, it was discussed what would be the definition for serious and complex medical conditions in order to seek the conditions that deserve analysis for expanding the use of drugs, including:

- Conditions that cause serious disability (e.g.: stroke, head and spinal cord trauma);
- Conditions that cause severe pain preventing normal daily activities (such as arthritis);
- Conditions that require frequent monitoring (such as schizophrenia and other psychoses);
- Conditions that could lead to serious complications and death (like cancer);
- It was also included the definition of serious adverse events research, whether they are situations that lead to hospitalization or its prolongation, disability, congenital anomalies or birth defects;

**ACCESS FUND**

In a competitive world of unstable nature, in which the excess of investment can be abruptly replaced by hard times even for the wealthy, as seen in the recent crisis 2008/09 country, there is urgent need to create mechanisms in which, in a concrete and consistent way, the access to drug is guaranteed in the required conditions for all countries (not only the poor ones).

Like some countries at the end of retroviral studies, which developed post-study assistance “funds”, such as “The HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT)” in order to seek a more immediate solution and seems attractive to us as something feasible, particularly in countries that still struggle with the distribution of drugs (post-studies or even
ABRACRO – Guarantee of Access to Post-Clinical Trial Drugs

marketed drugs). These funds may somehow be added to government programs, and ultimately benefit those who we, investigators, dedicate the best of our ability, our efforts and why not saying our lives, to benefit our patients!

CONCLUSION

The rhetoric and questions about who should be given the experimental drug after clinical trials should be replaced by an objective action of systematization of medical conditions in which the access to drugs must be provided, as well as to whom, how, and for how long the supply should last. Obviously this issue requires a comprehensive and transparent debate between all parties involved: authorities, researchers, sponsors and the Brazilian society. The creation of a support fund for the access to new drugs, diagnostic tests and medical devices may help the public and private healthcare system and strengthen it as a whole for further expansion of access, as stated in our Constitution.

REFERENCES


Dr Luis Augusto Tavares Russo MD. Ph.D
APCB Director - Associação de Pesquisa Clínica do Brasil [Brazilian Clinical Research Association]
Doctor by FioCruz in Children and Women Collective Health
Assistant Professor of Pontifícia Universidade Católica of Rio de Janeiro in Endocrinology and Diabetes IEDERJ
Director of CCBR Brasil Centro de Andilises e Pesquisas Clínicas [Clinical Research and Analysis Center CCBR Brasil]
**Guarantee of Access to Post-Clinical Trial Drugs**

The trend of globalization of clinical trials, as observed in recent years, brought up issues not previously discussed and the continued treatment with investigational drugs, after completing a research, is one of them. In Brazil, approximately five years ago, the Review Ethics Boards, CEPs (IRB/ERB), and particularly the Comissão Nacional de Ética em Pesquisa [National Commission on Research Ethics], CONEP, began to request the maintenance of study drug’s supply after the clinical trial completion. Although it is based on the main ethical documents that guide clinical research (Declaration of Helsinki and CIOMS, for example, and in Brazil, Resolutions 196/96 and 251/97), this request presents practical difficulties in implementation, especially in the case of chronic diseases.

The continuity of medical care, including treatment, is based on the ethical responsibility to compensate those individuals who voluntarily agreed to participate in the research for the development of science, and that were exposed to unknown risks, additional invasive procedures, questionings about their habits and personal life, among others. Additionally, the research participants may not have, upon completion of the study, access to the medicine in the healthcare service of their country or even the medical care they need. This concern is certainly greater in developing countries because the research participants (and the population itself) are particularly vulnerable as a result of poverty, illiteracy, limited resources, and insufficient access to healthcare, and lack of familiarity or inexperience with research.

In a thesis defended in May of 2011, at the Faculty of Medicine of USP (University of São Paulo), this topic was evaluated. The objective of the research was to identify the issues involved in the continuity of drug supply after the completion of trial and analyze the perspective of various characters that constitute the national clinical research scenario, i.e. researchers, members of Review Ethics Boards (IRB/REB), sponsors and patients. A sample by convenience was worked with, seeking to generate samples that represented, in an adequate way, the population from which they were extracted, and the integrant elements selected by value judgments and/or accessibility criteria, and not for reasons of statistical randomization.

Questionnaires based on literature and adapted to the project in question were prepared and sent by e-mail, along with their respective Free and Informed Consent Forms (ICF), between October, 2009 and January, 2010, to members of CEPs (IRBs/ERBs) (all accredited by CONEP by that date), researchers (in two therapeutic areas, HIV/AIDS and diabetes mellitus) and sponsors (all pharmaceutical companies performing research in Brazil and all Clinical Research Organizations, CROs). The researchers were asked to apply the questionnaire to their research patients through paper questionnaires.

The response rate of the IRB/ERBs was 20.7% (124 out of 599 questionnaires sent have responded), 20% for researchers (58 out of 290) and 45.3% for sponsors (24 out of 53). Fifty-four patients invited by their physicians have responded. With respect to information contained in the
ICF, the less informed item is about how to obtain the drug after the study for all groups surveyed. Regarding the motivation of patients to participate in a research, 96.2% of patients responded as "very important" in the decision, the search for better medical care and attention to their health; and 94.2% the fact to contribute to the development of science (altruism). However, the other groups interviewed did not feel the same way: for them, the patients' higher motivation to participate in clinical research is the search for better medical care and attention to their health, followed by the search for access to treatment alternatives for their disease.

When asked about who should receive the investigational drug after the study, patients responded that everyone should receive the drug after the study (60.4%); among researchers, most (43.1%) responded that the drug should be provided to the study participants and 39.7% responded that the drug should be given to people who would benefit from the study medication. The representatives of IRB/REBs agreed with the patients that all people should receive the drug, but in a much lower proportion (35.3%). The sponsors felt that the study medication should be provided to study participants who would benefit from it (50%). There was consensus among groups in that, with continued treatment, this should be provided by the sponsor at no charge. When answering the question of how long the drug should be given, researchers and sponsors considered that the drug should be provided until its availability in the public system, while the IRB/ERBs members have stated that this should happen during the period in which the patient is benefiting from it. Patients responded that the benefit should be kept for life.

Due to several study limitations (representativeness of the sample, population restricted to Internet users, study conducted only in Brazil, and only in two diseases), its results cannot be generalized, but they contribute to the discussion of the topic, analyzing the points of view of several characters in the national clinical research scenario.

Most international (and national) guidelines do not provide specific guidance to researchers about the post-study obligations. There are no explicit laws in this matter, so the discussions usually stick to ethical and/or moral standards and guidelines. The continued supply of investigational drugs, after the conclusion of the study, is mandatory when there is benefit to the patient and he/she has no alternative treatment. It would be inhumane, in addition to unethical, to discontinue a treatment that has been, so far, successful. This case sets up the situation of "necessity" and not simply the "benefit" and can, almost always, be embedded in the situation of expanded access (RDC 26/99). However, other situations require different approaches, such as in chronic diseases in which other treatments are available. In this situation specifically, besides the benefit, one must weigh the risk of continuing a treatment still under investigation outside the controlled environment of a research, even remembering that, according to Law 6360/77, no product can be used before regulatory approval by ANVISA, except for experimental use and under the control of a responsible physician. Ideally, after a phase III study, the patients who have benefited from the treatment could be offered an extension study protocol (optional), maintaining the characteristics of a controlled clinical trial. Outside this situation, the monitoring of patients and potential adverse events would be greatly impaired and, subsequently, also the safety of patients. One cannot think only about the benefits without considering the potential risks.
The subject is sufficiently large and complex for seeking a single recipe to meet all the diversity of situations, cultures and societies. Probably, the solution is not unique and simple, in that each research must have their own assessment, since it has its own specificities, the same way that every disease has its own characteristics, and each population, their needs. Ideally, a process in which the benefits, after the research, are clearly included in the initial evaluation of all clinical trials, like the others benefits and risks usually already considered, should be defined.

If healthcare is a commitment of every nation, the issue of post-study supply will always exist, but will always be a temporary issue, with definite end. This is the case of medications for HIV/AIDS in Brazil. The research is just a way to contribute to the improvement of healthcare. It cannot be, nor intended to be, the solution for all public health problems. For any developing country, the long-term supply for patients after clinical trials can only be realistically maintained after regulatory approval in the same country and incorporation into the local health system.

The responsibilities of researchers and sponsors do not end when the study ends; one should seek a responsible termination of research, as well as the relationship created between the researcher and patient.

Researchers and sponsors are therefore obliged to consider the issue of drug supply after the research, but not the obligation to directly provide them. Clinical research is essential in the generation of evidence that later will become, or not, treatment consensus and guidelines. And then we'll be already talking about medical care and no longer research.

Before that, it would be premature (and risky) to expand the use of an experimental drug without need and without the strict control that usually characterizes the research environment.

**SUGGESTED LITERATURE**


12. Shah S. Post-trial obligations in international research. Presentation done at the Department of Biethics, NIH Clinical Center, on Oct 27th 2010 as part of the Human Subject Research Course. [Cited on 27 Dec 10]. Available at: http://www.bioethics.nih.gov/hsrc/

Dr. Sonia Mansoldo Dainesi
Medical Director at Boehringer Ingelheim
Doctor in Preventive Medicine by Faculdade de Medicina da Universidade de São Paulo [School of Medicine of University of São Paulo]
Member of SBMF Board since 2003; Ex-president of SBMF (2004-2005)
Coordinator of the NAPesq project (Núcleo de Apoio à Pesquisa Clínica – Clinical Research Support Group) at HCFMUSP from 2005 to 2007, and member of the Rede Nacional de Pesquisa Clinica (MCT/MS/FINEP) [National Clinical Research Network], by HCFMUSP, in the same period
Dr. Nelson Keiske Ono - Traumatologist

ACCESS TO POST-STUDY MEDICATION

According to Resolution No. 251/97 of the National Health Council (CNS), patients who had benefited from use of investigational medication have guaranteed access to the medication provided by the sponsor. However, a significant number of protocols conducted in Brazil do not preconize their extension for these purposes. Thus, for cases in which the patient is benefiting from the drug, and the doctor feels this is the best therapeutic alternative and that there is no study extension, the Coordination of Research in Clinical Trials (CEPEC) and National Health Surveillance Agency (ANVISA) by reconciling the rules of the National Council of Ethics (CONEP) with health legislation, recommends that the sponsor gives access to the drug by the research subject, the Coordenação de Pesquisas em Ensaios Clínicos (CEPEC) and Agência Nacional de Vigilância Sanitária (ANVISA) [National Agency for Health Surveillance], conciliating the regulation of the Conselho Nacional de Ética em Pesquisa (CONEP) [National Commission for Ethics in Research] with the health legislation, it is recommended that the sponsor allow the access to this drug by the research subject.

This is still an issue that needs to be widely discussed and disclosed. Access to drugs as a way to compensate the volunteers who took investigational drugs and to continue the treatment may become a risk if the sponsor is the only party responsible for the health of the patient post-study.

In a country in which the income distribution is extremely uneven, and in which part of the population do not receive free medications, much less buy them, this Resolution may help to provide them. Thus, individuals in need, instead of interrupting their respective treatment, will continue it. But this becomes a problem when the supply of these drugs is used to camouflage the defects in the health system and drug distribution.

The access to these drugs is only guaranteed to the individuals who have participated in the study. That is, only a portion of people, and not the entire community, which may become unfair, since not everyone had the opportunity to participate in the clinical research, and then, benefit from it. Therefore, the Council for International Organizations of Medical Sciences (CIOMS) of 2002 supports the access for the entire population, as long as the medication is responsive to the health needs and priorities of that community.

The use of drugs before their registration at ANVISA is not recommended. Even if it the drug is proven to be effective, there is no support from any governmental body.

Since these drugs are under study or post-study, their adverse events and long-term consequences are not known for sure. The fact is that, based not only on exam results, but also on the patient, it is the healthcare professional’s responsibility to assess whether the benefits are greater than these possible harms. Due to this, in most cases, conventional medicines are usually chosen.
We conclude that this Resolution may benefit the research subjects, because even if the medication is not being marketed, it allows subjects to continue their treatment, as long as it demonstrates effectiveness. However, since they are clinical trial drugs, we do not know yet their adverse events that may occur during a longer treatment.

REFERENCES

1. www.apcb.com.br/upload/pdf/52.ppt
2. www.anvisa.gov.br/medicamentos/pesquisa/doacao_medicamento.htm

Dr. Nelson Keiske Ono

Assistant Professor, Doctor, of Faculdade de Ciências Médicas da Santa Casa de São Paulo [School of Medical Sciences of Santa Casa of São Paulo]
Coordinator of the Review Ethics Board of Santa Casa de São Paulo
Chief of the Hip Group of Santa Casa de São Paulo
Assistant Professor, Doctor, of Faculdade de Medicina do ABC
When conducting any clinical trial, it is virtually impossible to examine all elements of the population of interest. Therefore, we work with samples. A sample can be defined as a subset, a selected part of the total observations covered by the study population, through which inferences about the population characteristics can be made. A sample must be representative. Taking and handling a sample require special care so that the results are not distorted. The statistical inference provides elements to generalize, in a safe manner, the conclusions obtained from the sample to the population. These conclusions have a determined error, which is inherent to the variability present in the sample taken, in order to make decisions about the parameter that we are studying. A sample that is not representative of the population is said to be biased and its use can lead to misinterpretations.

The theoretical justification for scaling samples is practically mandatory in research protocols and has been a constant concern for journal reviewers and committee members that evaluate research projects.

Although we are often asked about this calculation, we should reflect on important issues such as ethical and logistical difficulties in obtaining data. For example, in studies of rare diseases or with limitations of laboratory kits, the key word is feasibility. The calculation is always possible, but noticing the number of patients estimated in the time period available for data collection may not be feasible.

If the feasibility should be considered, why do we worry so much about the sample size? Statistically speaking, in order to interpret the results of a statistical analysis with safety, we need to ensure that the statistical test is sufficiently powerful to detect real differences. In studies with statistically non-significant results, a concern that arises is: Is there really no significance or is the statistical power is low? In a review of 71 articles with results that were statistically non-significant, Freiman et al. (1974) concluded that more than the lack of significance, there was inability to detect differences. This inability is the low power that is directly related to the size of the sample. A major concern is the fact that significant therapeutic effects are being lost due to inadequate studies. Moher et al (1994) concluded that "information about the statistical power and the sample size need to be improved". In fact, it is natural to conclude that studies with many patients have greater power and studies with few patients are likely to have low power. At last, calculating the sample is a much more complex issue than one can imagine and largely depends on the researcher's knowledge and not just on the statistician.

The sample determination is a critical step in developing a research project and cannot be understood only as a theoretical calculation, but also as a procedure focused on the accuracy of the results to answer the scientific questions of the study. The main goal is to establish, objectively, what is the number of individuals that need to be studied in order to have a sufficient

Guarantee of Access to Post-Clinical Trial Drugs

Paula Goldenstein Strassmann and Maristela Precivale - Statistics

GUARANTEE OF POST-CLINICAL TRIAL ACCESS – STATISTIC POINT OF VIEW
sample to detect important differences. It is necessary to perform the calculation of sample size in order to not to study patients neither more nor less than the necessary to obtain a reliable conclusion of the research, as well as to meet the ethical and logistical problems.

It is very important that the researcher knows the true role of the calculation of sample size, which begins in the study planning, and can significantly contribute to the quality of their study. The choice of various methods of sample size calculations follows the methodological criteria. There are many different methods of calculating sample size that can be employed according to the type of variables studied, and they depend on the type or design of the study, which in turn depends on the research questions.

In poorly planned samples, there are always the two sides of the coin. Abnormally large samples, in addition to increasing the cost of the study could make differences that are clinically irrelevant to be statistically significant and, moreover, involve an unnecessary waste of resources (time, cost, or even lives). Even if the sample is large, it must not be biased and should be representative of the population from which it is derived. On the other hand, studies with a very small number of patients may not produce a definitive answer and allow important differences to go unnoticed. The results obtained with small samples are not necessarily wrong; however, the results obtained with small samples may sometimes be used as a form of statistical "mistake".

The fact that there is a positive result on the sample of one researcher in a multicenter study does not mean that it has any significance, isolated. Without the choice of an appropriate test and interpretation, which can (and should) use the help of statistics, but that depends mainly on the power of the sample considered, any conclusion or decision to be taken may be mistaken. This result may be completely different from that obtained after statistical analysis of the total sample. The use of a smaller sample size than the one calculated is directly related to the ability of the results to provide a reliable answer to the clinical question.

Regardless of ethical issues, the researcher’s judgment regarding the clinical benefits of the study drug based on observations made at its research center has no statistical supported and any extrapolation of results for the population is questionable. The results obtained with a smaller size of the sample calculated, without statistical analysis, may be unreliable since they can just the result of chance.
REFERENCES


Paula Goldenstein Strassmann
CEO of PGS Medical Statistics
Post-Graduated in Statistics by USP
Responsible for the strategic development and research methodology

Maristela Precivale
Graduated in Statistics by USP with specialization in Epidemiology - Faculdade de Saúde Pública [Public Health School].
Statistician of PGS responsible for the pharmaceutical industry protocols
ABRACRO – Guarantee of Access to Post-Clinical Trial Drugs

Dr. Angela Fan Chi Kung - Lawyer

GUARANTEE OF POST-STUDY ACCESS
LEGAL ASPECTS

Clinical research is "any research on human beings in order to discover or verify the pharmacodynamic, pharmacological, clinical and/or other effects of products and/or to identify adverse reactions to the research products in order to ascertain their safety and/or efficacy." (EMEA, 2007). Clinical research is intrinsically related to the development of medicine, and more recently, it represents a mandatory step in the development of the drug prior to the registration of the product before the health authorities.

The ethical principles governing clinical research with human beings are established in the Declaration of Helsinki. Among these principles are those that seek to ensure access to the research benefits for the subject after the conclusion of the study.

In Brazil, the post-study ethical obligations provided in the Declaration of Helsinki are reflected in the resolutions of the Conselho Nacional de Saúde [National Health Council] (CNS) that deal with the ethical standards for clinical research. Under CNS Resolution No. 196/96, the research involving human beings must ensure the benefits resulting from the research project, whether in terms of social return, access to procedures, products or research agents. It is complemented by the CNS Resolution No. 251/97, establishing that the sponsor or, in case of its inexistence, the institution, researcher, or promoter, must ensure access to the study medication, should its superiority to conventional treatment is proven.

The CNS Resolutions, however, do not define "access to the investigational drug", i.e., whether it would be an ethical obligation to release the drug on the market where the research was conducted, whether it would be free or expensive, if the provision would be limited until the market release of the drug, etc.

The Comissão Nacional de Ética em Pesquisa Clínica [National Commission of Ethics in Clinical Research] (CONEP) believes that after the study and before regulatory approval of the drug, upon the prescription of the investigational drug by the medical researcher or any patient’s doctor, the sponsor should provide it free of charge to the patient, regardless of the existence of other established treatments on the market or the actual benefit from the drug being tested by the patient.

Therefore, for CONEP, "access to the investigational drug" means the free and unconditional supply of the post-study experimental drug without time limitation. To ensure access to the investigational drug to the research subjects, CONEP requires, as a condition for ethical approval of clinical protocols, that the sponsor, institution or investigator present a statement in which they are committed to guarantee the supply of the experimental drug, allowing no type of restriction, either temporary or regarding the appropriateness of use.

Years may elapse between the conclusion of research and drug registration, or, even if the research result does not prove the drug safety or efficacy, it will not be marketed. Thus, the experimental drug, is a product still under development, which use outside the clinical trial scope should be limited to cases in which there is no other treatment available.

From the legal point of view, the experimental drug is a drug not yet approved by the registrant regulatory authority, Agência Nacional de Vigilância Sanitária [National Agency for Health Surveillance] (ANVISA).

Law No. 6.360/76, which deals with drug registration, determines in its article 12 that these can only be delivered to be consumed if they are registered at the Ministry of Health. The new drugs, exclusively intended for experimental use under medical supervision are exempt of registration for a period of up to three years and may be imported upon express authorization by the Ministry of Health. After the three years period, the product will is required to be registered, under penalty of confiscation, as determined by the Ministry of Health.

In this sense, the RDC Resolution No. 26/99 from ANVISA regulated the access of patients with serious and life threatening disease to potentially effective products, unregistered in the country or in studies under development in Brazil or in the country of origin, in the absence of satisfactory therapeutic options (expanded access program). Under Law No. 6.360/76, such programs are limited to the period of exemption from registration of three years.

Thus, in terms of Law No. 6.360/76 and the ANVISA RDC Resolution No. 26/99, the supply of a experimental drug not registered in Brazil, can only be accomplished: (i) through authorization by ANVISA and for the maximum period of three years (ii) for patients with serious diseases and if the medication presents threat to life, and (iii) in the absence of satisfactory therapeutic alternatives.

The supply of experimental medication in violation of the rules mentioned above features a sanitary infraction, pursuant to Law No. 6437/77 (Sanitary Infractions Law), as well as qualifies for crime against health, heinous crime, according to article 273 of the Penal Code, amended by Law No. 9.677/98.

Although it is possible to provide the unregistered post-study medication within the assumptions cited above, such supply is not required by Brazilian law system. According to the principle of legality, as expressed in section II of Article 5 of the Federal Constitution, “no one will be obliged to do or stop doing something except by virtue of law”. The CNS Resolutions are ethical standards and not legal norms.

It is noticed that the CONEP seeks to overcome the legal deficiency by requiring the unilateral declaration of guarantee of post-study access, compelling the sponsor to assume a contractual commitment, under risk of the non-ethical approval of the research protocol. In one hand, such procedure seems to meet the demand of ethics, but on the other hand, it undermines the principle of legality.
CONEP, by compelling the sponsor, institution or investigator to submit a statement, without allowing any type of restriction, including legal ones, overpowers its attributions and undertakes its own statement, since the validity of the legal business requires perfect legal act that, in turn, depends on a capable agent, a lawful object and form prescribed or not barred by law.

Due to the fragility of the ethical standards to effectively regulate the conduction of clinical research in Brazil, the Law Project No. 2.473/03 by Deputy Colbert Martins, PPS/BA, which aims to transform the provisions of Resolution CNS No. 196/96 under effect, is under processing, at the Deputy Chamber. In the opinion of the project’s reporter, Deputy Cida Diogo, she points out that the CEP/CONEP system is not supported by law.

To ensure that the ethical principle of ensuring “access to the investigational drug” is required without affront to the current legislation, Law No. 6.360/76 should be amended, or the law itself, such as the initiative of Law Project No. 2473/2003, should be enacted to establish a legal obligation, as well as the parameters of unregistered drug supply after the clinical research completion.

Dr. Angela Fan Chi Kung
Lawyer, partner of Pinheiro Neto Advogados office
Bachelor in Law by Faculdade de Direito da Universidade de São Paulo
[Law School from University of Sao Paulo]
Master (LL.M.) in Common Law Studies, by Georgetown University and Specialist in Health Law by Faculdade de Saúde Pública, da Universidade de São Paulo [Public Health School from University of Sao Paulo]
Professor of Regulation in the Pharmaceutical Industry in the Executive MBA courses of the Pharmaceutical Industry, FGV/SINDUSFARMA and Business School of Sao Paulo
Professor of Health Law in the Instituto de Direito Sanitário (IDISA) [Institute of Health Law]
ABRACRO – Guarantee of Access to Post-Clinical Trial Drugs

POV OF VIEW OF THE NATIONAL AGENCY FOR HEALTH SURVEILLANCE REGARDING THE ISSUE: GUARANTEE OF ACCESS TO POST-CLINICAL TRIAL MEDICATIONS.

In Brazil, the production, marketing and use of medications can only be made after the grant of health registration by the Ministry of Health. To obtain this registry, there are detailed and standardized guidelines involving aspects that address the quality of products (production and control), evidence of efficacy and safety (in case of new drugs) and interchangeability (in the case of generic and similar drugs).

However, there are situations in which the use of unregistered drugs is permitted, as in clinical trials, expanded access programs and in compassionate use and post-study donations. In such cases, the product is provided by the producing and/or sponsoring companies, promoting special access to patients or patient groups that otherwise would not have alternative treatment in the country.

This demand arose in the 1980s with the advent of the epidemics of Acquired Immune Deficiency Syndrome - AIDS. Groups of patients and family members have organized to enable the support use of drugs still under investigations by patients who did not participate in the studies because they did not meet the inclusion criteria and/or exclusion criteria or because they had no access to the study because they lived far from the research sites. The continuation of drug use after the end of the study have also been demanded by the participants who have benefited from the drug.

Specifically regarding the continuity of the medication use by research participants after the completion of clinical trials, the Declaration of Helsinki had already provided this alternative to propose that research protocols should describe mechanisms for post-study access for research subjects who have benefited the intervention studied. Resolution No. 251/97 of the Conselho Nacional de Saúde (National Health Council) (CNS), also states that the sponsor should ensure access of the investigational drug for patients who have benefited from its use. CIOMS (Council for International Ethical Guidelines) also states that the product should be reasonably available to the country or the inhabitants of the community that hosted the study after its completion. Resolution No. 196 of the CNS discusses the issue by citing that the research should "ensure the return of the benefits obtained through the research for the people and communities in which they have been perform”, besides "ensuring to the research subjects the benefits resulting from the project, whether in terms of social return, access to procedures, products or research agents."

In many cases, this right is guaranteed in the study extension, which is defined by ANVISA as the proposed extension or continuation of the research with the same subjects recruited, without essential changes in the objectives and methodology of the original project. However, a large number of protocols conducted in Brazil do not provide a study extension for these purposes.

In guaranteeing these rights, several issues are raised, like for example, how long should this post-study access last, who is responsible for providing and storing the investigational product, and
how to track, report and monitor adverse events outside the context of a controlled clinical trial. In addition to these issues, it is important to note that a single study hardly proves the efficacy of a particular intervention, and the individual benefits sometimes do not match the results obtained in the study as a whole. The superiority of a new drug must be proven by means of a statistical evaluation of the research data and not from the clinical evaluation of a single patient\textsuperscript{5,6}.

Another important item is related to risk management, because the safety of the continued use of the drug by those who have benefited from it cannot be adequately evaluated in studies in early stages. In these phases, the effects of the drug are monitored for short periods and the safety assessment refers to the study period and does not extend after its completion\textsuperscript{4}.

Some authors interpret the benefit of research as not only directly related to the research subject who has participated in the study, but also as a return of various benefits to the community, such as training of healthcare workers, improvements in the infrastructure of health facilities, provision of standard treatment available, provision of public health measures, among others\textsuperscript{5}. However, the legislations make clear that the subjects who have clinically benefited from the study have the right to continue receiving, without any costs, the medication that has brought a benefit for their health, in addition to the benefits that the study has brought to the community. In these cases, the responsibilities of the sponsors do not end with the conclusion of the study, because they must provide conditions of safety and monitoring the use of the drug for as long as necessary, while the research subject is benefiting from the experimental treatment\textsuperscript{7}.

Thus, in cases where there is a patient benefiting from the investigational drug; which the assistant physician deems to be the best therapeutic alternative and; that the study protocol which ends and has no expected study extension, ANVISA, seeking to reconcile its regulations with CONEP, recommends that the sponsor proceeds with the donation of the drug. This case also includes the donation of medication due to premature end of study.

The Agency’s understanding is that the treatment of patients with chronic diseases should be guaranteed while the patient is benefiting from it, according to the physician’s discretion. In the case of treatment of duration defined in the protocol, the necessary product should be provided for the complete treatment of the patient. It is the sponsor’s attribution to provide full and free treatment to the patient. Moreover, ANVISA’s concern is not just regarding the access, but also about the monitoring. Thus, the sponsor must submit periodic reports on the post-study donation program and should report serious adverse events to Anvisa. It is also a sponsor’s responsibility to provide the financial resource for comprehensive care for complications resulting from the risks foreseen in the post-study donation program.

The responsible physician must make a formal request for the sponsor’s product, for each patient to be treated, justifying the use by medical report, if interested in having patients in the post-study donation program; properly store the medication according to the manufacturer instructions; notify the sponsor about the occurrence of serious adverse events; provide the documentation necessary to monitor the post-study donation program and assume the
responsibility for providing comprehensive care, along with the sponsor, to the complications and
damage resulting from the expected risks.

Still, the expected benefits must outweigh the expected losses or damages and the principle
\textit{primum non nocere} - above all, do no harm, should be considered. In the same way, the principle
of justice which includes the merit (which is deserved) and right (something that someone has the
right to) should be preserved\textsuperscript{8}. The fair, equitable and appropriate treatment should be
guaranteed to these patients. This same principle also supports the requirement provided in the
CNS Resolution No. 196/96 that research in any area of knowledge should ensure that the
research subjects obtain the benefits resulting from the project, whether in terms of social return,
or access to the investigational treatment, referring to post-study donation.

\textbf{REFERENCES}

1. BRASIL. Lei n° 6360, de 23 de setembro de 1976. Dispõe sobre a vigilância sanitária a que ficam sujeitos
os medicamentos, as drogas, os insumos farmacêuticos e correlatos, cosméticos, saneantes e outros
1976.

2. BUSS, P. M.; CARVALHEIRO, J. R.; CASAS, C. P. R. Medicamentos no Brasil: inovação & acesso. Rio de

3. GROOPMAN, J. The right to a trial: Should dying patients have access to experimental drugs? The New

4. GOLDIM, J. R. O uso de drogas ainda experimentais em assistência: extensão de pesquisa, uso

5. DAINESI, S. M. Como assegurar benefício aos pacientes após sua participação em pesquisas clínicas?

6. DAINESI, S. M. Como fazer valer a máxima da ética médica Primum non nocere ao oferecer continuidade
de tratamento com drogas experimentais a pacientes de pesquisa clínica? Revista da Associação Médica

7. JÚNIOR, B. R. S. Acesso às drogas na pesquisa clínica. Revista Bioética, Brasília, Conselho Federal de

Mexico, like many other Latin American countries, is considered a major target of the pharmaceutical industry for the implementation of clinical trials both at hospital and ambulatory levels. This is because it is one of the countries with the largest population in the region, a high incidence of infectious and chronic diseases and physicians and researchers are relatively well trained. In addition, Mexico has a well established health infrastructure and laws governing the individual right to health as well as the conduct of researchers involved in clinical research studies. Chapter V of the Mexican General Health Law defines the legal bases for conducting clinical trials, which are consistent with the provisions of the Declaration of Helsinki and other international standards.

Compliance with these laws is guaranteed through two institutions: 1) Federal Commission for Sanitary Risks Protection (COFEPRIS) whose functions include regulation, control and health promotion at national level and 2) the National Bioethics Committee (CNB) whose function is to set standards for bioethics at state and institutional level, including research ethic committees, ultimately responsible for the review of clinical trials. According to current regulations, approval for clinical trials must be granted by both institutions, COFEPRIS and a research ethic committee.

According to the ClinicalTrials.gov database, Mexico is involved in 1370 clinical trials supported by the pharmaceutical industry and more than 70% of these trials are conducted in public hospitals and research institutions; however, Mexico still has no publically accessible data base of clinical trials for consultation by physicians, participants or general population The Declaration of Helsinki (paragraph 30) states that "at the end of the investigation, all subjects participating in a research study should be assured of the best proven prophylactic, diagnostic and therapeutic methods existing and identified by the study ". In the case of the Mexican General Health Law and its related regulation of Health Research in Human Subjects there is no article that regulates these aspects of the Declaration of Helsinki. This means that the sponsor / investigator is not required from a legal standpoint to provide the drug tested once participants completed the study, thus leaving the responsibility for ethics committees and COFEPRIS to ensure compliance with this recommendation.

COFEPRIS currently does not require compliance with this recommendation when a researcher requests authorization of a clinical trial and the ethics committees only guarantee that the test product is applied to the subjects involved in the control group (either placebo or treatment standard), once treatment is revealed. This situation poses an ethical problem particularly for products aimed at treating chronic and degenerative diseases such as cancer, diabetes, renal failure and AIDS, among others.
Therefore it is necessary to establish clear guidelines in Mexico that can be implemented to ensure access to medication after the end of clinical trials.

Dr. Julieta Ivone Castro Romero
Ph.D, Marburg University, Germany
Master in Bioethics, CIEB - Universidad de Chile [University of Chile]
Medical Sciences Researcher, INSP
President of Bioethics Commission of INSP since November, 2008
National Researcher Level I, CONACYT
Member of the Bioethics Committee of Estado de Morelos
Professor of Bioethics for post-graduate students, INSP