

Letters to the Editor/Cartas ao Editor

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What is phase 0 and phase I in clinical research?

Dear Editor,

The registration of research as an international trial has become a reality and a necessity. However, the categorization of different types of studies in International Trial Registries is badly defined for both researchers and editors. Thus, a clearer description is required.

According to the definition of the World Health Organization, Phase I clinical trials “test a new biomedical intervention in a small group of people (e.g., 20-80) for the first time to evaluate safety (e.g., to determine a safe dosage range and to identify side effects)” [1].

So when I sent a case report of about 15 patients submitted to established clinical treatment using an elastic stocking for vascular insufficiency to a well-known journal, I was surprised to hear the editor say that he required the registration number before it could be published, as this was a Phase I trial. And even more so when I tried to register the study as a Phase I trial in an International Trial Registry and was told it was not a Phase I trial. Why does the WHO state specifically that 20-80 people are a small group? How are trials of 15 individuals taking new drugs considered as Phase 0 while this study was considered as Phase I?

With the creation of the phase 0 classification, there seems to be no doubt when investigating drugs in small scale studies with about 15 patients. And, in general, it seems logical that we should be more careful with the prescription of new drugs than existing clinical therapies, such as elastic stockings or the evaluation of non-invasive complementary examinations.

There are many other ill-defined situations such as, for example, what is the classification of a series of five case reports – a “micro-study”, a phase 0, or a phase I? Some journal editors think that a series of five case studies should be classified as phase I.

I think it would be very beneficial if you, as Editor, would take the initiative to assist researchers, editors, and even the Research Ethics Committees by publishing a clear definition in your journal and to start a debate about the direction of clinical trials and their registration.

José Maria Pereira de Godoy¹, MD, PhD

1. Faculdade de Medicina de São José do Rio Preto/ Medicine School São José do Rio Preto (FAMERP), Department Cardiology and Cardiovascular Surgery and

National Council for Research and Development (CNPq), São José do Rio Preto, SP, Brazil.

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Comments on Letter to the Editor

Dr. José Maria Pereira de Godoy raises several questions:

1. Whether his study of application of elastic stockings to treat vascular insufficiency in 15 people should be qualified as a phase 1 or phase 0 trial?
2. Ethics of Phase 0 trial.

To answer these questions one has to define the intent of the trial. It is the formulated goal rather than the number of study subjects per se that determines the qualification. The stated goals of Phase 1 trials — establishing the maximal tolerated dose of the tested medication and the determination of its toxicity — require larger numbers of enrolled subjects and the emphasis of pharmacokinetics rather than the therapeutic effects and benefits (endpoints of Phase 2 and 3 trials). In contrast, the goals of Phase 0 trials avoid the determination of maximal tolerated dose and its toxicity, specifically lack the therapeutic intent, and focus mostly on establishing whether the proposed medication has the intended pharmacokinetic profile (e.g., interacts with the intended enzymes, or it is absorbed as anticipated). Therefore, Phase 0 trials involve “micro-dosing” (avoiding toxicity, and neither expected nor intended to produce therapeutic or diagnostic benefits) and require significantly lower numbers of enrolled patients.

It is important to understand that Phase 0 trial does not obviate the requirements of undergoing the full 3 phases of the required regulatory process. FDA created this process to alleviate the notorious problem of a “clogged pipeline” in development of promising medications, and allows early “weeding out” of (initially promising) medications.

Therefore, we would agree with the assessment that the scenario presented by Dr. Godoy probably does not satisfy the definitions for Phase 1 nor Phase 0 trials.

From ethical, statistical, and scientific standpoints, the introduction of Phase 0 trials elicited vigorous debates. Ethically, the controversy focuses on the dynamics of a trial, which enrolls patients not expected to derive any benefit from the intervention. Statistically, the challenge lies in maintaining the scientific rigor despite low number of patients who are subjected to an intervention which is neither toxic nor therapeutic. Consequently, Phase 0 trials may be applicable to a rather limited number of biological interventions. Additionally, linking Phase 0 with Phase 1 trials may be challenging as well. Therefore, we are grateful to Dr. Godoy for raising these issues. We believe that a thorough understanding of the regulatory process is vital for a proper description of a study and its qualification as a trial or a case review [1-5].

Edward Gologorsky¹, MD; Tomas A. Salerno¹, MD, PhD

¹ University of Miami Miller School of Medicine and Jackson Memorial Hospital Miami, FL, USA.

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Dear editor,

The questions presented by the researcher José Maria Pereira de Godoy seems quite relevant although some considerations should be observed.

The phase 0 studies, also known as exploratory first-in-human, follows the guidelines of the Food and Drug Administration (FDA) established in 2006 to guide the Exploratory Investigational New Drug Studies [1]. This modality also receives designation of a microdosing study, since the amounts of agents administered are too small to present any therapeutic effect. Thus, there is no evaluation of safety or efficacy, but only the pharmacokinetics and pharmacodynamics of the test agent [2]. The main purpose of phase 0, which includes 10 to 15 healthy individuals, is to streamline the process of molecular investigation or promising interventions, since they allow to obtain early data from human beings, besides those from animal research, which are often inconsistent and non-reproducible.

The phase I studies include from 20 to 100 healthy individuals, and discusses the pharmacodynamics and pharmacokinetics of the therapeutic agent, as well as their safety and tolerability. These studies are usually funded by the pharmaceutical or equipment industry and conducted in highly controlled locations known as Pharmacology Central Units. Interventions that succeeded at this stage will then have its efficacy tested in phase II, III and IV (postmarketing) [3].

Regarding the study proposed by Dr. Godoy, we do not believe it meets the definition of a clinical study, since a therapeutic measure with a known efficacy (by elastic compression stockings) was used in the treatment of venous insufficiency. We believe that such a study would be best characterized as a series of case report (descriptive study).

We still think that what is more important than the correct classification of the study within their evolutionary stages, is the facilitation of access of health professionals to the document known as Clinical Study Report (CSR) a wide and unrestricted report for the study, where individual data regarding safety and efficacy are presented in detail, such information that are commonly lost or just summarized in the tables present in numerous scientific publication, skewing the correct evaluation and application of evidence-based measures.

Marcelo Derbli Schafranski¹, MD PhD

¹ Universidade Estadual de Ponta Grossa, Ponta Grossa, PR, Brazil.

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Dear editor,

José Maria Pereira de Godoy raises interesting questions about the definitions of phase 0 and phase I clinical trials in his letter to the editor entitled “What is phase 0 and phase I in clinical research?”, which was published in this issue of the Brazilian Journal of Cardiovascular Surgery. His main arguments can be summarized as follows:

1. Bearing in mind that the study was conducted in order to assess the safety and effectiveness of a brand new product (elastic stockings designed to treat venous insufficiency), the author argues for considering the study as a phase I clinical trial.

2. The study could not be registered in an International Trial Registry as phase I because the number of patients evaluated was deemed insufficient.

In my opinion, there are pros and cons to Dr. Godoy’s clinical trial being regarded as phase I:

Pros:

1. What determines whether a clinical trial is phase I is primarily its goal, not the number of patients evaluated [1].

2. The definition of phase I clinical trials from the World Health Organization [2] states that a phase I clinical trial shall evaluate “a small number of patients”, without specifying the minimum or maximum number of participants.

Cons:

1. Usually, a phase I clinical trial evaluates healthy volunteers. Patients may be included in some cases: when the treatment being evaluated can make healthy individuals sick, such as cancer drugs, or when every existing traditional treatment known to man has been used without providing beneficial results to the patient [3]. The participants in Dr. Godoy’s trial do not meet any of those criteria.

2. The high risk involved in the early stages of clinical research demands strict regulations and careful monitoring during every single phase of the research [4]. As far as I know, the monitoring was not performed.

Dr. Godoy argues that a clearer definition of the different types of clinical research available should be made by the International Trial Registry. In my point of view, these definitions are designed mainly for the study of drugs, especially the newly created phase 0 [5]. The criteria used to determine the ideal number of participants have as their main goal the assessment of pharmacokinetics, pharmacodynamics and dosage of drugs; aspects involving diagnostics, medical equipment, and procedures are relegated to the background.

This distortion might explain, in part, the difficulties faced by Dr. Godoy to define his clinical study.

Lilia Nigro Maia¹, MD, PhD

1. Faculdade de Medicina de São José do Rio Preto, São José do Rio Preto, SP, Brazil.

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Phase 0, Phase I in clinical research and the registering of publications

In most countries, the structure of clinical research for the release of new drugs, biological drugs, and human health devices is, in general, similar to the provisions of the North American law. Food and Drug Administration (FDA) regulations started to evolve from the mid-1880s until 1997, when the Food and Drug Administration Modernization Act (FDAMA) was enacted. They continue to evolve, especially in order to guarantee safe access to newly developed products.

Primary regulations on drugs, biological drugs, and medical devices are part of the Code of Federal Regulations (CFR) Title 21. They were designed to avoid a series of problems of the past and to protect public interest and health in terms of new health products. Specifically, Investigational

New Drugs (IND) are governed by Part 312; Devices and In Vitro Diagnostics, by Parts 800 - 861.

The regulatory approach for drugs and/or biological drugs is different from the one for devices. In the latter, it is understood its action or result is not achieved through chemical actions in the human body or other animals and its treatment goal is not dependent on metabolism. New drugs and/or biological drugs follow specific development and evaluation steps [1].

In the USA, as mentioned, it starts with the IND Application, which is eventually followed by the New Drug Application (NDA). Initial exploration of the product in preclinical phases, usually in animals, supports the design of exploratory phases in humans. In general, the clinical stage is divided into three phases of pre-commercialization research aimed at examining the safety and efficacy of the drug and/or biological drug.

Phase I studies are comprised of small studies (20 to 100 individuals), with dose escalation, which may include either patients with certain conditions or healthy volunteers. Their main goal is to assess the safety of a particular route of administration. In addition, drug metabolism and pharmacokinetics can also be evaluated.

Phase II studies are comprised of one or more larger clinical studies, for a particular population of patients, whose main goal is to offer preliminary evidence of efficacy and dosage as well as additional data on therapeutic safety. After this phase, the regulatory authority and the sponsor should refine their strategy for subsequent studies in larger populations.

Phase III studies are larger in scale, usually multicenter and international. They are aimed at evaluating the risks and benefits of a product in a particular population of patients, with a given clinical indication. Safety and efficacy data from those last studies provide the product with the possibility of approval for commercialization as well as detailed instructions on usage for the particular condition [2].

As with any scientific research, methodology for each phase should be well established and meet the minimum requirements needed to accurately reflect results. Among the aspects to be considered are desired outcomes, study population, randomization, stratification, blinding, sample size, adherence, and statistical analysis techniques. All of these requirements are planned before the study.

The development of the clinical research lasts approximately two to ten years. After that, the product enters the post-commercialization studies phase (Phase IV studies), where, besides safety monitoring, new applications and recommendations are added to it. This phase continues throughout the life cycle of the drug [1,2].

Several mechanisms have been created to speed up the development and approval of drugs and biological drugs, especially those designed for patients suffering from serious, debilitating, life-threatening diseases, and without

complementary alternatives (21 CFR 312 Subpart E, 314.510 and 601.41). One of these mechanisms was created in 1998, in the Fast Track Guidance, and revised in 2004. It set out mainly to facilitate the development and review of new drugs and biological products for conditions which are health risks and show the potential to quickly reach unmet medical needs.

In the 2004 Critical Path Report, the FDA suggested new strategies were needed to help identify promising molecules, in an effort to reduce the time and resources spent on developing new drugs. As a result, in 2006 the FDA launched the new FDA Guidance on Exploratory Investigational New Drug (IND) Studies, in which an exploratory phase previous to Phase I studies is described. This phase is consistent with the regulatory requirements for the protection of human beings, involves few resources, and accelerates the development of promising components by defining, previously, if the behavior in human beings is the same as what it would be in the preclinical phase [3-5].

These studies were named “Phase 0” or “microdosing trials”, and they referred specifically to exploratory studies, prior to Phase I, with controlled human exposure and without diagnostic or therapeutic value. “Phase 0” studies are characteristically limited to a few individuals, usually 15, and they last a week. Their main goal is to collect preliminary pharmacokinetic and pharmacodynamic (PK/PD) data of the component being investigated, including image data of the bond to the receptor, and they do not allow inferences to be made about either safety or efficacy since non-therapeutic dosages are used. Preliminary data derived from a “Phase 0” study assist in the decision-making process and in judging potential candidates in the development of drugs. In general, this phase is limited to specific drugs whose target as well as the effects on their biomarkers must be known (2010 Qualification Process for Drug Development Tools). This approach in addition to methods of evaluating images of organs, tissues, cells, and molecules (Optical images, Positron Emission Tomography – PET, Single Photon Emission Computed Tomography – SPECT, among others) are essential to validate this phase and to either obtain proof of concept for the development of future studies or interrupt the clinical trial process [2-5].

Clinical trials of medical devices and equipment are not divided into phases in the way drug studies are. In the USA, they are governed by the Code of Federal Regulations (CFR), Title 21, Parts 800 – 861, and, in particular, Part 860.7 (Determination of Safety and Effectiveness) which deals with important aspects in clinical studies of these devices, prior to PMA (Premarket Approval). These aspects include: valid scientific evidence, safety, effectiveness, controlled clinical research, and data analysis, in accordance with the usual methodology for any scientific research [6].

In Brazil, the Brazilian Health Surveillance Agency (ANVISA) has very clear regulations governing the

development of drugs, biological drugs, and materials to be used in healthcare. As a result of its most recent development, they are similar to the provisions of the FDA [7].

In the USA, clinical studies of new drugs, biological drugs, equipment, devices, or procedures had to be registered in accordance with the 1997 Food and Drug Administration Modernization Act (Modernization Act), section 113, which had created the Clinical Trials Data Bank to regulate the registration of clinical trials of drugs which would be studied and commercialized in the country. Subsequently, this platform was transformed into ClinicalTrials.gov. As of 2004, the International Committee of Medical Journal Editors (ICMJE) and, in 2005, the World Association of Medical Editors established the registration of clinical studies as a prerequisite to publish in their journals. In 2006, the World Health Organization (WHO) started to reveal the importance of registering in their International Clinical Trials Registry Platform (WHO ICTRP). Information fed into the WHO platform comes from primary registries and worldwide collaborators, including ClinicalTrials.gov. As of 2007, BIREME recommended that journals indexed in the LILACS (Latin-American and Caribbean Center on Health Sciences Information) and SciELO (Scientific Electronic Library Online) databases should abide by the WHO and ICMJE provisions [8].

The Brazilian platform, Brazilian Clinical Trials Registry – REBEC (Registro Brasileiro de Ensaio Clínicos) [9], was launched in December, 2010 and was integrated into the WHO ICTRP in April, 2011, in accordance with all ICMJE provisions.

The WHO ICTRP, ClinicalTrials.gov, ICMJE, and REBEC guidelines emphasize the importance of registering every clinical study performed on human beings who are subject to diagnostic, therapeutic, or other procedures, whether interventional, observational, experimental or not. There is still some doubt about whether to register studies which are not characterized as clinical trials, as recommended by WHO and highlighted in the ICMJE guidelines below:

“...the ICMJE adopted the WHO’s definition of clinical trial: “any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.” Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. Purely observational studies (those in which the assignment of the medical intervention is not at the discretion of the investigator) will not require registration.”

“Those who are uncertain whether their trial meets

the expanded ICMJE definition should err on the side of registration if they wish to seek publication in an ICMJE journal. The ICMJE secretariat office is unable to review specific studies to determine whether registration is necessary. If researchers or others have questions about the need to register a specific study, they should err on the side of registration or consult the editorial office of the journal they wish to publish the study in” [10].

Overall, the Brazilian platform REBEC has accepted the registration of clinical studies that do not formally meet the criteria for clinical trials, as established, and it is formally recognized as a Primary Registry in the WHO ICTRP and ICMJE, which minimizes the issue for Brazilian researchers.

Carlos Antonio Caramori¹, MD, PhD

¹ Universidade Estadual Paulista Júlio de Mesquita Filho (UNESP), Botucatu, SP, Brazil.

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of patients to determine the outcome of the risk/benefit in the short- and long-term of the formulations of the active ingredient, exploring the type and profile of the most common adverse reactions;

d) Phase IV - are researches performed after marketing the product and/or medical specialty. These researches are performed based on the characteristics of which that drug and/or medical specialty was authorized. They are generally studies on post-marketing surveillance to establish the therapeutic value, the emergence of new adverse reactions and/or confirming the frequency of appearance of those already known, and treatment strategies.

Domingo Braile
Editor-in-Chief/BJCVS

EDITOR'S NOTE

Regarding the Letter to the Editor “What is phase 0 and phase I in clinical research?”, Authored by Dr. José Maria Pereira de Godoy, is timely to take readers' knowledge, as important information, a call from the Ministry of Science, Technology and Innovation (MCTI), along with the National Council for Scientific and Technological Development (CNPq), Ministry of Health (MOH) and Department of Science, Technology and Strategic Inputs (SCTIE) about Clinical Research on which it is defined in the context of different entities the clinical trials in phases I, II, III and IV nationwide.

It is considered a clinical trial any research on human beings, aiming to discover or verify the pharmacodynamic, pharmacological, clinical and/or other effects of product (s) and/or identify adverse reactions to the product (s) under investigation, with the aim of ascertaining its safety and/or efficacy (EMA, 1997). Clinical trials are classified into four stages (I to IV), as defined by Resolution No. 251/97 of the National Health Council, namely:

a) Phase I - the first study in humans, in small groups of volunteers, generally healthy, of a new active ingredient or new formulation to establish a preliminary safety and pharmacokinetic profile;

b) Phase II - aims to demonstrate the activity and establish short-term safety of the active ingredient, assessing the dose-response relationship in a limited number of sick patients;

c) Phase III – performed in a large and varied groups

Screening of fetal congenital heart disease: the challenge continues

Rastreamento das doenças cardíacas congênitas fetais: o desafio continua

Dear Editor,

The initiative of inviting a group of obstetricians to write an editorial for a cardiovascular surgery journal emphasizing the need of an adequate prenatal diagnosis of congenital heart diseases should be commended. The authors provide a comprehensive summary of the recent advances and advantages of intrauterine diagnosis, encouraging obstetricians not to limit the screening to those known to be at risk of developing a cardiac malformation. They also recognize the value and the limitations of the four chambers view with which the obstetricians feel comfortable. Furthermore, the authors stress the fact that there are a number of cases, particularly the cono-truncal anomalies, where the visualization of the great arteries is difficult and the pitfalls important. They also underline the importance of expanding the training, knowledge and abilities of those performing the studies to allow a broader detection of cardiac anomalies [1].

As in other specialties, there is an increasing interest in the newly developed technologies which will certainly improve the images and facilitate a precise detection and diagnosis. However, the key for an accurate screening continues to be the operator's knowledge of the cardiac anatomy and a proper

understanding of the unique and complex spatial arrangement of the cardiovascular system. The concept of spatial thinking — a cognitive skill used by architects and urban planners — can help in understanding the world around us by using the properties of space in everyday life, the workplace, as well as in science, to structure problems, find answers and articulate solutions [2].

While we firmly believe that a proper utilization of the present tools should enable us to improve detections, we recognize the importance of a conscientious labor force that makes excellent use of modern technologies as they become widely available and affordable. Whether we liked it or not, technology will continue to shape our practices.

Although it is not our intention to write a paper within a letter to the Editor, there are important concepts such as proximity, product space, structure of production, collaborative rationality, and team work that should be at least mentioned. Their application will improve our understanding of the complexity of the cardiovascular services and thereby enhance performance.

Proximity formalizes the idea that the ability of a center to generate a product depends on its ability to produce other ones — structure of production. When a center with many complex capabilities adds a new one, this can create a range of new, possible complex procedures. Conversely, adding a single new capability in a center that has few to begin with won't leverage an existing matrix of capabilities in the same way — it might not produce any new procedures at all [3].

As a pediatric cardiologist and a cardiovascular surgeon we strongly advocate the need of an inclusive team approach for the proper management of the neonate with congenital heart disease: a work structure in which all components of the cardiovascular services — a cluster of people focused on excellence according to their relatedness and interests — contributes to the quality of the final outcome with an integrated approach [4]. This leads to collaborative rationality, of getting better together, which is a different way of knowing and generating, of making and justifying decisions based on diversity, interdependence and dialogue [5,6].

It is a team integrated by pediatric cardiologists, neonatologists, cardiovascular surgeons, anesthesiologists, nurses and specialized critical care units in which obstetricians with imaging expertise have a place. The role of the latter should not be limited to the image detection but also to participate in the decision making process: that is, diagnosis, intrauterine treatment, time, type and place of delivery, etc. In other words, an effort centered in the fetus' health, encouraging collaboration among professionals and sharing knowledge that contributes to reciprocal medical education in a multidisciplinary environment.

How are we doing?

The use of information about one's business is vital

to understand, report on, and predict different aspects of performance. After making theoretical considerations, which, among practical people, has a connotation of impracticality, we feel compelled to include information about our policies as well as unpublished data on our experience.

Recently, we reviewed our findings on early detection of congenital cardiac anomalies in a group of 49 neonates under 30 days of life that underwent surgery [7]. Interestingly, in this cohort of the patients, 40% had prenatal diagnosis and 90% of them had severe forms of univentricular heart — the majority with hypoplastic left heart syndrome. In all cases, the malformations were detected by an obstetrician specialized in images and confirmed by a pediatric cardiologist, both aware of the importance of visualizing the outflow tracts and the great vessels, using a conventional four chambers view.

It is our policy to discuss all patients with prenatal diagnosis of heart disease by a group formed of general obstetricians, obstetricians specialized in images, pediatric cardiologists, neonatologists and cardiovascular surgeons. This team decides the management of the patient — that includes consulting the mother — with special consideration to the need of prenatal intervention, the time, type and place of delivery, and the timing for surgery. We strongly believe that a joint management benefits the patients and improves surgical results by diminishing morbidity and mortality. However, the findings disclosed in the Editorial as well as ours clearly indicate that there is room for improvement by training those involved in the screening process, realizing the need of a team approach, and the adoption of modern technologies. It is, among other things, the ability to recognize where there is room for improvement that allows an expert operator to reach great heights. "The ability to see room for improvement, however, is not of much use unless one also has a strong and continuing desire to improve" [8].

Neonates face unique incremental risk factors related to the patient's variables and to structural hospital characteristics that should be properly individualized and addressed in a timely fashion in order to improve surgical outcomes. An accurate prenatal diagnosis can make a significant contribution to accomplishing this goal.

Mariano Ithuralde¹, MD; Rodolfo Neirotti², MD, MPA, PhD

1 Clínica y Maternidad Suizo-Argentina, Buenos Aires, Argentina.

2 Michigan State University, East Lansing, MI, USA.

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