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## The challenges of clinical research in Brazil

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Reading the lay press in Brazil daily reveals both the importance and the difficulties of clinical research in the Twenty-First century in our country. The approval by the Congress of the so-called “cancer pill”, which is phosphoethanolamine-based and the doubts regarding arboviruses are two of the most emblematic challenges faced by clinical research in our field. It will always be about understanding the historical, circumstantial and structural limiting facts that prevent the full development of clinical research from happening.

### Defining “clinical research”

The first point to be discussed is precisely the term “clinical research”. By definition, clinical research means there is at least one human being being studied in a scientific project. It may have an observational origin only, as in the description of a clinical case, or it may be an intervention with tens of thousands of participants as in the modern clinical trials. However, in recent decades, the term “clinical research” has erroneously become synonymous with therapeutic trials with new (or old) drugs. This confusion of terms was not beneficial for the establishment of a culture of research in humans in Brazil. The second important point is to present what would the primary scientific research designs in the medical field be. Let us illustrate it didactically with studies related to high blood pressure.

1) **Clinical case or case reports:** The first is the description of a clinical case or series of cases in a situation of outpatient care, as the description of albuminuria syndrome by R. Bright was in 1836, even before the creation of sphygmomanometers<sup>1</sup>.

2) **Physical and chemical or biochemical studies:** A second example would be all the experiments that do not involve any living being, for example, the accepted proposal to shape and build a molecule to block the function of the autonomic nervous system, which was the case of the creation of the beta-blockers by James Black in 1962<sup>2</sup>.

3) **experiments in animals:** The third type of research involves animals in controlled experiments such as the traditional Goldblatt experiment in 1934, in which he clamped the renal artery unilaterally and discovered the association between the reduction in renal blood flow and high blood pressure and, later, renin.

4) **Observational or cohort studies:** The fourth type is only observational in a large sample of people for a long time, as it was for high blood pressure as a risk factor for cerebrovascular and coronary heart disease. The best example is the Framingham Heart Study, which was established in 1948 in the American city that gives this study its name and has since then opened a new universe of knowledge regarding cardiovascular risk factors<sup>4</sup>.

5) **Interventional studies or clinical trials:** As what has been happening with several diets and drugs tests

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as well as other actions to discover which of them would be effective to lower the blood pressure in hypertensive patients, as in the recent SPRINT showing new ideal limits for lowering blood pressure<sup>5</sup>.

6) **Secondary base studies:** they can be demographic studies, such as the identification of the evolution of mortality caused by high blood pressure-related diseases<sup>6</sup>.

## HISTORY

For decades, the Medical Sciences in Brazil have been a combination of experimental studies using animals and descriptions of cases or clinical series. This polarity reflected the division between “primary subjects” and “clinical subjects” in medical schools. During decades, this dichotomy was only the effect of splitting undergraduate medical between basic and clinical disciplines. Further, this dichotomous structure to teaching medicine became the cause a medical course divided between biology and medicine. The separation between these two areas has expanded over time, reducing the much-needed dialogue between science and medicine. The distance between who is practicing the “pure science” and who has involved in the “practical medicine” is the source of two recurrent problems observed reading publications, thesis or papers, from a medical school. One is the lack of statistical power for the description of a small number of surgical and non-surgical interventions. Another problem is from studies using animals without a great research question derived from the clinical practice. Although they can be designed with scientific rigor, the generalization of these results has been very low.

In the last decades, however, there has been a movement of progressive improvement in research in humans with the incorporation of practices coming from epidemiology and its basic designs, cohort, case-control, transversal that allowed the clinical trials to have a stable structure. Another aspect leading to considerable improvement in clinical research was the dissemination of the ethical principles of experimentation in humans that began at the end of World War II and which materialized in Brazil with the resolution 196/96 of the National Health Council, which is the regulatory milestone for clinical studies in the country.

However, the challenges to the full development of clinical research are still the lack of tradition and culture of all individuals involved in accepting that science is paramount to an effective and appropriate clinical practice. The greatest example of our low cultural level was the approval of phosphoethanolamine by the Congress, a farce in which the *Universidade de São Paulo* was the protagonist through a unit without any affinity with the medical field and through Professors without any tradition in clinical research.

## The current contribution of the USP Faculty of Medicine

Despite the huge disappointment, it was to see the name of the *Universidade de São Paulo* involved in such an unhappy episode of the “cancer pill,” the remaining schools and institute of USP – have shown numerous studies of high quality regarding clinical research. To mention only the current example of FMUSP and using the classification presented above we can provide some examples of excellent contributions from *Casa de Arnaldo*.

1) Clinical case or case reports: the Clinical Medicine Division of the University Hospital publishes an electronic magazine of enormous importance, “Autopsy and Cases Reports”, whose documentary value is scientific and educational<sup>7</sup>. The Institute of Psychiatry has a research line on images in the field of Alzheimer’s with paramount results for better knowing this and other diseases<sup>8</sup>.

2) Experiments in animals: research related to cancer with murine models performed at the LIM-Oncology, which become hypotheses to be developed at the Cancer Institute<sup>9</sup>.

3) Observational or cohort studies: the Clinical and Epidemiological Research Center based at University Hospital coordinates the largest study on cardiovascular diseases and diabetes in the southern hemisphere. The Brazilian Longitudinal Study of the Adult Health, ELSA - Brazil (Estudo Longitudinal de Saúde do Adulto ELSA - Brasil) with 15105 participants being monitored since 2008 with more than 100 original papers published and intense international collaboration<sup>10</sup>.

4) interventional studies or clinical trials: the comparison of electrical stimulation in depression that resulted in an article in “The New York Times”, which was

conducted at the Clinical and Epidemiologic Research Center of the University Hospital and is the most cited study in the field<sup>11</sup>. The Heart Institute created the “Medicine, Angioplasty, Surgery Study” (MASS), a clinical trial for angina of huge impact and with five developments, all of the vast importance in the scope of global cardiology<sup>12</sup>.

5) Secondary base studies: the Preventive Medicine Department published a necessary critical evaluation of

several studies and demographic bases linking depression to violent behavior<sup>13</sup>.

## CONCLUSION

Clinical research in Brazil is still in its early days and can grow greatly in the next decades not only with funding but mainly to the improvement of scientific culture in the country.

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