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A JOURNEY THROUGH THE MILESTONES OF CLINICAL RESEARCH

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Abstract: The evolution of clinical research, from its primitive forms to its current state, mirrors the development and evolution of humanity itself. Historical accounts extend to the present day, with current scientific knowledge providing detailed insights into the evolution of research methods. The history of clinical research is replete with instances that have marked its progression, particularly in the 20th century, leading to the necessity for the creation of regulatory documents for human experimentation. A full understanding of the current level requires an analysis of its evolution.
Keywords: History of Clinical Research; Clinical Investigation; Bioethics; Developing countries

INTRODUCTION

Clinical research is fundamental to the development of medicine, and an understanding of the current level requires an analysis of its evolution, from Antiquity to the present day.

Even though some of the practices analyzed occurred many years ago, many of the situations reported occurred in the last century, therefore in a relatively short time span. The analysis of the historical milestones of clinical research demonstrates a path in the search for safety, efficacy and ethics, and one objective of this research is to list errors and successes over time, as we consider that these milestones are essential to understand the challenges faced in the past and avoid future repetitions.

Examples of the need for standards and policies to focus on the protection of research participants are the introduction of ethical regulations such as the Nuremberg Code and the Declaration of Helsinki. Likewise, the development of randomization and double-blind trials are also developments that revolutionized clinical research.

Therefore, this research is justified by the need to understand the factors that have stimulated clinical research over time, allowing a critical assessment of the present and the formulation of future directions for the field, reinforcing the importance of ethics, innovation and methodological rigor in conducting clinical research, promoting reflection on the challenges and opportunities that clinical research still faces today.

METHODOLOGY

The study presented consisted of a bibliographical review, whose objective is to identify and analyze main milestones of clinical research from Antiquity to the present. To this end, a review of scientific articles and normative documents was carried out, describing the evolution of clinical research, including methodological, regulatory and ethical advances. The bibliographic research was carried out in the scientific databases PubMed, Scopus and Google Scholar, with articles selected that presented a chronological context of the most relevant events, and analyzing fundamental historical documents, such as the Nuremberg Code (1947) and the Declaration of Helsinki (1964).

RESULTS AND DISCUSSION

One of the first reports is present in the Book of Daniel (Bible), during the reign of King Nebuchadnezzar in Babylon, around the year 540 BC; it is described that the king ordered his people to adhere to a dietary regime consisting exclusively of meat and wine, as this was believed to enhance physical well-being. However, upon observing that some of the young, royal lineage individuals were consuming vegetables in defiance of the decree, the king permitted them to adhere to this dietary regime. A subsequent observation after a period of ten days revealed that the latter group exhibited superior nourishment, compelling

the king to mandate the adoption of this diet by his subjects. This event marks a significant departure in the realm of human experimentation, as it is among the earliest documented cases in history (Collier, 2009; Bhatt, 2010).

In the publication entitled "Canon of Medicine", Avicenna (1025 AD) highlights rules and principles that are intrinsic to clinical research. These include case comparison, the use of a control group, the presence of bias in experimental situations, and the significance of observational experiments, amongst others (Nasser & Savage-Smith, 2009).

Ambroise Paré, a French military surgeon largely responsible for the establishment of military surgery through his discoveries, during a military engagement in 1536, resorted to an unconventional approach due to the scarcity of oil, which, when boiled, constituted the primary treatment for bullet wounds. Utilising a combination of egg yolk, rose oil, and turpentine, Paré observed a substantial improvement in the condition of the soldiers, leading to the adoption of this novel treatment for their wounds (Bhatt, 2010; Domingues, 2024).

James Lind, while serving as a physician aboard several English naval vessels, in 1747 conducted what is widely considered the first controlled clinical trial, selecting sailors suffering from scurvy, dividing them into groups, and isolating them from the rest of the crew, treating each pair with a distinct treatment for scurvy, with the randomisation process ensuring equivalent symptoms and dietary conditions amongst the groups; cider, weak acid, vinegar, seawater, nutmeg and barley, or oranges and lemons where the "treatments". The pair of sailors receiving citrus fruits demonstrated the most favourable progression of the disease. Lind's meticulous attention to the accurate reporting of the findings aligns this research with contemporary clinical research standards (Bhatt, 2010; Milne, 2012).

The term "placebo" emerged in the late 18th century and is attributed to William Cullen (1710-1790), who introduced the term into medical language in 1772. Also John Coakley Lettsom (1744-1815), an physician of note who practised in London, used the term placebo in the same sense (Jütte, 2013).

The etymology of the term is unclear, but its purpose at the time, remained consistent: to satisfy the patient's desire for a drug, even if the doctor was not convinced of its necessity and pharmacological efficacy. The earliest recorded instance of the utilisation of the term 'placebo' in a medical context is believed to be in the 1785 edition of the New Medical Dictionary (De Craen et al., 1999). In 1801, John Haygarth documented the findings of what is believed to have been the inaugural placebo-controlled trial. At the time, metal rods (known as Perkins tractors) were commonly used to treat a variety of conditions, with the assumption that the electromagnetic influence of the metal would alleviate symptoms. Haygarth applied the treatment to five patients using a wooden imitation and found that four of them experienced relief. The next day, Haygarth repeated the procedure using the metal rods on the same five patients and obtained identical results: four out of five people reported relief of symptoms (De Craen et al., 1999).

A significant number of clinical trials were conducted between the beginning of the Great Depression (1929) and the end of the 20th century, especially on the period surrounding the Second World War. Significantly, numerous human rights violations were documented during this period, as described below:

1932-1972: The study of syphilis at the Tuskegee Institute in Alabama was initiated by the United States Public Health Service (USPHS) in a population of black men in their natural environment. The study comprised two groups: a control group of 201 men

who were disease-free and a treatment group of 399 men with syphilis who were not treated. The objective of the study was to observe the natural progression of the disease. The study ran from 1932 to 1972, interrupted only by court orders. Information regarding the possibility of withdrawing from the study was withheld, as was treatment, despite the efficacy of penicillin being demonstrated (Corbie--Smith, 1999; Tobin, 2022).

1937: Sulfonamides were the first systemic antibiotics, but due to their ease of availability, their use became unregulated and without control over the manufacturing process, eventually resulting in the death of 105 people from diethylene glycol poisoning, due to an incorrectly prepared batch of medication (Wax, 1995).

1939 - 1945: During World War II, Nazi forces conducted numerous experiments on concentration camp prisoners with no regard for human life and dignity, resulting in a significant number of direct and indirect fatalities. These experiments included genetic studies, musculoskeletal studies, environmental exposure, product testing, and mutilation, among others (Bansal et al., 2015).

1946-1948: During this period, Cutler (USPHS) conducted a study of syphilis in vulnerable populations in Guatemala. The study was sponsored by the National Institute of Health and carried out in collaboration with Guatemalan researchers such as Dr Juan Funnes of Guatemala Public Health. The research design entailed the intentional infection of study participants with syphilis (along with gonorrhoea and chancroid), followed by the administration of penicillin for the treatment of these infections. This experimental programme was meticulously structured, with subjects being exposed through infected sexual partners or via direct inoculation of infected tissue. Once the post-exposure results were complete, penicillin was used to try to cure the infections (Reverby, 2011).

1948: Bradford Hill, an English epidemiologist, was instrumental in introducing randomization, a method that allowed therapeutic interventions to be evaluated in large--scale clinical trials. One of his earliest studies described the efficacy of streptomycin in the treatment of pulmonary tuberculosis, and his most significant work, in collaboration with Richard Doll, was the design of the Smoking and Lung Cancer Trials, which provided compelling evidence of a link between tobacco addiction and subsequent health problems, including cancer and coronary heart disease (Yoshioka, 1998; Wendland, 2008).

1994: In the 1990s, placebo-controlled trials of zidovudine (AZT) were conducted in Africa. The trials used placebo controls as opposed to effective drugs in HIV-positive pregnant women with the goal of preventing vertical transmission. It is important to note that the trials did not provide the most advanced medical care available during the time of the research (Wendland, 2008).

1996: During an outbreak of meningococcal meningitis in Kano, Nigeria, the efficacy of the new antibiotic trovafloxacin was tested in an open-label trial involving 200 children, divided into two groups: one group receiving trovafloxacin and one group receiving the standard treatment for meningitis, ceftriaxone. The study revealed that five children in the trovafloxacin group and six children in the ceftriaxone group died from the disease. The research also identified violations of ethical guidelines, including the exploitation of vulnerable populations and the lack of access to information about the potential side effects of trovafloxacin (Wise, 2001).

Although many of the experiments presented already preserved the rights of human beings, with respect for ethical principles, the two most significant milestones in the advancement of human rights occurred in the 20th century are as follows:

1947: The Nuremberg Code is drafted, an important document in the history of clinical research ethics, based on ten fundamental principles to ensure human safety and protection, in opposition to unregulated Nazi experimentation, introducing concepts such as voluntary participation (Shuster, 1997).

1964: The Declaration of Helsinki constitutes a statement of ethical principles for medical research involving human subjects, covering research on identifiable human material and data, and including concepts such as informed consent, risk-benefit balance, and protection of vulnerable groups. The Declaration has been revised eight times since 1964, with the last revision taking place in Helsinki in 2024 (World Medical Association,1964).

FINAL CONSIDERATIONS

This article presents the perspective of the most relevant historical milestones in the evolution of clinical research, although pointing out the most relevant situations is always subjective. Something difficult to do and which can be considered a limitation of the study and a future area to be addressed, is the contextualization of each historical milestone in relation to the time in which it occurred, so that it is not decontextualized, something that we do not intend in this approach.

In the context of experimentation on populations and in countries with few resources, issues of an ethical nature are of particular importance. This is because there is a verifiable history of the exploitation of these weaknesses by the country sponsoring the research. In the aftermath of a significant incident, such as those documented above, governments frequently find themselves compelled to implement regulatory measures and establish guidelines of conduct and action. These measures are designed to avert the recurrence of the circumstances engendered by the experiment. The current practice of clinical research, in constant evolution and demand, requires revisiting past practices as a way of avoiding the repetition of clinical research conducted under conditions considered unacceptable from ethical and human perspectives.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHORIZATIONS/ RECOGNITION

By submitting the work, the authors assume responsibility for the entire content of the work.

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