Clinical Trials and Health Risks: How Can The Law Strengthen Participants' Rights In Algeria?

التجارب العيادية والمخاطر الصحية: كيف يمكن للقانون أن يعزّز حقوق المشاركين في الجزائر؟



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Abstract:

This paper explains the legal, regulatory, and ethical aspects of clinical trials in Algeria, emphasizing the paramount importance of participant safety and rights over scientific or societal interests, as mandated by national and international regulations. (Chapter I) defines key terminology based on Algerian Health Law No. 18-11 and provides a historical overview of medical research regulations. (Chapter II) discusses potential risks to participants, while (Chapter III) outlines the essential requirements and procedures for clinical trials. Finally, (Chapter IV) focuses on the purpose of good clinical practice in Algerian law, which is to safeguard the well-being, safety, and rights of trial participants.

key words: Clinical Trials Regulations; Human Subjects; Informed Consent; Good Clinical Practice (GCP); Medical Research Ethics.

الملخص:

تشرح هذه الورقة الجوانب القانونية والتنظيمية والأخلاقية للتجارب العيادية في الجزائر، مؤكدةً على الأهمية القصوى لسلامة المشاركين وحقوقهم بسموّها على المصالح العلمية والمجتمعية وفقًا لما تقتضيه اللوائح الوطنية والدولية. يُعرّف الفصل الأول المصطلحات الرئيسية استنادًا إلى قانون الصحة رقم 18-11 المعدل والمتمم؛ كما يُقدّم لمحة تاريخية عن لوائح البحث الطبي في الجزائر. يناقش الفصل الثاني المخاطر المحتملة على المشاركين، بينما يُحدّد الفصل الثالث المتطلبات والإجراءات الأساسية لهذه التجارب. وأخيرًا، يُركز الفصل الرابع على هدف الممارسات السريرية الجيدة في القانون الوطني، وهو حماية سلامة المشاركين في التجارب وحقوقهم.

الكلمات المفتاحية: لوائح التجارب العيادية؛ البشر المشاركون؛ الموافقة المستنيرة؛ الممارسات السريرية الجيدة؛ أخلاقيات البحوث الطبية.

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Introduction:

At the beginning of 2020, the Algerian government announced the creation of the Ministry of Pharmaceutical Industry[1]. The objective behind the creation of this Ministry was to promote the local production of pharmaceutical products, in view of bringing Algeria at the forefront of production and positioning itself as a regional hub in the sector, and as a leading country in North Africa. Moreover, the amended Health Law[2] of 2020 gave this new ministry the competence to grant authorizations for clinical trials on human subjects[3]. With the creation of the Ministry of Pharmaceutical Industry, quite a few authorizations have been issued since 2020. But Algeria was before that conducted 206 clinical trials out of a total of 26,329 patients from 2007 to 2017, of the 206 clinical studies or research conducted, 52 are observational studies only and 106 are Pharmaco-epidemiological studies[4]. The granting of authorizations by the Ministry of Health and Hospitals Reforms, for clinical trials of drugs previously was considered very lengthy. However, this time limit has been reduced a priori, notably with the creation of the Ministry of Pharmaceutical Industry which would give a new impetus to clinical research in Algeria. Since the first text governing good practice in clinical trials was published in 2009[5], more than 100 studies have been carried out in Algeria, as part of multi-center studies conducted in several countries around the world. In 2020, the time-limit of authorizations by the Ministry of the Pharmaceutical Industry for clinical trials of medicinal products was reduced to 3 months.

This is still acceptable compared to previous years when the authorization was only given after six months or more and sometimes never. This new provision has been incorporated into the amended and supplemented Health Law No. 18-11.

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[1] See: Executive Decree No. 20-271 of 29 September 2020 ***laying down the Minister's competences for the Pharmaceutical Industry***, Official Journal n° 58.

[2] See: Ordinance No. 20-02 of August 30, 2020 amending and supplementing Law n° 18-11 of July 2, 2018 relating to ***Health***. O. J. n° 50.

[3] According to article 381 of the amended Health Law (18-11) N° 20-02: "***Clinical studies shall be subject to authorization by the Minister responsible for the pharmaceutical industry, who shall take a decision within three (3) months, on the basis of a medical and technical file and a declaration of completion of clinical studies on humans, submitted by the sponsor. Any changes in the clinical studies file, once authorization has been obtained, shall be subject to the agreement of the Minister responsible for the pharmaceutical industry.***"

[4] See: Bouguelli Amina, intervention in title: "***Clinical trials in Algeria: assessment 2007-2017"***, the 5th training session organized by Roche Algeria for the benefit of journalists, Roche LAB, AXYLYS, Algiers, 2020.

[5] See: Decision No. 00200 of 25 July 2009, Amending Decision No. 112 of 22 October 1995, ***Establishing the Rules of Good Clinical Practices (GCP)***.

Clinical Trials and Health Risks: How Can The Law Strengthen Participants' Rights In Algeria?

With the current legislative and regulatory framework in place to oversee and monitor clinical trials on human subjects[1] in Algeria, many difficult questions are looming, especially about the adequacy of the existing regulatory and legislative framework with the aspirations, ambitions, and opportunism of the Contractual Research Organizations (CRO)[2], including companies that sponsor clinical trials, which in recent years have become focused on economic aspects, profitability and financial returns rather than on protecting and promoting the rights and welfare of human subjects who participate in these clinical trials? To what extent will current legislative and regulatory frameworks ensure a balance between ensuring the well-being and rights of people participating in clinical trials and protecting the financial and profitability interests of sponsoring companies and (CRO)?

For the purpose of answering these questions, and before moving on to discussing the specific legal and regulatory aspects of clinical trials in the Algerian health system, including the rights of participants, it is important to first establish basic definitions and understand what is being discussed. (**Chapter I**) of this contribution is devoted to explaining what is meant by the terminology used repeatedly throughout this paper and to providing a brief overview, taking into account the historical sequence of medical research regulations on human subjects. The terminology used everywhere will follow the Algerian definitions as stipulated in the Health Law N°18-11, its amendments and other legal and regulatory texts relevant to clinical trials on human subjects. This will be followed by a discussion of the risks that human subjects or participating in clinical trials may sometimes be exposed (**Chapter II**). In (**Chapter III**), further details are provided to identify and regulating the basic requirements, conditions and procedures for the clinical trial-related studies. (**Chapter IV**) will focus on

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[1] Some authors use the term 'participant' instead of 'subject' because they believe the term 'subject' is insulting. See: Iain Chalmers, "***People are "participants" in research: Further suggestions for other terms to describe "participants" are needed***", British Medical Journal, Volume 318, 24 April 1999, p 1141. While "participant" is sometimes used, this paper primarily uses "subject" for three reasons: its prevalence in WHO guidelines, its accuracy in describing passive involvement in research, and its reminder of potential exploitation, countering the feel-good connotation of "participant."

[2] The Contract Research Organization (CRO) is a person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of the trial-related duties and functions of the sponsor. A sponsor may transfer any or all of the trial-related duties and functions of the sponsor to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. See: Ralph B. D'Agostino, et al., "***Wiley Encyclopedia of Clinical Trials***", 1st edition, Wiley-Interscience, 2008, p 465.

explaining the basic purpose of establishing the rules of good clinical practice in Algerian law, namely to protect the well-being and rights of human subjects who are involved in these trials.

Chapter I: Clinical Trials on Human Subjects In Algerian Law: A Brief Historical and Definitions

First Requirement: Clinical Trial Regulations In Algeria: A Brief History

In Algeria, the human clinical trials was the subject of a draft decree drawn up in the 1990s, but never published, as it was deemed probably premature for the time. From 1995, clinical trials were regulated by:

- Helsinki Declaration[1] (World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects), last update Oct. 2013.
- The Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (ETS No 164). 4 April 1997, Oviedo, (Spain)[2].
- ICH E6 R1; R2; (R3- on DRAFT 19 April 2021): Good Clinical Practices[3]; version 4, last update Nov. 2018.
- Ordinance No. 20-02 of 30 August 2020, amending and supplementing Law No. 18-11 of 2 July 2018, relating to Health.
- Executive Decree No. 20-391 of December 19, 2020 amending and supplementing Executive Decree No. 19-190 of July 3, 2019, fixing the missions, organization and functioning of the national agency for pharmaceutical products (ANPP)[4]. O. j N° 78, of 27 December 2020.
- Decision of December 27, 2020 on the missions, composition, organization and functioning of the committee of clinical experts. O. j N° 78, of 27 December 2020[5].
- Decision No. 112/MSP/MIN of 22 October 1995 laying down Good Clinical Practice. Modified in July 2009, by (Decision No. 00200 of July 25, 2009).

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[1] See: World Medical Association (WMA) ***Declaration of Helsinki*** Ethical Principles for Medical Research Involving Human Subjects. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

[2] See : ***Oviedo Convention and its Protocols*** at: https://www.coe.int/en/web/bioethics/oviedo-convention

[3] ICH (International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use) harmonized guideline integrated addendum to ICH E6 (R1): ***Guideline for Good Clinical Practice ICH E6 (R2)*** ICH Consensus Guideline. https://ichgcp.net/

[4] The agency (ANPP) is a Regulatory public establishment with specific management, endowed with legal personality and financial autonomy, placed under the supervision of the minister responsible for the pharmaceutical industry.

[5] In application of the provisions of article 26 of executive decree n ° 20-324 and of article 23 of executive decree N° 20-325 of November 22, 2020, Decree of December 27, 2020 ***on the missions, composition, organization and functioning of the committee of clinical experts It specifies*** in article 2.

- Decision No. 44 of 21 September 1998 on a form for a declaration of intent to test a medicinal product or similar product.
- Decision No. 48 of 7 October 1998 on the form for reporting a serious effect likely to be due to biomedical research on a medicinal product or a pharmaceutical product.
- Decision No. 67 of 6 December 1998 Establishing the Clinical Trials Unit.
- Circular No. 1429 of 25 September 1999 Defining the Places where Clinical Trials are to be Carried Out.
- Circular No. 003 of 11 October 1999 on Guidelines for the Conduct of Medical Research on Humans.
- Circular No. 04 of 11 October 1999 Laying Down Rules for the Conduct of a Bioavailability and Bioequivalence Study.
- Decision No. 387 of July 31, 2006 Relating to Clinical Trials.
- Decision No. 388 of 31 July 2006, Related to the Clinical Trials Authorization Process.
- Decision No. 00200 of 25 July 2009 Modifying the Decision No. 112 of 22 October 1995 Setting the Rules of Good Clinical Practices.

Today, these last three decisions are applied. The existing body of law operates according to the basic principles agreed by WHO[1] and ICH.

Algeria's contribution to clinical research activity on a global and continental scale remains very limited, with only 55 clinical trials (1/1 million inhabitants) despite all the potential and assets available to make it an attractive country for clinical trials[2].

It is important to note that the clinical trials unit mentioned above was not actually created, as the National Pharmacovigilance and Toxicology Centers were created in the late 1990s and are under the supervision of the Ministry of Health.

First Section: Clinical Trials in Law: Concepts and Stakeholders Involved

Firstly: Clinical Trials

A clinical trial represents a forward-looking biomedical or behavioral investigation that engages human subjects and/or utilizes human-derived materials, such as behavioral data, questionnaire responses, or biological samples. These trials are structured to address a defined research query and aim to ascertain

[1] World Health Organization.

[2] See: Nadia Bouabdallah, "***The Reality of the Development of Biomedical Research in Algeria and the Organizational aspect***", Scientific Day on "Clinical Research: Algeria on the Path of Innovation", Algiers, December 21, 2021.

the safety, efficacy, and effectiveness of a novel biomedical or behavioral therapeutic or preventative measure[1].

Every clinical trial needs a main question it aims to answer. This question, and any related secondary questions, must be clear and decided beforehand. The main question should cover the key aspects (who, what, by whom, when, how long, and what result). This is the trial's focus, whether it's about comparing treatments, testing a new treatment, applying a treatment in a new way, or studying quality of life. The trial must be set up to properly answer this question, have enough statistical power to test it, and have a significant impact if successful[2].

In Algeria, Biomedical research consists of studies on human beings with a view to developing epidemiological, diagnostic, biological and therapeutic knowledge and to improving medical practices. These studies are designated by Law No. 18-11 under the name “clinical studies”[3].

According to Decision No. 00200 of 25 July 2009[4], Clinical trial is defined: any systematic trial of a drug in humans, whether in sick or healthy volunteers, in order to highlight or verify its effects and (or) to identify any effect and / or study its absorption, distribution, metabolism and excretion to establish its efficacy and safety. Articles 378, 379, and 380 of Health Law N° 18-11 set out the modalities of these studies. Clinical studies must imperatively respect the moral, scientific, ethical and deontological principles which govern medical practice. The clinical studies must be carried out in accordance with the rules of good practice in the matter in the structures approved and authorized, for this purpose, according to the methods fixed by the minister in charge of pharmaceutical industry. Clinical studies can only be performed in humans if:

- They are based on the latest state of clinical research, scientific knowledge and sufficient preclinical experimentation.
- The predictable benefit-risk ratio is favorable to the person included in the study.

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[1] See: Delva Shamley, Brenda Wright (Eds.), "***A Comprehensive and Practical Guide to Clinical Trials***", Academic Press, Elsevier, 2017, p 2.

[2] See: Peter R. Nelson, "***The Research Question and the Hypothesis***". In: Kamal M.F. Itani Domenic J. Reda (Editors), "***Clinical Trials Design in Operative and Non Operative Invasive Procedures***", Springer International Publishing AG, 2017. p5.

[3] Clinical studies can be observational or interventional, and relate in particular to:

- ***Therapeutic, diagnostic and preventive studies;***
- ***Bioequivalence and bioavailability studies;***
- ***Epidemiological and pharmaco-epidemiological studies***. The terms of application of this article are set by regulation. See: Art. 377 of ***Health Law N° 18-11*** modified and completed.

[4] See: Decision No. 00200 of 25 July 2009 Modifying the Decision No. 112 of 22 October 1995 **setting the rules of Good Clinical Practices**.

- They are carried out under the direction and supervision of an investigating physician, demonstrating appropriate experience**.** They shall be applied under human, material and technical conditions appropriate to the clinical study and consistent with the requirements of scientific rigor and the safety of those who are suitable for the clinical study.

Secondly: The (Sponsor) or (CRO) and Investigator

Clinical trials must be undertaken by a sponsor[1], who is defined as the natural or legal person who begins the clinical study, according to Article 384 of Health Law No 18-11. It might be a pharmaceutical firm, a Ministry of Health-approved contract research organization (CRO), a healthcare organization, a scientific society, a research institution, or a natural person with the requisite credentials and abilities. According to the Decision No. 387 of July 31, 2006 (Art. 4 and 5)[2], Clinical trials require sponsors, and/or research organizations called contract research organizations (CRO) and investigators. Sponsor is any natural or legal person who initiates a clinical trial. The term "contract research organization" (CRO) is understood to mean any company providing services in the field of clinical trials. This company is assimilated to a promoter. Investigator is understood to mean any general practitioner or specialist who directs and supervises the performance of the clinical trial. Article n° 381 of Health Law n° 18-11 amended in 2020, specifies that: Clinical studies are subject to the authorization of the Minister in charge of the pharmaceutical industry who decides within three (3) months, on the basis of:

- A medical and technical file.
- A declaration of completion of clinical studies on humans presented by the sponsor.
- Any modification in the clinical studies file, once authorization has been obtained, is subject to the approval of the Minister responsible for the pharmaceutical industry.

The sponsor of a clinical trial must submit a written protocol[3], signed by the investigating physician(s) after he (they) has (have) expressed his (their)

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[1] The clinical trial sponsor, who initiates and oversees the study, designates an Investigator Site under the direction of a Principal Investigator. This site executes the trial utilizing its Clinical Team, which may be sourced from a Clinical Trials Unit (CTU), a Contract Research Organization (CRO), or the site's research staff. Sponsors can be individuals, corporations, or institutions, including governmental or industrial entities, and may or may not provide financial support. See: Delva Shamley, Brenda Wright. Op.cit, p3 & p5.

[2] Decision No. 387 of July 31, 2006, **Relating to Clinical Trials.**

[3] The Protocol it's: ***a document describing the rationale, objectives, methodology and statistical methods of the test, and specifying the conditions under which this test must be performed and managed. A list of the elements to be included in the protocol is given in the annex to this explanatory note***. See: Decision No. 00200 of 25 July 2009.Op.cit.

agreement, signifying his (their) acceptance of the protocol and his (their) commitment to respect the conditions of realization, as stated in Decision No. 388 of July 31, 2006Furthermore, clinical trials must be conducted in compliance [1]. with the principles of good practices in this field in recognized and authorized organizations, as required by ministerial Decision No. 00200 of July 25, 2009, pertaining to good clinical trials practices (GCP).

Second Section: Medical Ethics Committee or Institutional Review Board (IRB)

Clinical trials require prior approval from an Institutional Review Board (IRB), ethics board, or Medical Ethics Committee. These boards, comprising clinicians, researchers, and community members, are crucial for ensuring ethical trial conduct and protecting the rights, safety, and well-being of participants, adhering to Good Clinical Practice guidelines and data protection regulations. The IRB reviews trial protocols to ensure medical safety and participant protection before granting approval[2].

Clinical trial protocols must also be approved by the Medical Ethics Committee[3], which is an independent body established at the level of external healthcare services and whose activities are overseen by the relevant departments of the Ministry of Health, and which will be gradually replaced by the National Agency (ANPP). The Ethics Committee is defined in the Glossary of Decision No. 00200 of 25 July 2009 as: A independent body comprising representatives of the medical and para-medical professions, as well as non-healthcare professionals, whose responsibility is to verify that the safety, protection and rights of the people participating in a given trial are insured, with the extension of reassuring the general public. Ethics committees must be constituted and operate in such a way that the aptitude and availability of investigators, logistical means and protocols, as well as the method of recruiting persons participating in the trials and the guarantees of confidentiality can be objectively assessed and impartially, with complete independence from the investigator, the sponsor and the authorities concerned. The legal status, constitution and regulatory requirements concerning ethics committees must comply with the provisions in force List of members of the ethics committee (specifying their function), as well as a description of its operating procedures and deadlines response, must be accessible to the public.

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[1] See: Decision No. 388 of July 31, 2006, related to the clinical trials authorization process.

[2] See: Delva Shamley, Brenda Wright. Op.cit, p5.

[3] According to ***Health Law N°18-11***, Art. 383: "***Clinical studies are subject to the opinion of the medical ethics committee, cited above***". Medical ethics committee is independent body created at the level of the external health services. Activities supervised by the competent services of the Ministry of Health. Missions, composition, organization and functioning remain to be determined by regulation.

Any clinical trial project must be submitted by the sponsor to the prior opinion of the ethics committee for clinical trials created in Article 25 of Decision No. 387 of July 31, 2006. The ethics committee for clinical trials has one month from the date of receipt of the draft to give its opinion. The Minister responsible for health creates, in each health region, one or more ethics committee (s) for clinical trials. Ethics committees for clinical trials are based in public health institutions (Art.25). The organization and functioning of the ethics committees for clinical trials are set by instruction. The ethics committee for clinical trials is an independent body, it is composed of eight (08) people (Art.26).

Firstly: The Human Subjects

As detailed further below, while clinical trials commonly involve healthy male subjects, patient participation is also possible. Human subjects are individuals who have voluntarily provided informed consent by signing the Informed Consent Document, thereby agreeing to the procedures to be performed during the clinical trial[1]. However, People who cannot participate in clinical trials are[2]:

- Persons deprived of their liberty by a judicial or administrative decision;
- Patients in emergency situations and people hospitalized without consent.

For clinical trials without direct individual benefit[3], the sponsor assumes, even without fault, compensation for the harmful consequences of the trial for the person who takes part and that of his beneficiaries, without the fact of being opposed. a third party or the voluntary withdrawal of the person who had initially consented to participate in this test.

Second Requirement: The Role of National Agency for Pharmaceuticals (ANPP) In Clinical Evaluation

In addition to the regulatory functions of the Minister of Pharmaceutical Industry, we find the National Agency (ANPP), which is the regulatory agency responsible for overseeing the safety of clinical trials and monitoring the benefit-to-Risk ratio of trials on human subjects. The Agency also plays the role of honest

[1] See: Delva Shamley, Brenda Wright. Op.cit, p3.
[2] See: Art. 14 and 15 of Decision No. 387 of July 31, 2006. Op.cit.
[3] Direct Individual Benefit (DIB) it is said that clinical research has direct individual benefit when patients included in the trial will directly benefit from any therapeutic benefit in the management of their condition. Conversely, all other clinical research is said to have no direct individual benefit when the healthy subjects or patients included in the trial do not derive any direct therapeutic benefit from the research in which they have agreed to participate. See: Decision No. 387 of July 31, 2006. Ibid.

advisor to the health authorities. The Missions of ANPP in Clinical studies according to the executive Decree No. 20-391[1] is:

- Scientific evaluation of the benefits, risks and therapeutic value;
- Opinions on requests for clinical studies and bioequivalence studies;
- Promotion of scientific research into pharmaceutical products;

Aspects of the evaluation	**Approvals**	**Methodology and conduct of the test**	**Data analysis**	**Clinical trial protocol**
- Administrative and regulatory aspects. - Methodology and conduct of the test. - GPC - Data analyses.	- Ethics - Authority - Consents of volunteers - Investigation reports	- Design - Comparators - Population - Judgment criteria - Procedure - Statistics	- Statistical analysis: Methods and tests - Areas and margins of acceptance - efficiency - Equivalence / Bioequivalence - Safety / Tolerance Requests for clinical studies and bioequivalence	- Goals-Plan - Population - Treatments - Judgment criteria - Procedure - Statistics

Table.1. By author: Clinical evaluation of ANPP

As a comparative example; the regulatory agencies like the FDA use phased testing (I-IV) to ensure drug safety and efficacy before approval[2]. Initial phases focus on identifying major safety concerns in small groups, while later phases expand to larger groups, refining safety assessments and emphasizing efficacy.

The figure below shows the various stakeholders involved in biomedical research studies, including clinical trials in the Algerian health legal system.

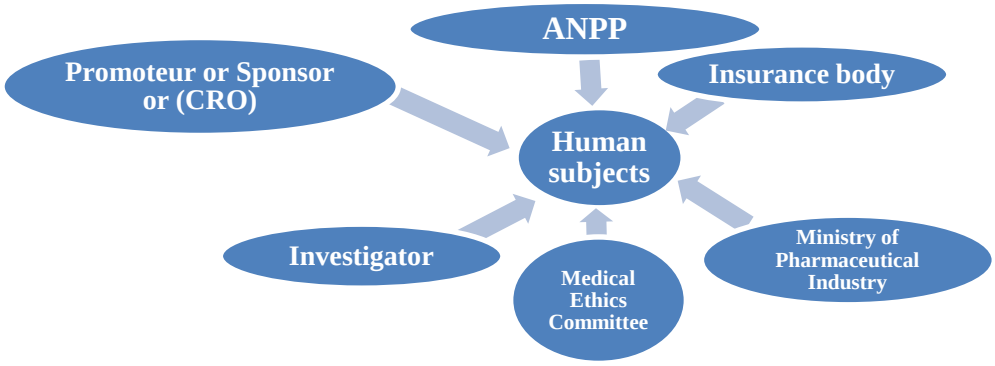


Fig. 1. By author**:** Stakeholders Intervening to Protect Human Subjects

Chapter II: Clinical Trial Management: Phases and Associated Risks

First Requirement: Trial Management

[1] See: Executive Decree No. 20-391 of December 19, 2020, amending and supplementing Executive Decree No. 19-190 of July 3, 2019, ***fixing the missions, organization and functioning of the national agency for pharmaceutical products (ANPP)***. O. j N° 78, of 27 December 2020.

[2] See: Domenic J. Reda, "***Clinical Phases of Device and Drug Evaluation with Emphasis on Early Phase Trials***". In: Kamal M.F. Itani Domenic J. Reda (Editors). Op.cit, pp 41-42.

Effective clinical trial management demands a flexible, multi-stage process. Throughout the trial, stakeholders fulfill specific roles, and the completion of prerequisite steps is essential before advancing to subsequent stages. The process is divided into three stages, as detailed below:

Firstly: Clinical Trial Stages

A) - Stage 1

Stage 1 encompasses the development of the investigational drug, definition of the research question, and fulfillment of regulatory requirements. While these processes may occur concurrently and not strictly sequentially, all must be completed before initiating the clinical trial[1].

B) - Stage 2

In Stage 2, the preparation phase of the clinical trial is detailed, encompassing planning and staff training. This phase involves the clinical team establishing the procedural framework, securing necessary documentation, agreements, and materials. The principal investigator oversees staff training and delegates specific responsibilities. While potentially time-intensive, thorough preparation is critical for a successful trial outcome.

C) - Stage 3

Stage 3 elucidates the implementation of the clinical trial and details the procedures executed upon trial completion[2].

Secondly: Clinical Trial Phases

Clinical trials are prospective studies in humans comparing an intervention's effects to a control. Participants are tracked over time from a defined baseline, unlike retrospective studies where individuals are selected based on a past event or condition. Leveraging widespread electronic health records, large-scale studies track patients undergoing therapist-chosen interventions. This non-randomized approach, unlike clinical trials, is often retrospective due to participant identification post-treatment, leading to potential data limitations.[3] Treatment outcomes are often confounded, even with adjustments. Electronic records can complement clinical trials which require standardized interventions (drugs, procedures, etc.) to change an outcome. Studies without intervention are observational, not trials[4]. Before clinical trials, research companies conduct preclinical studies for activity/toxicity. If successful, safety/toxicity studies begin

[1] See: Delva Shamley, Brenda Wright. Op.cit, p5.
[2] Ibid, p8.
[3] See: Lawrence M. Friedman, Curt D. Furberg, et al., "***Fundamentals of Clinical Trials***", fifth edition, Springer International Publishing Switzerland, 2015. P2.
[4] Ibid. p3.

in human volunteers. Clinical trials proceed in phases (I-IV) to assess safety, tolerability, and efficacy. Phases may overlap[1].

A) – PHASE I

Phase I studies are initial human trials assessing a new drug/vaccine's safety and tolerability in a small group (often healthy volunteers). Researchers determine the highest safe (maximum tolerated dose) (MTD), studying how the body absorbs and reacts to the drug, and monitor for side effects to determine the optimal dosage.

B) - PROOF-OF-CONCEPT TRIALS

Early-stage trials explore a drug's potential for new uses beyond its original purpose. These small-scale "proof-of-concept" studies, bridging Phase I and II, assess if further development or investigation into a "new indication" is justified[2].

C) - PHASE IIA AND PHASE IIB

If Phase I shows no safety issues, Phase II trials begin. These trials involve more participants to assess the drug's effectiveness, activity, feasibility, and toxicity. Safety is continuously monitored, and dosage is refined. The drug may be tested on different groups (e.g., adults then infants).

1) - PHASE IIA

Phase IIa trials expand safety assessments to larger groups and pilot efficacy tests in specific patient populations. Objectives focus on determining safe and effective dosing parameters like MTD.

2) - PHASE IIB

Phase IIb trials rigorously demonstrate a drug's efficacy at the prescribed dose. Sometimes called "pivotal trials," they provide key evidence for marketing approval, similar to Phase III trials, and lead to Phase III upon proving drug effectiveness[3].

D) - PHASE IIIA AND PHASE IIIB

Phase III trials, involving 1000-3000+ participants, definitively assess efficacy and safety versus existing treatments. They monitor side effects and optimize safe use, ideally via randomized, double-blind studies. These "pivotal trials" provide licensing data.

1) - PHASE IIIA

Post-efficacy trials gather safety/efficacy data in intended patients. This data informs drug labeling and package inserts before application submission.

2) - PHASE IIIB

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[1] See: Brenda Wright, "***Chapter 2: Clinical Trial Phases***", In: Delva Shamley, Brenda Wright, Op.cit, p11.
[2] Ibid.P12.
[3] Ibid.P13.

Phase IIIb trials happen after a drug application is submitted but before approval. They gather extra info sometimes needed by regulators before they approve a drug for marketing. These trials can add to or complete earlier trials, or be designed as a bridge to Phase IV studies.

E) - PHASE IV

Phase IV trials occur post-market to monitor a drug's effects across diverse populations and identify long-term side effects. They assess real-world effectiveness, explore new uses, and uncover rare safety concerns not seen in controlled pre-market trials, adhering to the same scientific/ethical standards.

Second Requirement: Clinical Risk Definition

Risk is the chance of harmful outcomes, with the degree of risk determined by the probability and magnitude of harm. A ranking system uses a seven-point scale to classify damage, ranging from "tiny" to "catastrophic," based on duration and magnitude[1]. While Algerian health legislation for ongoing clinical studies is "without direct individual benefit"[2] and in all cases, even without error, the applicant is required to incur compensation for the detrimental effects of the study for the benefit of the person under her control and those with his rights[3] - Noting that the legislator does not clarify how and by what amount this compensation is calculated.- whereas, for example, the US regulations don't mandate compensation for research-related injuries. However, participants facing more than minimal risk must be informed about available medical treatments and if compensation is offered (45 CFR 46.116a6).[4] Informed consent cannot waive legal rights or release researchers from liability (45 CFR 46.116). Due to potential bias, some advise against subjective probability estimates in research. Instead, unknown risks can be acknowledged without assigning numerical values, and potential unforeseen risks can be disclosed[5].

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[1] The Systematic Evaluation of Research Risks (SERR) assesses research intervention risks by comparing them to acceptable comparative activities. It involves: (1) identifying potential damages; (2) classifying damage magnitude (1-7); (3) estimating damage probability; and (4) comparing the research intervention's damage probability to that of the comparative activity. SERR aims to minimize cognitive biases and improve participant protection by quantifying and comparing risks. See: Annette Rid, et al., "***Evaluating the Risks of Clinical Research***", Journal of the American Medical Association (JAMA), volume 13, n° 304, October 2010. pp. 1472-1479.

[2] According to article 391 of the Health Law 18-11, Clinical studies, in particular those without direct individual benefit (DIB) must not involve any serious foreseeable risk for the health of the persons who do so. They must be preceded by a medical examination of the persons concerned. The results of this examination are communicated to them prior to expressing their consent.

[3] See: article 393 of the Health Law (18-11). Op. cit.

[4] See: David B. Resnik, "***The Ethics of Research with Human Subjects: Protecting People, Advancing Science, Promoting Trust***", International Library of Ethics, Law, and the New Medicine, Volume 74, Springer International Publishing AG, Switzerland, 2018.p 189.

[5] See: David B Resnik, "***What is a reasonably foreseeable risk?***", The American Journal of Bioethics, Volume 13, N°12, December, 2013. Pp 29-30.

Second Section: Types of Risk Related to Research Participation

Research participation carries potential risks: medical (mortality, bad reactions), psychological (pain, anxiety), social (discrimination, stigma), financial (medical bills), and legal (e.g., paternity issues)[1].

Firstly: Risk and Trust

Realized risks can erode trust in researchers, institutions, and IRBs because participants expect protection from harm[2]. Realized risks in science, especially harm to healthy research volunteers, can erode public trust in the scientific process[3]. The terminal patients in trials may face death, which, while regrettable, can be seen as a reasonable choice given the potential for treatment. However, a healthy volunteer's death elicits strong negative reactions due to its unexpected nature[4]. Data breaches also cause distress. Therefore, proper risk management is crucial for maintaining trust in human subject research.

Secondly: Assessing and Minimizing Risk

A) - Assessing Risk

To manage research risks, the IRB assesses risks, ensuring they're reasonable compared to benefits[5]. This involves identifying, estimating (assigning probabilities), and evaluating risks. The IRB relies on the investigator's proposal, potentially seeking outside expertise or conducting reviews. Risk evaluation is a moral judgment[6]. IRBs must differentiate between research risks and standard clinical care risks when assessing studies. All study activities and their combined risks should be considered in the risk assessment[7].

B) - Minimizing Risk

Risk management involves determining if studies have adequate measures to minimize potential harm[8]. Risk minimization in research varies based on study goals, population, and procedures. Some measures used to minimize risk include[9]:

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[1] See: David B. Resnik, "***The Ethics of Research with Human Subjects***". Op.cit, p166.

[2] See: Henry S Richardson, Leah Belsky, "***The ancillary-care responsibilities of medical researchers: An ethical framework for thinking about the clinical care that researchers owe their subjects***", Hastings Center Report, Volume 34, N°1, 2004, p-p 25-33.

[3] See: David B Resnik, "***Limits on risks for healthy volunteers in biomedical research***", Theoretical Medicine and Bioethics, volume 33, N°2, 2012, pp 137-149.

[4] See: David B Resnik, "***The Ethics of Research with Human Subjects***". Op.cit, p167.

[5] See: David Wendler, Franklin G. Miller, "***Risk-Benefit Analysis and the Net Risks Test***", in: Ezekiel J. Emanuel, et al., "***The Oxford Textbook of Clinical Research Ethics***", Oxford University Press, 2008. pp 503-514.

[6] See: Annette Rid, David Wendler, "***A framework for risk-benefit evaluations in biomedical research***", Kennedy Institute of Ethics Journal, volume 2, N° 21, 2011, pp141-79.

[7] See: D Wendler, F G Miller, "***Assessing research risks systematically: The net risks test***", Journal of Medical Ethics, volume 8, N°33, 2007, pp 481-486.

[8] See: David Wendler, Franklin G. Miller, "***Risk-Benefit Analysis and the Net Risks Test***", Op.cit. Pp 503-514.

[9] See: David B Resnik, "***The Ethics of Research with Human Subjects***". Op.cit, pp 170-171.

• To mitigate risks in early-stage drug trials, researchers review existing literature, initiate dosing at low levels and gradually increase it based on tolerance. For novel drugs, they begin with a small subject pool, expanding it only when deemed safe. They also collect medical histories to identify potential allergies.

• Protecting research participants involves: excluding at-risk individuals, careful monitoring during and after the study, using a DSMB (Data and Safety Monitoring Board) to assess safety and modifying/stopping the study if needed, and promptly reporting problems/events.

• Participant safety in research necessitates careful planning and execution. This includes minimizing radiation exposure (consulting safety committees), adhering to medication guidelines, limiting blood/tissue collection, ensuring MRI safety (no metal), implementing sedation safeguards, and providing counseling for studies involving sensitive topics.

• To minimize research risks, investigators should ensure trained staff, follow standard operating procedures (SOPs), and protect privacy/confidentiality. These are examples of measures used to protect research subjects.

In the Algerian health legislation, some provisions were added in 2020, on the occasion of the amendment of Health Law 18-11, In the case of a clinical study without direct individual benefit, the sponsor may pay to the persons who lend themselves to it an indemnity in compensation for the constraints undergone, under the terms and conditions set by the minister responsible for the pharmaceutical industry. The sponsor must declare to the Minister responsible for the pharmaceutical industry the persons who are suitable for clinical studies without direct individual benefit (DIB) before their registration in the national register provided for this purpose.

The sponsor is responsible for the ongoing safety assessment of the investigational drug. He is required to immediately notify any serious or unexpected adverse reaction, or any new safety fact, occurring during or after the end of the study, to the minister responsible for the pharmaceutical industry, to the medical ethics committee for clinical studies, concerned and to all the investigating physicians concerned, at the latest, within seven (7) days. He must submit an annual safety report to the minister responsible for the pharmaceutical industry and to the medical ethics committee for clinical studies. The investigating physician must declare any serious event likely to be due to research on a pharmaceutical product to the minister responsible for the pharmaceutical industry, to the sponsor and to the medical ethics committee for clinical studies.

The sponsor is required to draw up a final report of the study which it sends to the minister responsible for the pharmaceutical industry[1].

Chapter III: Clinical Trials In Algerian Health System: Regulatory Requirements and Procedures

First Requirement: The Basic Requirements

The companies providing services in the field of clinical trials are approved by the Minister of the Pharmaceutical Industry[2]. Any sponsor of a clinical trial on human beings must declare their intention to carry out it to the Minister of the Pharmaceutical Industry, who grants them an authorization for this purpose. The declaration of intent is formulated in accordance with the form attached at the (Annex B of Decision No. 388). The Minister of the Pharmaceutical Industry may, at any time, ask the sponsor for additional information on the clinical trial. It can also, at any time, suspend or prohibit a clinical trial.

No clinical trial can be performed on humans[3]:

- If it is not based on the latest state of clinical research, scientific knowledge and sufficient pre-clinical experimentation;

- If the foreseeable benefit / risk ratio does not benefit the subject included in the research. Clinical trials can only be performed:

- Under the direction and under the supervision of a doctor with appropriate experience;

- Under material and technical conditions suitable for the clinical trial and compatible with the requirements of scientific rigor and the safety of people who are suitable for this trial; Any serious effect likely to be due to research on a pharmaceutical product must be declared by the sponsor, to the Minister of the Pharmaceutical Industry. For clinical trials without direct individual benefit, the sponsor assumes, even without fault, compensation for the harmful consequences of the trial for the person who takes part and that of his beneficiaries, without the fact of being opposed, a third party or the voluntary withdrawal of the person who had initially consented to participate in this test.

For clinical trials with direct individual benefit, the sponsor assumes compensation for the harmful consequences of the trial for the person who takes part in it and that of his beneficiaries, unless he can prove that the damage is not attributable. At his fault or that of any intervening party without being able to be

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[1] See: articles from 391 to 394 of Ordinance No. 20-02 of August 30, 2020 amending and supplementing ***Law No. 18-11*** of July 2, 2018 relating to ***Health***.

[2] With the amendment of the Health Law of 2020, the previous tasks of the Minister of Health, Population and Hospital Reform were assigned to the Minister in charge of the pharmaceutical industry, and this is as explained in art 7 and 8 of Decision No. 387 of July 31, 2006, ***relating to clinical trials.***

[3] See: articles from 9 to 11 of Decision No. 387.ibid.

opposed the act of a third or the voluntary withdrawal of the person who had initially consented to take part in the clinical trial.

The promoter is required to take out insurance covering his civil liability for the activity he undertakes. The clinical trial does not give rise to any direct or indirect financial compensation for those who take part in it, other than reimbursement of costs incurred by the person who takes part in the clinical trial.

The performance of any clinical trial is subject to a financial agreement between the sponsor and the investigator. The sponsor enters into a financial agreement with the establishment in the event that the clinical trial generates additional costs. The financial means made available to the investigator must be invested, among other things, for the acquisition of materials and equipment for the department where the clinical trial is taking place. The procedures determining the standards and methods applicable to the testing of pharmaceutical products are set by order of the Minister of the Pharmaceutical Industry. Clinical trials must be carried out in accordance with the rules of good laboratory practice and the rules of good clinical practice[1].

First Section: Consent of the Person

Scientific research on humans is ethically and legally justified by respecting the individual's autonomy and physical/mental well-being. Informed consent is crucial; participants must fully understand the research before agreeing to participate and before their information is shared. Such persons shall have a right of access directly or through a doctor appointed for that purpose, a right of rectification and a right of opposition. They need to know the risks and benefits so that they can consciously decide whether to participate or not. Any adult may designate a trusted person who may be a relative, or attending physician and who would be consulted in case he or she is unable to express his or her will and receive the information necessary for this purpose, then he or she will account for the will of the person, his or her testimony will prevail over any other testimony. This formality shall be in writing and co-signed by the designated person. It may be reviewed and revoked at any time[2].

This principle is now contained in a multitude of international declarations since Nuremberg, including the Declaration of Helsinki[3] and the Convention for the Protection of Human Rights and the Dignity of the Human Being with regard to Persons. Applications of biology and medicine: Convention on Human Rights

[1] See: articles from 14 to 20 of Decision No. 387.
[2] See: articles 343 and 344 ***of Health Law N° 18-11***.
[3] See: ***Declaration of Helsinki***. Op.cit.

and Biomedicine (Oviedo Convention /Council of Europe: 04 April 1997) until today[1].

Second section: The Medical Ethics Committee

A Medical Ethics Committee has been created by the Ministry of Health for clinical studies and is located at the level of the external services responsible for health. It is "an independent body" but its activities are supervised by the competent services of the health ministry. All clinical trials are subject to the opinion of the medical ethics committee. The law insists on the principle of informed consent[2]. Clinical studies can only be carried out if the persons who lend themselves to them or, failing this, their legal representatives, have given their free, express and informed consent, in writing after having been informed, by the investigating doctor or the doctor who represents it, particularly on:

- The objective, the methodology, the duration of the research, the expected benefits, the constraints, the foreseeable risks, the possible medical alternatives.
- Their right to refuse to participate in research or to withdraw their consent at any time without incurring any liability and without prejudice to their therapeutic management.

The informed consent of the person undergoing the clinical study must be included in the study protocol. The individual's consent applies strictly and only to the study for which it is requested. The person undergoing the clinical study can withdraw their consent at any time, without incurring any liability and without prejudice to the therapeutic management. No one can participate in several clinical studies simultaneously. The sponsor is responsible for the ongoing safety assessment of the investigational drug. He is required to immediately notify any serious or unexpected adverse reaction, or any new safety fact, occurring during or after the end of the study no later than seven (7) days, at:

- Minister responsible for the pharmaceutical industry.
- To the medical ethics committee for the clinical studies concerned.
- All the investigating physicians concerned[3].

Before carrying out a clinical trial on a person, the free, informed and express consent of the person must be obtained after the investigator has informed him of:

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[1] See: (***Oviedo Convention***). Op.cit.

[2] Informed consent defined as: Free and formally expressed acceptance of a person to participate in clinical research. Consent is said to be "informed" when the person has received from the investigating doctor (or a doctor replacing him) all the information concerning: the objectives of the trial, the benefits, the risks and the constraints. The consent of the person can be withdrawn at any time without prejudice to himself. Consent is evidenced by the person signing a "consent form" signifying that they have received all the information they want regarding the clinical trial. See: ***Glossary in Decision No. 387, and Decision No. 388***, Op.cit.

[3] See: Article 386 et seq. Law No. 18-11.

- The objective of the trial, its methodology and its duration;

- The expected benefits, the constraints and the foreseeable risks, including if the trial is stopped before its end. The investigator must inform the person whose consent is sought of his right to refuse to participate in a research or to withdraw his consent at any time without incurring any liability. Consent is given in writing or, if this is not possible, it is certified by a third party. The latter must be completely independent of the investigator and the sponsor[1].

Second requirement: The Special Provisions for Clinical Trials without Direct Individual Benefit (DIB)

Clinical trials without direct individual benefit must not pose any serious foreseeable risk to the health of those who undergo them. They must be preceded by a medical examination of the persons concerned. The results of this examination are communicated to them prior to expressing their consent. In the case of a clinical trial without direct individual benefit to the people who participate, the sponsor may pay these people compensation in compensation for the constraints suffered. The number of clinical trials without direct individual benefit in which a volunteer may participate may not exceed three (03) per year.

No one can participate in several biomedical research simultaneously. Under no circumstances can clinical trials carried out on minors give rise to the payment of compensation. Clinical trials without direct individual benefit can only be carried out in structures approved by the Minister of Health, Population and Hospital Reform. Trials with no therapeutic purpose are subject to the prior opinion of the National Council for the Ethics of Health Sciences[2].

First section: The Request for a Clinical Trial

The request for a clinical trial may come from[3]:

- Pharmaceutical laboratories and medical practitioners in the context of research;
- Administrative authorities in connection with the registration of a pharmaceutical product;
- Research institutions within the framework of research projects;
- Service companies in the field of clinical trials. The clinical trial applicant submits a file to the department in charge of pharmacy of the Ministry of Pharmaceutical Industry, comprising the following documents:

- The declaration of intention to carry out a clinical trial in accordance with the form established for this purpose;

[1] See: articles from 21 to 23 of Decision No. 387. Op.cit.
[2] See: articles from 30 to 36. Ibid.
[3] See: articles 2 and 3 of Decision No. 388. Op.cit.

- The clinical trial protocol as provided for in Article 7of Decision No. 388[1].
- The observation book;
- The investigator's brochure;
- A copy of the civil liability insurance contract taken out by the promoter;
- A copy of the financial agreement between the sponsor and the investigator. The above documents must be submitted in duplicate. The dossier must be submitted at least two months before the scheduled start date of the trial.

Second section: Request Rejection Status

The request for a clinical trial may be rejected in the following cases[2]:

- When the file is incomplete;
- When the ethics committee for clinical trials has issued an unfavorable opinion;
- When the clinical trial protocol does not comply with the methodological principles described in good clinical practice;
- When the location of the clinical trial does not meet the conditions appropriate for the clinical trial as defined by instruction from the Minister of Pharmaceutical Industry. The sponsor appoints an investigator to direct and oversee the conduct of the clinical trial. In the case of a multicenter clinical trial, the sponsor entrusts the performance of the trial to several investigators, he designates from among them a principal investigator called the coordinating investigator**.** The investigator should inform the sponsor of any critical event that occurs during the clinical trial. In the event that this event results in a significant modification of the clinical trial protocol, this must be notified to the ethics committee for clinical trials.

The investigator and his team must remain available for the duration of the clinical trial. The investigator must inform the director of the hospital where the clinical trial is taking place, before it starts. When the products subject to the clinical trial do not have a marketing authorization in Algeria, an authorization for their customs clearance is issued by the directorate in charge of pharmacy of the Ministry of Pharmaceutical Industry. When there are products left at the end of the clinical trial, the pharmacy management issues an authorization for their destruction. At the end of the clinical trial, the sponsor must send the pharmacy department of the Ministry of Pharmaceutical Industry a report on the progress of the trial and the results obtained. The performance of a bioequivalence or bioavailability study is subject to the same procedure as the clinical trial. For the

[1] See: article 7: "***The clinical trial is the subject of a protocol which is signed by the investigator after he has expressed his agreement"***.

[2] See: articles 5, 6, and 8 of Decision No. 388. Op.cit.

performance of an observational study, the sponsor must only submit to the level of the directorate in charge of pharmacy of the Ministry of Pharmaceutical Industry, the clinical trial protocol and the form of declaration of intention to perform a trial. Clinic established for this purpose[1].

Pharmacological research is a crucial part of the strategy to enhance the quality of medical practice by expanding the available treatment options for a particular health issue. Advancement in the medical field cannot be realized, particularly given the present level of scientific understanding, without the use of clinical trials. This type of activity ensures advancements in pharmacology, enhances the quality of patients' lives, and improves their likelihood of functional recovery and outcomes. However, from the clinical research perspective, ethical and legal error problems appear when a doctor participating in clinical trials (referred to as "investigator") does not comply with the correct way of obtaining adequate informed consent, mismanages patient safety measures, or falsifies research data. These actions can lead to serious consequences for participants, undermine the validity of clinical trial results, and negatively impact the medical community and society as a whole through the decrease of individuals' chances of getting the optimal cure[2].

Chapter IV: The Basic Purpose of Establishing Good Clinical Practice (GCP)

First requirement: What Is Good Clinical Practice (GCP)?

GCP, based on ICH guidelines, is a global standard for clinical trial design, conduct, and reporting. It ensures data integrity, scientific validity, ethical soundness, and protects trial participant rights and confidentiality. GCP protects clinical trial participants' rights, ensures safety and efficacy, and demands thorough documentation (protocol, records, training, and facilities). It clarifies roles (sponsors, investigators, monitors) and uses quality assurance to guarantee standards are met, ultimately safeguarding subjects and data quality[3].

First section: The (GCP) In Algerian Health System

The Algerian health regulations insist, as stipulated in article 2 of the Decision No. 00200, the necessity of those involved in clinical trials must each ensure that they comply with good clinical practices defined by all the provisions to be put in place to ensure the quality and authenticity of their scientific data during the trial, on the one hand and respect for ethics on the other. The provisions

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[1] See articles from 9 to 14 Decision No. 388.

[2] Octavian Vasiliu, Andrei G. Mangalagiu, et al., "***A Review of the Ethical and Legal Challenges in Clinical Trials***", Romanian Journal of Military Medicine, Issue No.3, Vol. CXXVIII, May 2025.pp 225-233.

[3] See: Delva Shamley, Brenda Wright. Op.cit, p2.

and guidelines as set forth in the Decision No. 00200 of July 25, 2009, setting the rules of Good Clinical Practice, must be read and interpreted in the light of decrees 387 and 388 of July 31, 2006. Good practice in a clinical trial is an international ethical and scientific quality standard applying to the design and performance of trials in which human subjects participate.

Protection of human subjects and the recording and presentation of data relating to these tests and the compliance with such a standard guarantees to the public the protection of the rights, safety and well-being of the subjects participating in the trial in accordance with the principles deriving from the Declaration of Helsinki, as well as the reliability of the results of such clinical trials.

Second Section: Protection of Persons Participating In Tests and Consultation of Ethics Committees

The purpose of the Decision No. 00200 of July 25, 2009, is to establish the principles of good clinical practice for human clinical trials in Algeria. These principles concern mainly the pharmaceutical industry, but also all parties involved in the production of clinical data for the registration of medicinal products. They apply to all four phases of clinical drug evaluation including bioavailability and bioequivalence studies. Moreover, they can be applied more widely by anyone undertaking experimental studies in humans. All parties involved in the evaluation of medicinal products undertake to conduct these studies in accordance with these principles in an atmosphere of mutual trust. In order to guarantee the rights and protection of persons undergoing testing, to establish the credibility of the data and to improve the ethical, scientific and technical quality of testing, it is necessary to formalize in advance and in writing procedures concerning their organization and conduct, data collection, documents and verifications. A statistically sound project is essential; it is unethical to involve human beings in trials that are poorly designed and conducted. Compliance with such procedures is evidence that all data, information and documents have been properly generated, recorded and reported.

Second requirement: Protection Of Persons Participating in Tests

The current version of the Helsinki Declaration (2013) provides the ethical basis for clinical trials. It must be fully known and followed by anyone engaged in research in humans. The protection and well-being of trial participants is ultimately the responsibility of the investigator, but the existence of an ethics committee and the obtaining of free and informed consent provide independent safeguards for the protection of trial participants.

First Section: The Ethics Committees

According to the Decision No. 00200 of July 25, 2009, setting the rules of GCP, the sponsor and (or) the investigator must seek the opinion of an ethics committee on the suitability of the protocol (including its annexes) for the trial, as well as on the methods and documents used for the informing individuals and obtaining their informed consent. The ethics committee must be informed of any modification of the protocol and of any serious or unexpected adverse event occurring during the trial and which may affect the safety of persons or the conduct of the trial. Its opinion should be requested if a reassessment of the ethical aspects of the trial is essential. The trial cannot be started before the ethics committee has issued a favorable opinion on the procedures and documentation. The sponsor and the investigator must take into account the recommendations of the ethics committee. When submitting a clinical trial project to an ethics committee, the ethics committee should consider the following points:

a) The investigator's ability to perform the test, having regard to his qualifications, experience, team and logistical resources, taking into account the information available to the Committee;

b) The adequacy of the protocol to the objectives of the study; its scientific efficiency, that is, the possibility of reaching certain conclusions with as little exposure as possible for people; and the rationale for the foreseeable risks and harms versus the expected benefits for participants and / or others;

c) The quality and completeness of the written information to be communicated to individuals, their relatives, their guardians and, where applicable, their legal representatives;

d) The way in which the recruitment and information of people are carried out, as well as the methods of obtaining consent. All information intended for the solicited persons and / or their legal representatives must be submitted in its final form;

e) The provisions providing for compensation and / or treatment in the event of damage or death of a person if this can be attributed to a clinical trial, and any insurance or indemnity covering the civil liability of the investigator and the promoter;

f) The extent to which investigators and participants could be remunerated or receive compensation for their participation.

The ethics committee must give its opinion in writing, within a reasonable time, identifying with precision the test, the documents studied and the date of the examination.

Second Section: The Informed Consent

According to the Decision No. 00200 of July 25, 2009, setting the rules of GCP, the principles of informed consent contained in the current version of the Declaration of Helsinki (2013) must be observed in every clinical trial. Whenever possible, information should be given both orally and in writing. No one can be forced to participate in a trial. Individuals, their families, their guardians or, where applicable, their legal representatives should be free to inquire about the terms of the trial. The information should clearly state that refusal to participate in a trial or withdrawal from the trial at any stage does not result in any disadvantage to the person's subsequent management. She must have sufficient time to decide whether she wishes to participate in the trial.

The person must be informed that personal information may be examined during the audit by the competent authorities and authorized persons; they will be processed and stored in such a way as to maintain the strictest confidentiality. The person should be informed of the compensation and treatment procedures foreseen in the event that they suffer damage or disability as a result of participating in the trial.

If a person consents to participate, after having received full and understandable explanations of the trial (its objectives, the expected benefits for the participants and/or for third parties, the standard treatments or placebos, the risks and disadvantages - for example: invasive procedures - and, if applicable, an explanation of any conventional and recognized alternative treatment), his consent should be recorded in an appropriate manner. It must be confirmed either by the dated signature of the person or by the signature of an independent witness who certifies in writing the assent of the person concerned. In both cases, the signature confirms that the consent is based on well-understood information and that the person has freely chosen to participate in the trial, without prejudice to their legal and ethical rights, while having the option of opting out of the trial test without having to state the reason.

When the patient is unable to give personal consent (for example, in the event of unconsciousness, severe mental disorder or disability), inclusion in a trial may be acceptable if the ethics committee gives its approval in principle. And whether the investigator is of the opinion that the participation of that patient is in their best interests and will contribute to their well-being.

The accord of a legally qualified representative sharing this opinion must also be recorded in writing, signed and dated. The impossibility of obtaining either written informed consent or oral consent attested in writing by a witness must be

recorded and justified in writing by the investigator. A written and signed consent must always be obtained from the person himself in a trial without therapeutic purpose, i.e. when the person concerned cannot derive any direct clinical benefit from it. Any information which becomes available during a trial and which may have implications for those participating in the trial should be provided to them by the investigator.

Conclusion:

Despite the amendments introduced by the amended Health Act of 2020 regarding the reduction of administrative approval times, the formation of medical ethics committees at the central level, and strengthening the powers of the National Agency for Pharmaceutical Products, the clinical trials sector in Algeria still suffers from many shortcomings, particularly in terms of infrastructure and material resources, and a lack of funding, including private investment. With public and private hospitals focusing on healthcare rather than research and development, we are seeing difficulties in attracting and retaining patients.

The brain drain and shortage of qualified research personnel are also exacerbating these shortfalls. With a public social insurance system that compensates for medical and experimental errors on lump-sum compensation, we are witnessing a clear unwillingness on the part of patients to be the subject of clinical trials due to their lack of confidence in lump-sum compensation, which are often completely disproportionate to the damage caused by medical liability. Social rejection, preconceived notions, and prejudices in most Algerian minds about the risks of clinical trials, the opportunism of medical research companies, and the weakness of the insurance system remain challenges facing this emerging sector.

Although the current regulatory and legislative framework for the practice of biomedical research, including the achievement of clinical trials in the Algerian health system, appears to be fairly outdated, it is still able to fully guarantee the rights, safety, and well-being of the people involved in these trials. This paper briefly focused on highlighting the highly complex regulatory environment for conducting clinical trials in the Algerian health system. Emphasis has also been given - in brief - to the most important definitions, requirements, procedures and conditions of good practice for clinical trials on human subjects.

It is important to emphasize that this highly complex regulatory environment has contributed to a clear lack of investment in medical research in Algeria, which has led the public authorities to think deeply in order to re-update

the regulatory and legislative framework related to biomedical research which is being worked today.

Currently, an executive decree is being prepared aimed to harmonization of documentation of clinical studies; Implementation of forms simplifying deposit procedures; and posed a transparent and factual evaluation criteria.

On late 2021, The Minister of the Pharmaceutical Industry, chaired the official opening of the work of the Scientific Days on Clinical Studies, organized at the International Conference Center[1].In his speech, the Minister indicated that clinical studies are of extreme importance for the export of pharmaceutical services. Worldwide, the value of exports of these services is USD 70 billion, which is why the Ministry of Pharmaceutical Industry aims to reach an export volume more than of USD 250 million by 2026.

In addition to the financial value of this activity, the Minister highlighted the added value that clinical studies can bring to the patient by enabling him to access innovations in care that often the only solution in terms of treatment. For this reason, for the 2024 financial year, the Ministry of Pharmaceutical Industry plans to carry out 100 clinical studies, knowing that from 2017 to 2020 no studies were registered. Because of their importance and strategic nature, the Minister of the Pharmaceutical Industry has indicated that the country's high authorities consider clinical studies to be an important link in the development process of the national pharmaceutical industry, hence the amendment of the legislative framework governing this activity to promote research and development and promote access to innovative medicines.

A draft executive decree on clinical studies has been prepared by the services of the Ministry of Pharmaceutical Industry and tabled at the level of the General Secretariat of the Government after consultation and collaboration with all stakeholders in the field. Several areas were reviewed, including the requirement to conduct clinical studies in accordance with the Good Practice Guidelines (GCP) and in accordance with the procedures established by the Ministry's services.

But also the obligation to subject clinical trials to authorization by the pharmaceutical industry sector as well as any other substantial modification of the dossier relating to the clinical study. Other amendments include the obligation to subject the transport of biological samples, products and devices for clinical

[1] MPI (2021), "***The Ministry of the Pharmaceutical Industry (MPI) ambition to export 200 million dollars in 2024 through clinical trials***". Ministry of the Pharmaceutical Industry (MPI), December 21, 2021. At : https://www.miph-dz.org/dexporter-200-millions-de-dollars-en-2024-a-travers-les-essais-clinques/?fbclid=IwAR3X9f0SfTP6vxV4fNfiDpARISDCQVdwkOxYF9HlNLwnDHYso82vgBzli6g

studies to pre-authorization by the department responsible for issuing the transport authorization, in addition to measures defining the standards and methodologies applied to the studies of pharmaceutical products and medical devices and the procedures for carrying out clinical trials.

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