Romania's Regulatory Framework for Clinical Trials

Romania is located in Southeastern Central Europe, north of the Balkan Peninsula and on the western shore of the Black Sea. With a population of 20.1 million, it is the seventh most populous member of the European Union. Its capital and largest city, Bucharest, is the sixth largest city in the European Union.

Historically, Romanian researchers and inventors are well known and have made notable contributions to the scientific field. Henri Coandă discovered the Coandă effect of fluidics. Victor Babeș discovered more than 50 types of bacteria; biologist Nicolae Paulescu discovered insulin, while Emil Palade received the Nobel Prize for his contributions to cell biology. Lazăr Edeleanu was the first chemist to synthesize amphetamine, while Costin Nenițescu developed numerous new classes of compounds in organic chemistry.

After the fall of communism in 1989, the country experienced a decade of economic instability and decline, led in part by an obsolete industrial base and a lack of structural reform. From 2000 onwards, however, the Romanian economy was transformed into one of relative macroeconomic stability, characterised by high growth, low unemployment and declining inflation. Since 2000, Romania has attracted increasing amounts of foreign investment, becoming the single largest investment destination in Southeastern and Central Europe. In 2014, economic growth was at 1.8 % with Romania preceding countries like France, Germany and the United Kingdom, and unemployment was at 6.4 %, which is very low compared to other EU countries.

With the current favourable economic trend, and well-established and clear regulations, we thought about sharing with you some insights into the regulatory framework for clinical trials in Romania.

Clinical trials are experimental research on the administration of a drug or cosmetic product in humans. These studies must be conducted in accordance with GCP (good clinical practice) and the applicable law in the state where it takes place.

GCP is a set of rules of good clinical practice, which is an international standard for ethical and scientific quality in the design, management, recording and reporting of clinical trials involving human subjects, facilitating mutual acceptance of data by the competent authorities in the field of medication.

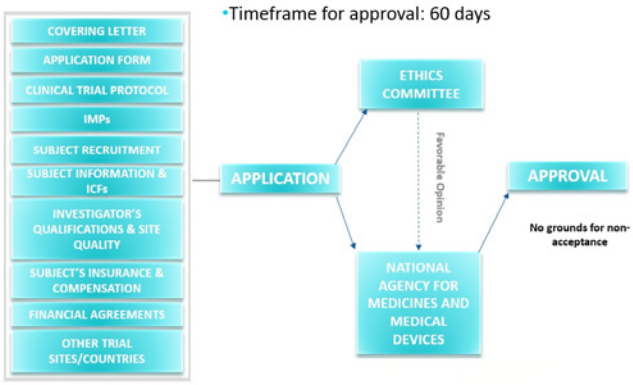
In Romania, according to Regulation (EC) Nr. 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products, clinical trials in human volunteers do not represent a requirement for placing these products on the market. For products that do not fit into the category of cosmetics, approval must be requested from the National Agency for Medicines and Medical Devices (NAMMD) in accordance with law 95/2006 on reform in the field of health, Title XVII - Drug, with subsequent modifying.

The Cosmetic Directive 76/768/EC which has been replaced by the Cosmetic Products Regulation 1223/2009 and which harmonises and simplifies the cosmetics regulations across the EU member states including Romania, provides strict guidelines controlled by authorities in each member state, harmonising the requirements for cosmetics in the European Community. A "cosmetic product "means any substance or preparation intended for placing in contact with the various external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and mucous membranes of the oral cavity with the view exclusively or principally to cleaning them, perfuming them or protecting them in order to keep them in good condition, change their appearance or correct body odours" (Cosmetic Directive 76/768/EC).

Studies involving skin measurement methods and testing of cosmetic products on humans are similar to medical research. They involve the use of humans as research subjects and also deal with pure scientific research, whose primary purpose is to contribute to generalised knowledge about the human skin physiology and active substances, and with applied research, aimed to evaluate the safety and efficacy of new cosmetic ingredients and finished products. In both studies, the ethical considerations are related to the relationship between the physician/the investigator and the human subject/the healthy or sick volunteer and their main objective is the protection of the human being. So, the ethical considerations for cosmetic testing and use of skin measurements are similar to those for medical research on humans, particularly non-therapeutic research. They are subject to the ethical principles of the Declaration of Helsinki and the guidelines for good clinical practice (GCP), and are integrated into the research design.

There are several guidelines for testing cosmetics on human subjects, whose indication is found in the guidance DG - Health and Consumer Protection - Scientific Committee on Consumer Product (SCCP). The SCCP's Notes of Guidance for the Testing of Cosmetic Ingredients and Their Safety Evaluation.

As previously mentioned, in Romania, the competent authorities in the field of medicine are the NAMMD and Ethics Committee.



Clinical trials on drugs are regulated in Romania in accordance with international law (Order MS no. 904 of 25 July 2006) "approving the Rules relating to the implementation of good practice in the conduct of clinical trials on medicinal products for human use" transposing Directive 2001/20 / EC of the European Parliament and of the Council of 4 April 2001; MS Order no. 903 of 25 July 2006 "Principles and detailed guidelines for the approval of good clinical practice for medicinal products for human investigational, and requirements for the manufacture and importation of these drugs", transposing Directive 2005/28 / EC of 8 April 2005; Order no. 905 of 25 July 2006 "on the approval of the principles and guidelines of good manufacturing practice for medicinal products for human use, including for clinical investigation" transposing Directive 2003/94 / EC of 8 October 2003.

The NAMMD is a public institution subordinated to the Ministry of Health, set up through Government Emergency Ordinance no. 72 of 30 June 2010 on reorganisation of certain healthcare facilities and amendment of public health legislation, as a result of the merger of the National Agency for Medicines and the Technical Office for Medical Devices. The NAMMD organisation and operation have been approved by Government Decision No. 734 of 21 July 2010.

For over 50 years now, the NAMMD has represented the medicinal product regulatory authority in Romania. Initially known as the Institute for the Control Medicines and Pharmaceutical Research on its setup in 1956, the name of the institution was further changed in 1960, to become the State Institute of Drug Control and Pharmaceutical Research (ICSMCF) and later on, between 1999 and 2010, by reorganisation of the former ICSMCF, the institution operated as the National Medicines Agency. The National Agency for Medicines and Medical Devices (NAMMD) is established through Emergency Government Decision no. 72/2010, as result of the merger of the National Medicines Agency with the Technical Office for Medical Devices.

The ICSMCF was the first institution in Romania to comply with the modern definition of a medicines regulatory authority, whose main duties were: authorisation and registration of medicinal products,

yearly development of the Product Index, complex control of medicinal products manufactured nationally and abroad, pharmaceutical inspection, development of the Romanian Pharmacopoeia and its Supplements, development of national standards and reference materials, etc.

According to Scientific Council Decision no. 2/2014 on Regulations for authorisation of units able to perform clinical trials in the field of the medicinal product for human use (approved on 22 April 2014), the applications for authorisation of units able to perform clinical trials on medicinal products for human use shall be submitted to the NAMMD.

For each approval of clinical trial on drugs, a dossier is submitted to the NAMMD after getting a favourable opinion from the National Committee of Ethics. A clinical trial on pharmaceutical products cannot start until the Ethics Committee has issued a favourable opinion and the NAMMD has not informed the sponsor of any grounds for non-acceptance. The study dossier addressed to the National Committee of Ethics and the one addressed to the NAMMD can be sent in parallel. Both the National Committee of Ethics and the NAMMD should express their opinions taking into consideration the same versions of the submitted documents. The timeframe for approval is 60 days from the submission of a complete and updated dossier.

Upon approval, the signed order indicates the institution where the study will be conducted, and the principal investigator responsible for conducting it.

For more information about clinical trials, the links for the European Union Authorities (http://www.ema.europa.eu/ema/), USA (http://www.fda.gov/) and the World Health Organization (http://www.who.int/en/) can be accessed.

Compliance with these standards and regulations assures the public that the rights and safety of the trial subjects are protected under the principles based on the Human Rights Declaration of Helsinki, amended.

Clinical trials are conducted in a variety of locations, such as hospitals, universities, offices or clinics accredited for research by medical authorities.

A clinical trial may be mono-centric (occurs in one centre or one country), or multi-centric, taking place in several centres and countries. The multi-centric studies take place simultaneously in European Union countries, the United States, CIS countries, etc. whose volunteers contribute to international clinical research.

Clinical trials sponsors are usually companies or government agencies that investigate and produce drugs or cosmetic products. They design the strategy and finance the conduct of clinical trials. If the sponsor does not have sufficient internal resources to organise clinical trials, they outsource (contract) the organising of clinical trials to specialised companies called clinical research organisations (CROs).

Between the organisations and clinical investigators conducting the study are contractual relationships in accordance with the rules of good clinical practice. These relationships determine the amount of funding for investigators and differ from project to project, depending on the length and complexity of each. Payment to the investigator is an international practice, a remuneration for a specific work of great scientific value which involves a major responsibility.

Even though Romania is estimated to have the fourth fastest-growing demand for travel and tourism in the world, it is also becoming a very popular destination for performing clinical trials, mainly due to its accessibility, and the availability of highly-trained medical practitioners and investigators, scientific technicians and researchers most of whom are fluent in both English and French, and last but not least, to the important availability of volunteers and patients.

Things are moving quickly in Romania, and with Bucharest being the safest city on the European continent, you may rest in peace that your clinical trial will unfold in a climate of public safety.

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