

# Interventional Clinical and Chemical Studies in Romania, Legal Guarantees

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*The risks of medical treatment are due not only to the patient's anatomic and physiological state, but also to the scientific and technical level of medicine when providing the medical service, which may progress through interventional clinical studies. In Romania, between 2012-2016 were issued annually between 192 and 221 authorizations for performing interventional clinical studies, the majority being phase III studies and almost half in oncological, respiratory and nervous diseases, although the pathology which represents the main mortality cause is the cardiovascular one. The goal of this study is the analysis of the legal requirements for the patients to participate to these interventional clinical studies, within the ample proceedings that aim to the approval of chemical substances as human use drugs. At present, the legal guarantees for interventional clinical studies are offered by the EU Regulation 536/2014 of the European Parliament and of the Council of 16 April 2014 regarding interventional clinical studies with drugs for human use, which through art. 4-27 of the Regulation settles a preliminary authorization procedure meant to avoid any deviation from public order and good morals, and through art. 28-36 of the Regulation protects the patient's private interest through a special regulation of his consent when accepting an unusual clinical practice.*

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The scientific and technical level progress of medicine implies interventional clinical studies meant to discover, verify, identify, study the clinical, pharmacological, pharmacodynamic effects, side effects, absorption, distribution, metabolism, the elimination of medicines by administering them to human subjects who are subjected to a therapeutic strategy, which does not belong to usual clinical practice, and a diagnosis or monitoring procedure besides the usual clinical procedure. Physico-chemical characteristics and physiological properties as rate of dissolution, solubility, pKa, lipophilicity, and molecular weight, can directly interfere with the distribution, metabolism, absorption, and elimination of a substance [1,2].

Ensuring medical assistance is not an obligation of result (meaning the doctor is not compelled to give or maintain the patient's life, health, body integrity); but it is an obligation of means, through which the doctor is obliged just to search (with diligence and prudence, using all the necessary means) to maintain life, health, the patient's body integrity. However, since in the case of interventional clinical studies this search does not follow the usual clinical practice, that is the regular treatment used for treating, preventing or diagnosing a disease or affection, they benefit from a special regulation through Regulation (EU) 536/2014 [3] of the European Parliament and the Council from 16 April 2014

regarding interventional clinical studies with human use medicines and the abrogation of Directive 2001/20/CE.

The goal of present study is the analysis of the legal requirements for the patients to participate to these interventional clinical studies in Romania, within the ample proceedings that aim to the approval of chemical substances as human use drugs.

## Experimental part

For the current study we used the data regarding interventional clinical studies carried out in Romania which are posted on the site of the National Agency of Medicine and Medical Devices and the Reports of its Board between 2012-2016 [4]; and we analyzed the number of requests submitted and the authorizations issued, the affection groups, the legal aspects and the phases of the clinical studies: phase I (assesses the action, the metabolism and the side effects of the medication on healthy subjects), phase II (exploratory studies for the best security and tolerability dose), phase III (assesses the efficiency, security and compares with placebo or other medications), phase IV (post-authorization).

## Results and discussion

From the analysis of ANMDM data it results that between 2012-2016 were issued annually between 192 and 221 clinical authorizations (fig 1).

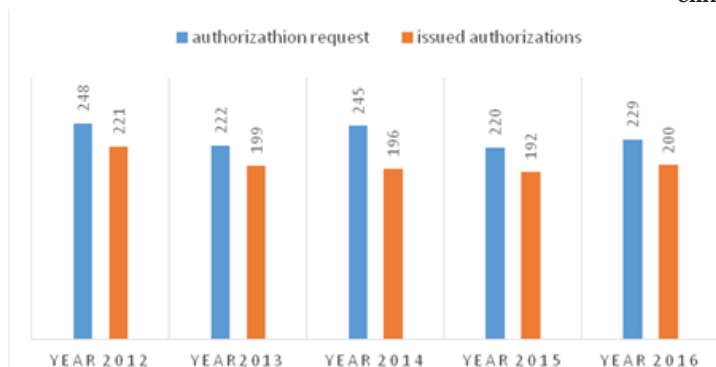


Fig. 1. issued authorizations/ requests for clinical studies in Romania

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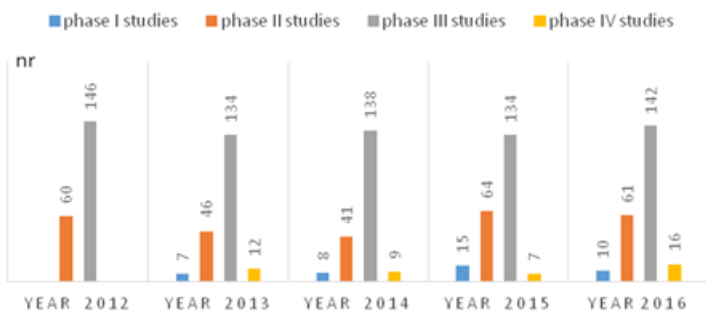


Fig. 2. Type of clinical studies for which authorization was issued between 2012-2016

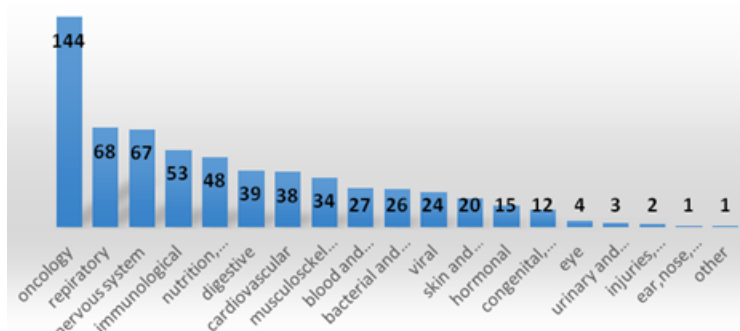


Fig. 3. Groups of affections for which clinical studies are being performed

From the analysis of the type of clinical studies for which an authorization was issued between 2012-2016 it can be noticed that phase III studies dominate (48.31%), followed by phase II (26.88%). Studies in phases I and IV appear in almost equal percentages and significantly smaller (fig 2).

Analyzing the groups of affections comprised in the clinical studies between 2014-2016, we can notice that oncological affections dominate, followed by respiratory ones, nervous system, the only ones which exceed 10%. Between 5-10% we found studies about nutrition and metabolic diseases, of the immune, digestive, musculoskeletal and cardiovascular systems. The rest, which are mentioned in figure 3, are to be found in percentages below 5%.

Between 2012-2016 a number of 3134 amendments were submitted, most of them in 2015 (fig 4).

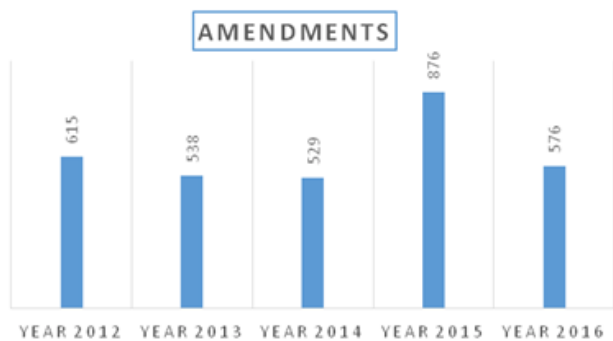


Fig. 4. Submitted amendments

We can notice that in 8% of the studies under age people are comprised, and in this subgroup the most frequent are the studies for respiratory affections 22.2 %, the nervous system 18.5%, bacterial and mycotic 11.1 % and nutrition

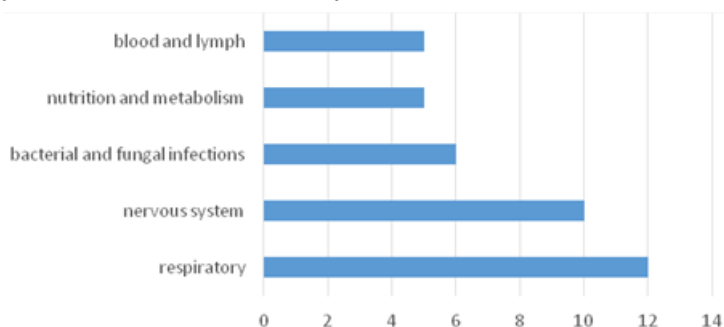


Fig. 5. Groups of affections for which clinical studies are being performed on children

and metabolic affections 9.25%. Out of the studies mentioned 77.7% are in phase III.

Interventional clinical studies carried out in Romania, after their authorization by ANMDM, represent a very small percentage of such studies in the world (mainly phase III of drug pre-authorization). This indicates that the authorization procedure is not only formal, but also restrictive, in order to avoid hazardous studies. However, the diseases included in these studies do not correlate well with the clinical reality in our country, in which cardiovascular diseases are predominant, mortality by cardiovascular diseases being one of the highest in Europe. Thus, according to Eurostat[5] data on the standardized mortality rate in 2014, Romania is in second place of the 28 member states of the EU regarding circulation diseases, with a rate of 951.3 /100.000 population, compared to the UE mean rate of 373.6, only Bulgaria being higher. On ischemic heart disease Romania holds the 5th place with a mortality rate of 320.5/100.000 compared to UE rate 126.3/100.000, exceeded by Lithuania, Latvia, Slovakia and Hungary, with rates over 350/100.000. However, in the Romanian clinical studies the first places are held by oncological, respiratory and neurological diseases. Eurostat data evidence that Romania is the first for cervical cancer mortality, with a rate of 16.4/100,000, much higher than the EU average 3.9/100,000. Romania is below the average EU rate on nervous system disease mortality, a rate of 21 vs. 38.4 (place 19/28) and uterine cancer, place 20/28, and very close to the EU mortality rate regarding cancer in general, colorectal, lung, breast, respiratory. To be noted also that 8% of the studies include under age subjects.

The original principle of medical law is represented by the principle of human body inviolability [6], stipulated in

the Romanian law system through art. 64 from the current Civil Code: (1) *The human body is inviolable.* (2) *Any person has the right to physical and psychical integrity. One cannot touch the integrity of the human being except the cases and conditions expressly stipulated by the law*. By its virtue it is imperative that the beneficiary of the medical service should express a valid consent prior to the performance of the medical service.

However, even before the present Civil Code, the Romanian legislator particularly stipulated that medical care is performed based on the patient's consent through art. 124 of Law no. 3/1978[7]. Later, through art. 1 letter. a) from Law no. 46/2003[8], the term *sick person* (a physical state) is replaced by the *patient* notion which represents a *legal notion* [9], because through this law the consent of the medical service beneficiary (the premise for performing the medical service), regulated in detail through art. 13-20 from Law no. 46/2003, is just one in a series of rights: the right to information (art. 4-12 from Law no. 46/2003), the right to a second opinion (art. 11 from Law no. 46/2003), the right to interrupt any medical intervention (art. 13 from Law no. 46/2003), the right to the confidentiality of medical data (art. 21-25 from Law no. 46/2003), rights to which are added those stipulated directly or indirectly in Title XVI of Law no. 95/2006[10] and in the Health Minister's Order no. 482/2007[11]. But, more than that, this legal state supposes, besides rights, correlative obligations either to the doctor's rights: the patient's gratitude obligation towards the doctor[12] and the obligation to inform the doctor, or to the medical service provider's rights (the doctor who practices his profession as a liberal profession in one of the forms regulated by OG no. 124/1998[13] or the employer unit of the paid doctor): the payment obligation for the medical service and the payment obligation for the hotel services connected to the hospital medical services.

Exercising the rights and assuming the obligations are the legal effects of the patient's consent which, consequently, is a legal consent and must be validly expressed. In this respect, art. 1204 from the Civil Code imposes three cumulative conditions for the validity of the consent: a) the consent must be serious (it should not be expressed as a joke or by way of friendship, should not be too vague or expressed under a mental reserve known by the doctor); b) the consent must be expressed knowingly (should be expressed by a person with discernment); c.) the consent must be free (it should not be affected by one of the faults of consent: error, fraud, violence, lesion).

In order to avoid error (the false representation of an element considered by both parties as essential) or fraud through reluctance (the purposeful induction through fraudulent omissive workmanship of a false representation of a situation), the legislator regulated expressly and largely both the framework for the patient's decision making through the possibility of exercising the medical rights which reflect the self-determination principle (the right to information - art. 4-12 from Law no 46/2003 and the right to a second opinion - art. 11 Law no. 46/2003); and the legal way of showing will only be in written form according to art. 660 from Law no. 95/2006 and art. 8 from the Annex to Order no. 487/2007, wherefrom results the solemn character of the medical contract [14]. In the content of the patient's information right there are two categories of information. First, the patient has the right to general data about the medical service provider: identity - name and address, registration number in the trade register or the unique register of medical practices and the fiscal identification code; professional status: the professional

preparation level and/or didactic and/or academic titles, experience etc. of the tenure doctor or employed/collaborator doctors, internal order regulations; and the medical services which they provide: specialization, technical endowment, costs. Second, the patient's right to information supposes data about his own concrete situation: health condition, diagnostic and prognosis of the sickness in the absence of treatment, the nature and risks of the treatment or viable alternatives with their risks and consequences. Those are due not only to the patient's anatomic and physiological condition, but also to the scientific and technical level of medicine when the medical service is provided, and can be reduced through medical research, which implies interventional clinical studies meant to discover, verify, identify, study the clinical, pharmacological, pharmacodynamic effects, side effects, absorption, distribution, metabolization, the elimination of medicines by administering them to patients who are subjected to a therapeutic strategy, which does not belong to usual clinical practice, and a diagnosis or monitoring procedure besides the usual clinical procedure.

Ensuring medical assistance is not an obligation of result (meaning the doctor is not compelled to give or maintain the patient's life, health, body integrity); but it is an obligation of means, through which the doctor is obliged just to search (with diligence and prudence, using all the necessary means) to maintain life, health, the patient's body integrity. However, since in the case of interventional clinical studies this search does not follow the usual clinical practice, that is the regular treatment used for treating, preventing or diagnosing a disease or affection, they benefit from a special regulation through Regulation (EU) 536/2014 of the European Parliament and the Council from 16 April 2014 regarding interventional clinical studies with human use medicines and the abrogation of Directive 2001/20/CE. The importance of this regulation is emphasized by the fact that although the European Union does not have a common policy in the field of health which is left, on the basis of subsidiarity principle, at the appreciation of member states, however for interventional clinical studies was adopted a regulation, that is a general rule, which is compulsory and directly applicable, meaning that it has autonomous validity without the interposition of the national states power [15], in comparison with the former Directive which must be transposed in the national law system by the national legislator. Concretely, this regulation settles two legal filters for clinical studies in order to ensure the public interest of the society and particularly of the patient.

First of all, Regulation (EU) 536/2014 ensures the legality of the object of the medical contract. This represents, on basis of art. 1225 par.(3) and 1226 par.(2) Civil Code, a validity condition of the legal acts in general consisting of the fact that the legal operation (in our case, providing a medical service which does not follow the usual procedure) is according to public order and good morals because the respect for the human being (life, health, body integrity) is a necessity for the whole society and not only an individual's private interest. In this respect, for example, cell, organ, tissue sampling and transplant cannot be made for a material purpose, but only for a humanitarian purpose [16]. It is the same with interventional clinical studies as the end goal cannot be a sadist one (a person can dispose of their own body only in a legal framework and cannot allow any other person, not even willingly, to mutilate, torture or kill them) or a mercantile exploitation of the human body for profit purposes exclusively. Generally, this condition is respected because, on one hand, from the financial point of view, the investments are considerable, and out of all

the verified products only 10% become medicines, and on the other hand the scientific results are significant. For example, in CANTOS study (sponsor NOVARTIS), performed on 10,061 patients from 40 countries [17], investigating the effects of canakinumab on patients with a history of heart attacks and inflammation markers (increased CRP) was demonstrated the reduction of cardiovascular events and were opened new research paths due to the results in the protection of patients with lung cancer [18]. However, in order to avoid any deviation from public order and good morals, the prior legal guarantee of the interventional clinical studies is represented by the preliminary authorization procedure of the interventional clinical study regulated by art. 4-27 Regulation (EU) 536/2014.

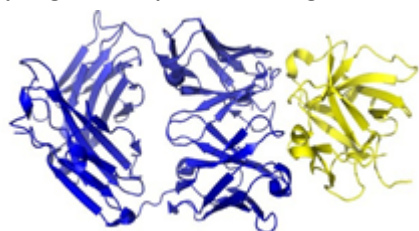


Fig 6 Ribon diagram of canakinumab (blue) bound to proinflammatory cytokine IL-1 $\alpha$ 4. Canakinumab- chemical and physical data: formula C<sub>6452</sub>H<sub>9958</sub>N<sub>1722</sub>O<sub>2010</sub>S<sub>42</sub>; molar mass 145.2kg/mol.[19]

Secondly, even if an interventional clinical study does not infringe the dignity and respect for the human being in general, this does not represent an obligation for the patient, who has the right to freely appreciate if an interventional clinical study is according to his concrete interest. The preliminary legal guarantee of the patient's private interest represents a special regulation of the consent art. 28-36 from Regulation (EU) 536/2014.

## Conclusions

In Romania, during 2012-2016 between 192 - 221 authorizations were issued for interventional clinical studies, most of them phase III and almost half related to oncological, respiratory and nervous system diseases, though the highest mortality rates are given by cardiovascular conditions. At present, the legal guarantees

for interventional clinical studies are provided by the EU Regulation 536/2014 of the European Parliament and Council of 16 April 2014 regarding interventional clinical studies with drugs of human use; art. 4-27 of the Regulation instituted a prior authorization procedure meant to avoid any deviation from public order and good morals, while art. 28-36 of the Regulation protects the patient's private interest by a special rule on his consent to be submitted to an unusual clinical practice.

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