Regulatory Framework for Developing Clinical Trials in Romania

Romania is a country located between Central Europe and Southeastern Europe, bordering the Black Sea. Romania shares a border with Hungary and Serbia to the west, Ukraine and Moldova to the northeast and east, and Bulgaria to the south. At 238,391 square kilometres (92,043 sq mi), Romania is the eighth largest country in the European Union by area, and has the seventh largest population of the European Union with 20,121,641 inhabitants (20 October 2011). Its capital and largest city is Bucharest – the sixtieth largest city in the EU.

The country attractiveness index for clinical trials (as ranked by the top 12 pharmaceutical companies)\(^1\) has taken into consideration advantages such as:

- Patient availability,
- Cost-efficiency,
- Relevant expertise,
- Regulatory conditions,
- National infrastructure and environment.

Besides being a large country, Romania has other attractive prospects for pharmaceutical companies which deserve to be taken into consideration when pursuing a clinical study in this part of the world. To mention a few: the size of the Romanian population among CEE and EU countries, with a high number of eligible and participating compliant patients and high enrolment rates; the epidemiological profile; the low level of healthcare expenditure and consumption per capita with a high percentage of treatment-naïve patients; regulatory and legislative reforms following EU accession; trial start-up times and requirements which are comparable with other EU countries; competitive costs per patient; high standards of medical education; highly concentrated and specialised healthcare services; experienced personnel (including eCRF and IVRS solutions); supportive infrastructure; good regulatory and protocol compliance with good-quality data, certified by audits and inspections conducted by sponsor, regulatory or third parties. All of the above make Romania an attractive destination for big pharmaceutical companies.

It is worth mentioning that almost all European guidelines and rules governing medicinal products in EU have been transposed into national legislation in Romania. Three main European directives are in place in Romania as follows:

- Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice in regard to investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products – transposed by MHO No. 903/2006

The relevant Eudralex Vol 10 guidelines were also translated and transposed into national legislation (NAMMD Scientific Council Decisions, MHO).

Here is a comprehensive list of European guidelines\(^2\) which have been transposed into national legislation, useful for any submission of documents by a sponsor requesting permission to open their trial in our country.

- CT1: Detailed guidance on application for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial – transposed by NMA SCD No. 22/2010
- CT2: Detailed guidance on the application format and documentation to be submitted in an application for an ethics committee opinion on the clinical trial on medicinal products for human use – transposed by NMA SCD No. 50/2006
- CT3: Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use (‘CT-3’) – transposed by NMA SCD No. 27/2011
- ICH guideline E2F - Note for guidance on development safety update reports September 2010 (not transposed, applicable as such)
• Good Manufacturing Practice for Medicinal Products - Annex 13: Investigational Medicinal Products - transposed by NMA SCD 5/2012
• Guideline on the requirements to the chemical and pharmaceutical Quality documentation concerning investigational medicinal products in clinical trials – transposed by NMA SCD 15/2008
• Guidance on investigational medicinal products (IMPs) and ‘non-investigational medicinal products’ (NIMPs) - transposed by NMA SCD 20/2011
• Detailed guidelines on good clinical practice specific to advanced therapy medicinal products (not transposed, applicable as such)
• Clinical investigation of medicinal products in the paediatric population – transposed by NMA SCD 41/2006
• Ethical considerations for clinical trials on medicinal products with the paediatric population
• Recommendation on the content of the trial master file and archiving – transposed by NMA SCD No. 51/2006

There are also specific national regulations for conducting clinical trials in Romania:
• NAMMD SCD no. 29/2011 on approval of the Regulations concerning authorisation by the National Agency for Medicines and Medical Devices of clinical trials/notification to the National Agency for Medicines and Medical Devices of non-interventional clinical trials conducted with medicinal products for human use in Romania - provides procedure steps for assessment and approval of an Application for a Clinical Trial.
• MHO no. 912/2006 on approval of the Regulations for the authorisation of medical units for conducting clinical trials on medicinal products for human use - provides rules and standards for authorisation of clinical trials sites (medical units and investigators)

The regulatory framework in Romania is very well-structured, where all international or European rules of conducting clinical trials find their place. Immediately after the 1989 December Revolution, Romania first set up the Bioethical Committee in 1992, followed in 1997 by the approval of the first Ministry of Health Order to make ICH-GCP compliance mandatory. In 1998, the National Ethics Committee for clinical trials was established, and 1999 saw approval of the first Medicine Law and assignment of the National Medicines Agency as Competent Authority for Clinical Trials. In the years since 2000, Romania has begun the translation and adoption of new European legislation in clinical trials as seen above.

The measure of Romania’s success lies in the rapid evolution of the regulatory framework, which was promptly transposed from EU rules and regulation into national legislation. It has been observed that this regulatory environment was one of the principal reasons why the number of completed and active studies in Romania increased from 75 in 1994 to 214 in 2004, and to 1484 in February 2014.

As a result of the activity report by the National Agency for Medicines and Medical Devices (NAMMD) for 2011, the number of requests for authorisation of developing clinical trials is registering a small decrease in comparison with the number of requests received annually in previous years (i.e. 246 for 2011 against 266 for 2010, 253 for 2008 and 275 in 2008). Phase III studies have the greatest percentage, which means that the respective experimental drugs are in an advanced phase of development, and close to receiving market approval. They are followed by Phase II studies. As for Phase I studies, NAMMD has received a limited number of requests as there are few Phase I units located in Romania. Bioequivalence clinical trials were also conducted in Romania in 2011.

The principles of conducting clinical trials are driven by the Declaration of Helsinki of the World Medical Association: entities involved in running clinical trials and GCP inspections.

If we talk about the role of entities involved in running a study in Romania, we have to underline the investigator’s role in Romania. As study teams are usually well-structured, Romania has experienced investigators, a competitive speed of recruitment, one of the lowest costs per patient, and supportive infrastructure.

Regarding GCP inspections, there are national inspections programmes in place - NAMMD having its own standard operating procedures made in accordance with the guidelines for inspection, vol 10 Eudralex - Clinical Trials - Chapter 4 – Inspection. The purpose of any inspection is the verification of protection of the rights and comfort of the study subjects, compliance with GCP, and data quality. The National Inspections Programme contains routine inspections for ongoing clinical trials at the sponsor/CRO investigation centres, and triggered inspections. The Romanian inspectors have also conducted GCP inspections in the context of the centralised procedure of the European Medicines Agency (EMA).
Data extracted from NAMMD shows that in the period 2008-2011, the total number of GCP inspections was 96 (both announced and unannounced) with the distribution per year shown below (Fig.6), indicating a low number of critical findings. An analysis of findings observed during 2010-2011 GCP inspections shows a percentage of 22.98% in the source documents; findings related to other areas of clinical trials conduct are below 10%.

From a financial perspective, clinical trials relieve part of the social burden on the national healthcare system, and ensure treatment with active medication for therapeutic areas which the national healthcare system cannot support. Clinical trials represent an alternative (sometimes the only) option for patients to have access to innovative, new-generation molecules. There is truth in the fact that the Romanian pharma market is small and usually endures several years of delays in registering and ensuring commercially available new molecules, and that national treatment programmes/reimbursement plans are generally not 100% able to meet the needs of the population. But that is why the running of clinical studies in this country is an option for patients registered on “waiting lists”: to gain access to the latest medication, and sometimes gain a cure for their disease. In regard to therapeutic study areas and medical conditions, the leading place is taken by oncology studies, but psychotic disorders, neurology, respiratory, haematology, diabetes, endocrinology, cardiology, and viral and bacterial infections are also studied in Romania (Fig.7).

<table>
<thead>
<tr>
<th>Country</th>
<th>Population (millions)</th>
<th>Number of clinical trials</th>
<th>Trials / million inhabitants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romania (EU)</td>
<td>21.4</td>
<td>143</td>
<td>6.7</td>
</tr>
<tr>
<td>Serbia Montenegro</td>
<td>10.5</td>
<td>50</td>
<td>4.8</td>
</tr>
<tr>
<td>Macedonia</td>
<td>2</td>
<td>7</td>
<td>3.4</td>
</tr>
<tr>
<td>Bosnia-Herzegovina</td>
<td>3.9</td>
<td>10</td>
<td>2.5</td>
</tr>
<tr>
<td>Ukraine</td>
<td>46.2</td>
<td>112</td>
<td>2.4</td>
</tr>
<tr>
<td>Russia</td>
<td>142.5</td>
<td>304</td>
<td>2.1</td>
</tr>
<tr>
<td>Moldova</td>
<td>3.8</td>
<td>3</td>
<td>0.8</td>
</tr>
<tr>
<td>Belarus</td>
<td>9.7</td>
<td>6</td>
<td>0.6</td>
</tr>
<tr>
<td>Albania</td>
<td>3.2</td>
<td>2</td>
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Some of the identified findings were distributed as per the chart below:

![Fig.3 Experienced investigators by country](image)

**Table 1:**

<table>
<thead>
<tr>
<th>DEFICIENCY CATEGORY</th>
<th>PERCENTAGE (%)</th>
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<tbody>
<tr>
<td>Source documents</td>
<td>22.98</td>
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<td>Facilities and equipment</td>
<td>0.04</td>
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<td>SOP</td>
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<tr>
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![Fig.4 Cost per patient](image)

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**Fig.5 Supportive infrastructure in Europe**

**Fig.6 GCP inspections in Romania**

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From a public and media perspective, there is still room for improvement in developing clinical trials in our country. The public is rather unaware of the existence of clinical research, and lacks knowledge with regard to the legal framework, guidelines and rules involved, which may lead to some negative views over using humans as “laboratory animals”, etc.

So, why do Romanian patients participate in clinical trials? Because they offer access to innovative medication; sometimes they are the only option for treatment; patients hope that partaking in the trial will improve their quality of life; the laboratory tests are performed in accredited laboratories (located abroad or in Romania); patients can get more attention from medical site staff; and last but not least, many patients hope that their involvement will help others with the same disease in the near future.

In conclusion, the development of clinical trials in Romania is very promising, and the country’s existing legislative framework and organisation is inviting to any pharmaceutical company wishing to conduct studies on its patients/subjects. This development is a positive step for both the medical profession, and for patients whose access to treatment has thus advanced.

References
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13. Cristina Florescu Moraid, “Clinical Research in Romania” ppt, slide 59, Postgraduate Course in Clinical Trials Management, May 2013, Bucharest

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