BANTAO Journal 2009; 7 (2): 1-3

BJ

BANTAO Journal

Editorial

Clinical Trials in the Balkan Region: Still Under-Discovered Potential?

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The term clinical trial refers to the entire biography of a drug from its inception in the lab to its introduction to the consumer's market and beyond. Synonyms for clinical trials include clinical studies and clinical research. Once the promising candidate or the molecule is identified in the lab, it is subjected to pre-clinical studies where different aspect of the drug including its efficacy and toxicity are studied. Clinical trials are commonly classified into four phases. Each phase of the drug approval process is treated in a separate clinical trial. The drug developing process will normally proceed through all four phases over many years. If the drug successfully passes through Phases I, II, and III, it will usually be approved by the national regulatory authority for use in the general population. Phase IV are 'post-approval' studies.

Clinical trials were first introduced in Avicenna's *The Canon of Medicine* in 1025 AD, in which he laid down rules for the experimental use and testing of drugs and wrote a precise guide for practical experimentation in the process of discovering and proving of the effecttiveness of medical drugs and substances [1]. He proposed some rules and principles for testing the effectiveness of new drugs and medications, which still form the basis of modern clinical trials [2,3].

One of the most famous clinical trials was James Lind's demonstration in 1747 that citrus fruits cure scurvy [4]. He compared the effects of various different acidic substances, ranging from vinegar to cider, on a group of afflicted sailors, and found that the group who were given oranges and lemons had largely recovered from scurvy after six days. Frederick Akbar Mahomed (1884) who worked at Guy's Hospital, London [5], made substantial contribution to the process of clinical trials during his detailed clinical studies, where "he separated chronic nephritis with secondary hypertension from what we now term as essential hypertension". He also founded "the Collective Investigation Record for the British Medical Association"; this organization collected data from physicians practicing outside the hospital setting and was the precursor of modern collaborative clinical trials [5]. Many years later, it becomes obvious that clinical trial is the best, legal and highly controlled way on how to produce the new drug.

The process of the drug development is very long, complicated and costly and they have to fulfill regulatory requirements. In the United States, it is the function of the Food and Drug Administration (FDA) to establish these regulatory requirements. The European Medicines Agency (EMEA) and Japanese Pharmaceutical and Medical Devices Agency (PMDA) are important authorities in drug development. The rising costs of meeting demands of different regulations led to the establishment of an International Conference on Harmonization of Technical Requirements for Registration of Pharmaceutical for Human Use (ICH) in an attempt to coordinate and synthesize international regulatory requirements. These systems of new drug approvals are extremely rigorous and costly. It takes 12 years on average for an experimental drug to travel from the laboratory to the medicine users. Only five in 5,000 compounds that enter preclinical testing will actually progress into human clinical trials and of these five, only one is likely to be approved by the regulatory authorities.

Having in mind all mentioned above, it is reasonable that selection of sites that will conduct clinical trials is one important step during the whole process called clinical trial. The most of the company have 'their sites' for years and it is very difficult to break this 'closed system'. Their trust, positive experience and personal contact are a warrantor of the trials' success. The most of these countries are from the Western world and from clinics experienced in clinical trials and approved to work according to GCP protocols.

During the last decade, the number of clinical trials in Balkan countries markedly increased. The convenient local procedures, along with the highly motivated and educated stuff and compliance of patients are the reasons why more and more companies are interested to conduct clinical trials in this region. Relationship between doctor, nurses and patients are very close and trusty, therefore the majority of patients do agree to participate in these clinical trials. On the other hand, a potential patient's benefit of participation in these clinical trials is possibility for treatment with a novel therapy (such as phosphate binders or calcimimetics) in the region where these drugs are yet unavailable or not recognised by the health-care system. In addition, the

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shortage of some expensive drugs or restriction by local authorities due to the drug cost may be over-passed by the studies that include these developing drugs (e.g. ESAs).

Table 1. Data on regulatory bodies and clinical studies in some countries from the Balkan region

	Serbia	**Bosnia& Herzegovina**	**Albania**	**R. Macedonia**	**Croatia**	**Bulgaria**
No of dialysis Units	46	25	5	18	52	64
No of centers that perform HD/PD	46/10	25/5	5/1	18/1	52/18	64/7
Ethic Committee	Local	Local/Central	Local	Local/Central	Local	Local/Central
Meetings of EC	Monthly	In 2 months	In 3 months	Monthly	Monthly	Monthly
Time for Decision	Two days	One months	2-3 months	2 weeks	One month	One-two months
Fee for EC	500 E	50 E	No fee	1000 E	No fee	200 E - 1500 E*
Meeting of MOH/Regulatory Body	~ 2 Months		In 3 months	1-2 months	One months	
Fee for MOH/Regulatory Body	confidential		800 E	500 E	3500 E	Up to 1500 E
Time for Decision	2-3 weeks		8-12 months	2 weeks	1-3 months	2 months
No of studies in nephrology, last 10 years	24	10	20	23	22	24
Nephrologists with > 50 indexed scientific papers (alphabetic order)	Dimkovic N Djukanovic Lj Peco-Antic A Stefanovic V Stojimirovic B			Grcevska L Polenakovic M Spasovski G Tasic V	Bašić Jukić N Duraković Z Gašparović V Kes P	Belovezhdov N Dimitrakov D Robeva R

*Depending on the phasys and the type of the study (pharmacokynetics, bioavailability etc.) concerning the central ethic commitee; different in each hospital concerning the local EC

Recently, an interesting survey was performed with a simple questionnaire about some regulatory issues, and the former experience with the clinical trials in a few Balkan countries. As it could be seen from the Table 1, there is a growing interest for mutual participation in these clinical trials from the side of sponsors as well as the Balkan researchers. This breakthrough was done in the last decade of the previous century, but the real expansion happened over the last decade. Here, the motivation for the clinical studies in the Balkan countries was best explained by the sponsors of clinical trials who described their positive experience with the countries already involved. Sites from Balkan countries could show very good compliance with the proposed timelines, they could always recruit among the highest number of patients (as per center practice) and could raise substantial number of reasonable queries. Communications with the CRO companies and sponsors were evaluated as excellent one and investigators from the region became even members of the Advisory or Scientific Boards in various companies, being involved in the planning of the drug development through further clinical research. In addition, these already performed clinical trials have generated a higher scientific impact for a few nephrologists from the region who become well known by their publications in Medline cited journals. Hence, the last row of the Table 1 was fulfilled with the Balkan researchers who have in their Medline portfolio more than 50 papers in the indexed journals. This could be considered as a good promotion of the scientific level in the Balkan area, and an easy accessible communication towards nephrologists linked to the various fields of nephrological research.

On the other hand, the recognised shortcoming of the Balkan scientific horizon is still the lack of regional cooperation in nephrology as well as very few regional meetings needed for the guidelines implementation. This is in despite of the currently similar condition of the health-care systems and availability of the local resources. It is up to us all to accomplish these tasks in the future.

Finally, in the light of 'saturation' of western countries with numerous clinical trials, countries from the Balkan region offer the solution for the time to come. Favorable location, highly experienced staff and motivated patients, convenient local regulatory procedure, all together is the formula that guarantees success in the long and complicated issue named as clinical trial.

Conflict of interest statement. None declared.

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