

The Clinical Trial Hub

Dr Georg A Mathis at Appletree Ltd reviews a model for successful co-operation between clinical service organisations in Western and Eastern Europe



Georg A Mathis is a trained Doctor of Veterinary Medicine with a PhD in Pharmacology (both received from the University of Zurich, Switzerland) and an MBA from the State University of New York at Albany. He has experience in clinical practice, as well as basic research in cell biology and cellular metabolism, and clinical pharmacology. Georg has spent the last 15 years in the pharmaceutical and healthcare industry, mainly in executive positions. Since 2002 he has been CEO of Appletree Ltd, a contract services organisation specialising in ophthalmology, which he founded with two partners.

From the early 1990s, performing clinical research in Central and Eastern Europe (CEE) has become increasingly popular. Initially, cost was the major driver for this trend, and the studies were principally intended for local registration or marketing support. Recently however, and especially since the beginning of the new decade, clinical trials in CEE became more and more part of international registration dossiers compiled for Western authorities, such as the US Food and Drug Administration (FDA), the European (Union) Medicines Evaluation Agency (EMA) or other Western European regulatory agencies. As a consequence, clinical trial sites and contract services organisations (CSO) in CEE have become the target of audits by Western authorities, especially the FDA. The outcome of such audits was mostly quite favourable and in any case no worse than audits of Western institutions.

The major opportunity when performing clinical studies in CEE is the fact that they are extremely efficient (see Table 1). Large eligible patient populations are cared for by highly dedicated investigators, who are very well trained. As a general rule, a markedly higher proportion of the eligible patients will participate in a clinical trial than is typical in the Western world. In our experience, in an ocular infection study, the rate of recruitment of eligible patients was approximately five per cent in Western Europe, whereas in several Central European countries the average was at least 10 times higher. This is, on the one hand, due to the fact that modern, Western medications and technologies are generally not within reach of the average patient in CEE, and on the other hand that the medical profession has a higher and undisputed standing in these countries, resulting in less hesitation to comply with a doctor's suggestion. This, at least in part, also influences compliance with the trial requirements, which, as a general rule, is very high. In summary, the resulting quality of data and the cost

effectiveness due to rapid recruitment make it worthwhile considering the inclusion of sites in CEE in any worldwide development plan.

These advantages might be seen as a threat to clinical trial institutions and the business of established CROs in Western

Table 1: Major Opportunities of Performing Clinical Trials in Central and Eastern Europe

- Large eligible patient populations
- Large proportion of participating patients
- High recruitment rates
- Dedicated investigators
- High standard of medical education
- Motivated patients
- Excellent compliance

Table 2: Major Risks Associated with Clinical Research in Central and Eastern Europe

- Investigators lacking clinical research and cGCP experience
- Lack of state-of-the-art medical equipment at the study sites
- Hospital staff and services inexperienced in clinical trial conduct
- Local monitors, often working two jobs, being overwhelmed by the workload and demands of the study sponsors
- Unclear and rapidly changing regulatory environment
- Comparatively long trial start-up times
- Little experience of most involved parties in dealing with Western business culture
- Monetary compensation becoming an all-important motivator for participating in a clinical study

medical doctors working as clinical research associates (CRA) in order to improve their meagre official salary. While, on the one hand, this results in very high level CRA personnel, they are often overwhelmed by the double workload and extensive demands of the study sponsors.

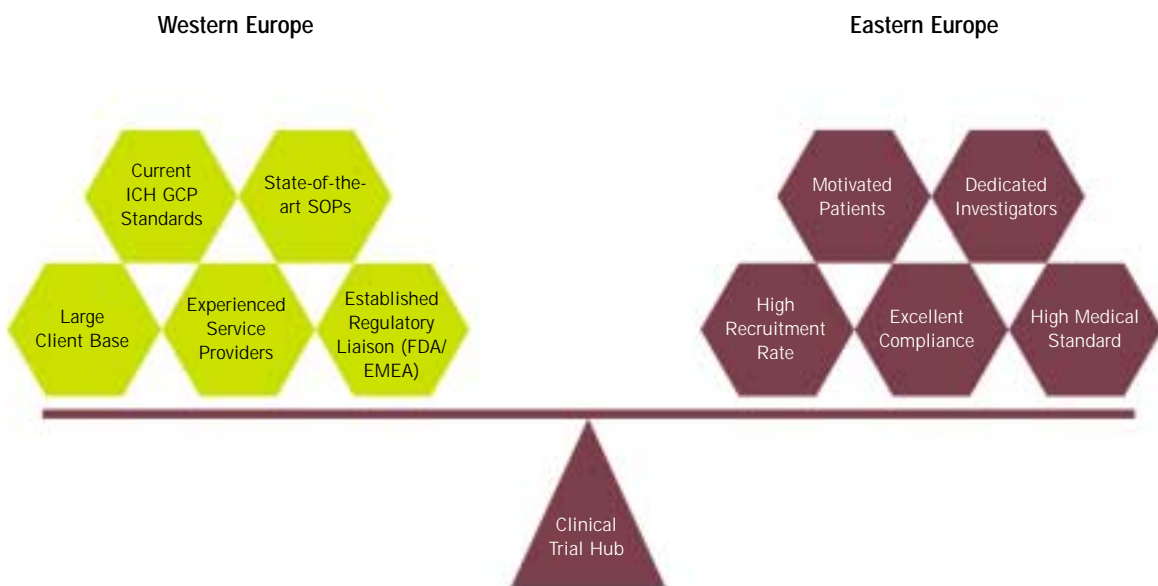
Another drawback is the potential lack of state-of-the-art medical equipment at the clinical study sites – for example the gold standard equipment for measuring intraocular pressure, the Goldmann tonometer, can basically not be found in Russian ophthalmology clinics. The CEE countries have opened up to Western businesses only within the last 10-15 years; most involved parties in clinical research

Europe and the US. However, there are small drawbacks and risks associated with clinical research in CEE, which need to be carefully balanced against the opportunities (see Table 2). In general, most investigators in CEE lack the long term clinical research and GCP experience of their Western peers. In our experience, even today it is extremely rare to find investigators in CEE with a history of more than three or four fully GCP compliant clinical studies. The same is true for the supportive hospital functions and the clinical staff, such as hospital laboratories, pharmacies or nurses. Similarly, many CSOs in this area have only limited experience of working according to Western standards of quality and customer service. What is more, it is not uncommon for such organisations to be staffed by part-time employees, such as

often have very little experience in dealing with Western business culture and expectations. Further, the regulatory environment is rapidly changing in some countries and often subject to individual interpretation. For example in Poland, a country which has recently joined the European Union (EU) and which is supposed to be subject to the EU guidelines and regulations for clinical trial conduct, the rules for clinical trial authorisation have in our experience repeatedly changed in the process, causing delays and uncertainty. As a result, trial start up times in CEE countries can be comparatively long.

The cost of conducting clinical trials should clearly no longer be the decisive factor for performing clinical research in CEE

Figure 1: The Art of Balancing the Assets of Clinical Research in Central/Eastern and Western Europe



It is vital that every CRO has experience and know-how of managing complex clinical trial organisations, along with the ability to implement, if needed, state-of-the-art GCP and clinical research standards, plus use the clinical research network, as well as its connections, to service providers and study sites in Central and Eastern Europe

countries. Investigators in the area are by now fully aware of the honoraria paid in the Western world for clinical research and expect to be remunerated at the same level. In fact, one has to be mindful of the fact that monetary compensation may be becoming an all too important motivator for an investigator to participate in a clinical study in CEE, thus possibly causing ethical issues. In our experience, the overall cost for study conduct in CEE countries may be between 10 and 20 per cent below the corresponding Western European figures. However this cut is seldom all but annihilated by additional costs for translation, more extensive travel and the need for local support. Having said that, we are convinced, and have proven, that clinical studies in CEE are very cost effective. Costs generally similar to those in Western Europe are matched by significantly better performance. The trick is to manage the risks in order to profit fully from the opportunities in CEE. Or, in other words, it is essential to be capable of balancing the assets of Western and Central and Eastern European clinical research (see Figure 1).

In the course of a number of clinical studies we have succeeded in developing a co-operation model with CROs in Central and Eastern European countries: the clinical trial hub (see Figure 2, page 54). The model combines the best of both worlds. The CRO acts as the link and turning point between the different providers in the clinical study in Eastern and Western Europe, liaising and contracting with the clinical trial sites and local service providers on behalf of the sponsor. Local CROs or freelance consultants contribute their staff, local network, national regulatory knowledge and clinical research experience. Most importantly, it can act as the sole point of contact for all study related issues and questions for the sponsor, thus facilitating trial management on the sponsor's side.

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Figure 2: The Clinical Trial Hub Concept Facilitates Complex Trial Management for Corporate Sponsors

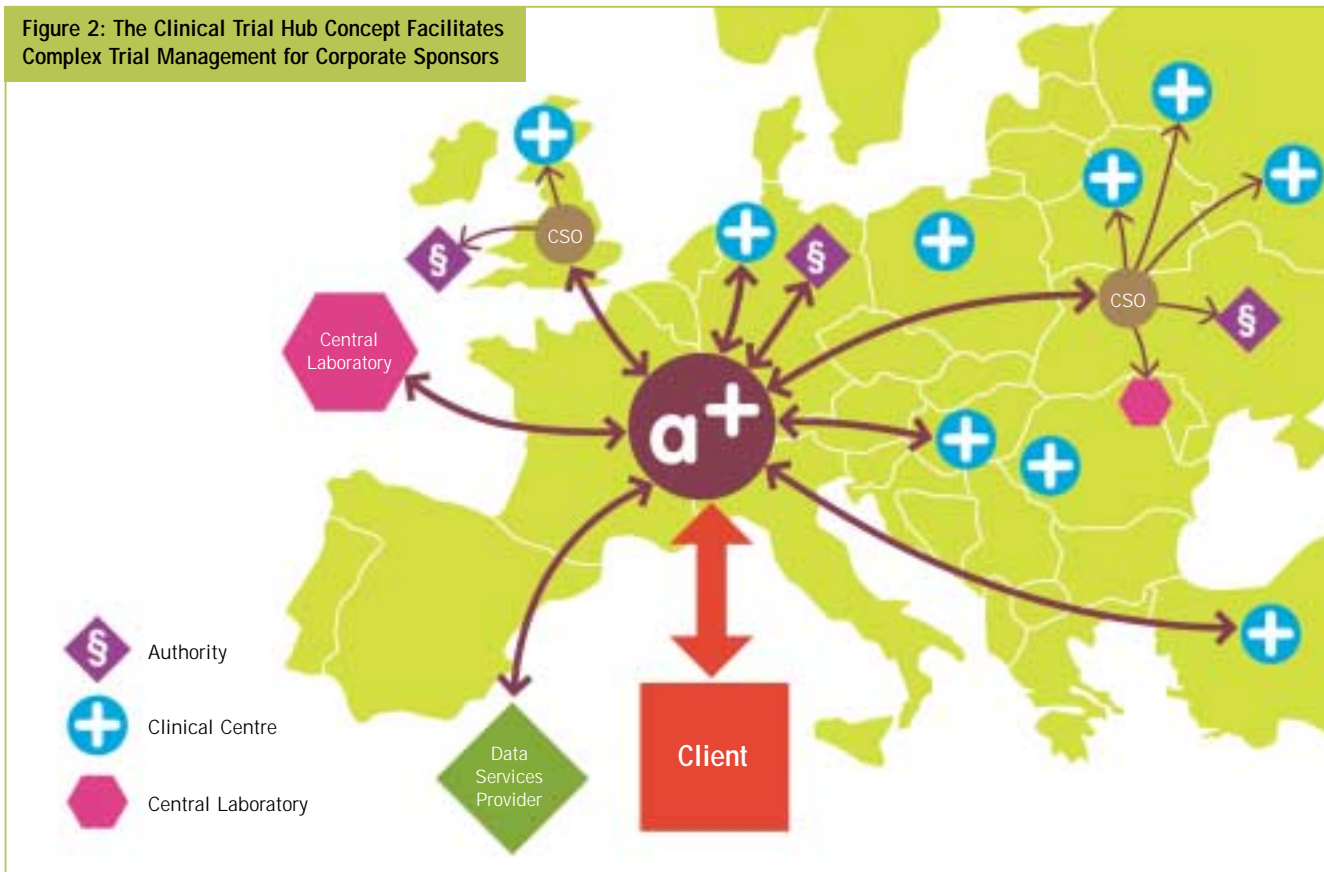


Table 3: Treatment of Ocular Infection

Clinical study phase	III
Sponsor	Western European mid-size enterprise
Clinical trial hub	Niche Western CRO
Countries	Poland, Czech Republic, Bulgaria, Romania
Clinical sites	14
Local laboratories	6
Data management	By sponsor
Medication supply	Co-ordinated by niche Western CRO
Local contract services organisations	3, non-specialised in indication (Czech Republic and Poland, Bulgaria and Romania)
Specifics	Part of a global trial: Asia, Western Europe, Central Europe and North Africa
Duration	Start-up: 8 months; in-study phase: 4 months
Outcome	Recruitment of 191 patients in 9 active sites; average rate of 5 subjects/site/month versus less than 0.5 patients/site/month in Western Europe; high quality results; average costs

Table 4: Treatment of Glaucoma

Clinical study phase	IV
Sponsor	Global pharmaceutical company
Clinical trial hub	Niche Western CRO
Countries	Poland, Czech Republic, Hungary, Bulgaria, Romania, Slovenia, (plus Greece and Turkey)
Clinical sites	10
Local laboratories	None
Data management	By sponsor
Medication supply	By sponsor's affiliate; co-ordinated by niche Western CRO
Local contacts	8, local subsidiaries of sponsor in each country
Local CSOs	1, non-specialised in indication (Greece)
Specifics	One of three identical trials in US, Western Europe, Central Europe
Duration	Start-up: 10 months; in-study phase: 9 months; 192 subjects recruited; 20 subjects/site/month in Czech Republic, Romania, Bulgaria and Slovenia
Outcome	Although last trial to be initiated, first to complete study; high quality results; below average costs

clinical research standards, plus use the clinical research network, as well as its connections, to service providers and study sites in Central and Eastern Europe. In the particular case of clinical research in ophthalmology, a niche market with very few specialised service providers, CROs can contribute their specific knowledge, thus enabling non-specialised contract service organisations to perform professionally in this context. Two case studies shall illustrate the concept (see Table 3 and 4).

In conclusion, by applying the concept of the clinical trial hub to ophthalmological clinical research in Central and Eastern Europe, it is possible to combine the assets of clinical research in Western and Central and Eastern Europe, thus delivering top quality clinical study results within timelines unheard of in Western Europe, as well as the US. ♦

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