

Look East

Luca Cantini and Simona Colazzo at Crom look at the quality of clinical data from sites located in Central and Eastern Europe

There is currently an increasing number of requests from sponsors for accelerated recruitment times in clinical trials without reducing quality, and with optimal cost-efficiency. To meet these expectations, pharmaceutical companies and CROs are setting up a growing number of clinical trials in central and eastern Europe (CEE). The need for data quality and cost-efficiency has led to the regular evaluation of clinical research performance and the capacity of CEE investigational sites. Several factors have contributed to the significant increase in the number of clinical trials conducted in CEE over the past few years (1). Although reports available in the Literature have used different methods in the assessment of levels of quality and benchmarking in clinical trials, there is evidence that the contribution in terms of sample size, the quality of the data obtained, the ethical care and the compliance with good clinical practice (GCP) guidelines in CEE sites is generally higher than that obtained in Western regions, including the US.

MULTINATIONAL CLINICAL TRIALS: THE PUBLISHED CEE EXPERIENCE

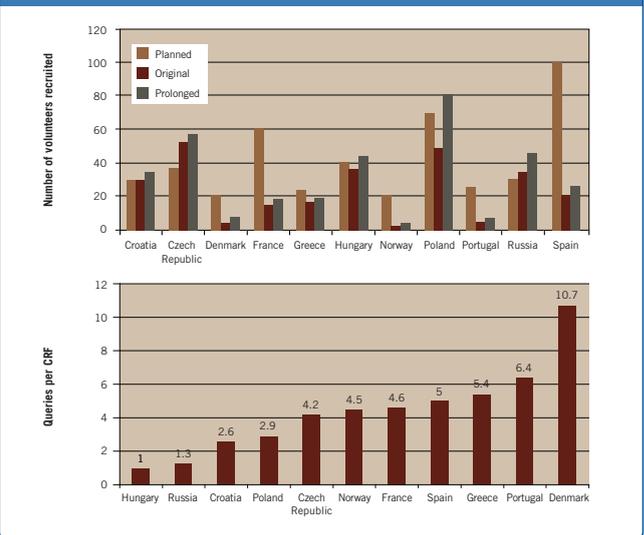
Conducting pan-European clinical trials, possibly also involving countries outside of Europe, allows the comparison of key performance indicators (speed, quantity and data quality) across CEE and western European countries in the same trial.

The results from a trial conducted in 11 countries (five in CEE and six in western Europe) have shown that CEE countries recruited more subjects than originally planned and were available for a prolongation of enrolment in replacement of low recruiting countries. In addition, sites in CEE countries had fewer queries than those in western Europe (see Figure 1) (1).

The analysis of another multinational trial that included 45 sites in Western countries (the US, Canada, Australia and New Zealand), 25 sites in western Europe (Ireland, Greece, Italy, Spain and the UK) and 48 sites in CEE (the Czech Republic, Georgia, Poland, Romania and Russia) showed clear differences between regions in data quality and recruitment rate (2). In this study, the majority of participants (520 subjects, 63 per cent of the total population) were enrolled in eastern European countries, while western countries enrolled 219 subjects (27 per cent) and western European countries enrolled 85 subjects (10 per cent). The analysis showed that the numbers of generated queries decreased as the rate of recruitment increased, was higher in western than in eastern countries, and was higher in regions with native English speakers than in non-English language countries (see Figure 2) (2).

Other pan-European clinical trials conducted between 2001 and 2003 permitted the analysis of a number of indicators (such as the number of patients, number of sites, average number of patients per centre, queries per 10 case report form (CRF) pages), allowing the comparison of results between western Europe (Italy) and CEE countries (Poland and Ukraine). In these studies, 1,435 patients (90 centres) were randomised in CEE countries, compared to 1,019 patients (193 centres) in western European countries, in various therapeutic areas. Comparing western European and CEE countries, the average numbers of patients enrolled by an individual site are

Figure 1: Recruitment and queries per CRF in participating countries (1)



15.9 and 6.6 respectively, and the percentage of queries for each CRF page processed is 0.22 per cent and 0.80 per cent respectively (see Figure 3, page 38) (3).

An overview of the results of FDA inspections conducted on a worldwide basis has recently been published (4). A 10-year period (1994-2004) was selected for the analysis of the results of FDA inspections in different world regions (inspections in eastern Europe started in 1994). Of the inspections reviewed in 2004, 2,765 were conducted in the US and 413 in non-US sites. In this analysis, countries were grouped into the following geographical regions: the US, Asia, Africa, western Europe, CEE, Latin America, the Middle East and West (Australia, Canada and New Zealand). CEE included the Czech Republic, Croatia, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Russia and Slovenia. The Middle East (Egypt and Israel) received only one inspection per country, and the vast majority of inspections in Africa took place in South Africa, hence results in these regions were not considered. The outcomes of the FDA inspections were compared for three variables:

- Classification codes: 'no action indicated', 'voluntary action indicated' (no further regulatory actions), 'official action indicated' (regulatory actions indicated)
- Deficiency codes: description of the inspection deficiency
- Average number of deficiencies across regions

Figure 2: Relationship between the query generation rate (QGR) and the subject recruitment rates shown for all investigators (A), split by region (B) and by native English versus non-native English language countries (C) (2)

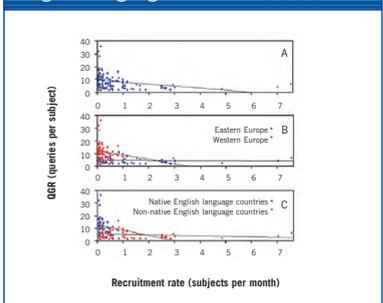


Figure 3: Comparative indicators – international multicentre clinical trials, 2001-2003 (3)

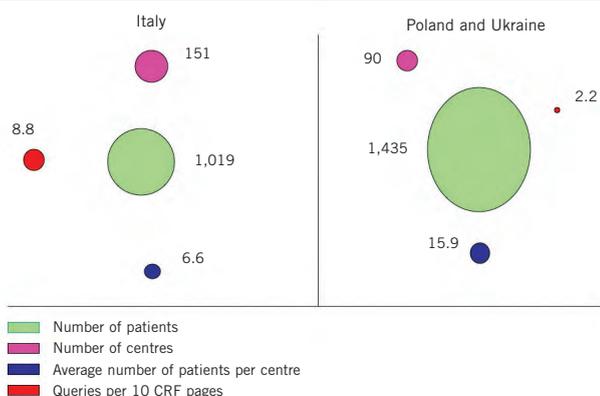
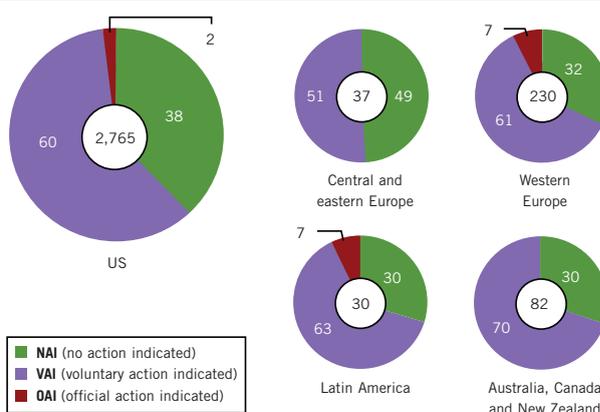


Figure 4: Outcome of FDA inspections by classification codes in the US and in the four largest regions (per cent) (4)



The results showed that:

1. CEE countries had no ‘official action indicated’ and had the highest rate of ‘no action indicated’ (see Figure 4) (4)
2. In the CEE countries, inadequate or incorrect records were the most common finding, accounting for 47 per cent of all deficiencies, while other problems (such as protocol violations or negligence in drug accountability) were less frequent compared with other regions
3. There were no substantial differences in quality across the examined CEE countries

Following this 10-year survey, the growing number of trials taking place in CEE countries led to the increase in FDA activity in these regions. An update one year after this review revealed 14 new inspections in CEE, five of which were in Russia, five in the Baltic states and four in Poland and the Czech Republic. This exponential increase in FDA activities in the CEE reflects growing attention to this region and corresponds with the increasing amount of data produced in this area. It has been highlighted that the FDA has not rejected any study from data collected in Eastern Europe (4).

PERSONAL EXPERIENCE IN MANAGING CLINICAL TRIALS IN CEE

Several pan-European trials conducted in different therapeutic areas have allowed a comparison of patient contribution and

overall quality across western European and CEE countries.

Table 1 summarises the number of planned and enrolled patients and the number of major protocol violations in studies in western and eastern Europe. Major protocol violations were defined as those protocol deviations potentially able to affect the efficacy and safety results of the trials, and can be considered as more reliable than the number of generated queries (data clarification forms) in the estimation of the overall quality of a trial. Patients with major protocol violations were generally excluded from the ‘per-protocol’ population for analyses. The results reported in Table 1 show that sites in CEE countries generally provided more patients than requested, in most cases compensating for a lower number of patients than expected from western European countries, or as rescue intervention. The overall quality of trials, as measured by major protocol violations, was generally very good, and CEE countries contributed significantly to achieving this goal. Importantly, the low number of protocol violations allowed the target population to be reached not only on an ‘intention-to-treat’ basis, but also in the ‘per-protocol’ analysis. This allowed the efficacy results of the studies to be consistent in the two analysed populations.

Therefore, personal experience of the assessment of speed, protocol adherence and general quality of clinical trials managed in CEE countries is consistent with that reported in the Literature.

PERSONAL EXPERIENCE IN AUDITING CLINICAL TRIALS IN CEE

Over the past few years, the audit is considered positively as a ‘standard practice’ performed on the system, the documentation and the investigational site. The audit, as a part of the quality system, is the method used to verify compliance with the applicable regulations and organisation standards, to determine validity and credibility of data and to identify areas for improvement. A substantial number of audits performed in the CEE area, together with other evidence, has confirmed the high quality of the sites located in these countries.

In general, the site staff appear to be highly familiar with clinical study conduct and compliant with the protocol and procedures. With reference to clinical study conduct, all required source documents are accurate, legible, consistent, complete and available. Any source data verification required can be conducted by easy

Table 1: Patient contribution and quality (measured by protocol violations) in a sample of clinical trials conducted in western European and CEE countries (yellow-shaded studies were conducted in both regions)

Type of study (Phase)	Western Europe			CEE			Total major protocol violations rate (per cent)
	Number of sites	Planned	Enrolled*	Number of sites	Planned	Enrolled*	
Respiratory (III)	21	170	53 (31.2)	55	550	650 (118.2)	3.4
Respiratory (III)	17	200	151 (75.5)	12	300	315 (105.0)	5.5
Cystic fibrosis (II)	11	74	5 (6.8)	8	60	54 (90.0)	5.1
Musculoskeletal	4	50	34 (68.0)	10	334	390 (116.8)	<1
Cardiovascular (III)	7	180	155 (86.1)	34	324	495 (152.8)	5.7
Metabolic (IV)	6	150	116 (77.3)	15	300	326 (108.7)	6.4
Cardiovascular (III)	-	-	-	13	224	251 (112.1)	6.8
Respiratory (III)	-	-	-	45	396	457 (115.4)	5.5
Respiratory (III)	-	-	-	19	240	276 (115.0)	1.8

* Data indicate number of patients enrolled, with the rate of enrolled versus planned in brackets

direct access to the subjects' notes that allow the auditor to collect a consistent quantity of data in order to confirm its quality. The process for obtaining informed consent is generally performed according to regulations and protocol requirements. Accurate document management reveals that sites are in control of the procedure for following the protocol and the management of investigational products (such as the availability of instrument outputs, instrument calibration and maintenance documents, temperature recording and comprehensive investigational product accountability records). With reference to adherence to the study protocol, the available documents support evidence that the subjects have the condition under investigation and that they participate in the study as per protocol requirements. Although protocol violations do occur, they are noticed promptly, and the requested corrective actions are undertaken during the course of the clinical study.

Additionally, the facilities appear adequate to carry out protocol procedures and to ensure the correct management of investigational products and essential documents.

In the personal experience of the authors, audits in CEE countries have resulted in only minor critical findings or none at all (defined as those findings that heavily affect the integrity of the study, system or process), which is consistent with the results of FDA inspections.

CONCLUSION

Current evidence indicates that the CEE region remains a solid and reliable arena for the efficient and high-quality conduct of clinical trials. Investigators are well-educated, experienced and highly motivated physicians who have opportunities for professional development, international networking and publication as a result of the trials. CEE nations offer a huge pool of easily reachable patients interested in participating in clinical studies thanks to free access to modern therapies and medical equipment. Overall, trial costs are lower than those in western Europe. For the most part,

well-defined regulatory processes make it possible to obtain all of the necessary approvals in a relatively short time. Although regulatory and import license procedures vary across CEE countries and require special attention in the organising phase of the studies (which requires locally-based organisation), there has been no experience of marked differences between CEE countries in overall speed and general quality of studies. The selection of CEE countries should be based mainly on an eligibility criteria and hence potential for recruitment (patient population varies across countries), as equipment and facilities have reached a satisfactory standard in all countries. There are no critical issues in central reading and transportation for assessment. Therefore, based on literature evidence and personal experience, CEE countries continue to offer an important contribution for investment in future clinical research.

References

1. Kucerova I and Babic D, Benchmarking Clinical Trials Practices in Central and Eastern Europe, *Applied Clinical Trials*, May 2003
2. Platonov P, Clinical trials in Russia and Eastern Europe: recruitment and quality, *Int J Clin Pharmacol Ther* 41 (7): pp277-280, 2003
3. Carmosino G and Malkowska W, Clinical trials in Central and Eastern Europe, *European Pharmaceutical Contractor*, Autumn 2004
4. Varshavsky S and Platonov PG, FDA Inspections Outside the USA: An Eastern European Perspective, *Applied Clinical Trials*, Sep 2004

About the authors



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Luca Cantini is the Medical Leader of CROM srl. His background includes 12 years' experience in a major pharmaceutical company where, as Head of Corporate Clinical Research, he was responsible for national and international clinical trials in a variety of therapeutic areas. From 1990 to date he published several scientific articles and he is certified as a medical writer by major multinational companies. Luca is now a consultant in clinical research and development with experience in project management and expertise in medical writing. Email: cromsource@cromsource.com



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