

Speeding the Critical Path

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Central and Eastern Europe's potential 300,000 CRFs per year could reduce drug development times and costs worldwide

Pharmaceutical research and development costs are growing faster than the market.¹ This trend is important, because pharmaceutical companies finance R&D from a relatively fixed percentage (10%–20%) of global revenues. As revenues stabilize and costs increase, the industry thus finds itself in a cash squeeze.² Given the current economic environment, it is unlikely that revenues will increase to keep pace with unmanaged increases in development costs. For this reason, costs must be contained or the industry will face unwanted program and personnel cutbacks.

Factors limiting market growth relate to the tightening of public healthcare purse strings in developed countries and to the natural limits on voluntary consumer spending for drugs. R&D productivity continues to decline, and costs continue to rise. The following statistics only underscore this perilous trend:

- The potential for success of a new chemical entity at the beginning of Phase I is still only 10%
- Nearly 90% of clinical trials are completed with significant delays.

These setbacks do not come cheaply. For a drug destined to make half a billion dol-

lars in annual sales, a one-day delay costs about \$1.3 million. Any avoidable delays to market are therefore unacceptable to anyone accountable for running a profitable business.

Targeting R&D cost savings

The industry has certainly responded to other fiscal crises. For a quarter of a century, i.e., since the emergence of good clinical practice (GCP), we have streamlined the drug development process, aiming to increase the overall success rate of R&D, as well as to shorten the timelines. If we are to remain fiscally sound and attractive to investors, we must find additional economies.

Largely, the industry has benchmarked and optimized each phase and task within the development process. At efficient companies, SOPs have transformed the actions of every clinical, data management and regulatory operations staff member into coordinated clockwork, moving clinical trials forward with Swiss precision. Protocol writing takes a few weeks. Case report form (CRF) assembly occurs within days. Computers code the data and generate tables and listings shortly after database lock.

One might think that little room remains for improvement, believing that we can no longer reduce development timelines in any significant way. Realistically, we probably cannot systematically shrink the time required for interstudy decision-making, although some companies try. Nor can we alter the protocol-driven patient treatment and follow-up periods. Within single studies, we have compressed the duration of individual phases to the minimum. In what phase, then, can we find the potential for greater efficiency?

The key phase

The patient enrollment period is the key phase where we believe the industry has the least control. Current enrollment tactics do not respond to our need for consistent, on-time enrollment; we need a broader strategy. If we could consistently reduce the patient enrollment period in clinical trials, we would take another major leap forward in optimizing the drug development process and preserving our economic health.

The sum of the duration of each clinical trial along the critical path, including the time related to interstudy decision-making, results in the overall time for clinical development of a new drug. We define a study along the critical path as a trial that must be completed before another time-critical study can begin. The critical path begins with the decision to launch “first-in-man” trials and ends with the decision to submit an application for marketing authorization. A clinical program may involve as many as 80 different clinical trials, however only 20% of these studies might actually be on the critical path. On the grand scale, it follows that any delay in any study on the critical path would lead to a delay in the completion of the entire development program. Since close to 90% of clinical trials experience a delay, not a single program completes on schedule.

Slow enrollment is the number one reason for the failure of clinical trials.³ Eighty-six percent of studies slip behind schedule.⁴ Furthermore, 60% of studies have delays of at least one month and 13% of studies are completed six months or more behind schedule. Because most clinical trials on the critical path each incur months of delays, overall development programs incur years of delays.

We can no longer afford to ignore this poor performance. We have developed the pernicious habit of routinely pushing back deadlines, giving ourselves the illusion that we are successfully meeting timelines while project schedules, if left unchanged, are almost never met. The practice must stop if we are to remain a financially viable industry.

Quantifying Lasagna’s Law

We systematically ascribe the cause for deadline pushback to a many-fold overestimation of the patient recruitment potential by clinical investigators. The cliché “Lasagna’s Law” was coined in the 1970s to describe this methodological error in enrollment estimates (see Figure 1). It is now the most popular rationale for delays in clinical projects. To compensate, many project managers think that the enrollment estimates from investigators are too optimistic by definition, and this leads to ultraconservative recruitment projections. Industry blames investigators, collectively, for the chronic delays in drug devel-

opment, viewing slow enrollment as an external factor totally beyond the control of project managers; more like a quasi “act of God.”

Efficient project managers must, therefore, focus on beating Lasagna’s Law at both the clinical trial and overall program levels. Better yet, project management should try to shorten the cumulative duration of patient recruitment in all studies on the critical path. Given that the enrollment period currently represents about 50% of the duration of a clinical trial, the overall development program would take 25% less time if the enrollment period shrunk by half. Reducing an eight-year clinical development program by two years translates into savings of approximately \$1 billion (2 years x 365 days x \$1.3 million/day), enough to finance the research and development of a new drug from inception! Faster enrollment, when achieved, would accelerate the drug development process to speeds not yet seen globally and restore the competitive edge to the industry.

(a)
$$T(P) = \sum_{i=1}^{i=n} T(CT)_i$$

where T = duration; P = program; CT = clinical trial; n = number of CTs in a P; which are on the critical path.

In the formula below, we define the duration of a clinical trial as the sum of durations of all phases, including inter-study decision-making:

(b)
$$T(CT) = T(\text{setup}) + T(\text{FPI-LPI}) + T(\text{LPI-LPO}) + T(\text{closeout}) + T(\text{decision-making})$$

If all phases of a clinical project are already proceeding at optimal speed, except for the enrollment period [T(FPI-LPI)], the sum of all other times can equal a constant, C:

(c)
$$C = T(\text{setup}) + T(\text{LPI-LPO}) + T(\text{closeout}) + T(\text{decision-making}), \text{ and}$$

the duration of any clinical trial then becomes a function of this constant and a variable, which is the enrollment period:

(d)
$$T(CT) = C + T(\text{FPI-LPI})$$

If C + T(FPI-LPI) from formula (d) replaces T(CT) within formula (a), the duration of a program appears to clearly depend upon the cumulative duration of all enrollment periods of all studies on the critical path:

(e)
$$T(P) = nC + \sum_{i=1}^{i=n} T(\text{FPI-LPI})_i$$

Figure 1. The time to develop a new drug in the clinic (duration of a program) arises from the sum of the durations of each clinical trial in the program.

The status quo

Drug developers and contract research organizations (CROs) still place most clinical trials in North America and Western Europe. The concentration of studies in these regions has led to site saturation and declining productivity. It simply will not help us to increase the number of participating sites in the traditional clinical research regions. This would inevitably lead to fewer patients enrolled per site, because recruiting additional sites often means accepting smaller centers and less experienced investigators. Worse yet, statisticians have calculated that this strategy might lead to a loss of statistical power.⁵ The difference in size between the smallest and largest sites would increase too, thus magnifying the risk of center effects. If the larger and more productive sites have to wait for the smaller ones to complete a block of patients, this may even nullify the advantage of having lined up a larger number of investigators.

The solution

We propose that the only effective solution is to seek and find large sites in new territories and pool them with large sites in the traditional regions. This strategy will resolve the productivity crisis by reducing the overall duration of enrollment.

If investigators in the customary locations cannot deliver, where might we look for investigators with a greater enrollment potential? For the most part, we have preferred to use sites in areas where we see well-organized healthcare systems, well-trained physicians, and GCP-compliant regulatory and ethical standards. Russia, the Ukraine, and the Balkans offer the conditions for major participation in global drug development. With the efficiency concerns of today, it is time we considered the huge opportunity that this region presents.

One hundred and fifty million inhabitants live in the Russian Federation, the largest country in Europe, both in terms of geography and population. Fifty million people reside in the Ukraine. The Balkans, including Romania (24 million), Serbia, Bulgaria, and Croatia, together represent another 50 million citizens. These countries firmly anchor themselves, culturally

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and economically, within the northern hemisphere, employing the same evidence-based medical systems and the same school of medical thought. They adopted GCP standards along with Western Europe and the United States, and they have a large, well-organized healthcare delivery system. Most important is

Table 1. Average Productivity Ratios by Indication between Sites in Russia, the Ukraine, and the Balkans Compared to Sites in the United States and/or Western Europe (1997–2002)

Indication	Average Productivity Ratio (comparison based on patients/site/month)
Hypertension	10.2
Asthma	5.2
COPD	4.9
Rheumatoid arthritis	4.8
Osteoarthritis	4.7
Atopic dermatitis	4.5
Myocardial infarction	4.2
Stable angina pectoris	4.0
Osteoporosis	3.9
Hepatitis C	3.8
Type II diabetes	3.7
Multiple sclerosis	3.6
Breast cancer	3.2
Overactive bladder	3.1
Colorectal cancer	3.0
Atrial fibrillation	2.9
Pancreatic cancer	2.9
Community-acquired pneumonia	2.8
Renal cell carcinoma	2.7
NSCLC	2.4

the region's demonstrated ability to produce evaluable patients at a rate at least two times faster than the United States or Western Europe.

Russia, the Ukraine, and the Balkans represent a catchment area for patient recruitment as large as North America or Western Europe. Today, the research-based pharmaceutical industry taps less than 15% of the region's clinical trial enrollment potential. It is the underutilized area of the world that can give us the answer to our patient enrollment stalemate. We have inventoried some 12,000 hospital-based sites in this region. With recruitment of just one patient per site every other week, which would not be too bold an assumption, the capacity of the region could easily reach 300,000 CRFs per year.

Based on about 50 international Phase II and III clinical trials, for which precise enrollment data per center and per month were available, we have derived site productivity comparisons between this region and the United States and Western Europe, in a variety of indications (see Table 1).

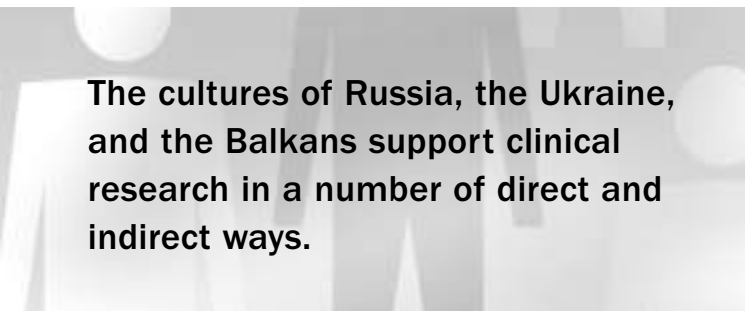
The table is based on enrollment statistics provided by the sponsors or CROs monitoring the trials considered in addition to our own data. The productivity of sites was defined as the average number of patients enrolled per site per enrollment month (i.e., during the available enrollment period).

Russia and Central and Eastern Europe (CEE) could them-

selves become exhausted, and therefore subjected to Lasagna's Law. We estimate that the remaining potential of Russia and CEE is 200,000 new CRFs/year. Given that an average of 4,000 subjects are needed per new chemical entity (NCE) registration, this reserve, which is available each year, represents the complete clinical development of 50 NCEs. Less than 10–12 were registered in 2002 in Europe.

Because the average site productivity in Russia, the Ukraine, and the Balkans is at least twice as high as that in the traditional clinical research regions, it is possible to halve the enrollment period in all clinical trials on the critical path. The industry must seize the powerful economic benefits of this potential.

Many factors contribute to the high average site productivity in the region. It has inherited a centralized healthcare system from the Soviet era, with therapeutic area hierarchies and vertical referral systems. Principal investigators, at the top of a medical specialty pyramid, can funnel patients from a large base of urban populations connected via vast and inexpensive public transportation systems. Due to a very small percentage of private medical practices, competition for patients does not exist between general practitioners and specialists in private practice or at city, regional or academic hospitals. Hospitals specialize by therapeutic area and enjoy, therefore, a semimonopolistic control of patient flow for research purposes. This



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allows sites to enroll previously unselected populations, whereas their Western counterparts in academia sometimes recycle the same pool of (often therapy-resistant) cases from trial to trial.

Culture and clinical trials

The cultures of Russia, the Ukraine, and the Balkans support clinical research in a number of direct and indirect ways. Since residential movement of the population is low, long-term follow-up is possible with little attrition. Patients also have lifetime medical records, segmented over various specialty hospitals and affiliated outpatient clinics. Clinical research, including pediatric studies, still enjoys a high degree of public acceptance. A well-educated population wants a high standard of care. Therefore, patients view clinical trials as a way to satisfy their desire for access to important new drugs. Excellent patient compliance arises from this motivation.

Study staff and monitors are, invariably, physicians. The collaboration of highly educated professionals makes it possible to conduct very complex scientific protocols. This results in consistent adherence to study schedules, significantly fewer proto-

col deviations, and lower screen failure and dropout rates.

Regarding the standard of healthcare, Russia, the Ukraine, and the Balkans are making a comeback in terms of Western expectations. The Russian economy is growing, and its pharmaceutical market is the fastest growing pharma segment in Europe. The per capita purchasing power in Russia (2001 per capita GDP at purchasing power parity of USD \$8,300)⁶ is less than one half that of the Central and lower range in the European Union—comparable to that of Poland and many other Central and Eastern European countries. However, it is 30% higher than that of Brazil, more than double that of China, and more than 3.5 times the purchasing power of the Indian population. In prosperous cities, such as Moscow, St. Petersburg, Kiev, and Bucharest, but also in some secondary cities, Russian purchasing power is closer to that of the European Union average. Hospitals in the national healthcare systems can be highly specialized by therapeutic area (e.g., oncology, cardiovascular diseases, hematopoietic tumors in children). This guarantees the best standard of care for the available budget and a better use of limited resources for the benefit of more patients.

The remaining options

Industry has tested other regions of the world for their clinical research capabilities, but several factors limit a significant contribution to the resolution of the enrollment problem. Reliable sites and countries quickly experience saturation beyond capacity. Some countries with large population bases suffer from a lack of sufficient healthcare infrastructure. Others ascribe to a non-Western medical philosophy. Finally, some regions have not yet resolved issues of quality.

Sponsors and CROs have been setting up studies in South Africa, Israel, Australia, and New Zealand over the past two decades. However, these countries have relatively small populations and are already inundated with clinical trials. For example, study placements in South Africa are currently declining.

Central and South America have been involved in clinical trials since a few HIV studies were successfully conducted there in the early 1990s. Today, the region endures profound financial turmoil. In addition, the quality of data conducted in the region has been questioned.

Over the last decade, countries in Central and Eastern Europe have successfully performed numerous small and medium-sized clinical trials. However, the relatively small populations of these countries limit major contributions. Poland has a sizeable citizenry of 38 million, but the other countries range from small (maximum 10 million) to very small (less than 2 million). The regulatory cost of setting up and monitoring studies in nations with a few million inhabitants presents a burden in terms of translations, language barriers for source document verification, varying regulatory systems, etc. Together, the three Baltic States, the Czech and Slovak Republics, and Hungary do not represent a greater patient extraction area than the Benelux (Belgium, the Netherlands, and Luxembourg). As a result, the number of clinical trials set up per year has reached a plateau.

Generally, attempts at developing significant clinical research capacity in India, China, and the Far East have not yet

Table 2. Percentages of FDA Audits with an OAI Outcome

Region	% Inspections with OAIs
Eastern Europe	0
Western Europe	7
Asia/Pacific	7
Africa	10
South America	>20

been successful, with the exception of a few major cities such as Hong Kong and Singapore. On the African continent, little capacity exists north of South Africa, for lack of ethical and healthcare infrastructures.

Speed and quality

Fast enrollment, by itself, would mean little if it did not generate high-quality data. So far, the quality of clinical research in Russia, the Ukraine, and the Balkans, as well as in all of Eastern Europe, has been unaffected by the speed of patient recruitment. At the DIA 2002 meeting in Chicago, an FDA delegate presented statistics on ex-US clinical inspections it had conducted; in particular, the percentages of inspections with major findings, leading to data rejection (so-called OAI, “Official Action Indicated”), on a by-region basis (see Table 2).⁷

There is a caveat about these statistics, however. The denominator, i.e., the number of inspections per region, differs greatly between regions. Whereas the FDA has conducted a few hundred inspections in Western Europe, it has inspected many fewer sites in the other listed regions. For instance, the FDA calculated Eastern European statistics based on 26 inspections, i.e., less than one-tenth in Western Europe. Nevertheless, the lack of OAIs for Eastern Europe signifies impressive data quality. Over the last 10 years, the FDA has received thousands of 1572 forms sent from this region. Most studies placed there, particularly in Russia, operate under IND regulations. National and foreign authorities are continuously inspecting clinical sites in the region. For example, in 2002 the Ukrainian Ministry of Health conducted 32 GCP inspections.

Pharmaceutical sponsors routinely audit sites in the region because it invariably contributes a large number of top-enrolling sites. Auditors from pharmaceutical companies have published statistics evidencing the high quality of clinical data from the region.⁹ Auditors from global CROs, as well as freelancers, have reported similar findings.¹⁰⁻¹¹

The tools

Russia, the Ukraine, and the Balkans represent the largest concentration of highly productive sites in the world. Harnessing this potential for faster drug development requires specialized knowledge, staff, skills, and infrastructure.

Expertise in local regulatory affairs is critical to the success of studies in the region. Russia, the Ukraine, and the Balkans have a tradition of complex bureaucracies going back some 200 years. The region accepted ICH GCP at about the same

time as the founding ICH countries adopted it. Hence, complex legislative apparatuses now exist to regulate clinical trials to the world standard. Naturally, each legislative body creates its own system for compliance. Knowledge of the systems, gained through years of experience and interaction, can greatly affect study startup timelines, compliant serious adverse event (SAE) reporting, and other key events.

Local legal expertise is necessary to establish contracts with each of the parties involved in the conduct of a clinical trial. Hospital management and investigators call for special provisions. Patient insurance brokers speak their own professional language. Drug and clinical supplies need to be imported and cleared through customs. Biological samples require export licensing. An organization with special expertise in managing the contractual obligations inherent in the clinical trial process will ensure that each element proceeds efficiently, and without interruption to the timeline.

Like everywhere in the world, it is of paramount importance to have a good rapport with opinion leaders. As a matter of culture, clinical research associates (CRAs) need a medical background to have sufficient educational leverage vis-à-vis the principal investigators. Training investigators yields stable contributors of high-quality data over time, establishes and maintains rapport, and ensures adherence to ICH GCP standards.

It takes a critical mass of dedicated people to deploy a large study quickly and then manage highly productive sites on a continuous basis. If a trial has 100 sites, each enrolling at a rate of four patients per month, sheer manpower and intense oversight is needed to maintain the necessary level of control. Monitoring will certainly be much more labor-intensive due to high patient enrollment numbers, the necessity to coach inves-

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tigators, the travel time, an abundance of source records, and very detailed clinical narratives.

A centralized drug storage facility offers a huge advantage in Russia, the Ukraine, and the Balkans. Although costly to set up and maintain, it is nevertheless indispensable for ensuring the availability of sizeable stocks, on the right side of the import barriers, with environmental controls in place (temperatures can swing from +40°C to -50°C). The ability to supply high-enrolling sites with study drug quickly, and across eleven time zones, mitigates the costs of such a system.

Finally, everyone who has ever placed studies in the region says that the most challenging issues relate to the logistics of conducting clinical trials. Indeed, this region is a paradise for problem-solvers. Those who can systematically manage the innumerable practicalities of efficiently running clinical

research in Russia, the Ukraine, and the Balkans will be able to elicit their fullest enrollment potential.

The productivity predicament facing the pharmaceutical industry can be solved by significantly increasing the speed of patient enrollment in studies on the critical path. Russia, the Ukraine, and the Balkans have the capacity to produce the CRFs needed to accelerate clinical drug development by 25%, the amount required to revive the pharmaceutical industry's R&D productivity on a global scale. Large organizations with extremely robust operational systems exist to produce CRFs in such volumes with uncompromising quality, trial after trial. This is a noble challenge for responsible investigative sites and monitoring organizations operating in the field.

References

1. J.C. Kreger, Research Analyst, William Blair & Company LLC. Session 117, CRO Market Snapshot: Analysts' Perspective. DIA 38th Annual Meeting, Chicago, July 2002.
2. J. Drews and S. Ryser, "Innovation deficit in the pharmaceutical industry," *Drug Information Journal*, 30, 97-107 (1996).
3. G. Lightfoot, E. Moench, J. Adelglass, K. Getz, F. Harwood, M. Hovde, P. Reilly. *ACRP's White Paper on Future Trends. Their impact on Sponsors, CROs and Investigative Sites*. January 1997.
4. G.D. Lightfoot, K.A. Getz, M. Hovde, S.M. Sanford, P.M. Stepp, J.R. Vogel. *ACRP's White Paper on Future Trends*. Spring 1999.
5. Z. Lin, "The number of centers in a multicenter clinical study: effects on statistical power." *Drug Information Journal*, 34, 379-386 (2000).

6. <http://www.cia.gov/cia/publications/factbook/geos/rs.html#Econ>
7. A.N. El-Hage. Session 170, International Clinical Trials: GCP Compliance and Regulatory Agency Experience in International Inspections. DIA 38th Annual Meeting, Chicago, July 2002.
8. A.N. Chashin. National Ethics Committee, Ukraine. Presentation of Current activities in the Ukraine. Forum of Ethics Review Committees in the Confederation of Independent States (FERCCIS). Conference on ethics Review Committees in the CIS. Almaty, Kazakhstan, 26-28 September, 2002.
9. S.I. Behrens, "Do ethics committees in CEE countries meet internationally recognized GCP standards and obligations?" 11-12 September, 2000. IBC Global Conferences Ltd., Budapest, Hungary.
10. P.B. Brunier and G.R. Nahler, "GCP deficiencies in clinical trials in Western and Eastern Europe," *Applied Clinical Trials*, March 1998, 46-51.
11. H. Neal, "The contract research organization perspective: audits in Central and Eastern European countries," *Drug Information Journal*, 35, 475-480 (2001).

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