Wrong Turn

An analysis of Good Clinical Practice inspections by Russian regulators sheds light on the main areas of non-compliance by investigators and local ethics committees – pointing to shortcomings in study management that are similar to problems encountered in the West

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The clinical trials market in Russia took shape as a result of the Federal Law on Drugs No. 86 in 1998, which defined the basic principles for R&D, manufacturing and distribution of pharmaceutical products – including requirements for the planning, conduct and control of trials. In the subsequent development of this legislation, the Russian Ministry of Health introduced a number of additional regulations governing issues around the drug R&D process. Particularly important was Executive Order No. 266 in 2003, which approved the rules of Good Clinical Practice (GCP).

In 2004, a subordinate agency of the Ministry of Health, Roszdravnadzor, was established to oversee various healthcare activities, including clinical research. It started to initiate checks of medical entities certified to carry out trials. Between 2005 and 2014, Roszdravnadzor performed 619 scheduled and random inspections of clinical sites across Russia. Since 2011, the results of site inspections have been published on its public internet domain.

GCP Violations

An analysis of freely available information on the results of these inspections provides useful insight. During 2011-2014, Roszdravnadzor carried out 372 checks of sponsors/CROs and clinical sites, including 316 primary inspections (scheduled and triggered by complaints of non-compliance with regulations); and 56 secondary checks on corrective and preventive actions undertaken by sites. In this time, 280 violations of national legislative requirements were found at 83 clinical sites. The average number of violations per certified research centre was 3.4.

With respect to the structure of violations, 164 findings (55.4%) were related to GCP non-compliance by investigators – the average number of violations was 2.1 per investigator – and 67 findings (22.6%) were the result of non-GCP compliance by local ethics committees (LECs). Tables 1 and 2 give further details on the observed findings, along with the relevant references to the ICH Guideline for Good Clinical Practice E6(R1) which these non-compliances relate to.

Summary of Concerns

The data provided in Table 1 demonstrates that the principal concern cited in investigators' work was inadequate maintenance of trial documents (29.3%). An improper process for obtaining informed consent forms (ICFs) ranks in second place (15.9%), and poor study drug accountability, dispensation and storage comes third (12.8%). Non-compliance with the protocol (12.2%) and unsuitable allocation of duties (12.2%) share fourth place.

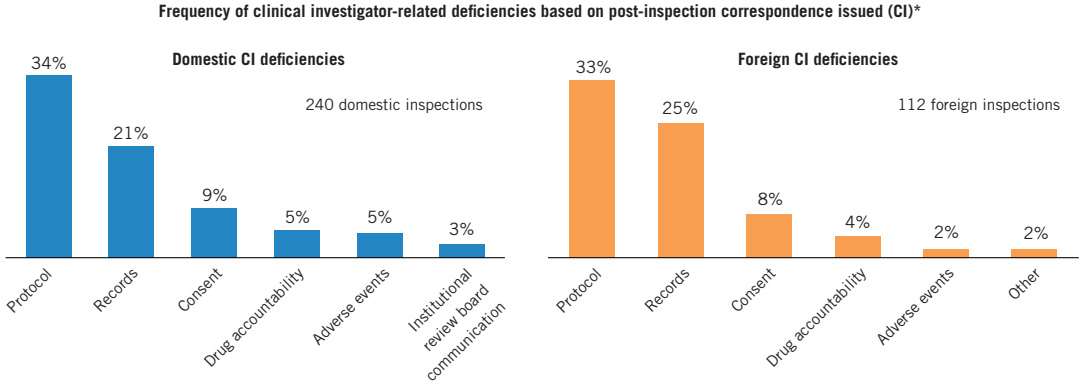
It is informative to compare the results with investigator-related deficiencies that are revealed by FDA domestic and foreign inspections (see Figure 1). This indicates that non-compliance with protocol was the most frequent GCP violation, followed by lack of maintenance of study documents, below standard processes for obtaining ICFs, and inadequate drug accountability. It appears that trends identified by inspections from both regulatory agencies are similar, except for violations related to protocol compliance.

The data in Table 2 demonstrates that the main concern with the work of LECs in Russia was the lack of documentation

Table 1: Roszdravnadzor inspections: investigator GCP non-compliance

Investigator GCP non-compliance	ICH GCP E6(R1) relevant section	Finding	
		Absolute number	%
Improper maintenance of trial documents	4.9.1, 4.9.2, 4.9.3, 4.9.4	48	29.3
Improper process for obtaining ICFs	4.8.1, 4.8.2, 4.8.8	26	15.9
Improper study drug accountability, dispensation and storage	4.6.1, 4.6.2, 4.6.3, 4.6.4, 4.6.6	21	12.8
Non-compliance with protocol	4.5.1, 4.5.2, 4.5.3, 4.5.4	20	12.2
Inadequate allocation of study-related responsibilities	4.1.5, 4.2.4	20	12.2
Improper storage of trial documents	4.9.4, 4.9.5	13	7.9
Inadequate qualification and experience of personal	4.1.1, 4.2.3	7	4.3
Trial participants' non-compliance with study requirements (non-compliance with inclusion criteria)	No matching relevant sections	4	2.4
Inadequate communication with LEC	4.4.2, 4.10.1	2	1.2
Non-compliance with randomisation procedures	4.7	1	0.6
Improper maintenance of study participants' confidentiality data	2.11	1	0.6
Non-compliance of adverse events reporting	4.11	1	0.6
Total		**164**	**100.0**

Figure 1: FDA inspections: investigator GCP non-compliance



* Based on letter issue date; inspections may have multiple deficiencies

Note: this does not denote number of inspections completed, but rather the number of inspection reports evaluated and closed in FY2013

Source: www.fda.gov/downloads/aboutFDA/centersoffices/officeofmedicalproductsandtobacco/CDER/UCM256376.pdf

of internal activities (32.9%) or non-compliance with regulations (17.9%). Substandard assessment of investigators' qualifications (14.9%) ranks third and improper maintenance of written records of LEC activities and minutes (10.4%) fourth.

Poor Governance

It should be noted that the Russian GCP regulations (approved by Executive Order No. 266) do not fully comply with ICH GCP E6(R1), and some violations could not be qualified by relevant provisions from international guidelines. Moreover, 49 violations (16.5%) related to non-compliance of clinical site administration. For example, there were 21 findings (42.8%) of an appropriate written appointment of the principal investigator and personnel to a clinical trial not being issued; and 16 findings (32.6%) where an appropriate written notification of study initiation was not sent to the Ministry of Health.

Problems in allocating responsibilities were found in 12.2% of cases (see Table 1). Furthermore, 75% of these also featured other GCP violations, such as issues with maintaining and storing documents, drug accountability, dispensation and storage, and ICF-obtaining processes, as well as non-compliance with the protocol. In breaches relating to assigning responsibilities, the average number of violations was 3.8 per investigator – almost twice as much as at inspected clinical sites that were compliant with requirements of the relevant sections of ICH GCP E6(R1). These findings indicate shortcomings in trial management by principal investigators: poor study governance, which started with a lack of adequate allocation of duties, resulted in a larger number of GCP violations.

Wider Picture

The identified trends generally correspond to the results of an analysis of 114 multicentre trials, STEPS, funded by the UK's Health Technology Assessment programme and the Medical Research Council. This research demonstrated that 45% of multicentre studies failed to reach 80% of the pre-specified sample size. Less than one third of the trials recruited their original target number of participants within the time originally specified, and around one third had to be extended in time and resources. One factor observed in trials that recruited successfully was that they were properly managed by a dedicated trial manager.

Arguably, the significance of adequate trial management at the level of clinical site will increase with the implementation of risk-based monitoring (RBM), which requires a higher level of investigator independence in study conduct and personnel duty execution.

Table 2: Roszdravnadzor inspections: LEC GCP non-compliance

LEC GCP non-compliance	ICH GCP E6(R1) relevant section	Finding	
		Absolute number	%
Inadequate standard operating procedures	3.2.2, 3.3	22	32.9
Non-compliance with charter (regulations)	No matching relevant sections	12	17.9
Inadequate assessment of investigator's qualification	3.1.3	10	14.9
Improper maintenance of written records of its activities and minutes of meetings	3.2.2, 3.4	7	10.4
Non-compliance with meeting quorum requirements	3.2.3	5	7.4
Inadequate continuing review of ongoing studies	3.1.4	4	6.0
Non-compliance with requirements for meeting participation (participation of non-members)	3.2.4	2	3.0
Inadequate review of information regarding payments to participants	3.1.8	3	4.5
Non-compliance with voting procedures (investigator vote)	3.2.1, 3.2.5	1	1.5
Inadequate composition	3.2.1	1	1.5
Total		**67**	**100.0**

Russian System

Traditionally, two types of clinical studies are defined in Russia. International multicentre trials undertaken according to a single protocol in more than one country are usually initiated by foreign sponsors, and represent part of the R&D programme for original pharmaceutical products. In general, substantial funds are put aside for these studies and appropriate monitoring is anticipated. In the second type, local registration studies are initiated by foreign and domestic pharma companies for the purposes of subsequent marketing authorisation application in Russia. Typically, sponsors of these trials prefer a cost-saving strategy for monitoring activities.

A comparison of these types of studies, in terms of quality, was carried out by looking at Roszdravnadzor's inspection results. Some 390 clinical trials were inspected between 2012 and 2014: 304 (78%) were international multicentre trials and 86 (22%) were local registration studies. GCP non-compliance was found in 40 (13.2%) of the international multicentre trials and 49 (57%) of the local registration studies.

The differences revealed were statistically significant. It turns out that investigators whose work has been thoroughly controlled by a monitor provided a higher level of GCP compliance. But, unfortunately, this data does not mean that all of these highly GCP-compliant investigators will be as good in the new monitoring environment and able to independently manage their studies in an effective way.

Practical Advice

Based on the data presented, some practical advice can be given to foreign sponsors of clinical trials based in Russia:

- Room should be made in the study budget to make it possible to provide for routine monitoring of research centres, and on-site visits should be scheduled. This will ensure an acceptable level of study conduct quality
- Sponsor/CRO employees who will be engaged in monitoring visits or on-site audits should be informed of the most frequent GCP violations
- If a scheduled planned trial in Russia does not anticipate routine monitoring visits, the sponsor may want to implement RBM so that thorough site selection procedures, including on-site visits, will be undertaken. Local offices of foreign pharma companies or local CROs should be entrusted with resolving this issue (or site selection procedures), mostly because of their better understanding of local subtleties
- When clinical sites for RBM are selected, advanced training for principal investigators should be provided. This should comprise not only study-related and GCP issues, but also basic principles of project management

Certainly, there are no established criteria by which one can determine a good trial manager at first glance. Nevertheless, there are some indicators that presuppose the presence of an appropriate level of study management at the clinical site. In particular, the principal investigator should:

- Clearly understand their present research workload and be able to predict it for the near future
- Maintain a database of subjects that could be involved in clinical studies, with profiles that correspond with the investigator's professional background
- Collaborate with referrals and patients' communities for the purposes of speedy recruitment
- Use social networks for faster recruitment and maintaining patient commitment to an ongoing trial
- Utilise computerised systems which allow scheduling of study-related diagnostic and treatment procedures, and control their execution
- Employ study coordinators that are not engaged in routine medical work
- Be well-informed about the cost of medical services needed for calculating the trial budget
- Assess regulatory risks of the scheduled trial in terms of legislative requirements for the type of investigational drug and as specified by protocol nosology

It is essential to pay close attention to a clinical site's working environment. High staff turnover and personnel dissatisfaction with remuneration for participation in trials indicate inadequate clinical site management. Separate clinical trial departments that exist within the structure of medical institutions should be seen in a positive light; these could potentially take over certain investigator activities, such as site contract negotiation, and study team preparation for external audits and regulatory inspections.

References

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