

Best friends forever: A pattern of collaboration between medical writers and biostatisticians within the Russian CRO

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Abstract

The Russian clinical trial industry and Russia's local regulatory requirements are developing rapidly. Within Russian contract research organisations, medical writers must take on non-traditional roles and, in particular, must collaborate closely with biostatisticians within their organisations. This article describes the special relationship between medical writers and biostatisticians within Russian contract research organisations and the special expertise that medical writers in Russia need to develop.

Clinical trials industry in Russia

The world is undergoing a boom in clinical trials, with annual increases between 1% and 14%.¹ Considering that the average annual growth in recent years has been 4-5%, the number of approved clinical trials may reach 30,000 by 2020 (Figure 1).

The Russian Federation is an attractive and fast-growing market for pharmaceutical products. The number of approved clinical trials could increase by 20% by 2020 to

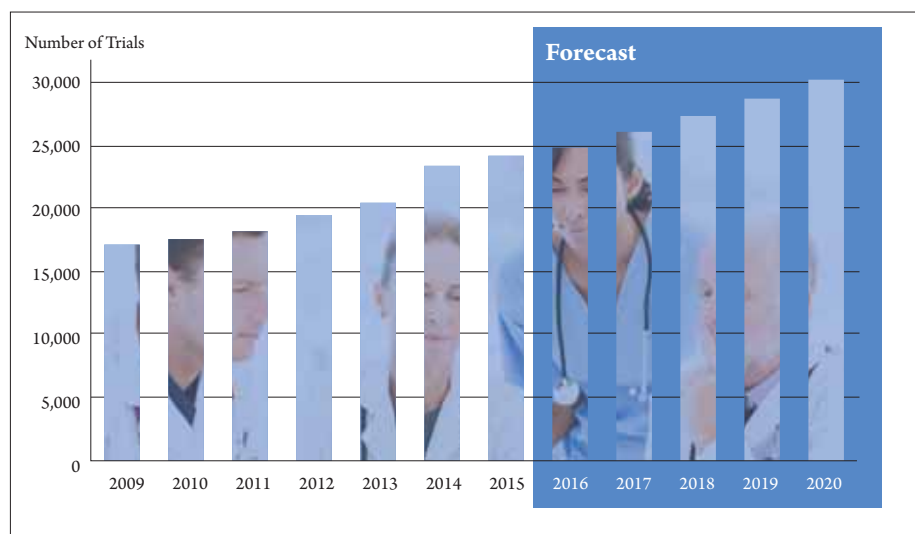


Figure 1. Number of clinical trials approved worldwide between 2009 and 2015 and forecast for 2016 to 2020. Data were from ClinicalTrials.gov.

reach 1,000 (Figure 2). The Russian government continues to invest in pharmaceutical manufacturing and drug development, with implementation of many economic measures and programmes in the last few years.

A main reason for this rapid growth in clinical trials in Russia is the 2010 Federal Law on Drug Circulation.² This law imposed new regulatory requirements on the clinical trials industry and stipulated that well-controlled, evidence-based confirmative clinical trials must be performed as part of the drug registration process in Russia. This law applied to most drug categories and included products that had already been investigated and registered in other countries. The result has been a considerable increase of so-called “local registrational” phase III studies. These now represent approximately two-thirds of all clinical trials carried out in Russia (Figure 2).

These new regulations resulted in a rapid

increase in demand for regulatory and trial-related documents and therefore the development of the medical writing industry in Russia.³ At the same time, pharmaceutical companies have lacked experience in planning and conducting clinical trials, have not been able to liaise with and obtain scientific advice from regulatory authorities, have not had enough personnel knowledgeable about study design and methodology.

Medical writers in Russia therefore need to be able to provide not only writing but also scientific advice on drug development and regulatory affairs as well as different aspects of study design and methodology. This means that medical writers must have a good understanding of basic biostatistics and statistical methodologies applied to clinical trials. This demand for high-level knowledge of biostatistics means that medical writers need to work in close

collaboration with biostatisticians, especially within the contract research organisations (CROs).

In this article, we describe the collaborative work between medical writers and biostatisticians within Russian CROs and give a brief overview of local regulatory environment in which these specialists operate.

Key regulatory documents in Russia

Federal Law #61-FZ “On circulation of medicines”, which was passed in 2010, is the main act controlling drug manufacturing, non-clinical and clinical studies, pharmacovigilance, and drug registration in Russia.¹ This regulation is still developing, and more than 10 amendments have been made to date. This law defines the essential documents required for clinical trial approval that must be submitted to the Ministry of Healthcare of the Russian Federation. These documents are assessed by the Ethics Council and the Federal State Institution Scientific Center for Expertise of Medical Products. Since 2012, the Scientific Center for Expertise of Medical Products has published a series of guidelines on different aspects of study planning and conduct, including the content and structure of study protocols and clinical study reports (CSRs), statistical principles for clinical studies, and study design and methodology for different therapeutic areas.^{4,5}

In addition to Federal Law #61-FZ, the

National Standard of the Russian Federation GOST 52379-2005 contains key guidance for the conduct of clinical trials in Russia.⁶ It stipulates that all clinical trials in Russia must be conducted according to Good Clinical Practice and includes a translation of the International Conference on Harmonisation Guideline for Good Clinical Practice.⁷ This act harmonises Russian clinical trials with the rest of the world.

Besides these documents, the Eurasian Economic Union (EAEU), which includes the Republic of Armenia, the Republic of Belarus, the Republic of Kazakhstan, the Kyrgyz Republic, and the Russian Federation, is developing legislation on pharmaceutical drug development. The EAEU member-states have agreed to establish a single pharmaceutical market and are in the process of developing unified regulatory principles and rules for drug development, approval, and marketing. The first EAEU regulations on clinical studies came into force in December 2015 and included detailed regulations for drug expertise and registration in the EAEU and Good Clinical Practice, along with requirements for the content and structure of CSRs.^{8,9}

Generally, the Russian and EAEU regulations and guidance are in harmony with the international guidelines and standards implemented by International Conference on Harmonisation, the US Food and Drug Administration, and the European Medicines Agency.

At the same time, there are some local differences that can lead to challenges and concerns at different stages of drug development. Moreover, the Russian legislation is still being developed, so to provide optimal services for clients, CROs should continue to track the changes and trends.

Medical writers and biostatisticians in the Russian CRO: collaboration towards study success

A successful clinical study is one that provides accurate, reliable, and valid data and that allows regulatory authorities to make accurate regulatory decisions about the safety and efficacy of the medicinal product. To achieve this, the multi-disciplinary team must collaborate effectively from development of the study concept to data analysis and reporting. In Russian CROs, medical writers and biostatisticians must take on non-traditional roles and collaborate closely to reach the objective of a successful clinical study.

Collaboration during study concept development

Developing the scientific concept is one of the most challenging aspects of a clinical study but is also the most important for determining its regulatory, scientific, and financial success. In the Russian CRO, medical writers and biostatisticians are responsible for ensuring that the study is in compliance with



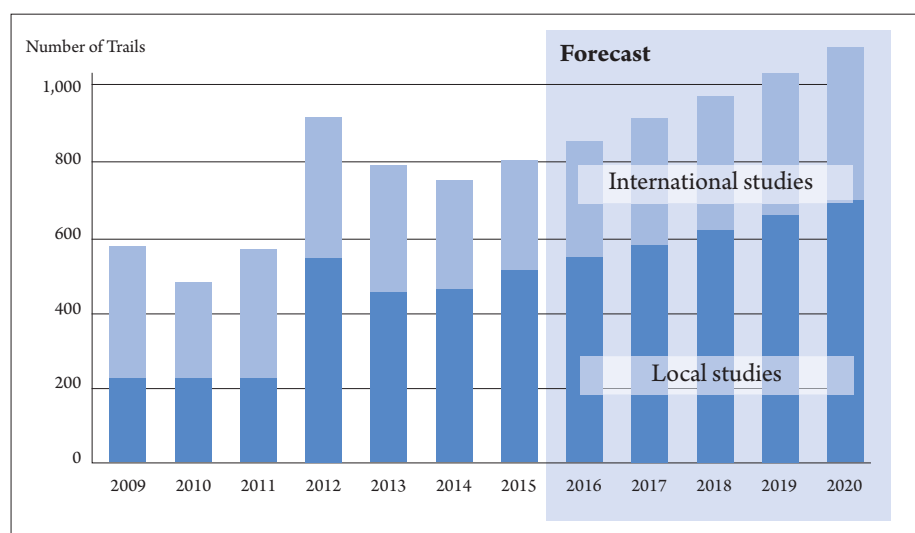


Figure 2. Number of clinical trials approved in Russia between 2009 and 2015 and forecast for 2016 to 2020. Data were from the Russian Registry of Approved Clinical Trials (<http://grls.rosminzdrav.ru/CIPermissionReg.aspx>) and the Association of Clinical Trials Organisations (<http://acto-russia.org>).

local and international regulatory requirements, applicable scientific guidelines, and trends and tendencies in the specific therapeutic area. In addition, medical writers and biostatisticians are responsible for ensuring not only that the study is feasible and time – and cost-effective but also that the results it produces are internally and externally valid. The medical writer and the biostatistician must work together to research and select the study population, the primary and secondary endpoints, and the types and time points for study assessments in the context of the requirements for the specific phase of clinical development.

As part of this, medical writers within Russian CROs need to be aware of the basic approaches and regulatory requirements for sample size calculations. To this end, Russian medical writers need to be aware that the Russian regulatory authority has been focusing much more attention on the details of study design and on the statistical aspects of the study, including assumptions used for sample size calculation. For instance, for phase III confirmatory studies, the most common concerns raised during regulatory review are the choice of primary endpoint, study hypothesis, justification of non-inferiority/equivalence margin, and clinical and statistical assumptions supporting a sample size calculation. This part of the study concept often becomes particularly challenging when developing “local registrational” phase III studies for

products that have been registered in other countries for a long time and for which clinical trial data may be limited or absent. Such cases usually require extensive literature searches and a great deal of creativity and thought to develop arguments to support the study concept and design.

Collaboration during protocol development

Once the study outline is finalised, medical writers are responsible for developing the clinical study protocol, which defines all aspects of the study and, in large measure, influences the quality of future data resulting from the study.¹⁰ The statistical part of the protocol is usually written by a biostatistician and reviewed by the medical writer to ensure that the terminology, text style, and formatting are consistent and follow the appropriate templates and style guidelines. Therefore, within Russian CROs, medical writers must be able to understand the main statistical aspects of the study to be able to provide comments and suggestions related to the statistical methods in the protocol.

After the clinical study is approved by the regulatory authority, the medical writer and the biostatistician must continue to work together to develop a statistical analysis plan, and to review of the case report form, which is usually generated by the CRO’s data management department. Medical writing review of the statistical

analysis plan is essential for planning and outlining the CSR and for avoiding late changes to statistical outputs.¹¹

Collaboration during study conduct

Medical writers and biostatisticians within the Russian CRO continue to be a part of the process after the protocol has been implemented at the clinical study sites. The medical writer and biostatistician may consult with the clinical trial team and sponsor on questions and difficulties in the practical application of the protocol during clinical research, such as a high rate of premature withdrawal loss to follow-up, difficulty in performing assessments, and problems related to data analysis or reporting. The participation of medical writers and biostatisticians in these discussions helps guarantee that decisions are made in accordance with the protocol and are aligned with needs of future statistical analysis and data reporting.

Collaboration during data review

After a clinical study is complete and database is cleaned, medical writers and biostatisticians within the Russian CRO participate in data review before database lock and before starting statistical analysis. This is an important step that should not be underestimated because it helps to ensure the data are clean and complete for the final analysis. A detailed preliminary review of raw data can save the medical writer and biostatistician time later by avoiding problems with final data analysis and interpretation. Although they collaborate, the biostatistician and medical writer have different roles during data review: the biostatistician performs statistical review checks to identify outliers and to find missing or inconsistent data, while the medical writer searches for errors and inconsistencies in coding of adverse events, medical history, and concomitant medications and looks for underreporting of clinical descriptions, which could complicate interpretation of the collected data.

The medical writer and biostatistician within Russian CROs must also take part in data review meetings during which final decisions about data issues are made in conjunction with the various stakeholders.

For phase II and III studies, the medical writer is expected to work in close collaboration with the biostatistician on issues related to the distribution of patients in data analysis sets, especially in cases requiring clinical judgement and opinion.

Collaboration during development of the CSR

The success of the CSR depends on having carried out effective reviews of the statistical analysis plan, the final raw data, and the statistical output. To allow timelines to be respected, issues and concerns related to the database and analysed data must be resolved before statistical output can be included in the core text and appendices of the CSR. Substantial time can be saved by having the medical writer review the prepared statistical output before they start writing the CSR, even if an output is considered final after the quality check procedures. This allows discrepancies, errors, and confusing results to be identified, discussed, and corrected, reducing complications and confusion during writing. Once the first draft of the integrated CSR is prepared, the medical writer and the biostatistician carefully go through the core text to ensure that the results are interpreted correctly from both a statistical and clinical perspective.

Factors of successful collaboration

Working conditions have a great influence on team effectiveness. Having the majority of employees of the medical writing and biostatistics departments work at the same office facilitates communication and allows issues to be resolved quickly so that project timelines are respected. Regular face-to-face meetings beginning from study start-up and shared training on standard operation procedures enhances understanding about project plans, milestones, and specific project requirements.

When team members work closely, professional skills and knowledge are easier to attain. Within the CRO, a collaborative learning environment can be maintained by sharing and discussing useful literature publications, conference materials, and new regulatory information.

Conclusion

Thanks to new regulations and on-going changes, the Russian pharmaceutical industry is rapidly developing. Because of these changes, medical writers and biostatisticians within Russian CROs must play non-traditional roles: in addition to their usual functions, they act as a source of expert knowledge on the scientific and regulatory aspects of study design and methodology. Close collaboration between them improves the efficiency and quality of the drug development process. This can be fostered by creating an environment of discussion, support, and shared learning.

Conflicts of Interest and Disclaimers

The opinions expressed in the article are those of the authors and do not necessarily reflect the views of their employers.

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