Compliance mechanisms available in Russia to ensure adherence to ethical guidelines

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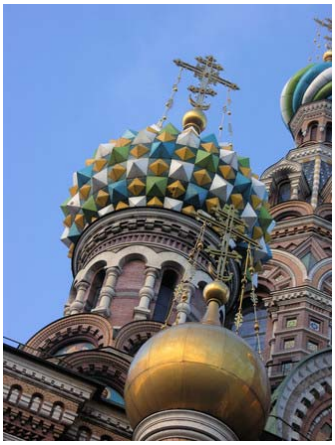
Executive Summary

The protection of trial participants in medical research rests on ethical guidelines and a functioning ethical review system. Compliance mechanisms to ensure adherence to ethical guidelines should rest upon legislative, normative, administrative, educational, social and cultural mechanisms, and should be based on well-developed monitoring/evaluation practices. A detailed review of these aspects, as available in Russia, is presented in this Report.



St Petersburg
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Legislative & normative compliance mechanisms

Modern legislative and normative resources in Russia require close collaboration between international processes in the protection of human rights in research, and the local establishment of a national legislative system in compliance with it. For this reason, Russian laws in this field identify a system of state guarantees ensuring the protection of human rights, dignity, autonomy and wholeness for biomedical research participants.

The Russian legislative system relies on the statutory provisions of the State Constitution and corresponds to the principles stated in the main international documents (*International Code of Medical Ethics* (WMA), *Declaration of Helsinki*, *Convention on Human Rights in Biomedicine* (CE), *CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects*, UNESCO Declaration on Bioethics and Human Rights, WHO and ICH *Guidelines for Good Clinical Practice*, and WHO *Operational Guidelines for Ethics Committees that review biomedical research*).

The conduct of biomedical research is regulated separately by corresponding national legislative Acts, and by international agreements signed by the State. It is important to indicate that cooperation in the field of international legislation is based not only on the passive adoption or adaptation of global principles and standards. From the beginning, collaboration functions as a "*two way street"* because of equivalent representation, and the contribution from Russia to the global process of the establishment and development of universal ethical mechanisms. On the other hand, the national ethical normative Acts accept the humanistic and moral heritage of Russian medicine, and rest on a strong historical and cultural background.

Taking into consideration the status of mechanisms to ensure that ethical guidelines are adhered to, legislation in Russia covers the whole range of medical research involving human participants, whether or not they imply any intervention. State legislative policy regarding ethical guidelines for the protection of human rights and dignity in medical research is directed towards providing conditions for safeguarding participants' health, providing appropriate medical care in line with the status quo of current science, and preventing any discrimination in the course of the research. State laws provide the general requirements for ethical evaluation, establishment of the Ethics Committee (EC) and its operation, and monitoring and evaluating ethical review practices. The list of normative Acts is available[2] on websites and is demonstrated in the specific areas of the ethical guidelines presented below.

Administrative/methodological compliance mechanisms

The establishment of ECs as responsible bodies to guarantee the protection of human rights, and the obligation to obtain the written voluntary consent of human participants in research were legalized

[2] http://acto-russia.org/; http://www.minzdravsoc.ru/find; www.grls.rosminzdrav.ru; http://www.roszdravnadzor.ru/; legislative base "Consultant plus"; www.pravo.gov.ru

by the Federal Law *Fundamental Principles of Legislation of the Russian Federation on Healthcare 158*, from 22.07.1993; upgraded N 323-FZ, 21.11.2011 and N 112-FZ, 26.04.2016.

In general, Russian legislation does not require obligatory local ethics committees (LECs) in each medical organization. According to the Federal Law *On Circulation of Medicines* N 61-FZ, 12.04.2010 (last updated 29.12.2016) it is obligatory for a planned clinical trial to be reviewed by the Council of Ethics at the Ministry of Health and Social Development (from an ethical point of view), as well as by the Federal State Institution Scientific Center for Expertise of Medical Products (from a scientific point of view). Both of these authorities present the official approval process. At the same time, according to the rules for accreditation, the establishment of a LEC at the research sites where clinical trials could be performed is a necessary part of the accreditation agenda. Usually, after receiving State approval, ethical review relies on LECs within medical organizations, or so-called 'umbrella' ethics committees, whose decisions are applied simultaneously to several clinical sites. The main function of a LEC is the ethical monitoring of clinical trials at the site.

Regarding compliance with global ethical standards, many international acts of both universal and regional character which concern ethical evaluation and the practice of ethical expertise, and play a guiding role in the process of development of ethical guidelines in Russia were originally created with the direct participation of experts from Russia. As an important step in the development of a mechanism to ensure the quality of ethical review by promoting internal quality control, monitoring, and evaluation of EC performance, the Federal Service on Surveillance in Healthcare of the Russian Federation (FSSH, Roszdravnadzor) was founded in 2004, with responsibility for the oversight of various healthcare activities comprising clinical trials.

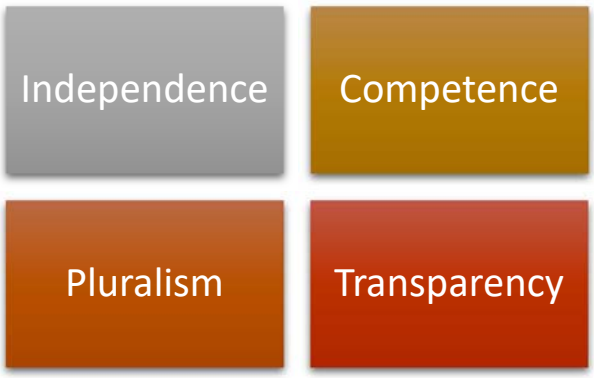
Another fruitful activity connected with the standardization of ECs' operation was the creation of *Standard Operational Procedures for Ethics Committees* (SOP). The current situation for establishing an EC and its operation includes standard requirements on the structure, membership, education and rotation of EC members; the procedure for submitting review applications, conducting the review, decision-making and communicating a decision; follow-up review of research, and the order of maintaining documentation, and archiving.

One special aspect to ensure compliance with international frameworks is that the first version of *Standard Operational Procedures for Ethics Committees* was created within the frame of the TDR/WHO project, Strategic Initiative for Developing Capacity in Ethical Review (SIDCER). Discussion, consultation and analysis of the main statements for the organization, composition, and activity of ethics committees, and progress in the methods of ethical review processes that take place in international ethical research practice were founded in the dynamic improvement of the standards and criteria for ethics committee activity. Preparation of the SOPs utilised universal definitions, norms on bioethics, international documents and guidelines. The logistic order of the description of the different procedures of the EC's performance and the different stages of the ethical review of the

study guarantee that the ethical review process is both reasonable and useful for the different partners involved in ethical review of biomedical research.

The SOPs are available in Russia as the instrument to ensure the EC fulfils its specific role, and functions according to the four basic principles of ethical review: independence, competence, pluralism, and transparency (see Figure 1). Based on these principles, an EC provides independent guidance, advice, and decisions on medical research or other specific research protocols involving human participants, with due regard for universal ethical standards, the requirements of the relevant regulatory agencies, and applicable laws and regulations (local, national, and international).

Figure 1: Four basic principles of ethical review



Educational compliance mechanisms

One essential mechanism to ensure that ethical guidelines are adhered to is high quality teaching of bioethics at the level of university curricula, reading material, and case studies that are appropriate to the country's needs. It is a logical process for the enhancement and unification of the system of bioethics education in Russia to participate in a global cooperation with UNESCO. This concept includes the comprehension and implementation of the *Ethics Education Programme* (EEP) as a target for teaching existing courses in bioethics in UNESCO member countries, with their subsequent harmonization.

In the frame of this review it is particularly important to present the special direction for setting up educational tools and programmes that integrate with national educational and healthcare frameworks and consist of ongoing education for EC members. Training possibilities for EC members are available at national, regional and institutional levels. According to the national guidelines, members of ECs should be trained and have certificates confirming their education. One example of an international contribution to the highest ethical and scientific standards in the process of such training is the development by WHO of the IEC/IRB *Recognition Program* and its implementation in Russia.

In general, according to the training programme, the education of EC members covers a few modules, which include lectures and working groups. Special attention focuses on the issues of human participant protection, conducting and following SOPs, and inspection and monitoring of the EC. The educational materials are based on universal ethical principles, and international and national guidelines on the ethical review process. The program includes questions of research methodologies and ethical issues in various types of health research; privacy and confidentiality of health information; research among vulnerable groups, and other aspects of protecting human rights in the process of independent ethical review. SOPs provide an overview of the guidelines for constituting an EC, review procedures and contributing to the implementation of good practice in ethical review, and organization of the EC's activity. A special training course includes a monitoring training workshop with a series of lectures and practical self-training for inspection and conducting actual surveys of the EC.

It is important to discuss international cooperation with the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in the training for inspectors. This cooperation includes sharing inspectional information, collaborations on numerous joint and observational inspections, participation in multi/bilateral training, and keeping each other informed of GCP-related legislation, regulatory guidance, and related documents. From Russia's side, the Federal Service on Surveillance in Healthcare (Roszdravnadzor) is responsible for this activity. The value of this collaboration was presented in the European Union's GCP "Inspectors Working Group Workshop", which took place in Paris, 17 – 19 November 2014, and was mentioned in July 2015 EMA/INS/GCP/434373/2014 in *Compliance and Inspections Annual report of the Good Clinical Practice Inspectors* Working Group 2014, which was Adopted by the GCP IWG on 5 March 2015. This collaboration has facilitated improvements in the Russian agencies' inspection coverage and decision-making processes and has contributed greatly to each agency's understanding of the other's inspection procedures.

Informational/social compliance mechanisms

One of the main universal principles of bioethics which contributes to the understanding and acceptance of medical research by society is transparency. It is important to mention here that all information concerning medical research in Russia is open by inclusion in the official databases of the Ministry of Health and its presentation on the available websites.[3] The information includes the following data: accredited sites where research could be conducted; the list of planned, ongoing and past Clinical Trials; agenda and decision of EC (national and local); the list of planned inspections, findings and results (see Figure 2). One of the points for guarantee is open information about all 1,127 accredited sites located in different Russian cities, mostly in Moscow (252), and Saint Petersburg (157). Besides availability on official websites, this information is also published in scientific articles and analysis by the Association of Clinical Trials Organizations (ACTO).[4]

[3] www.roszdravnadzor.ru, clinic@roszdravnadzor.ru
[4] http://acto-russia.org/files/ACTO

Figure 2: Publicly available information on clinical trials in Russia

Objective and open knowledge of the status of medical research in Russia unveils a whole range of opportunities for all stakeholders to receive the information, to understand it and to search for ways to improve the situation through national and international collaboration in this sphere.

A special point should be made regarding the course of education on bioethics for journalists, which has been created in Russia. [5] All these opportunities are based on adherence to universal values and ethical principles.

It is important that according to the duties of social responsibility, information concerning medical research, with full presentation of achievements as well as important problems, is now available to parliaments, governments, public institutions and corporations.

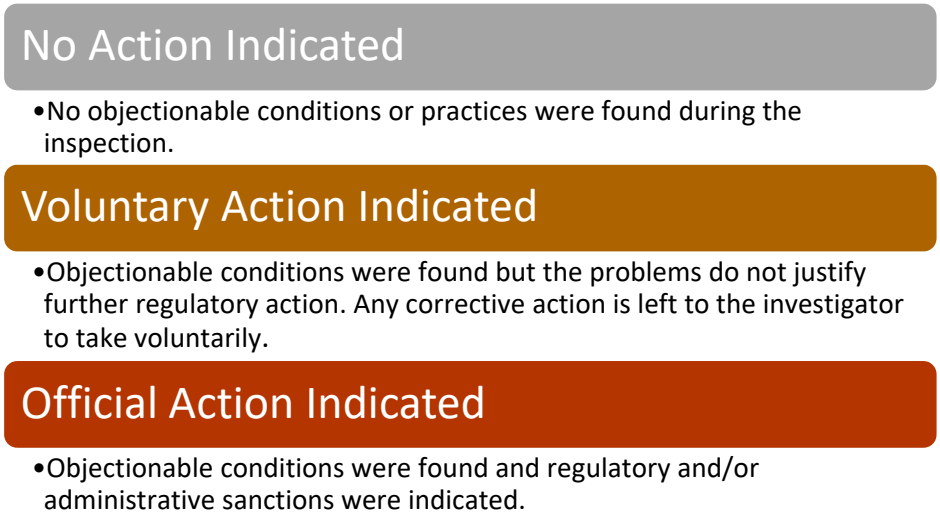
Control compliance mechanisms (audit, inspections)

In accordance with the ICH GCP standards and essential national regulations, various internal (monitoring) and independent controls (audit, inspection) take place for medical research conducted in Russia. The main purpose of an independent control system is protection from falsification, misconduct and fraud in research; to ensure that the study has been conducted in accordance with the protocol, appropriate SOPs, ICH GCP and the principles of the *Declaration of Helsinki*, and that the clinical trial data are credible. In general, the main value of an independent control system is based upon respect for human dignity, rights and freedoms; recognition of the achievements of scientific and technical progress; facilitation of equal access to scientific achievements through free flow of information, and the protection of the interests of all stakeholders in medical research, including society in general.

[5] Pavel Tishchenko & Boris Yudin Bioethics and Journalism: Moscow: Publishing House “Adamant”, 2011. – 76 pp. English translation and editing by Liza Shurik ISBN 978-5-86103-110-3 ; http://lms.iite.unesco.org/

The first international inspection was carried out by the FDA in 1995. From that time until July 2014 there have been 99 inspections of Russian trial centres in total. Following analysis of the information presented by ACTO, the results of 65 inspections were NAI (No Action Indicated. No objectionable conditions or practices were found during the inspection.). The results of 33 inspections were VAI (Voluntary Action Indicated. Objectionable conditions were found but the problems do not justify further regulatory action. Any corrective action is left to the investigator to take voluntarily.). One inspection resulted in OAI (Official Action Indicated. Objectionable conditions were found and regulatory and/or administrative sanctions by FDA were indicated.).[6]

Figure 3: Possible ACTO Inspection Results



As has been mentioned above, national inspection was established in 2004 by an agency independent from other national authorities responsible for the approval process; the Federal Service on Surveillance in Healthcare of the Russian Federation (FSSH, Roszdravnadzor). This agency is guided by the *Constitution of the Russian Federation* and essential national laws, as well as international standards, in accordance with ICH GCP and WHO GCP,[7] and uses definitions compliant with the US Food and Drug Administration *Inspection Guide: Detecting Fraud in Bioresearch Monitoring Inspections*, April 1993.[8]

According to the data from Roszdravnadzor, there were 714 inspections of accredited trial centres in 62 Russian cities between 2005 - 2015. Roszdravnadzor carries out systematic (planned) inspections, posted on its website a year in advance.[9] The reasons for these inspections are: 3 years from the last planned inspection, or from the date of the site's registration/accreditation.

[6] Detailed information is available on http://acto-russia.org/files/ACTO.

[7] http://www.who.int/medicines/areas/quality_safety/safety_efficacy/gcp1.pdf

[8] US Food and Drug Administration. Inspection Guide: Detecting Fraud in Bioresearch Monitoring Inspections. April 1993

[9] http://www.roszdravnadzor.ru

The reasons for so-called “by cause inspection” (not planned) are: the deadline for the recommendation from the last inspection; urgent information about risks/harm to the life/health of participants/citizens; or the order of the President of the Russian Federation on the basis of the request of the prosecutor's office of RF.[10]

Information on the commencement of such unplanned inspections is provided 24 hours beforehand, except for inspections based on the risk/harm to life/health of citizens. Inspections are also conducted according to the SOPs of the Federal Service on Surveillance in Healthcare, Roszdravnadzor, which define all essential actions before, during and after the inspection. 49% of routine inspections found mistakes had been made; they were connected with the activity of the LEC (25% cases), sponsors (8% cases), or sites (67% cases). As a rule inspectors find routine mistakes in Informed Consent Forms, Case Report Forms (CRFs), medical notes, and other study documentation and study procedures. Detailed information about all former, ongoing and planned inspections is updated by Roszdravnadzor quarterly on its website,[11] which contains precise information about the results of inspections of organizations conducting pre-clinical and clinical trials of medicines. The annual analysis of inspections conducted by Roszdravnadzor is made by ACTO, and is available at http://acto-russia.org/files/ACTO.

Conclusion

This Report summarised the compliance mechanisms which are available in Russia to use as tools to ensure adherence to ethical guidelines. The complex of mechanisms is based on:

- a well-developed legislative system,
- appropriate administrative procedures,
- the operation of responsible bodies according to SOPs, which follow universal principles of transparency and acceptability for society, and
- an independent monitoring agency.

Important elements of the compliance mechanisms are based on access to education and training for members of ethics committees as well as other specialists who are involved in the process of the appropriate functioning of the ethical review system (e.g. inspectors and media). The training courses are available at national and international levels.

The monitoring system to ensure compliance analyses mistakes and fraud in biomedical research, and develops mechanisms for their prevention. The role of collaboration with international organizations holding similar responsibilities has been highlighted.

[8] http://www.genproc.gov.ru
[11] clinic@roszdravnadzor.ru