Research Results in Pharmacology

Research Results in Pharmacology 10(3): 43–51
UDC: [615.038:174:061.24:34](100)
DOI 10.18413/rrpharmacology.10.496

Review Article

Ethical aspects of clinical trials in Russia and BRICS countries: An overview

Sergey Y. Simeniv[1], Alexander L. Khokhlov[2], Olga N. Soldatova[3], Nathalia V. Pyatigorskaya[1]

1 I.M. Sechenov First Moscow State Medical University of the Ministry of Healthcare of the Russian Federation (Sechenov University), 8 Trubetskaya St., Bldg 2, Moscow 119991 Russian Federation
2 Yaroslavl State Medical University, 5 Revolutionerov St., Yaroslavl 150000 Russian Federation
3 Sanatorium Buran - branch of the joint-stock company Russian Railways-Health, Trekhselishche village, Sergiev Posad district, Bldg. 50, Moscow region, 141330 Russian Federation

Corresponding author: Sergey Y. Simeniv (sergey.simeniv@gmail.com)

Academic editor: Tatyana Pokrovskaia ♦ **Received** 12 April 2024 ♦ **Accepted** 21 July 2024 ♦ **Published** 17 September 2024

Citation: Simeniv SY, Khokhlov AL, Soldatova ON, Pyatigorskaya NV, (2024) Ethical aspects of clinical trials in Russia and BRICS countries: An overview. Research Results in Pharmacology 10(3): 43–51. https://doi.org/10.18413/rrpharmacology.10.496

Abstract

Introduction: In the context of the globalization of the clinical trials market, the rapid growth in their number, the fast development of biomedical research using new technologies, and insufficient control over their conduct by state regulatory authorities and independent ethics committees, ethical aspects of conducting clinical trials and the issue of protecting patients' rights remain relevant. **The aim of the study:** To review and compare the legislative frameworks and regulations of ethical aspects of clinical trials in Russia and the BRICS countries, which possess significant scientific, industrial, and economic potential – China, India, and Brazil.

Materials and Methods: The search was conducted using PubMed, Medline, and Google Scholar databases, with descriptors including ethics in clinical trials, legislative regulation of clinical trials, and ethic committee. The selection criteria included publications from 2010 to 2024 and articles focusing on the regulation of clinical trials in Russia, China, India, and Brazil, along with their histories and evaluation forms.

Results and Discussion: In Russia, the work of Ethics Committees is based on the European model, grounded in modern international ethical norms and regulatory documents of the Russian Federation and the Eurasian Economic Union (EAEU). A drawback is the lack of structured interaction between Ethics Committees at both national and local levels. The work of Ethics Committees in China and India faces several problems, such as weak organizational structure, unjustified membership composition, low training, incompetence, weak control and management mechanisms, and flawed systems for obtaining informed consent. The Brazil's ethical and regulatory system meets global requirements and ethical standards, aimed at protecting the rights of clinical trials participants. However, in all developing countries, there remains a potential danger for clinical trial participants with a low socio-economic standard of living.

Conclusion: The experience of BRICS countries, which are intensively developing in the field of clinical trials, is interesting in terms of developing possible approaches to monitoring activities, ensuring interaction, certifying Ethics Committees, and centrally training Ethic Committee members in Russia.

Graphical abstract

Protection of the rights, health, and safety of clinical trials participants

- Legislative framework
- Regulatory authorities
- Qualified work of Ethics Committees
- Globalization of clinical trials
- Socio-economic standard of living in the developing countries

Keywords

clinical trials, developing countries, ethic committee, ethical principles, rights of participants, safety

Introduction

Ethical standards for conducting clinical trials (CTs), guaranteeing respect for all research subjects and the protection of their health and rights, such as the Nuremberg Code, the Declaration of Helsinki, and ICH GCP guidelines, are based on the tragic history of human rights violations in CTs. Precedents of human rights violations in human research have laid the foundation for modern ethical standards, which must continue to improve alongside the development of biomedical technologies and science.

Currently, the best standard for conducting CTs is Good Clinical Practice (GCP) – a standard of ethical and scientific requirements for planning, organizing, conducting, monitoring, auditing, documenting, analyzing, and presenting CT results, ensuring the reliability and accuracy of the obtained data and presented results, as well as protecting the rights, health, and confidentiality of clinical trial subjects (Kravchenko et al. 2022).

Independent ethics committees (IECs) play an important role in ensuring the protection of the rights, health, and safety of CT participants. IECs, both at the local and national levels, must evaluate the effectiveness of measures to protect the rights of CT participants and decide on the feasibility of conducting CT as well as monitor ongoing CTs. Although all IECs are guided by the same international regulatory documents, the legal status, composition, functions, and activities of IECs can differ in various countries. Russia has adopted foreign experience and chosen the European model of ethics committees (ECs), which have a public character and have advisory powers. ECs dealing with CT issues began to be established at major research centers in Moscow in the early 1990s. Sometimes, their creation was initiated by international pharmaceutical companies interested in creating conditions that complied with GCP (Gurylyova and Nezhmetdinova 2020; Komissarova 2020).

In the context of the dynamic changes in the political and economic situation in the world and the shift in the vector of international relations, the experience of legislative regulation in the field of clinical research in several countries friendly to Russia is of interest. Particularly interesting for Russia in the sphere of political and economic cooperation are the BRICS countries – an interstate association of 9 countries (Brazil, Russia, India, China, South Africa, the United Arab Emirates, Iran, Egypt, and Ethiopia). The BRICS member countries are characterized as the most rapidly developing large countries, playing a key political and economic role in extensive regions of the world and collectively possessing the largest resource potential in the world, enormous domestic markets, and labor reserves (Nekhoroshih 2016). These factors also make the BRICS countries attractive in the competitive global CT market.

The pharmaceutical industry has adopted a strategy of internationalization, wherein CTs are usually conducted simultaneously at several research centers in multiple countries. The tendency for the participation of several countries in the same study is influenced by the need to reduce costs, either by the possibility of using an infrastructure and skilled labor of relatively lower cost (especially when compared to the values practiced in European and North American countries) or by the ease and speed to recruit volunteers for the studies (Gouy et al. 2018). Ethical issues related to the internationalization of CTs must be considered, primarily due to the vulnerability of populations in developing countries.

The globalization of the market and the rapid growth in the number of CTs, including those conducted by international pharmaceutical companies, the fast development of biomedical research using new technologies, insufficient control over the conduct of CT by state regulatory authorities and IECs, potential conflicts of interest on the part of sponsors and Investigators, the planning of international CT protocols and informed consent forms without considering the ethnic and cultural differences of populations in different countries, and restrictions on access for research participants from developing countries to high-tech treatment after the end of CTs can lead to violations of participants' rights. Thus, the ethical aspects of conducting CTs and the issue of protecting patients' rights remain relevant.

The aim of this work is to review and compare the legislative frameworks and regulations of ethical aspects of conducting CTs in Russia and BRICS countries, which have significant scientific, industrial, and economic potential – China, India, and Brazil.

Materials and Methods

The search was carried out using PubMed, Medline, and Google Scholar databases, with descriptors including ethics in research, CT, legislative regulation of CT, and EC. The selection criteria included publications from 2010 to 2024 and articles focusing on the regulation of CTs in Russia, China, India, and Brazil, along with their histories and evaluation forms.

Results

The Russian Federation

In Russia, with the aim of integrating into the international pharmaceutical market, current legislation in the field of CT and research quality has been aligned with the rules of the most authoritative international and national regulatory agencies, such as European Medicines Agency and U.S. Food and Drug Administration. In 1998, OST 42-511-99 "Rules for Conducting Quality Clinical Trials in the Russian Federation" was adopted, based on ICH GCP. In 2005, an adapted version of ICH GCP was adopted in Russia as the national standard GOST R52379-2005 "Good Clinical Practice". To establish uniform GCP rules with the countries of the European Union, the USA, and Japan for the member states of the EAEU (Armenia, Belarus, Kazakhstan, Kyrgyzstan, Russia), the EAEU GCP Rules https://docs.eaeunion.org/docs/en-us/01411924/cncd_21112016_79 were developed in 2014-2016, which are maximally harmonized with ICH GCP, facilitating the functioning of the common drug market within the EAEU, and the recognition of CTs data by the authorized bodies of the EAEU member states and at the international level (Hasanova and Iskhakov 2016; Alikov and Marchenko 2018).

The work of IECs at both the federal and local levels in Russia is based on ethical principles outlined in the current Russian legislation and the key international and domestic regulatory documents governing biomedical research involving humans, as well as IEC's own established standard operating procedures (SOPs). The federal-level IEC (Ethics Council under the Ministry of Health of the Russian Federation) organizes and conducts the ethical review of the possibility of conducting CTs of drugs for medical use to issue a conclusion on the ethical justification for conducting CTs, while local ethics committees at medical institutions and research centers further monitor the studies approved by the Ministry of Health of the Russian Federation in the supervised territory. However, to date, there is no legislative regulation of the interaction between IECs either vertically or horizontally in Russia. Similarly, there is no scheme for their interaction with each other. In case of detecting research ethics violations, a local ethics committee can report this to the Ministry of Health, affecting the possibility of registering the investigational drug, but such information is not requested, and the procedure for its submission has not been developed. Similarly, there is no scheme for interaction between ECs: if approval is not obtained from one Local ethic committee, it is possible to turn to another in the hope of lower ethical review standards, lower qualifications, or less attentiveness of the experts (Gurylyova and Nezhmetdinova 2020; Komissarova 2020).

The People's Republic of China

High-profile cases in the ethical aspects of clinical trials, such as the "golden rice" study (a study of genetically modified rice on children aged 6-8 years without obtaining informed parental consent) (Qiu 2012), the "HEAVEN" study (transplantation of a donor's head into a recipient's body) (Suskin and Giordano 2018), a study of germline genome editing in human embryos for clinical use (Li et al. 2019), and the "cancer treatment with malaria microbes" in 2012-2019, revealed insufficient protection of CT participants in China (Li et al. 2019). With the quick development of human research and a large number of international CTs for drugs and medical devices in China, the laws and regulations related to human participant protection are constantly improving, yet the protection of participants during ethics review and supervision needs to keep pace with this development. Therefore, China is a typical example of a developing country that urgently needs to establish a Human Research Protection Program, which could serve as a model for other developing countries (Zhou and Liu 2021). Current policies and regulations in China cannot keep up with the rapid development of biomedical human research and their varied contexts (Lei et al. 2019). The use of new technologies has not only provided different tools for human research but has also highlighted higher requirements and challenges for the protection of human participants (Zhou and Liu 2021).

Legal protection of clinical trial subjects is stated in

national laws of China. Article 26 in the Law of the People's Republic of China on Medical Practitioners (implemented on January 5, 1999) provides that physicians should obtain the approval of hospitals and the consent of patients themselves or their family members for experimental treatments. Article 29 in the Law of the People's Republic of China on Progress of Science and Technology (implemented on January 7, 2008) provides that the state should prohibit scientific research and technological development that undermine national security, harm public interests, endanger human health, or violate moral principles and ethics. In China, no specific laws on the protection of human subjects have been legislated. Enforcement agencies at all levels have laid down general or specific rules and regulations, establishing a roughly complete legal system dominated by administrative rules and normative legal documents for the protection of clinical trial subjects in China. Since China has not yet enacted independent legislation for the legal rights of subjects, ethical review censorship is generally believed to safeguard clinical subjects' rights. The ethical committee ensures the safety and interests of subjects from an ethical perspective (Ren et al. 2018).

The effectiveness of ethical review directly impacts the scientific, authentic, accurate, and reliable nature of CTs, making effective supervision essential. However, current supervision is unsatisfactory, with many issues in ethics committee review, including loose organizational structures, unreasonable personnel compositions, inadequate training, incompetence, non-standard member recruitment, weak supervision and management mechanisms, and unqualified informed consent systems. Therefore, an independent supervision system should be established to ensure the efficiency of ethics committees, along with ethical review project records for tracking and management (Ren et al. 2018).

Informed consent is critical in safeguarding the rights of clinical trial subjects, and a well-prepared informed consent form is essential for ethics committees to improve protocol review quality. Clear and accessible wording is crucial for potential participants to understand. Meanwhile, China has not fully established a damage insurance system, leaving CT participants in need of strong legal guarantees and social support. Participants often face difficulties providing evidence in legal proceedings when they suffer physical damage. Legally, informed consent does not exempt sponsors and researchers from liability. Compensation scope is determined by personal damage criteria based on civil law and regulations, with appropriate compensation for mental damage also considered (Ren et al. 2018). According to Ren et al. (2018), legal protection of human subjects' rights in China remains unsatisfactory, necessitating the improvement of existing general laws and special regulations, and the enactment of specific laws to protect human subjects' rights.

The Drug Supervising and Regulatory Department of China has formally joined the International Council for Harmonization (ICH) of Technical Requirements for Pharmaceuticals for Human Use, and has become a member of the ICH council. ICH-GCP, known as E6 in the Efficacy E Series of ICH, is the international standard for ethical integrity and scientific quality for conducting trials involving the participation of human subjects. An updated framework, GCP-2020 was officially published in April 2020 by the Chinese National Medical Products Administration (NMPA) and the National Health Committee (NHC). https://www.nmpa.gov.cn/xxgk/ggtg/qtggtg/20200426162401243.html. However, due to rapid developments in drug research and a consolidation of system reforms in drug examination and approval, a disparity between the GCP-2003 framework and more recent international codes now exists. Amongst other things, disparity in safety report management in drug clinical trials is essential to the comprehensive and objective evaluation of a trial drug (Yang et al. 2021).

Recently, the quality of clinical trials conducted in China has made considerable progress, partly due to major reforms in 2016 by the China Food and Drug Administration to modernize its regulatory processes by decreasing the review and approval times, encouraging innovative medical product development, and promoting international standards (Chen and Zhao 2018). However, some authors believe that CTs in China still fall below the global average standard. A systematic review by Fan et al. (2022) analyzed 90 studies published between 2000 and 2021 in 58 Chinese and foreign journals. Problems were identified in the registration process (7 CTs), ethical review (14 CTs), conducting clinical trials (54 CTs), and submitted reports (19 CTs). Major violations associated with the operation of ECs in China included unreasonable member composition, incomplete reviews, non-standard records, inadequate consideration of ethical issues, and neglecting follow-up reviews and ethical acceptance checks (Fan et al. 2022).

The Republic of India

India has become an emerging hub for CTs due to the abundance of patients, a heterogeneous genetic population, availability of trained human resources, and low expenditure, along with various facilities provided by the Government of India (Das and Sil 2017; Tanushya 2022). Since 2004, the number of new trials has increased at a 31% compound annual growth rate, and the clinical trials market has grown by 30%, almost double the global average (Das and Sil 2017). However, concerns have been raised about the ethical implications of the globalization of clinical research in developing countries, exacerbated by incidents of rule and ethical violations in international CTs (Glickman et al. 2009; Tanushya 2022). Notable cases of ethical violations include the cervical cancer screening trial conducted in 1998, which involved randomized clinical trials of cervical screening on Indian women in Mumbai, Tamil Nadu, and Osmanabad by a U.S.-based company and foundation. Among the 138,624 unscreened women, 254 died as a result of the clinical trials. Those women were not adequately informed about the experiment or whether they were in the screened or unscreened group. It was also found out that women from the lower socio-economic strata were not screened, which led to the question of whether it was ethical to deprive women of screening, which was available, merely based on their socio-economic status (Bagcchi 2013; Tanushya 2022). The clinical trials on 1984 Bhopal Gas Tragedy victims, beginning in 2004, also stirred controversies due to violations of the international ethical principles, putting vulnerable and already ill patients at more risk (Tanushya 2022). The HPV vaccine trials in 2009-2010 involved 24,000 girls aged 10-14 in Andhra Pradesh and Gujarat receiving vaccines provided by GlaxoSmithKline (United Kingdom). The girls experienced side effects, and seven died, with many cases lacking informed parental consent

(Mudur 2013; Tanushya 2022). The resulting public outcry led to a Public Interest Litigation filed at the Supreme Court against multiple entities, highlighting that over 150,000 people were involved in at least 1,600 clinical trials from 2006-2011, with at least 2,163 deaths reported (Tanushya 2022).

In 2013, the Supreme Court criticized the government, the Ministry of Health and Family Welfare, and the Central Drugs Standard Control Organization (CDSCO), suspending clinical trial approvals and mandating videotaped consent from participants. This led to prolonged approval timelines and a significant drop in clinical trials conducted in India, from 529 approved trials in 2010 to 83 in 2016 (Bagcchi 2013; Tanushya 2022). Major violations detected during site inspections included data credibility issues, inadequate records, failure to follow the investigational plan, and failure to notify the Institutional Ethics Committee of changes or submit progress reports. There were also concerns over areas of subject protection, namely, consent, Institutional Ethics Committee approval, and reporting of adverse drug reactions (Das and Sil 2017).

The work of ECs in India is regulated by various documents. The Indian Council of Medical Research (ICMR) first released a policy statement on ethical considerations in human subject research in 1980, revised in 2000 and amended in 2006. The ethical guidelines are given legal status by Schedule Y of the Drugs and Cosmetics Rules, 1945 (Bhatt 2012).

It was revealed that an approval letter of Institutional Ethics Committees has deficiencies in various aspects, including composition, quorum, and review of insurance and clinical trial agreement. This highlights the gaps in education and training of Institutional Ethics Committees members. With reports of Institutional Ethics Committee malfunction pouring in the media, CDSCO has taken stern steps in streamlining the Institutional Ethics Committee functioning. The Schedule Y is amended by inserting a rule 122DD which specifies the detail procedures for the registration of ethics committee. As per rule 122DD, all ethics committees have to be registered with Drug Controller General of India (DCGI) without which they cannot approve of any clinical trial protocol and has come into effect from February 25, 2013. For the purpose of registration, application has to be sent by the ethics committee to CDSCO as per the requirement specified in Appendix VIII of Schedule Y [Annexure I] along with a checklist available from CDSCO website. The Institutional Ethics Committee must have a minimum of seven members and appoint a Chairman (from outside the institution) and a member secretary from among its members. Registered committees must have at least seven members, including diverse representatives such as medical scientists, doctors, legal experts, social scientists, philosophers, and laypersons. If an institution specializes in certain areas of research, it is desirable to include representatives of specific patient groups on the EC (eg. HIV-AIDS, genetic diseases, etc.). If necessary, experts in the field may be invited to provide their opinions without the right to vote. The EC must have appropriate gender and age representation. As per Indian GCP, ICMR guidelines and Annex Y, the work of Institutional Ethics Committee shall be conducted through formal meetings and shall not resort to decision making by circulating proposals or emails. The Institutional Ethics Committee should meet at regular intervals and the decision period should not be >3-6 months, which should be specified in the SOP. Proper records of all meetings and decisions taken must be kept. The Institutional Ethics Committee is tasked with not only reviewing proposals, but also reviewing ongoing clinical trials by reviewing periodic progress reports, monitoring and writing internal audit reports, and/or conducting independent site visits to study sites. In the event of trial-related injury or death of a clinical trial subject, the Institutional Ethics Committee must also consider and recommend compensation to the sponsor within a specified period of time. A clinical trial can only be started after a written approval has been obtained from the Institutional Ethics Committee. Any amendments to the approved study documents require new Institutional Ethics Committee approval. To comply with the regulatory framework in India, the Institutional Ethics Committee must have records and access to written SOPs on the work of the committee as a whole, on vulnerable populations, regarding the training of new and existing members, and monitoring and preventing conflicts of interest; details of any previous EC audit or inspection. The licensing authority (CDSCO) upon satisfaction of the requirements grants registration for a period of 3 years from the date of issue, after which the Institutional Ethics Committee must apply for re-registration within 3 months from the date of expiry. For re-registration, it has become mandatory for each Institutional Ethics Committee member to have a GCP certificate and information about the monitoring of the ongoing study. By registering with CDSCO, the I Institutional Ethics Committee undertakes to protect the rights, safety and welfare of research participants by reviewing and approving clinical trials in accordance with Appendix Y and GCP, and to conduct an ongoing review of clinical trials at appropriate intervals. In the event of any serious adverse event, the Institutional Ethics Committee is required to review it and provide its opinion in accordance with the procedures specified in Section XII of Annex Y. The IEC is required to maintain adequate and accurate records and retain them for a period of at least 5 years from the date of completion or termination of the study (both in hard and soft forms). Authorized inspectors or CDSCO officials may inspect any Institutional Ethics Committee records, data or documents relating to the clinical trial and provide adequate responses to any inquiry regarding the conduct of the clinical trial (Bhatt 2012; Das and Sil 2017; Singh et al. 2019).

On March 19, 2019, the New Drugs and Clinical Trials Rules 2019 https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=OTg4OA== were passed by the Government of India. These rules regulate new drugs, clinical trials, new investigational drugs, bioavailability and bioequivalence studies, and ECs. The rules mandate timely reviews of ethical aspects, informed consent of participants, and the need for permissions from the Central Licensing Authority for manufacturing or importing new drugs. Applications for conducting clinical trials must also be submitted to the Central Licensing Authority. The 2019 Rules include provisions for compensation to participants for injuries or other harm caused during trials. These rules aim to expedite trial approvals and the introduction of new drugs, with specific timelines for approvals: 30 days for drugs manufactured in India and 90 days for drugs developed

outside India (Tanushya 2022).

Despite regulatory efforts, India lacks codified laws specifically protecting CT participants' rights. Apart from the 2013 Supreme Court mandate for videotaped consent, there have been no concrete measures to ensure these rights (Tanushya 2022). The traditional social structure, the hierarchical caste system (Anikeeva 2020), leaves lower castes and those with low living standards and education particularly vulnerable. These populations often participate in trials for monetary rewards without understanding the risks or their rights (Tanushya 2022).

Informed consent is crucial for ethical clinical trials, involving clear communication of all essential details to potential participants. However, consent forms are often complex, and a study revealed that even medical students struggled to remember the key details from consent forms (Kamath et al. 2014; Tanushya 2022). The language barrier further complicates comprehension, as various dialects are used across India, making it difficult for participants to understand the consent forms. Ensuring participants understand their right to withdraw, maintain privacy, and know how to file complaints is essential (Tanushya 2022).

The Federative Republic of Brazil

Brazil, the largest country in Latin America both in area (8.5 million square kilometers) and population (about 200 million people), has a powerful, rapidly growing economy. Brazil has become one of the three most dominant emerging countries, along with India and Russia, attracting the highest number of international biopharmaceutical companies outsourcing CTs. Advantages include a large, fast-growing, mainly treatment-naïve and diverse patient population, lower costs, and geographic proximity to Western biopharmaceutical companies. Improved ICH-GCP compliance and shortened approval times have also contributed to growth in Brazil's clinical research sector (Virk 2010; Ukwu et al. 2011). The ethnic and racial diversity of the Brazilian population has increased pressures on the CT industry to ensure patient diversity, recognizing that therapeutic effectiveness and toxicity may vary significantly among racial/ethnic groups (Burroughs et al. 2002). Furthermore, due to the fact that the Hispanic population, currently the largest ethnic minority in the US, is significantly under-represented in US clinical trials, the US FDA has encouraged growth of clinical research in Latin American countries such as Brazil (Virk 2010).

Brazil's ethical and regulatory system complies with global and national requirements, following modern ethical standards and technologies. The Federal Regulatory Agency ANVISA (Agência Nacional de Vigilância Sanitária – National Health Surveillance Agency) is included in the list of members of the ICH, indicating international recognition of the agency's and the country's technical capacity. ANVISA, created by Law No. 9,782 of January 26, 1999, evaluates the technical and medical aspects of CTs, issues permits for the import of materials and medicinal products for trials, and operates with administrative and financial autonomy (Gouy et al. 2018).

The assessment of ethical aspects of clinical research in Brazil is the responsibility of the Comitês de Ética em Pesquisa (CEP) (Research Ethics Committees) and the Comissão Nacional de Ética em Pesquisa (CONEP) (National Commission for Research Ethics), collectively known as the CEP/CONEP System. Regulation began with Resolution 1 of June 13, 1988, creating ECs to issue opinions on research ethics. This was replaced by Resolution CNS 196 of October 10, 1996, which standardized an ethical assessment system, including regional CEPs and the federal body CONEP. This resolution was further updated by Resolution CNS 466 of December 12, 2012, aimed at consolidating the CEP/CONEP System through decentralized cooperation to protect research participants in Brazil. CONEP, responsible for ethical and normative aspects, coordinates and supervises the CEPs, accredits and registers these committees, and requires semi-annual reports from CEPs on approved projects. The entire communication process and document submission for ethical appraisal is done via "Plataforma Brasil", an online platform ensuring agility and transparency. Some projects, after CEP approval, must also be appraised by CONEP, depending on the thematic area, such as genetic material sent abroad, changes in the genetic structure of human cells for in vivo use, research on human reproduction genetics, irreversible dissociation of data, manipulation of gametes, pre-embryos, embryos, and fetuses, fetal medicine with invasive procedures, new therapeutic equipment, new invasive therapeutic procedures, studies with indigenous populations, and research involving genetically modified organisms or high collective risk (Gouy et al. 2018).

The RDC 219/2004 required an approval document, known as a "comunicado especial" (special communiqué - CE) for each participating center in multicenter clinical trials. This format allowed for thorough assessments but increased the period for obtaining CE. This was repealed by RDC 39 of June 5, 2008, which established a single CE for each study, allowing evaluations by ANVISA based on the ethical approval from the coordinating center's CEP (Gouy et al. 2018).

The RDC 36 of June 27, 2012 was published complementarily to the RDC Anvisa 39/2008. In general, this resolution allowed the simplified analysis of studies that had already begun to include patients in another country or been analysed and approved by another regulatory agency, including FDA, EMA, the PMDA of Japan, or the Health Canada. In addition, the submission of clinical trials to databases of the Registro Brasileiro de Ensaios Clínicos (Brazilian Registry of Clinical Trials - ReBEC) was started. Studies that had been registered prior to the validity of the resolution on the primary registries of the International Clinical Trials Registry Platform (ICTRP) of the World Health Organisation (WHO) https://www.who.int/clinical-trials-registry-platform/network/primary-registries would also be accepted. ReBEC is publicly owned and managed by the Fundação Oswaldo Cruz - Fiocruz (Oswaldo Cruz Foundation), the leading Brazilian governmental research organization operating on a non-profit basis and composing the ICTRP/WHO network as primary registry. For this reason, registration with ReBEC meets the requirements of the International Committee of Medical Journal Editors (ICMJE) (Gouy et al. 2018).

RDC 9, published on February 20, 2015, revoked RDC 39/2008 and RDC 36/2012, significantly altering ANVISA's analysis of CTs in Brazil. The Dossiê de Desenvolvimento Clínico do Medicamento (DDCM) (Clinical Drug Development Dossier) includes all CTs carried out in the country for the registration of a

Table 1. Number of clinical studies in the BRICS countries (Gomes et al. 2012)

Country	Number of studies, n		Number of studies, %		Compound annual growth rate, %
	2001	2011	2001	2011	
China	14	354	26	34	38
India	9	158	17	15	33
Russia	5	263	9	25	49
RIC†	28	775	53	74	39
Brazil	25	269	47	26	27
BRICS‡	53	1044	100	100	35

Note: † RIC – Russia, India, China; ‡ BRICS – Brazil, Russia, India, China

pharmaceutical drug, except bioequivalence and bioavailability studies. This framework reduced the regulatory deadline for evaluation by approximately five months, without compromising the quality of the technical evaluation. Any documentation for analysis in Brazilian ethics and regulatory proceedings must be submitted in Portuguese and, in the case of studies with a country of origin outside Brazil, the time for a quality translation should be taken into account at the time of the planning study in the national territory (Gouy et al. 2018).

Brazil's stringent regulations restrict placebo-controlled trials, prohibiting trials where placebo is the sole treatment if an approved treatment exists as a comparator, unless justified by usual care standards (Ukwu et al. 2011).

Access to experimental drugs is a possible benefit; however, in some cases, sponsors do not ensure access to treatment at the end of the study for participants who benefited. Resolution 466/2012 ensures all participants have free access to effective prophylactic, diagnostic, and therapeutic methods indefinitely after a study (da Silva et al. 2016). The Brazilian government has also implemented programs, one of which involves increased reimbursement and free drug coverage for patients in the public healthcare sector. Brazil was the first developing country to provide free and universal treatment to HIV-infected people, when the Brazilian Ministry of Health guaranteed free access to anti-retroviral drugs for people infected with HIV. In 1999, the Brazilian government established a legal basis for generic drugs in Brazil. This has led to an increase in the number of bioequivalence studies, or clinical studies used to demonstrate the therapeutic equivalence of generic drugs (Virk 2010).

Despite these efforts, the globalization of CTs poses threats to participants' safety and rights due to Brazil's significant social inequalities. According to 2004 statistics, Brazil has a 63.4% degree of income inequality, with vast differences in lifestyle and education among populations, and many have limited access to medical care. Brazil's illiteracy rate means that about 10% of the population aged 15 and older are still illiterate, with higher rates in certain regions and racial/ethnic groups. Many lower-income patients participate in trials primarily for access to treatment, posing ethical challenges (Virk 2010).

Discussion

Over ten years (2001-2011), the number of CTs conducted in the BRICS countries increased almost 20 times from 53 to 1,044, with the CTs market in Russia characterized by the highest compound annual growth rate among the countries considered (Table 1) (Gomes et al. 2012).

The advantages of globalization are to bring resources to developing countries to standardize conduction of clinical research, the training of researchers in the requirements necessary to conduct research in accordance with GCP, which is consistent with good professional ethics. Governments of many developing countries have recognized the interest in global CTs and have taken steps to attract investment, reduce bureaucracy, and improve their regulatory systems (da Silva al. 2016). In China, for example, the centralization of the regulatory authority has helped reduce conflicting regulations between central and local authorities and has led to shorter approval times for CTs (Chen and Zhao 2018). However, the economic benefits resulting from globalization have been overly emphasized to the detriment of the ethical aspects of conducting CTs. Thus, several serious violations of ethical principles in conducting CTs have occurred in India and China, as mentioned above.

All CTs should consider the epidemiology of diseases, access to medical resources, the health status of the country's population, and bring benefits to the community. Access to experimental drugs is a potential advantage; however, sometimes patients were not provided with access to treatment after the end of the CT. This is a serious problem, as providing treatment at the end of the study to those participants who benefited from the drug should be standard practice. In Brazil, Resolution 466/2012 ensures that all participants, at the end of the study, shall have free access, for an indefinite period, to the best prophylactic, diagnostic and therapeutic methods shown to be efficacious (da Silva et al. 2016).

Conclusion

In the regulatory frameworks for ethical aspects of clinical trials in the BRICS countries described above, similar problems were observed: underqualified and incompetent work of IECs, data concealment, and violations of the rights of study participants. Currently, Russia and Brazil have developed the most progressive and organized requirements for ethical review, respecting the rights of trial participants and the work of IECs. The development of biomedical technologies and the presence of socially vulnerable populations with low living standards require a more careful legislative approach to regulating the rights of study participants. The experience of the BRICS countries, which are intensively developing in this area, is valuable for developing possible

approaches to monitoring activities, organizing and ensuring interaction among ECs from local to national levels, and certifying and centrally training EC members in Russia.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Funding

No funds were received in support of this work.

Data availability

All of the data that support the findings of this study are available in the main text.

References

- Alikov AV, Marchenko SD (2018) Normativnaya baza provedeniya klinicheskih issledovanij v mire i v Rossii [Regulatory framework for conducting clinical trials in the world and Russia]. Farmaciya [Pharmacy]. 67(8): 3-8. https://doi.org/10.29296/25419218-2018-08-01 [in Russian]
- Anikeeva EN (2020) Cultural Anthropology, Cast Hierarchy and Religious Values in Modern India. 4th International Conference on Culture, Education and Economic Development of Modern Society. 2020 (ICCESE 2020), March 2020. Atlantis-Press, 416: 493–496. https://doi.org/10.2991/assehr.k.200316.109
- Bagcchi S (2013) Indian Supreme Court halts approval of new clinical trials until regulatory framework is set up. British Medical Journal News 347: f5996. https://doi.org/10.1136/bmj.f5996 [PubMed]
- Bhatt A (2012) Indian clinical trials: Paradigm shift from speed to quality? Perspectives in Clinical Research 3: 1–3. https://doi.org/4103/2229-3485.92299 [PubMed] [PMC]
- Bhatt A (2017) International Council for Harmonisation E6(R2) addendum: challenges of implementation. Perspectives in Clinical Research 8(4): 162–166. https://doi.org/10.4103/picr.PICR_124_17 [PubMed] [PMC]
- Burroughs VJ, Randall WM, Richard AL (2002) Racial and ethnic differences in response to medicines: towards individualized pharmaceutical treatment. Journal of the National Medical Association 94(10): 1–26. [PubMed] [PMC]
- China National Medical Products Administration, National Health Committee. Notice on the publication of Good Clinical Practice (no. 57 of 2020) [EB/OL]. April 23, 2020. https://www.nmpa.gov.cn/xxgk/ggtg/qtggtg/20200426162401243.html [accessed on 23.05.2024]
- Chen J, Zhao N (2018) Recent advances in drug development and regulatory science in China. Therapeutic Innovation & Regulatory Science 52: 739–750. https://doi.org/10.1177/2168479018764661 [PubMed]
- da Silva RE, Amato AA, Guilhem DB, Novaes M (2016) Globalization of clinical trials: Ethical and regulatory implications. International Journal of Clinical Trials 3(1): 1–8. https://doi.org/10.18203/2349-3259.ijct20160472
- Das NK, Sil A (2017) Evolution of ethics in clinical research and ethics committee. Indian Journal of Dermatology 62(4): 373–379. https://doi.org/10.4103/ijd.IJD_271_17 [PubMed] [PMC]
- Fan J, Liu X, Li Y, Xia H, Yang R, Li J, Zhang Y (2022) Quality problems of clinical trials in China: Evidence from quality related studies. Trials 23: 343. https://doi.org/10.1186/s13063-022-06281-1 [PubMed] [PMC]
- Glickman SW, McHutchison JG, Peterson ED, Cairns CB, Harrington RA, Califf RM, Schulman KA (2009) Ethical and scientific implications of the globalization of clinical research. The New England Journal of Medicine 360: 816–823. https://doi.org/10.1056/NEJMsb0803929 [PubMed]
- Gomes RDP, Pimentel VP, Landim AB, Pieroni JP (2012) Ensaios clínicos no Brasil: competitividade internacional e desafios. In: BNDES Setorial. Rio de Janeiro, September 2012. Banco Nacional de Desenvolvimento Econômico e Social 36: 45–84. http://web.bndes.gov.br/bib/jspui/handle/1408/1504 [in Spanish]
- Gouy CML, Porto TF, Penido C (2018) Evaluation of clinical trials in Brazil: History and current events. Revista Bioética 26(3): 350–359. https://doi.org/10.1590/1983-80422018263254 [in Spanish]
- Gurylyova ME, Nezhmetdinova FT (2011) Introduction of ethical standards in practice of clinical researches in the Russian Federation through system of ethical committees (summary). Medical Anthropology and Bioethics [Meditsinskaya Antropologiya i Bioetika] 2(2): 11. [in Russian]
- Hasanova GM, Iskhakov ER (2016) Legal regulation of clinical trial and its problems. Bulletin of Ufa Law Institute [Vestnik Ufimskogo Yuridicheskogo Instituta MVD Rossii] 3(73): 22–26. [in Russian]
- International Clinical Trials Registry Platform (ICTRP) of the World Health Organisation (WHO) https://www.who.int/clinical-trials-registry-platform/network/primary-registries [accessed on 25.05.2024].
- Kamath A, Up R, Shenoy K (2014) Willingness to participate in a clinical trial and understanding of informed consent information among medical students. Indian Journal of Medical Ethics 11: 16–18. https://doi.org/10.20529/IJME.2014.005 [PubMed]
- Komissarova VA (2020). Obzor sistem natsional'nykh eticheskikh komitetov v stranakh zarubezh'ya i Rossii [Review of the systems of national ethics committees in foreign ccountries and Russia]. Medicinskaya etika [Medical Ethics]. 1: 65-71. https://elibrary.ru/download/elibrary_42564929_55035378.pdf [in Russian]
- Kravchenko DV, Bronskaya KV, Mazak IG, Kravchenko SS, Novik DK (2022) Conduction of clinical investigations: historic aspects and current state. Medical and Biological Problems of Life Activity [Mediko-Biologicheskie Problemy Zhiznedeyatel'nosti] 1: 23–30. [in Russian]
- Lei R, Zhai X, Zhu W, Qiu R (2019) Reboot ethics governance in China. Nature 569(7755): 184–186. https://doi.org/10.1038/d41586-019-01408-y [PubMed]
- Li JR, Walker S, Nie JB, Zhang XQ (2019) Experiments that led to the first gene-edited babies: the ethical failings and the urgent need for better governance. Journal of Zhejiang University 20(1): 32–38. https://doi.org/10.1631/jzus.B1800624 [PubMed] [PMC]
- Mudur G (2013) Indian MPs criticise HPV vaccination project for ethical violations. British Medical Journal 347: f5492. https://doi.org/10.1136/bmj.f5492 [PubMed]
- Nekhoroshih IN (2016) Analysis of competitiveness factors in the global economy using the example of the BRICS countries. Proceedings of the Southwest State University. Series: Economy. Sociology. Management [Izvestiya Yugo-Zapadnogo Gosudarstvennogo Universiteta. Seriya: Ekonomika. Sociologiya. Menedzhment] 1: 27–34. [in Russian]
- New drugs and clinical trial rules 2019. CDSCO https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=OTg4OA== [accessed May 23, 2024]
- Opendata.eaeunion.org: Decision of the Council of the Eurasian Economic Commission No. 79 03.11.2016 "On approval of the rules of good clinical practice of the Eurasian Economic Union". https://docs.eaeunion.org/docs/en-us/01411924/cncd_21112016_79 [accessed on 23.05.2024]
- Qiu J (2012) China sacks officials over Golden Rice controversy. Nature. https://doi.org/10.1038/nature.2012.11998
- Ren YP, Jin XR, Jiang S, Jiang BS (2018) Legal protection of the rights of clinical trial subjects in China. The Journal of Biomedical Research 32(2): 77–80. https://doi.org/10.7555/JBR.32.20170073 [PubMed] [PMC]
- Singh N, Madkaikar NJ, Gokhale PM, Parmar DV (2020) New drugs and clinical trials rules 2019: Changes in responsibilities of the ethics committee. Perspectives in Clinical Research 11(1): 37–43. https://doi.org/10.4103/picr.PICR_208_19 [PubMed] [PMC]
- Suskin ZD, Giordano JJ (2018) Body–to-head transplant; a "caputal" crime? Examining the corpus of ethical and legal issues. Philosophy, Ethics, and Humanities in Medicine 13: 1–6. https://doi.org/10.1186/s13010-018-0063-2 [PubMed] [PMC]
- Tanushya BS (2022) Regulation of clinical trials and rights of participants in India: An analysis. International Journal of Law Management & Humanities 5(4): 848–857. https://doij.org/10.10000/IJLMH.113417
- Ukwu H, Parma M, Guimaraes A, de Oliveira CF, Más AP, Villeponteaux E (2011) Clinical trials in Latin America. In: Global Clinical Trials. Academic Press, 271–308. https://doi.org/10.1016/B978-0-12-381537-8.10014-7

- Virk KP (2010) Addressing issues affecting clinical trials in Brazil. Clinical Research and Regulatory Affairs 27(2): 52–59. https://doi.org/10.3109/10601333.2010.480974
- Zhou J, Liu D (2021) Development proposals of Human Research Protection Program. Nursing Ethics. 28(4): 554–562. https://doi.org/10.1177/0969733020952114 [PubMed]

Author Contributions

- **Sergey Y. Simeniv**, Senior Lecturer of the Industrial Pharmacy Department, I.M.Sechenov First Moscow State Medical University, Russia; e-mail: sergey.simeniv@gmail.com; **ORCID ID** https://orcid.org/0000-0002-2867-2840. The author was engaged in developing the concept of the work, processing literature sources, and writing the text of the manuscript.
- **Alexander L. Khokhlov,** Dr.Sci (Med), Professor, Member of the Russian Academy of Sciences, Rector of Yaroslavl State Medical University, Russia; e-mail: rector@ysmu.ru; **ORCID ID** https://orcid.org/0000-0002-0032-0341. The author was engaged in editing and approval of the final version of the manuscript.
- **Olga N. Soldatova**, Cand. Sci (Med), The chief physician of the Sanatorium Buran - branch of the joint-stock company Russian Railways-Health, Russia; e-mail: soldatovaon13@gmail.com; **ORCID ID** https://orcid.org/0009-0007-2454-989X, RSCI SPIN code: 1884-7206. The author was engaged in processing literature sources and writing the text of the manuscript.
- **Nathalia V. Pyatigorskaya**, Dr.Sci (Pharm), Professor, Corresponding Member of the Russian Academy of Sciences, Head of Chair of the Industrial Pharmacy Department, , I.M.Sechenov First Moscow State Medical University, Russia; e-mail: pyatigorskaya_n_v@staff.sechenov.ru; **ORCID ID** https://orcid.org/0000-0003-4901-4625. The author was engaged in editing, formulation of conclusions, and approval of the final version of the manuscript.