Russia: The Mirage of Swiss Clinical Trials

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For strategic reasons and to maximise profits, industry-sponsored clinical drug trials on human subjects are increasingly offshored in developing and emerging countries. In those countries, pharmaceutical companies can find a large pool of vulnerable people willing to take part in drug trials as it represents often their only treatment option. In addition, weak regulatory environments enable the pharmaceutical multinationals to shorten clinical trials duration. This increases significantly the risk of ethical violations. Concerned about this situation, the Berne Declaration launched several investigations in 2012 and 2013. Four field studies took place in Argentina, India, Russia and Ukraine to better understand these contexts in which numerous clinical trials take place. How is the regulatory system performing? Are the ethical standards respected? How do Swiss firms conducting clinical trials behave in these countries? A research was also carried out in Switzerland to understand how Swissmedic – the Swiss medicines agency – functions and carries out the ethical control of clinical trials that were conducted in third countries. The field studies were done by investigative journalists and by an NGO specialised in the field. The five investigation reports are available on www.ladb.ch or upon request at info@ladb.ch.

This report is based on the research conducted in Russia by **Anastasia Kirilenko**, an investigative journalist.

IMPRESSUM

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The Russian context of clinical trials

Although clinical drug trials have been conducted in Russia since the early 1990s, their number has significantly increased since 1997, almost tripling from one year to the next[1]. In 2011, 33% of drugs authorised by the United States' FDA *(Food and Drug Administration*, the US medicines agency) and 48% of those licensed by EMA (*European Medicines Agency*) were based on data generated by clinical research in Russia and the Ukraine[2]. According to a CRO working in the sector (CRO: *Contract Research Organisation*, i.e. a private body that conducts clinical trials, or studies, on behalf of pharmaceutical companies)[3], the Russian Ministry of Health approved 916 new clinical trials (all types) in 2012; this represents a 60% increase compared to the previous year. Swiss sponsors launched 52 new clinical trials in 2012 (23 of which were for Novartis and 23 for Roche), putting Swiss companies in third place behind Russian sponsors (430) and US sponsors (143). Almost half of these new tests were phase III clinical trials[4].

Some important legislative changes

In 2005, Russia adopted a "National Standard", an adaptation of the Good Clinical Practice (GCP) Guideline issued by the International Conference on Harmonisation (ICH)[5].

In 2010, a new law "on the circulation of medicines" was enacted, replacing the federal law on medicines of 1998[6]. Intended to rationalise the system for licensing drugs, including the authorisation process for clinical trials, the new law spread confusion among the players involved in trials.[7]. The following are some of the measures criticised by the pharmaceutical industry and the CROs:

- The obligation to conduct clinical trials in Russia before the drug or medicine being tested can be licensed and marketed, even if it has been approved in another country.
- A refusal by the national ethics committee, attached to the Ministry of Health, to authorise a clinical trial is categorical and does not leave room for direct scientific dialogue with the companies concerned.
- Medicines/drugs developed outside Russia cannot be tested in Russia in phase I clinical trials.
- All sites that host clinical trials must be officially (re)accredited by the Ministry of Health.

The number of clinical trials conducted in Russia fell sharply after the new law entered into force, particularly tests sponsored by Russian companies. However, the situation has since returned to normal. International clinical trials in which one branch is conducted in Russia, which are less exposed and for which there are concessions, have hardly been affected by this new law, at least in quantitative terms. On the contrary, as the figures mentioned above show, the number of clinical trials conducted in Russia has been growing sharply since 2012. On average, almost two-thirds of drugs trials conducted in Russia are branches of international multi-centre clinical trials sponsored by multinational pharmaceutical companies.

Russia and the European Union: the same standards?

The European Commission report entitled "*Analytical report – cooperation (with Russia) in the field of clinical trials*"[8], dated July 2012 (only available since early 2013), establishes that, in general, clinical trials practice and associated monitoring measures in Russia match those of the European Union. However, certain rules are less strict than in the European Union, whilst others are more so: for example, Europe does not have a rule that every hospital in which trials are conducted must have special accreditation from the Ministry of Health. A well-known peculiarity of the Russian system is that direct contact between patients and ethics committees is not allowed. However, if a problem arises during a clinical trial, it is essential that a patient be able to consult an independent body. Currently, Russian patients can only turn to the trial's principal investigator, the same investigator who has an interest, particularly a financial interest, in successfully completing as many trials as possible. The low basic salaries of doctors exacerbates the risk of a financial conflict of interest, as confirmed by our investigation, conducted in Moscow, Saint Petersburg, Novosibirsk and other cities in Russia.

1. Peculiarities of the Russian clinical trials system

1.1 Overview

Medical consultations in Russia are free and patients are "allocated" a doctor according to where they live. Patients are often recruited for clinical trials by their doctor, who suggests they take part in a trial as part of a standard treatment. A second avenue of recruitment is via the internet (hospital websites, forums etc.). Patients can also contact the hospital or investigating physician on their own initiative. They are given several days to complete the form of informed consent. Patients who agree to take part must go frequently to the hospital to give blood samples and undergo medical examinations. The trial promoter is required to pay health insurance for every participant, according to a Russian government decree of 13 September 2010 "regarding the rules governing types of compulsory life and health insurance for patients participating in clinical trials".

All hospitals and other sites that host clinical trials, such as universities, must obtain special accreditation from the Ministry of Health, according to the Russian Federal Law on the Circulation of Medicines. The CRO or the pharmaceutical company then sends the relevant documents (protocol, informed consent form, patient's information sheet) to the Ministry of Health (Decision of the Russian Minister of Health of 31 August 2010 "on the ethics committee"). Three or four months later, the Ministry of Health conveys its decision. If the trial is approved, the recruitment of patients can start. This normally takes place in several cities, in order to guarantee a sufficient number of subjects. The information relating to each trial is generally published in English in the United States register of clinical trials (http://clinicaltrials.gov). Other registers exist (e.g. http://clinical-trials.ru), but they are not as comprehensive. The local ethics committee linked to the site of the trial plays a consultative role, in accordance with the Russian national standard GOST 52379-2005, the Russian equivalent of the ICH GCP (the good clinical practice guideline of the International Conference on Harmonisation on the criteria for licensing drugs for human use).

In the event of a death, the CRO contacts the next of kin to obtain a copy of the death certificate, in order to establish whether there was a link between the death and the drug being tested, and to report the death to the ethics committee. It is often not possible to establish a link because the patients tend to be seriously ill. However, where a link can be established, compensation should be paid. The promoter must then update the informed consent form with information on the death.

If the clinical trial is successfully concluded, the pharmaceutical company proceeds to license the drug, a process which can take several months. In Russia, clinical trials can only be conducted within the framework of this registration procedure.

Monitoring in the hospitals conducting clinical trials takes the form of various checks: audits by the pharmaceutical companies, inspections by the Russian medicines agency and, finally, by the FDA. While the checks carried out by the FDA are strict, they are rare.

1.2. Inadequate ethics monitoring

There is only one "official" (central) ethics committee in Russia, attached to the Ministry of Health. Since 2010, local ethics committees are obligatory and have been set up in every hospital and medical faculty which host clinical trials. The local ethics committees are comprised of representatives of civil society, including experts, journalists and priests. In theory, this system should meet the monitoring requirements. In reality, it is dysfunctional. For example, the central ethics committee has the power to prohibit a trial, but it is bureaucratic and permanently overloaded with work. Local committees are more thorough, but do not have the power to prohibit. They can only issue recommendations. Also, local committees have not yet been set up in all locations. Finally, in some cases, the principal investigator on a clinical trial also chairs the local ethics committee. This is notably the case in one Moscow hospital. When questioned, the doctor in question did not judge this situation as problematic.

In theory, international ethical standards relating to clinical research are formally respected in Russia, particularly with regard to consent, insurance and ethics committees. But these regulations clash with the reality on the ground, as shown by the stories we gathered from patients and others.

1.3. Russian patients' motives for participating in clinical trials

The doctors and employees of pharmaceutical companies whom we questioned[9] have noticed a considerable increase in the number of clinical trials conducted in Russia in the last three years, in particular trials by Swiss companies. In their opinion, Russian patients are motivated to participate for "scientific or curative" reasons. Members of ethics committees whom we questioned believe that patients are motivated by the prospect of receiving more attention from the doctor, which "is not guaranteed in Russia" outside of clinical trials because of the decaying public health system.

However, some patients explained to us that they chose to participate in a Swiss drug trial because of the government policy of imposing low-quality, or even "mortally dangerous" medicines (known as "generics" or "analogs bio"), even if that meant going to the doctor more often than they would like to or need to if receiving ordinary treatment. Unlike the generics

produced in Russia, Swiss drugs enjoy a good reputation in Russia, even when they are still at the experimental stage. In general, patients view an experimental Swiss drug as less dangerous than a Russian drug that has been authorised.

1.4. Financial motives and conflicts of interest on the part of doctors

The average salary of a doctor in Russia is very low. The remuneration for conducting drug trials can amount to several times a doctor's salary, providing a strong financial motivation and creating the potential for conflicts of interest. The Hippocratic oath is the only protection for patients. According to one account gathered during this investigation, there are also cases of corruption among investigating physicians, although, according to the same source, it is limited to a "few crooks". According to information provided by Veronika Skvortsova, the Russian Minister of Health, on the average, a doctor earns the equivalent of several thousand euros per month. But according to surveys conducted by specialist online agencies[10], the average salary of a neurologist in Moscow or Saint-Petersburg varies between 600 and a thousand euros per month, while an ophthalmologist in a small provincial town can earn as little as 200. The chief medical officer of a hospital can earn as much as 2500 euros per month in the provinces and 5000 per month in Moscow, which is still much less than his or her counterpart in the United States or Europe.

When recruiting patients on the internet, doctors do not always use the word "trial", but instead advertise that they are recruiting for an "observation programme", which requires the participants to take a drug and entitles them to receive the doctor's private attention. They encourage people to decide quickly whether or not they wish to participate. Such is the case of the trial of Novartis's drug Gilenya, for the treatment of multiple sclerosis, in which neurologist Alexander Ilves of Saint Petersburg is involved. Since 2010, in an online forum dedicated to this serious disease, Dr Ilves has been describing a "free observation programme" for Gilenya. He gives his mobile phone number and advises patients to "hurry" because of the limited number of places on the programme. He also claims that this is a unique chance to receive an innovative drug that the body tolerates well and that cannot be accessed by any other means[11]. When we contacted him by telephone, Dr Ilves gave us very general responses, claiming, for example, that people always sign the informed consent form. He recruits patients from two hospitals in Saint Petersburg, the Institute of the Human Brain and the Military Medical Academy. According to Artyom Golovine, who works for the All-Russian Multiple Sclerosis Society, an NGO working in the interests of patients suffering from multiple sclerosis, it is primarily in these two institutions *"that it is suggested to patients in crisis that they take part in a trial, promising them an improvement if they do; but when their state of health deteriorates they are not withdrawn from the trial because this would compromise the statistics. Once the trial is over, no further interest is taken in the patients".*

It is, in fact, at the Institute of the Human Brain that a female patient became disabled during a clinical trial (see Evgeni Evdochenko's account, item 7.2.).

Alexander Globenko, Clinical Trials Manager at Proxy Group Research, a CRO, also highlights the problem of recruitment using fallacious claims, such as describing trials as "free observation programmes" guaranteeing private attention from the doctor. He said that such cases have become rarer in recent years, but still occur in the provinces, away from Moscow and Saint Petersburg.

As clinical trials have become the main source of revenue for some doctors[12], it is entirely in their interest to continue conducting them on a permanent basis. Such financial motivation can also encourage them not to withdraw patients from trials when problems occur. The case of Anna N. from Oufa, who suffers from multiple sclerosis, illustrates this phenomenon very well. She described the difficulties she experienced in leaving a clinical trial. Despite her suffering from a significant side effect (depression), the doctor advised her not to leave the trial unless she experienced suicidal thoughts. She finally decided to leave the trial on her own initiative, for which she was censured by her doctor.

1.5. The difficulty of leaving a trial

Believing that Russian drugs are harmful, the majority of trial participants fear not being able to continue participating in a clinical trial. Some patients are afraid to leave a trial even in the face of grave doubts. One female patient confided to us: *"I know that afterwards I'll never be offered another trial and I won't get any treatment".*

It would therefore appear that patients only leave a trial if they suffer from very serious side effects (very high fever, hospitalisation, etc.). As the example of Anna N. shows, leaving a trial can annoy the principal investigator, which patients wish to avoid. Most patients questioned as part of this research refused to give their family name or to name the hospital in question, for fear of causing problems for their doctor and being excluded from future clinical trials[13]. Referring to clinical trials of a Russian drug, Ronbetal, a generic of Bayer's Betaferon (interferon β-1b), used in the treatment of multiple sclerosis, Artyom Golovine, from the NGO the All-Russian Multiple Sclerosis Society, confided to us that:

> *"In the worst cases, patients have hoarded drugs at home, preferring not to say anything to their doctor and to remain without treatment rather than compromise their chances of being used in a subsequent trial, which they hope will be more beneficial".*

Ronbetal and Sinnovex – drugs licensed on the basis of proof judged to be insufficient

Artyom Golovine complains that the Russian Law on the Circulation of Medicines was changed to allow trials of Ronbetal using an accelerated procedure, involving only 40 participants, of whom 16 were receiving Betaferon. Although limited, this study enabled the drug to be licensed in Russia.

"Worse still, for the Iranian drug Sinnovex (another generic of Betaferon)" Golovine adds, *"the clinical trial wasn't conducted in Russia at all, in spite of two court decisions on the subject"*. His NGO even went to court which, in March 2013, confirmed the absence of clinical trials of Sinnovex. The view of the public prosecutor's office, however, was that *"the accelerated procedure for registering generics of existing drugs is legal."*[14]

1.6. Ethics and falsification

It should be possible through a routine analysis of blood and urine for doctors to detect when patients are not taking their medicine. However, these checks are not always very strict, and falsification occurs, particularly for the purpose of hiding "absentee" patients. Alexander Globenko, Clinical Trials Manager at the CRO Proxy Group Research confirmed this:

> *"I don't know the statistics, but falsification happens quite frequently in Russia".*

According to him, there are two types of falsification. In the first type, patients are not recruited at all, but *"the urine of a laboratory assistant is used to replace the urine of a patient"*. The motivation in this case is financial. In the second type of falsification, the data for the trial is falsified in order to mask the fact that a patient has not taken his / her medicine.

However, Globenko believes that the problem of falsification of clinical trials in Russia is *"the same as in Europe"*. What is more, the doctors and members of ethics committees and NGOs we questioned explained that *"there is international monitoring, and the results of the inspections carried out by the FDA in Russia are encouraging"*. It is worth highlighting Alexander Globenko's claim that inspections of clinical trials by the pharmaceutical companies, the Russian drugs agency Roszdravnadzor and the FDA are aimed *primarily* at detecting falsified studies, with ethics being a secondary priority. For example, the inspectors are suspicious if the number of patients recruited is too high.

1.7. Limited access to treatment following trials

In most cases, continuation of treatment after a trial is not guaranteed. Even if the drug in question is subsequently licensed in Russia, the administration has to select it for inclusion on the list of drugs subsidised by the State. Otherwise, it is very expensive, and unaffordable for most. And, at least for the time being, treatments that are subsidised are mostly Russian generics, which contain less active substances (and therefore less effective) and are cheaper.

1.8. Compensation in the event of harm: statistics speak for themselves

Health insurance may be compulsory for participants in clinical trials in Russia, but compensation is very rarely paid. It must be acknowledged that Russian patients are so grateful for the treatment they receive from the testing of drugs that, even after serious health problems lead them to decide to leave a trial, they do not demand financial compensation. According to statistics from the association of bodies that conduct clinical trials in the country, ACTO Russia (Association of Clinical Trials Organisations)[15], there was not a single case of payment of compensation from among the 71,089 patients insured between 2007 and 2009 (see Annex III for the statistics). ACTO Russia has no recent statistics, but other accounts confirm this same phenomenon: hardly a patient or doctor questioned remembers a single case of compensation being paid (see witnesses' accounts further in the report), even when the trial in question caused serious disability.

2. Inspections by the Russian medicines agency

Obtaining comments from the Russian health authorities is extremely difficult. However, we did manage to question a few people on the inspections conducted by Roszdravnadzor, the Russian drug regulatory agency. This agency has a special monitoring department, but it only employs three full-time inspectors. Around 200 inspectors are employed on a part-time basis and do other work in parallel. Yuri Afonchikov is a former executive director at Roszdravnadzor and still works there as an inspector. Although he defended the Russian clinical trials system overall, he did express the following reservations.

Firstly, Russian law does not allow for serious fines to be imposed on investigating physicians who do not respect all provisions of the law, *"nor are the sites used for such trials denounced"*. The inspectors can only request that mistakes are corrected. Secondly, there is no specific training system for investigating physicians, so every doctor has a different level of knowledge: *"One doctor attends a 42-hour course, another a 72-hour one and a third a 144-hour one"*. Further, the courses are organised by the pharmaceutical companies and are not regulated by the state. For example, in Saint Petersburg, one agency that specialises in the recruitment of "clinical trials specialists" explained to us that candidates must be qualified doctors and that pharmaceutical companies offer clinical research training courses once candidates are hired[16]. The faculties of medicine also sometimes offered workshops [17].

Unlike Alexander Globenko, Clinical Trials Manager at the CRO Proxy Group Research, Yuri Afonchikov does not think that the quality of trials is generally higher in Moscow or Saint Petersburg:

> *"In Moscow and Saint Petersburg they even speak of 'phantom research'. Some researchers are juggling so many jobs and functions at once – as local education officers, professors, experts, consultants for the state on drugs purchasing – that they have no time left for clinical trials – and their teams do the same, always in a rush. But as these are renowned doctors, patients are clamouring to be recruited by them. In the end, they don't have enough time for everyone. For the doctors themselves it isn't really a problem: in Moscow and Saint Petersburg, even if certain patients are in pain and are likely to end up withdrawing from a trial, there will always be others to take their place. Generally speaking, people from all over Russia try to get treatment in the capital rather than in the small towns, including via clinical trials. It's why there are too many requests to take part in trials."*

He added:

> *"It's clear that in certain small towns doctors have less experience, but their attitude towards patients is often better."*

Even though he defends the Russian clinical trials system, Yuri Afonchikov concluded by stating that "ethics must be improved in Russia".

Irina Rogova, both a member of a local ethics committee and an inspector for Roszdravnadzor, believes that "*there could be even less monitoring of clinical trials, because if you're looking for faults you'll always find them."* According to her, Russian inspectors tended not to be very well qualified in the past, but are better qualified now thanks to the training courses organised by the FDA.

Roszdravnadzor's official communications about their inspections of clinical trials, such as the bulletin it publishes on the internet[18], are very "institutional" and uninformative. We are told, for example, that in 2011, "observations" relating to the work of the local ethics committees had been made. No further details have ever been provided.

Grigory Arutyunov, a Moscow doctor, admitted that the Roszdravnadzor inspectors warn of their visit two weeks in advance and only work on the basis of documents. Direct contact between inspectors and patients is not allowed. Only inspectors from the FDA are allowed to meet patients.

Svetlana Zavidova of ACTO Russia and Alexander Globenko of the CRO Proxy Group Research were also rather critical: according to them Roszdravnadzor does not carry out enough inspections, and the competence of the inspectors leaves something to be desired. However, Alexander Globenko still thinks that *"the essential duty of assuring the safety of patients is fulfilled"*.

3. How the ethics committees operate

3.1. Division of work between the central and the local ethics committees

Since 2010, local ethics committees are obligatory and operate in addition to the so-called central ethics committee within the Ministry of Health.

Alexander Arutyunov, an investigating physician from Moscow, explained to us how ethics committees operate in Russia:

> *"Every research clinic in Russia is organised in a university or hospital. In most cases, there is a local ethics committee on site. In certain rare cases, a local ethics committee can delegate its tasks to the central ethics committee of the Ministry of Health. 100% of research is approved by the central ethics committee first, and 70 - 80% is approved subsequently by local ethics committees. When trials are prohibited, it is done in 99.9% of cases by the central committee. The central committee prevails over the local committees."*

This situation makes Yuri Afonchikov, an inspector for Roszdravnadzor, somewhat sceptical with regard to the way the ethics committees operate. The central ethics committee, which takes the decisions, is reportedly quite bureaucratic, and composed of "star doctors" who tend to be less zealous, while the local committees, which take things more seriously, are not authorised to take decisions.

Its approval of an unethical trial of Saphris (asenapine) appears to confirm such doubts about the quality of work of the central ethics committee. Conducted by the United States firm Merck, predominantly in developing and emerging countries, this trial put the schizophrenic adolescents who were the subjects of the trial in grave danger, depriving half of them of all treatment in order to administer placebo. The trial was suspended in Argentina after being the subject of a complaint[19].

According to Alexander Globenko, Clinical Trials Manager at the CRO Proxy Group Research, still more troubling is the corruption within the central committee:

> *"Corruption is rife from the moment a request for authorisation of a trial is received from a pharmaceutical company. There are two bodies at the Ministry of Health that deal with such requests: the central ethics committee, which rules on matters of ethics, and the State Centre for Drug Expertise, which gives an opinion on the safety and quality of the drug being tested. It is not possible to get an expert opinion in advance, or to ask for advice from either body. The only possibility is to submit documents relating to trials to the Ministry of Health. An expert opinion takes four months, and these bodies can keep refusing to authorise until every comma is in the right place. In the meantime, the rules on punctuation change! For this reason, it's common practice to buy authorisations for individual trials. But despite that, I wouldn't say that unethical trials are accepted. Where there are serious infringements, even if some sort of bribe has been paid, the pharmaceutical company must keep correcting the protocol until it's acceptable".*

It is hard to verify such accusations, as no enquiries into corruption are made in this sector[20]. It is worth noting that the Russian press reports that it takes the Ministry of Health 115 days to examine a clinical trial dossier, much longer than in Europe – and new amendments proposed in 2013 could prolong that period by as much as a year[21].

3.2. Structure and work of the central ethics committee

Approximately twenty new members of the central ethics committee were designated between December 2012 and March 2013 (the Ministry of Health having changed in 2012). Even on the basis of the Ministry's official press releases, it is impossible to establish for certain who chairs it: Alexander Chuchaline, pneumologist and academic, or Igor Tyurin, radiotherapist. Also, it is possible to replace the chair with another member in the event of the former's absence. Neither Alexander Arutyunov nor Alexander Globenko, both involved in conducting clinical trials, could say who chairs the official ethics committee: *"We send them documents, but direct contact is not allowed"*.

According to the investigating physician Grigory Arutyunov, all members of the central committee are very busy. They hold several positions at the same time and it is *"impossible to contact them"*. In an interview in the government newspaper Rossiyskaya Gazeta, Alexander Chuchaline admits that:

> *"A lot of mistakes are still made. Our aim is to embed high ethical standards, professional and otherwise, in the Russian medical profession. We organise working meetings with the experts to discuss the best way of doing this. I would like to see set up in Russia a similar system of ethics committees to that in Germany, France and the United States, and for us to ensure the respect for ethics throughout the whole system."*[22]

In another interview granted to the same newspaper, Alexander Chuchaline speaks of *"orthodox medicine"* and the potential for religion and places for prayer in hospitals to encourage greater respect for ethical standards in general in the healthcare sector in Russia[23]. He calls on Russian doctors in general to respect moral values, but makes no mention of flaws in the legislation.

In a register[24] intended for the purpose, the official ethics committee is obliged to publish the main data on approved clinical trials, namely the pharmaceutical company concerned, the country of origin, the number of trials, and essential features such as use of placebo. What are not published are the names of the sites where trials are taking place and the active substance being tested.

According to this register, by 27 March 2013, the official ethics committee had examined 75 trials, of which 6 were rejected and 69 approved. The register also shows that Roche had two changes in protocols approved, and that Novartis and Europharma Russia are conducting a joint trial comparing generics with the original drugs. Only the codes of those drugs are given.

The Russian journalist Irina Nevinnaya, who was a member of the last official committee, provided us with some information on how it operated:

> *"We used to make a lot of comments about the insurance companies. Other than that, as some medical terms are very technical, we could ask questions, of course, but sometimes even the specialists couldn't answer them, and the chair of the committee then had to call on specialist doctors in whatever field to fill in the gaps. The main thing was to ensure that there were no conflicts of interest. But it was rare to refuse authorisation of a trial. And even then, the company concerned could re-submit the application, and we would re-examine it and approve it."*

4. Interviews: the perspective of members of local ethics committees

4.1. Grigory Arutyunov, investigating physician and chairman of a local ethics committee

How the ethics committees operate

In addition to being a chief researcher, Grigory Arutyunov is also the chairman of the local ethics committee of the Chair of Therapy at the Faculty of Medicine at the State University of Moscow. He told us that as chairman of the committee he does not have a vote: his role consists of presenting trials to the other members and encouraging them to vote. His committee is composed of 15 members, one of whom is a priest. Arutyunov regrets the presence of non-professionals (*"For the priest, everything comes from the devil"*). He added: *"The official ethics committee is comprised mostly of doctors and lawyers. It's easier*".

4.2. Yelena Volskaya and Irina Rogova, members of local ethics committees

Yelena Volskaya and Irina Rogova represent two committees at the medical university in Moscow – the Inter-University Ethics Committee, of which Yelena Volskaya is a member, and the Independent Interdisciplinary Committee, of which both women are members. Irina Rogova is also an inspector of clinical trials for Roszdravnadzor. Both these ethics committees supervise clinical trials conducted in faculties of medicine.

"In some of the faculties of medicine there are certified centres that conduct clinical trials", Yelena Volskaya told us; *"The pharmaceutical companies organise training courses there"*. When asked about the practices of the Swiss companies conducting clinical trials in Russia, the two women confirmed that they deal with clinical trials conducted by Roche and Novartis, but refused to give specific examples. Their only comment was that *"there's more to criticise with Novartis than Roche"*, because Roche works with large medical centres, whereas Novartis conducts trials almost anywhere, in small, less experienced hospitals. Questioned as part of this research, Evgeni Evdochenko, a doctor from Saint Petersburg, was also more critical of Novartis, but did not provide us with any more details (see below).

How the ethics committees operate

Yelena Volskaya and Irina Rogova explained that when their ethics committees examine a consent form and find that it puts pressure on participants – "*which could be considered an unethical way of encouraging a patient to participate in a trial"* – the committees recommend to the pharmaceutical companies that the text be altered and the trial is not approved until the changes have been made. They gave us the following concrete example of a recommendation from an ethics committee, without specifying which pharmaceutical company they were referring to[25]:

> *"In the 'importance of the trial' […] section, the risks linked to certain infections for pregnant women and new-borns are described in great detail. This emotive description can cause a lot of anxiety and worry for pregnant women, and can therefore be considered to be an unethical way of encouraging them to participate in a trial, in violation of the principles of good clinical practice (GCP) [...]. We recommend that these paragraphs should be amended."*

According to Yelena Volskaya, Roche, Novartis and other Swiss companies are among the companies to which recommendations of this kind are made – and the companies are obliged to adopt the recommendations. Yelena Volskaya also said that the pharmaceutical companies sometimes consult the local ethics committee before the central ethics committee.

Both women assured us that approval from the ethics committee is compulsory in Russia: Roszdravnadzor will not grant authorisation to conduct a clinical trial without that expert opinion. As mentioned earlier, before 2010 there was only one ethics committee, attached to the Russian Ministry of Health; now it is obligatory to set up a second, local ethics committee. Some local ethics committees have in fact been in existence since 2000, but were not compulsory at this time. According to Yelena Volskaya, the work of the ethics committees is based on the principles of the Declaration of Helsinki, the Russian transposition of the ICH GCP (GOST 52379-2005), and the Russian Law on the Circulation of Medicines (cf. Annex I). It should be mentioned, however, that according to Maya Brodskaya, a former Roche employee (see account below): *"There have been a lot of amendments to that law, and nobody knows what's in it."*

Yelena Volskaya also told us that the central committee is not effective because it has to deal with a 100 to 200 protocols in one meeting. This is in contrast to the local ethics committee, which meets every month to deal with about 15 trials – 18 at the most. *"We are thinking of meeting every two weeks, to improve the effectiveness even more – no more than 12 protocols per session"*, she told us. However, some local ethics committees examine up to 45 protocols in a session.

Russian patients' motives for participating in clinical trials

According to Yelena Volskaya, the motives for Russians to participate in clinical trials vary. She cites access to innovative technologies and more private attention from doctors in the care they receive as participants in the testing of medicines. The existence of cheap "analogs bio", which are imposed on Russian patients by Russian Federal Law No. 94, was again mentioned by Yelena Volskaya. Patients receive drugs, paid for by the Russian state, which are "ineffective" (for example, they only contain 40% of active substance), and this encourages them to participate in an international clinical trial instead.

In Russia, many people are deprived of good quality treatment. Yelena Volskaya reminded us that the Programme of Supplementary Medicines (DLO in Russian) for the treatment of cancer was set up 5 years ago. This programme, for example, limits the categories of cancers for which treatment is financed by the state. Although access to high quality treatment paid for by the state might be conceivable in Moscow, a number of patients living in rural areas have seen their benefit reduced to ten euros a month, which is not nearly enough to cover their treatment. The number of patients signing up for international clinical trials of cancer treatment has risen considerably since the DLO was established.

A financial incentive is only allowed for Phase I trials (in which only the use of Russian drugs is permitted). These trials are governed by the Russian Federal Law on the Circulation of Medicines (Annex I).

Russian doctors' motives for conducting clinical trials

Yelena Volskaya told us that international clinical trials represent for the doctors *"the possibility of better fulfilling their professional duty"*.

Patient consent

Informed consent forms can contain up to 45 pages. When asked whether all patients understand these forms, Yelena Volskaya shrugged her shoulders and said: *"No-one checks"*, and *"Patients come from different socio-economic backgrounds, but none are from the margins"*.

She admits that *"certain professors at faculties of medicine are approached by acquaintances wanting to sign up for a trial*". This networking and pulling of strings dates back to the Soviet era.

Continuation of treatment at the end of a trial

It is difficult in Russia to continue treatment once a trial is over. Irina Rogova cited one positive example: in 2004, her committee asked the company Bristol to continue treatment against HIV/AIDS for the subjects of a trial and the company agreed. She also said that Novartis offers the possibility of patients being included, post-marketing, in research known as "observation", which lasts ten years and is of a drug used in the treatment of multiple sclerosis. But, aside from these few cases, patients will no longer have access to the drug being tested if it is not selected for subsidy by the government. Also, if the drug being tested has not been authorised, its use beyond the trial is illegal.

Compensation in the event of harm

Insuring participants in a clinical trial is compulsory. The company concerned is obliged to compensate the patient in the event of a serious health problem, and their close relatives in the event of their death. However, neither Yelena Volskaya nor Irina Rogova could remember any cases where compensation was paid, or even applied for.

Use of placebo

According to Yelena Volskaya, placebo is used in only 30% of cases*, "as often as before"*. We should mention, however, that higher figures are quoted in other accounts (see below). This 30% refers to large-scale international research projects in which the efficacy of the drug cannot be proved by any other means.

5. Interviews: the perspective of associations linked to clinical trials

5.1. Svetlana Zavidova, Executive Director of ACTO Russia

ACTO Russia, the association of organisations that conduct clinical trials in Russia, has been registered since 2007. It brings together 26 CROs and pharmaceutical companies, including Novartis. ACTO Russia's aim, notably, is to promote clinical research in Russia and to *"denounce the myths surrounding clinical research in developing countries"*[26]. The executive director of this association, Svetlana Zavidova, believes that the standards of clinical research in Russia match research conducted in Switzerland, except for certain peculiarities in Russian clinical trials.

Peculiarities of the Russian system

We have established that there are two types of ethics committees in Russia. The so-called central ethics committee examines the dossiers of clinical trials before authorising them. Svetlana Zavidova admitted to us that the pronouncing of its expert opinion is purely bureaucratic. This is why there is a second type of ethics committee in Russia, called the "local ethics committee", attached to the hospital concerned in each case. Since 2010, the agreement of the local ethics committee is obligatory before a clinical trial can be conducted. We were told by Roche's former Head of Development, Siberia and the Far East, Maya Brodskaya (read her account below) that, in the case of a study conducted by Roche in Tuva, for example, the central committee in Moscow approved the protocol for the trial, whilst the local ethics committee, on the spot, made the patients sign the informed consent form. It is worth mentioning that Alexander Globenko, Clinical Trials Manager at the CRO Proxy Group Research, told us that local ethics committees are not active and present in 100% of cases, which was confirmed by doctor Alexander Arutyunov.

Another peculiarity of the Russian system explained by Svetlana Zavidova is the absence of any monitoring by the country's health authorities with regards to respect for the Declaration of Helsinki. This failing is apparently due to a lack of inspectors, who are also, apparently, not paid well enough. This was confirmed by Irina Rogova, another inspector (quoted above). For Svetlana Zavidova, that does not pose a problem in itself, because the FDA conducts international inspections in Russia, the findings of which are positive.

Svetlana Zavidova confirmed that direct contact between trial participants and ethics committees is not possible in Russia. Alexander Globenko told us that, although the telephone number of the official ethics committee is given on the informed consent form, it is impossible to reach it – which is why ACTO Russia has set up an emergency telephone line for participants in clinical trials. Svetlana Zavidova is proud of this initiative. She explained to us that it is the only emergency number in Russia for participants in drugs trials, because the local and central ethics committees *"work on documents"* and never speak to patients. However, she herself answers calls to the emergency number, and admitted that they do not receive many calls from participants. It should also be stated that this number is not official and patients have to find it on the internet. "*Once, someone called saying that they had a fever. I suggested they call their doctor"*, she told us. Some people call the number or send her emails in order to register for trials. But, as she said: *"There aren't enough places for everyone."*

She refused to give us any more information, hiding behind duty of confidentiality, an argument used constantly in the clinical trials sector. Throughout the interview she was careful not to reveal any of the phone number of people who had called the emergency line[27].

Compensation in the event of harm

Zavidova shared her own statistics with us regarding compensation paid. They show that since 2008, not one (!) of the thousands of insured clinical trial participants has received compensation (see Annex III). According to her, this is because no-one required compensation.

5.2. Alexander Saverski, President of the Russian League for the Protection of Patients

Reliability of the clinical trials system in Russia

According to Alexander Saverski, President of the League for the Protection of Patients, *"the Russian mentality is not conducive to a high degree of scientific rigour"* in clinical trials. He claimed, for example, that doctors do not sufficiently report negative results, and work with documents rather than with people.

He also said that a number of trials are organised in hospitals as part of doctoral theses. Negative results damage the trial from a scientific point of view and are therefore not desirable. It is true that many trials are conducted by faculties of medicine. However, doctor Alexander Arutyunov believes that while the practice of using clinical trials in doctoral theses was once common, it is now almost non-existent.

6. Interviews: the perspective of patients

6.1. Anna, 25 years old, Oufa, Bachkirie, suffering from multiple sclerosis – trial of Novartis' Gilenya

Anna started participating in the Gilenya study conducted by Novartis in May 2012. She had to stop taking the drug in October 2012, following problems with her health. Our initial interview took place just before this, in September.

Informed consent

"I don't remember how many pages there were in the informed consent form. But, strangely, I had to stay in the hospital for six hours after taking the drug for the first time, and only after did they make me sign the consent form, i.e. after the trial had started."

Motives for participating

"I have to take part in a clinical trial. This is already the fourth drug I've taken in its test phase. As you perhaps know, Betaferon was taken off the Russian market. It was the only drug that helped me. After that, they gave me Kopaxon, but I'm allergic to it. My doctor at the multiple sclerosis centre in the Republic of Bachkirie suggested this phase IV trial, as I wasn't getting treatment anymore and my condition got worse in May. I didn't have a choice."

Continuation of treatment at the end of a trial

"I don't know if I will have access to this drug once the trial is over. I know that there are precedents in which the regional budget covered the costs of a drug like this. I hope so."

Side effects and leaving a trial

"Side effects of Gilenya are depression. I did suffer from that, and a disrupted menstrual cycle. The depression got so bad that I could hardly speak to anyone. I called my doctor, and he said he'd ask Novartis some questions and call me back. He didn't call back. I left the trial and stopped taking the drug. When I told the doctor, he was annoyed and gave me a long lecture, saying I should have come and seen him before, or gone to the hospital, etc., etc. It was very unpleasant: not only did he not help me, but he made me feel guilty. I'd prefer not to say which hospital it was - I'm scared."

6.2. Natalia, 50 years old, Saint Petersburg, suffering from multiple sclerosis – trial of Novartis' Gilenya

Natalia took part in the phase III clinical trials of Gilenya for five years, starting in 2006. She left the trial in 2011, as *"the side effects outweighed the therapeutic effect"*.

Motives for participating

"My doctor, whom I've known for sixteen years, suggested this trial to me. He didn't hide anything from me. He said: 'I could give you a hundred arguments for this trial and a hundred arguments against it'. I've already lived with my multiple sclerosis diagnosis for 30 years. I've had a number of drugs tested on me, both Russian and foreign ones. I know I´ve been 'a lab rat'."

Side effects and leaving a trial

"There were thirty or forty of us; the trial took place at Hospital No. 25 in Saint Petersburg, where my doctor worked. They divided us into three groups: One third received placebo, one third 0.25 mg of the drug and one third 0.5 mg (no-one knew which group they were in). But after experiencing considerable side effects, I knew I hadn't been receiving placebo."

Natalia was hospitalised twice – with a temperature of 40° due to pyelonephritis. Her doctor advised her to stop taking Gilenya for ten days while she had these symptoms, but each time she started taking it again the side effects returned.

"I finally decided to leave the trial. The doctor was neither for nor against it; he said 'it's your right'. According to the informed consent form, you are allowed to leave the trial."

Informed consent

Natalia did, however, notice one strange thing: the informed consent form was renewed every six months: *"In the end, I didn't have the strength to read it any more"*. One of the last versions of the form (written in June 2010 and signed in April 2011), which Natalia showed us, runs to 25 pages. The document mentions insurance and gives the contact details of the doctor. It also states that the drug caused a death from chicken pox. The conclusion stated on the form is that all participants in the Gilenya trial must have had chicken pox as a child.

Difficulty accessing "standard" treatment

Since she left the trial in 2011, Natalia has been desperately searching for a treatment in the form of a standard drug, immunoglobulin in particular, which was working well for her before she agreed to take Gilenya. But her doctor refused to

prescribe her immunoglobulin, saying that it was a treatment reserved for pregnant women. Instead, he offered her a new clinical trial, which she refused.

According to Natalia, Gilenya strongly attacks the immune system in order to combat multiple sclerosis (a disease caused by excessive immunity), whereas the action of immunoglobulin is more gentle.

On 2 April 2012, Roche organised a meeting in Saint Petersburg entitled "*Roche Briefing and Recruitment Update Investigator Meeting: Opera I and Opera II studies*" to discuss two clinical trials. Natalia went to it out of curiosity. She explained, somewhat ironically, that there could not be much of a difference between "Opera I" and "Opera II", and that, regardless, she did not want to participate in any more trials, even if it was a year and a half since she had been able to obtain a prescription for a "standard" drug.

When we last spoke to her, Natalia was still not receiving any treatment. She told us that she was, at least *"regaining her health after Gilenya"*. She felt better than she did during the clinical trial. She had never thought about whether she was entitled to compensation or of asking for insurance. She considers herself to be a voluntary guinea pig who had been warned of possible side effects: *"The responsibility is wholly mine."*

6.3. Natalia, Rostov-on-Don, suffering from multiple sclerosis– trial of Sanofi-Aventis' teriflunomide

This other Natalia also suffers from multiple sclerosis. She is testing a drug, teriflunomide, developed by Sanofi-Aventis (phase III trial), but thinks she is receiving placebo.

Motives for participating and informed consent

"Since I haven't been able to take Rebif [interferon beta-1a, developed by Merck-Serono], I have no choice. In Russia, you understand, this is a common situation. I decided to sign up for a clinical trial in February 2012, to try to avoid that my condition deteriorates without treatment. This drug was recommended to me by my doctor, whom I've known for 19 years. I'd rather not name the hospital, as I don't want to cause problems for my doctor. She gave me a month to think about it. I signed an informed consent form – I understood everything. What was important for me was to be able to leave the trial at any time. But I don't have the signed form in my possession, which I find strange: once it was signed, the doctors (there are two in charge of the trial) took it back."

"One of the patients wanted to keep it; he asked the doctor, but the doctor didn't give it to him. That patient later had problems. As for me, I don't want to have problems with the doctor; that's why I'm not asking for the document back."

"This is my second clinical trial (the first was for Rebif), and I was able to keep the form. My doctor is often busy - she's the manager of a hospital. But yes, if I insist, I can speak to her on the telephone."

Side effects, compensation and continuation of treatment following trials

"I had symptoms of neuropathy. My doctor sent me for an examination but the symptoms weren't confirmed."

"It's a trial using placebo, and I'm really frightened that I'm receiving the placebo. I don't think I'll be able to have access to this drug once the trial is over."

"Perhaps insurance is mentioned in all the papers I've signed, but no-one drew my attention to it, so I don't know; they took the papers back. Luckily, I don't need that insurance, but I heard of one patient who asked for insurance and was refused."

"It's a trial over two years. I'm a bit annoyed at having to see my doctor more often than for a normal treatment, but I have to."

"I haven't noticed any improvement. Nobody's forcing me to stay on the trial, but I understand that there'll be problems for my hospital if I leave – because the pharmaceutical companies won't want to use that hospital in future; everyone understands this. If I stop this trial, I won't be asked to take part in other research."

6.4. Yulia, Moscow, multiple sclerosis

Motives for participating

Yulia has multiple sclerosis and is desperately searching for a Swiss clinical trial. This spring she took a test for Gilenya but wasn't recruited. She explained her motives to us:

"I have no choice. In Russia, with the new law, only ineffective drugs, or even mortally dangerous ones, are offered. My friend died just after having taken Ronbetal (produced in Russia, an "analog bio"). Why did she agree to take it? Between taking that drug and nothing at all, I know what my choice would be: to take nothing at all.

"I went to Switzerland to consult some doctors. Several doctors there advised me to sign up for a trial of Gilenya. I think that the quality of Swiss drugs is better than the quality of Russian drugs. I'm going to keep trying to register for a trial. At the moment, I'm not getting any treatment."

7. Interviews: the perspective of investigating physicians

7.1. Maya Brodskaya, former Roche employee

Maya Brodskaya is a former Roche employee in Novosibirsk. Until May 2011, she was Head of Development, Siberia and the Far East, responsible for supervising phase IV clinical trials (post-marketing) in those regions. She agreed to give her views.

How the ethics committees operate

"There was only one local ethics committee that focused only on patients' signatures on the informed consent form and not with trial protocols: these were approved in Moscow, by the central ethics committee."

Motives for participating

"Patients have various motives for participating in trials. They are often seriously ill, and a trial represents a real chance for them. They come from different backgrounds. Russian patients are ideal for the Swiss companies: they want to take part in clinical trials, there are lots of them and many of them are "naïve" – that's to say, they've had no other treatment before, apart from aspirin or ibuprofen. In Siberia, not far from the Altai, is the little mountainous republic of Tuva. There, in one year, Roche recruited a very large number of participants for a clinical trial of an anti-rheumatoid arthritis drug (Mabthera – rituximab). If they'd had to conduct that trial in Switzerland, it would have taken them several decades. It would appear that the inhabitants of Tuva are genetically predisposed to rheumatoid arthritis, although this medical fact is not reflected in the official statistics. Where there are no doctors, there are no statistics."

The trial in question was of Mabthera (rituximab) and was called "Arbitr". For Maya Brodskaya, recruiting patients for a trial of this type is motivating. By doing so, she is giving Russians in the provinces access to an experimental drug, which might be their only access to medical treatment.

Patient consent

"All patients sign an informed consent form. They must all understand it. In any case, idiots – excuse the term – aren't selected: IQ is important, in order that a patient doesn't forget to take a drug, and is capable of giving feedback to the doctor. I regret having recruited a gentleman in a remote village in the Altai: he developed a fever, but couldn't go to see his doctor because there was too much snow. He left the trial. I think it was a mistake to recruit him from the start. But on the whole, it's very rare that people leave a trial."

Side effects and compensation

"If there's a health problem, the doctor has to prove the link between the drug and the unwanted effects. I've never encountered such a case during my time in practice."

Use of placebo

"Placebo is not always used. It depends on the trial protocol. It's customary to use placebo for serious pathologies."

Continuation of treatment at the end of a trial

"The drugs being tested are not available on the Russian market as a matter of course. If the drug is not subsidised by the state (as was the case with the drug Poulmazine, for the treatment of cystic fibrosis), it's practically impossible to get it. I do remember one case in which the ex-husband of a participant in a clinical trial in Vladivostok paid for her drug once the trial had finished. According to the new law in Russia, every drug has to have been tested in the country for it to be marketed here – trials abroad aren't sufficient. So for Russians, trials make sense."

Inspections by Roszdravnadzor

According to Maya Brodskaya, Roszdravnadzor carries out inspections mainly in Moscow and not in the provinces, because *"all the documents are in Moscow"* and the inspectors are only interested in documents. She is also unhappy that hospitals have to obtain special accreditation to be able to conduct clinical trials: *"The documents that a hospital has to submit to the Ministry of Health are the same as for a license to practice general medicine. It just produces more paper."*

7.2. Olga Jeludkova, doctor in pediatric oncology

Olga Jeludkova conducts drug trials for various pharmaceutical companies in the field of pediatric oncology. She told us that she works primarily with CROs and that she *is "considering working with Novartis"*. She conducts phase II and III trials which, according to her, represent a chance for patients to have access to innovative treatment.

Use of placebo

Olga Jeludkova explained that the use of placebo in oncology is unethical and so she does not use it. She acknowledged that the use of placebo was suitable for other illnesses.

Compensation in the event of harm

"Every participant in a study has insurance that provides for compensation for damage caused by the pharmaceutical company. We fill in a separate form for

each side effect and send it both to the research centre and the pharmaceutical company. We have never had side effects that had to be compensated. It's incumbent upon the doctor in charge of the clinical trial to prove the link to the drug being tested."

Inspections by Roszdravnadzor

Olga Jeludkova told us that she had not had a Roszdravnadzor inspection in her hospital. Although she told us that she only takes part in ethical studies, she would not tell us which unethical ones she had declined.

7.3. Evgeni Evdochenko, neurologist, head of the Multiple Sclerosis Centre in Saint Petersburg

Evgeni Evdochenko conducts trials himself and helps "victims of clinical trials that have failed".

Participants' motives and informed consent

"We give the informed consent form to patients for a day or two so that they can study it at home. After that, they come back to me and I spend an hour explaining all the details of the research to them – what molecule we're dealing with, etc. Most patients agree to participate, but there are a few who refuse to after speaking to me.

"Phases II, III and IV of the research represent a chance for patients to receive a new drug if a standard drug is not helping them. Doctors suggest these trials. Some patients refuse, saying that they don't want to take part in an experiment."

Continuation of treatment at the end of a trial

"Continuation of treatment at the end of a clinical trial is possible if the drug is registered in Russia. If not, the participant receives standard drugs." Evgeni Evdochenko pointed out that even when trials are successful, the marketing process is longer than in Europe: *"There's a lot of bureaucracy, which delays the accessibility of the drug."*

Compensation in the event of harm

"As far as insurance is concerned, doctors are on the side of the patient. No-one can influence us; if a death is linked to the drug being tested, we say so, and the insurance company has to pay up."

He could not remember any cases where compensation was paid.

Evgeni Evdochenko is known among his patients as a doctor who takes care of "*victims of clinical trials"*. Accordingly, this investigation has revealed that he is currently looking after a patient of 19, disabled after a clinical trial conducted by other doctors, at the Institute of the Human Brain in Saint Petersburg[28]. We asked him if that patient will be compensated. He replied that he knows nothing about it, and that the patient must start the process herself, adding: *"Perhaps then she'll get something."*

Ethical protocols and placebo

Evdochenko insists that he only agrees to conduct ethical international trials involving US or European companies. This is what he said:

"Me, I only accept ethical protocols. I work with Roche, Novartis and Actelion, and everything I say relates to those companies. Everything depends on the principal investigator. When I work with Novartis, especially, I only accept ethical protocols without the use of placebo. I take note of the doses of the drugs prescribed and of the monitoring mentioned in protocols. For example, I didn't agree to conduct a trial of Gilenya."

"However, the use of placebo is necessary for diseases for which there is no known treatment (such as the primary resistant form of multiple sclerosis)."

7.4. Grigory and Alexander Arutyunov (father and son), doctors, Russian Medical University, Moscow

7.4.1. Alexander Arutyunov, assistant researcher and chairman of an NGO

Alexander Arutyunov, an assistant researcher, is also the chairman of an NGO, "The "scientifico-medical" Society of Therapists of Russia", the aim of which is to consolidate the efforts of doctors (cardiologists, gastroenterologists, etc.), including in the field of clinical trials. When asked about the aims of this NGO, Alexander Arutyunov gave the following reply:

"The era of clinical trials started in 1994 in Russia. The aim of our NGO is to help young specialists participate in clinical trials in their field, to help Russian companies, for example, write protocols, and to conduct our own trials, etc."

In actual fact, the association's aim seems simply to be the exchange of experience between doctors.

"We also try to explain to doctors the necessity of observing good clinical practice guidelines (GCP) – with regard to archiving, for example."

Compensation in the event of harm

"*I have been working on clinical trials since 2004; most of them were sponsored by foreign pharmaceutical companies. As regards Switzerland, I've had one experience with a Swiss CRO called Averion (Hesperion), and with Novartis."*

"We encountered difficulties with Averion (Hesperion). In one of their trials, we noticed undesirable side effects caused by the drug [a drug developed in the United States,

though he did not specify which one, for reasons of confidentiality] – *including the death of one patient. There was a very long enquiry afterwards. The promoter asked about ten times if we were sure that there was a connection between the drug and the undesirable effect. After that, recruitment of patients was stopped in our hospital. The FDA did register our results, though. That was five years ago."*

Patient consent

"In our hospital, the informed consent form is given to patients in advance so that they have enough time to look at it properly. It's noted in patients' medical records, because it would be a serious violation of ethical principles for a patient to sign something without knowing what it was, or without having read it."

With regard to the possibility of consent forms being signed by doctors instead of patients, Alexander Arutyunov only admitted to the existence of "rumours":

"Sure, there are rumours to that effect, but I personally don't know of any doctors who sign informed consent forms for patients."

"It's compulsory for the patient to keep a copy of the document. The time allowed to read the form in advance varies from one hour (when it's an emergency) to one week. We even had a patient who discussed their informed consent form with their relatives for a whole month before agreeing to take part in the trial. And, of course, a lot of patients refuse after they've read the document, which mentions all the risks and side effects. I would say 40 - 45 % of candidates refuse after reading it."

Patients' motives for participating

"In Russia and developing countries, patients are motivated by the possibility of having an alternative method of treatment, which means a chance to improve their health, although some patients say they are "happy to help science". Older people participate in trials more often than other groups (unless, of course, the study is aimed at young people). They come from a variety of social classes, and can be anything from sales assistants in small shops to radio presenters. As I say, it varies."

"We have noticed that sometimes the prospect of accessing a foreign drug can also be a motive, as it is assumed that it will be better than its Russian equivalent."

Continuation of treatment after a trial

"With emergency treatments – for example, for a heart infarct – the question of prolonging treatment doesn't arise, as the patient receives the drug only once. With a chronic illness, the trial can last for a long time – up to five years. Of course, patients get used to a treatment. They can decide whether or not to continue taking the drug at their own cost. In a few cases, a certain period of prolongation of treatment, even after the end of the trial, is provided for, but such cases are rare. The doctor can't help the patient if the drug is very expensive once it's registered. Sometimes the drug is paid for by the state, and the patient can access it. But there's obviously no guarantee that a drug will be subsidised by the state."

Compensation in the event of harm

"All participants in clinical trials are insured – against disablement, damage to health, or death (in the latter case, the money is paid to the close relatives). The assessment of the link between the drug tested and the undesirable effect may only be carried out by the principal investigator. It is he (or she) who is responsible for ticking the appropriate box with reference to the link: 'possible', 'highly probable' or 'acknowledged'. It's practically impossible to contest the principal investigator's decision, even if commissions or panels of experts are convened. In our case [see above, difficulties with the CRO Averion/Hesperion], *we ticked the 'acknowledged' box, which led to arguments, experts' opinions, etc., but it was impossible to change our decision. The Hippocratic oath guarantees that doctors don't lie about these things."*

"I know of one court case following the death of a patient (not in our hospital). It was in 2005. The conclusion at the end of the proceedings was that the death hadn't been caused by the drug."

Ethical protocols and placebo

"The ethics committees reject unethical protocols, or return them for modification. The use of placebo is necessary. You need to be able to judge whether a drug is more effective than no treatment. I think that placebo is used in more than 50% of studies. There are fields in which the use of placebo is not allowed: in emergency cardiology, in oncology. When it's a matter of emergency medical aid, a placebo is practically never used."

Inspections by Roszdravnadzor

"We've been inspected by Roszdravnadzor twice. All documents were checked. We have conducted almost 200 studies since 1995, and we've had about 30 audits by a CRO – and never once has a 'major irregularity' (informed consent form not signed, etc.) been found."

"Unlike the list of trials conducted in Russia (which you can find on the US register of clinical trials[29]), the list of researchers is not published. It's confidential information held either by the CROs or the pharmaceutical companies."

Trials in the provinces

"Not all trials can be conducted in Moscow. Treatment methods aren't always the same in the various provinces – different medicines are prescribed, the epidemiology is different. It's therefore reasonable for trials to be conducted regularly in all the regions. Moscow, Saint Petersburg, Novosibirsk, Vladivostok and Chelyabinsk are leading destinations."

7.4.2. Grigory Arutyunov, chief researcher

Grigory Arutyunov has been involved, most notably, in trials conducted by Merck-Serono (CIBIS, 1996), Novartis (pulmonology) and Roche.

Compensation in the event of harm

"When we worked with the CRO Hesperion and we had problems (in 2007 or 2008), the ethics committee debated the matter for almost 24 hours. It was very serious. Then an external council of experts, called in by the promoter, studied the problem. But in 99% of cases the decision of the principal investigator can't be overturned. The drug wasn't banned after the trial, but it was recommended that a CT scan of the brain be carried out on each patient (which is an undesirable result for the pharmaceutical company)."

"Clearly, it's not in the interests of the pharmaceutical companies to have patients die, and that's why it's important to prove that there's no connection between a death and the drug being tested."

Inspections by Roszdravnadzor

"We've had inspections by Roszdravnadzor. The inspectors give us two weeks' notice of when they're coming. They only study documents in the archives (which we keep for fifteen years after the end of a trial). They consult the documents with the person responsible for the archives – in my presence – but I don't say anything."

Patient consent

"From time to time we change the text of the informed consent forms, but each new version must be approved by the ethics committee."

According to Grigory Arutyunov, this procedure is tiresome, as it takes three to four months, during which time recruitment is suspended.

"Of course, patients are free to leave a trial. I had one patient, a chauffeur, who salivated heavily as a side effect and didn't want to continue. When I give patients the informed consent form, I suggest to them that we read it together, so that I can explain it to them. Patients come from different social classes – perhaps not from among the richest, but they do include middle class people".

7.5. Irina Bondar, chief diabetologist for the region of Novosibirsk

Irina Bondar works at the city's central hospital and teaches at the local University of Medicine. She has been collaborating with Roche for at least fifteen years. She gets inspections from the ministry every five years. She told us that *"all the patients are insured; if they're not, the health authorities won't authorise the study in question.*" Placebo is used *"almost always, though it depends on the protocol"*. She admits that the drugs tested remain inaccessible to patients because of their high price, adding: *"But there are generics."* She is quite indignant generally about the increasing number of checks and audits by the pharmaceutical companies and inspections by the FDA: *"I don't understand what they're looking for."*

7.6. Alexander Globenko, Clinical Trials Manager at the CRO Proxy Group Research

Between 2008 and 2011, Alexander Globenko worked as an investigating physician at Hospital No. 64 in Moscow, for the Chair of Therapy at the People's Friendship University of Russia in Moscow. He participated in Novartis trials of drugs for the treatment of cardiovascular disease, which, in his estimation, were "*no different from any others*"[30].

Compensation in the event of harm

"The minimum insurance accepted by the Ministry of Health provides cover of 10,000 dollars for a disability and up to 50,000 euros in the event of death. A disability can be irreversible, as I have seen myself: the patient fell and broke his teeth. I told him to claim on his insurance, which he did. But generally, the Russian mentality is such that patients don't demand compensation, even when I tell them to.

"A reversible condition (diarrhoea, nausea, etc.) that nevertheless leads to a deterioration in health won't be considered for compensation."

"The link between the drug being tested and the undesirable effect is recorded by the doctor. Within 24 hours, the doctor informs the ethics committee and the Ministry of Health. Then, compensation is provided."

"I conducted trials for the Russian generic of Gilenya. We had lots of cases where the immunity of the patient was compromised. However, my patients recovered three weeks after the end of the trial and it wasn't necessary for them to claim on their insurance. My colleagues in Saint Petersburg had a serious case of hypoleukocytosis [dangerous diminution in the number of leucocytes, or white blood cells], *and one patient had a serious*

generalised infection. He had to spend a long time in hospital. In a case like that compensation should be paid."

Consent of participants

"There are cases where doctors don't let patients keep the informed consent form. Such cases are rare in Moscow but are apparently more common in the provinces. That constitutes a violation."

Doctors' motives and conflicts of interest

According to Alexander Globenko, conducting clinical trials is very much in doctors' financial interests. For some, it has become their main source of revenue: "*They forget everything – their normal clinical practice in the hospitals, conferences in the universities – they devote themselves exclusively to trials*." The amount they are paid varies.

Continuation of treatment following a trial

"Most drugs are licensed following the completion of a trial, although some aren´t due to political problems [for example, as a result of tensions with other countries]*; it can happen."*

Respect for ethical standards

"I think only four centres in Moscow and one in Saint Petersburg comply with European and US standards (in any case, they're the only ones the big international CROs work with). In the provinces, the number of falsifications, serious violations, etc. is higher."

Conclusion

Despite the difficulties in trying to expose clinical trials conducted in Russia, the information and witnesses' accounts we were able to gather led us to conclude that the Russian system for conducting and monitoring clinical trials is far from perfect. Russian doctors sometimes use enticing but unethical incentives to recruit patients. Busy promising "private attention" to patients, doctors fail to sufficiently explain the negative aspects of a trial, such as use of placebo. They tend to present a trial as a great opportunity, stressing the fact that there are not enough places for everyone and that only a lucky few will be able to participate. This verges on a serious ethical violation. Further, some doctors do not give their approval for patients to leave a trial, and do not always report it when patients do. The "possibility of leaving the trial at any time", guaranteed in the informed consent forms and required by ethical standards, is not quite so simple. Doctors are so motivated by financial concerns that some have even abandoned their own practices to focus solely on clinical trials. This is quite different from the situation in Europe and the United States, where doctors' remuneration for conducting clinical trials is comparable with their salaries – or lower. The Russian press, which follows the subject in spite of difficulties presented by duty of confidentiality, also cites financial incentives as one of the problems of clinical trials[31]. In such a context, conflicts of interest are numerous.

Contrary to the arguments of clinical trials actors anxious to protect their reputations, unethical incentives and cases of intimidation and manipulation are frequent in Russia. However, any attempt at independent observation is blocked by "confidentiality". There is no independent authority that patients can contact as participants in a clinical trial – only the principal investigator. However, this is the very same doctor who, alone, decides whether the undesirable effects in question are linked to the drug or not. The official communications of Swiss pharmaceutical companies usually record the absence of any link between deaths and the drug being tested. This may be the same throughout the world. But in Russia, it is the doctor alone who takes the decision, even when there are numerous conflicts of interest involved. Further, it is entirely in the interest of these doctors that a trial be continued – much more so than for their European colleagues. Access to treatment outside a trial is almost impossible: Swiss drugs are not available or are unaffordable for Russian patients. Russian patients, therefore, prefer to navigate their way from one trial to the next in order to receive continuous treatment. However, the drugs being tested are experimental. NGOs are being set up for the protection of patients, to ensure that people who participate in trials can exercise their rights. However, these organisations do not yet have much influence.

The intention of the Russian State to regulate everything is clear, but its regulations are, for the most part, inadequate. Although local ethics committees exist since 2010 to ensure oversight of clinical trials by local bodies of a more diverse composition, it is not possible to circumvent the central ethics committee. It alone has the power to decide, but is completely overwhelmed with work. As for Roszdravnadzor, the Russian medicines agency, its inspectors do conduct regular checks, in which participation is obligatory, but doctors are forewarned of their arrival. A further problem is that only documents are subject to investigation. The inspectors check that the correct forms are used and the content of these forms, but they do not talk to the participants. This prevents an investigation of the "human" aspect of trials. It also prevents a deeper understanding of what is really happening on the ground.

Appendix I – Russian legislation relating to clinical trials

- Law on the Circulation of Medicines N° 61-FZ, passed 12 April 2010 and in force since September 2010
  http://www.rg.ru/2010/04/14/lekarstva-dok.html
  English translation (unofficial): http://acto-russia.org/files/en_circulation_medicines_02072013.doc

- Resolution of the Government of Russia of 13 September 2010 "regarding the rules governing types of compulsory life and health insurance for patients participating in the clinical trial of a drug"
  http://www.rg.ru/2011/02/01/pravila-site-dok.html
  English translation (unofficial): http://acto-russia.org/files/Goverment_Decree_714.doc

- Russian National Standard for "good clinical practice", GOST R 52379-2005
  http://www.pravo-med.ru/legislation/fz/8881/
  http://www.gosthelp.ru/gost/gost2925.html

- Bioequivalence Studies, Ministry of Health guideline of 10 August 2004
  http://www.webapteka.ru/phdocs/doc8032.html

- Ukase of the Russian Ministry of Health of 31 August 2010 "regarding the ethics committee"

Appendix II – Example of recommendations issued by a local ethics committee

Комментарии к Информационному листку пациента и форме информированного согласия:

- На стр.1 документа указана версия 1.0 от 12.09.2011г., на стр. 2-12 – версия 1.0 от 06.12.2011. Следует устранить это несоответствие.
- В разделе «Актуальность исследования (стр.1-2) подробно описаны риски для беременных женщин и для новорожденных, связанные с инфекционными заболеваниями. Это эмоциональное описание способно встревожить и напугать беременных женщин, что можно расценивать как некорректный метод воздействия с целью склонить участию в исследовании, и это противоречило бы требованиям GCP (см. п.4.8.3). Например, «…у таких детей с большой степенью вероятности в периоде новорожденности могут развиться любые инфекционные заболевания, тяжесть которых… заранее прогнозировать нельзя» (стр. 1, предпоследний абзац). Рекомендуем Вам отредактировать эти фрагменты.
- В разделе «Характеристика исследуемого препарата» (стр. 2-3) рекомендуем указать, что препарат разрешен к применению в России, в том числе у беременных (за исключением I триместра) при урогенитальных инфекциях.
- В тексте документа неоднократно упоминается врач-исследователь, но при этом применяются разные термины – исследователь, врач, проводящий исследование, врач. В то же время есть и упоминания лечащего врача. Желательно, чтобы не путать пациента, выбрать и применять для один и тот же термин, например, врач-исследователь.
- Обращаем Ваше внимание на то, что в разделе «Затраты/компенсации» (стр.7), говорится о «застрахованной деятельности - исследовании» (конец 5-го абзаца). В досье копии договора страхования ответственности производителя или врачей-исследователей нет.
- Раздел «Конфиденциальность» (стр. 9) рекомендуем дополнить информацией о том, что медицинские данные пациентки, которые будут передаваться спонсору, будут обезличены (закодированы) (в соответствии с протоколом, стр. 70-71).
- Рекомендуем также вычитать текст и справить опечатки, в частности: стр. 4, последний абзац – уточните управление «…пастилок от боли…», стр.5, абз.5 – «…форму…, в которой…».

Unofficial translation:

Comments to a patient's information and to an informed consent sheet:

- Page 1 of the document specifies the version 1.0 dated 12.09.2011, the pages 2-12 specify the version 1.0 dated 06.12.2011. This discrepancy should be eliminated.

- In the chapter "Relevance of Study" (pp.1-2), the risks for pregnant women and new-borns linked to infectious diseases are described in detail. This emotional description can cause troubling and worries among pregnant women, which can be considered as an undue method of influence in order to induce participation in the study. This could contravene the GCP requirements (see par. 4.8.3). E.g., "…any infectious diseases can occur and affect these children with higher degree of

probability in the neonate period, the severity of those… is impossible to forecast in advance" (p.1, second last paragraph). We recommend you to edit these abstracts.

- In the chapter "Characteristics of a Study Drug" (pp.2-3) we recommend you to specify that the drug is approved for use in Russia, also during pregnancy (with the exception of the 1st trimester) in cases of urogenital infections.

- The text of the document repeatedly refers to a physician-researcher; however, different terms are used like a researcher, a physician, one conducting research and a doctor. At the same time an attending physician is also mentioned. To avoid confusion it is advisable to choose and apply only one term, e.g. a physician-researcher.

- We would like to draw your attention to the fact that the chapter "Costs/ Compensations" (p.7), mentions "insured activity-study" (the end of 5th paragraph). However, the dossier does not contain a copy of a liability insurance contract of manufacturer or of physicians-researchers.

- We recommend to complete the chapter "Confidentiality" (p.9) with information that the medical data of a patient, will be anonymised (encoded) before being transferred to a sponsor. (according to the protocol, pp.70-71).

- We also suggest to do proof reading and correct typos, in particular: p.4, last paragraph – specify handling "… pastilles against pain…", p.5, par. 5 – "… form…, in which …".

Appendix III – Results of a study conducted by ACTO into compensation and insurance in Russia

ACTO
ASSOCIATION OF CLINICAL TRIALS ORGANIZATIONS

Результаты опроса членов АОКИ по страхованию в клинических исследованиях

Цель опроса: оценка риска наступления страховых случаев исходя из имеющейся практики страхования в России

Дата опроса: апрель 2010

Параметры оценки:
Оценивались данные по количеству застрахованных пациентов, стоимости страховой премии и количеству признанных страховых случаев. Учитывались данные за три года (с 2007 по 2009 г.г.)

Результаты опроса:
В опросе приняли участие 17 компаний
Суммарные результаты отражены в Таблице 1.
Подробные результаты (по годам, по фазам исследований, а также в процентном соотношении к данным Росздравнадзора по выданным разрешениям) представлены на Листе 2

Таблица 1

	суммарно за 2007-2009 годы
	всего
количество застрахованных пациентов	71 089
сумма страховых премий ($)	3 141 978
количество страховых случаев	0
средняя стоимость страховки на 1 пациента ($)	44

	2007 год								2008 год							
	I фаза	I/II фаза	II фаза	II/III фаза	III фаза	III/IV фаза	IV фаза	всего	I фаза	I/II фаза	II фаза	II/III фаза	III фаза	III/IV фаза	IV фаза	всего
количество исследований (по результатам опроса членов АОКИ)	4	2	54	2	87	0	4	153	7	1	55	2	113	1	10	189
количество разрешенных КИ (по данным Росздравнадзора)	21	8	146	11	228	6	58	478	28	11	136	16	278	3	63	535
кол-во КИ: доля данных АОКИ по отношению к данным Росздравнадзора	19,0%	25,0%	37,0%	18,2%	38,2%	0,0%	6,9%	32,0%	25,0%	9,1%	40,4%	12,5%	40,6%	33,3%	15,9%	35,3%
количество застрахованных пациентов (по результатам опроса членов АОКИ)	68	27	5 424	120	19 559	0	1 900	27 098	395	130	5 363	176	16 260	120	1 276	23 720
количество пациентов (по данным Росздравнадзора)	458	314	13 324	547	39 251	1 090	6 800	61 784	1 042	728	11 136	1 714	40 162	605	5 256	60 643
кол-во пациентов: доля данных АОКИ по отношению к данным Росздравнадзора	14,8%	8,6%	40,7%	21,9%	49,8%	0,0%	27,9%	43,9%	37,9%	17,9%	48,2%	10,3%	40,5%	19,8%	24,3%	39,1%
сумма страховых премий ($)	1 456	2 630	245 180	5 040	734 504	0	44 676	1033486	21 962	2 327	249 674	33 925	808 553	4 200	34 768	1 155 409
средняя стоимость страховки на 1 пациента ($)	21	97	45	42	38		24	38	56	18	47	193	50	35	27	49
количество страховых случаев	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

	2009 год							суммарно за 2007-2009 годы						
	I фаза	I/II фаза	II фаза	II/III фаза	III фаза	III/IV фаза	IV фаза	всего	I фаза	I/II фаза	II фаза	II/III фаза	III фаза	III/IV фаза	IV фаза	всего
количество исследований (по результатам опроса членов АОКИ)	4	3	56	0	102	0	20	185	15	6	165	4	302	1	34	527
количество разрешенных КИ (по данным Росздравнадзора)	27	16	132	17	251	1	47	491	76	35	414	44	757	10	168	1 504
кол-во КИ: доля данных АОКИ по отношению к данным Росздравнадзора	14,8%	18,8%	42,4%	0,0%	40,6%	0,0%	42,6%	37,7%	19,7%	17,1%	39,9%	9,1%	39,9%	10,0%	20,2%	35,0%
количество застрахованных пациентов (по результатам опроса членов АОКИ)	181	100	3 828	0	14 737	0	1 425	20 271	644	257	14 615	296	50 556	120	4 601	71 089
количество пациентов (по данным Росздравнадзора)	664	1 372	10 087	1 225	30 289	440	4 285	48 362	2 164	2 414	34 547	3 486	109 702	2 135	16 341	170 789
кол-во пациентов: доля данных АОКИ по отношению к данным Росздравнадзора	27,3%	7,3%	37,9%	0,0%	48,7%	0,0%	33,3%	41,9%	29,8%	10,6%	42,3%	8,5%	46,1%	5,6%	28,2%	41,6%
сумма страховых премий ($)	23 813	8 223	233 012	0	623 607	0	64 429	953 083	47 231	13 180	727 866	38 965	2 166 664	4 200	143 873	3141978
средняя стоимость страховки на 1 пациента ($)	132	82	61		42		45	47	73	51	50	132	43	35	31	44
количество страховых случаев	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Unofficial translation of the ACTO survey:

Results of the survey of members of ACTO regarding insurance in clinical trials

Aim of the survey: assessment of risk of occurrence of insurance claims based on existing experience in Russia

Date of the survey: April 2010

Evaluation parameters: The data was evaluated according to the number of insured patients, costs of insurance and number of accepted insurance claims. The data for a period of three years was evaluated (from 2007 to 2009).

Results of the survey:

17 companies have taken part in the survey. Summary of the results is presented in the Table 1.

The detailed results (by years, by phases of study, as well as a percentage regarding the data of permits issued by the Russian Federal Service on Surveillance in Healthcare (Roszdravnadzor)) are presented on Sheet 2.

Table 1

	Total for 2007-2009
Number of insured patients	71 089
Sum of insurances ($)	3 141 978
Number of insurance cases	0
Average cost of insurance per 1 patient ($)	44

Tables 2 and 3

[*Note: items in the tables on pages 2 and 3 are identical except for the time period (fiscal years). Reproduced below are only the total columns for each time period (in yellow in the original table). The other columns of the original table represent the figures broken down into the different trial phases: phase I, phase I/II, phase II, phase II/III, phase III, phase III/IV, phase IV*].

	2007	**2008**	**2009**	**For the whole period 2007-2009**
	Total	Total	Total	Total
Number of studies (according to the survey results of ACTO)	153	189	185	527
Number of authorised CT (according to the data of Roszdravnadzor)	478	535	491	1 504
Number of CT: proportion of the ACTO data in relation to the Roszdravnadzor data	32,0 %	35,3 %	37,7 %	35,0 %
Number of insured patients (according to the survey results of ACTO)	27 098	23 720	20 271	71 089
Number of patients (according to the data of Roszdravnadzor)	61 784	60 643	48 362	170 789
Number of patients: proportion of the ACTO data in relation to the Roszdravnadzor data	43,9 %	39,1 %	41,9 %	41,6 %
Sum of insurances ($)	1 033 486	1 155 409	953 083	3 141 978
Average cost of insurance pro 1 patient ($)	38	49	47	44
Number of insurance cases	0	0	0	0

Appendix IV – List of people questioned

Associations

- Svetlana Zavidova, Executive Director, Association of Clinical Trials Organizations (ACTO)
- Artyom Golovine, Executive Director, All-Russian Multiple Sclerosis Society
- Alexander Saverski, President of the Russian League for the Protection of Patients

Doctors

- Evgeny Evdoshenko, neurologist, head of the Multiple Sclerosis Centre in Saint Petersburg
- Irina Bondar, diabetologist, Novosibirsk Central Hospital; teaches at local University of Medicine; has been working with Roche for at least 15 years
- Alexander Ilves, neurologist, St Petersburg, involved in a Novartis clinical trial (Gilenya)
- Alexander Arutyunov, assistant investigating physician and chairman of NGO "Scientifico-medical Society of Therapists of Russia"
- Grigory Arutyunov, chief investigating physician, Faculty of Medicine at the State University of Moscow
- Olga Jeludkova, pediatric oncologist; conducts clinical trials for several pharmaceutical companies and CROs

CRO

- Alexander Globenko, Clinical Trials Manager, Proxy Group Research

Supervision of clinical trials

- Maya Brodskaya, former Head of Development at Roche in Novosibirsk

Roszdravnadzor (the Russian drugs agency) inspectors

- Yuri Afonchikov, inspector and former executive director at Roszdravnadzor
- Irina Rogova, clinical trials inspector for Roszdravnadzor

Ethics committees

- Yelena Volskaya, member of the Inter-University Ethics Committee and the Independent Interdisciplinary Committee at the medical university in Moscow
- Irina Rogova, member of the Independent Interdisciplinary Committee at the medical university in Moscow and an inspector for Roszdravnadzor

Patients

- Anna, Oufa
- Natalia, St Petersburg
- Yulia, Moscow
- Natalia, Rostov-on-Don

Appendix V – Clinical trials in the Russian press

The results of one of the first **investigations into clinical trials** in Russia were published in 2009 by the renowned journalist Svetlana Reiter. In her article she gives examples of recruitment to clinical trials by a hospital, not accredited by the Ministry of Health, which demanded money from the patients for the treatment. Another example concerns a minor who received an experimental vaccine unknowingly (the parents also did not know). At the same time, the doctors stated that the "signed informed consent form" existed. However, according to Reiter, clinical trials conducted by western companies in Russia do provide a last chance for desperate patients; it is therefore up to each individual to decide whether to participate.
http://bg.ru/society/delo_vrachey-8218/

The article entitled **"Very golden pills"**, which appeared on 11 February 2013 in one of Russia's biggest newspapers, MK, deals with a financial audit carried out recently in several Saint Petersburg hospitals where clinical trials take place. As part of this audit, doctors were required to show the inspectors their contracts with pharmaceutical companies. Some refused, citing confidentiality. But the author claims that, generally, doctors can earn between 1.5 and 17 euros per patient. The author also claims that patients in the third or fourth stage of cancer are most often recruited for trials, because they cannot bring complaints. Also, doctors do not pay taxes whilst using hospital equipment. The author claims that these financial incentives contradict a doctor's commitment to the Hippocratic oath: "The commercial interest is obvious". However, this audit has not yet led to any kind of criminal investigation, despite the claims of the author that "the Governor of Saint Petersburg has been informed."

http://www.mk.ru/social/health/article/2013/02/10/810304-ochen-sladkie-pilyuli.html

Endnotes

[1] http://acto-russia.org

[2] http://www.prweb.com/releases/2013/3/prweb10499405.htm

[3] http://www.synrg-pharm.com/modules/news/article.php?storyid=135

[4] Ibid

[5] http://www.pravo-med.ru/legislation/fz/8881/

[6] http://www.rg.ru/2010/04/14/lekarstva-dok.html

[7] See, in particular: Schofield I, *Confusion reigns in Russia*, 2012 Scrip 100, 21 December 2011; Schofield I, *The red, white, blue and grey of Russian trials*, Scrip Clinical Research, 24 November 2011; Sheftelevich Y & Tripathi SC, *Drug registration in Russia and the new law*, Regulatory Affairs Professionals Society (RAPS), September 2010; Katsnelson A, *Russian drug law hinders clinical trials*, Nature 2012 Jan 18;481(7381): 250.

[8] http://ec.europa.eu/health/international-activities/bilateral-relations/index_en.htm#fragment4

[9] See Appendix IV, List of people questioned.

[10] To view one of these surveys (in Russian), go to: http://www.med-otzyv.ru/zarplata-vrachey

[11] http://rscleros.ru/forum/viewtopic.php?f=3&t=1388&start=30

[12] According to press articles and some of the people we spoke to during the investigation.

[13] An NGO for the protection of patients attested to the credibility of the patients questioned.

[14] Decisions of the Court and the Public Prosecutor: http://yopapipa.livejournal.com/28854.html

[15] http://acto-russia.org. Constituted in 2007, ACTO Russia brings together 26 CROs and pharmaceuticals companies, including Novartis.

[16] The recruitment agency Yappi. See: http://www.yappigroup.ru/index.php?page=2.

[17] For example, one faculty of medicine in organises two-day workshops on "good clinical practice" (http://www.cito03.ru/trening.html).

[18] See: http://www.roszdravnadzor.ru/main/gurn/gurnalv?year=2013.

[19] This was trial P05896, approved 23 April 2012 by the official ethics committee. For further information on this case, see also: Berne Declaration (Ed.), *Clinical trials in Argentina: the pharmaceuticals companies are exploiting the flaws in the system of regulation*. Lausanne/Zurich (2013), pp. 14 - 15, available on: www.ladb.ch/essaiscliniques.

[20] It should be noted that in 2012, in terms of press freedom, Russia was ranked 142nd according to Reporters sans frontières (Reporters Without Borders) and 172nd according to Freedom House.

[21] http://www.rg.ru/2013/05/13/proekt-site-anons.html

[22] http://www.rg.ru/2013/02/15/sovet-site-anons.html

[23] http://www.rg.ru/2012/03/01/chuchalin.html

[24] http://clinical-trials.ru

[25] See Annex II for an extract from the report issued by the ethics committee concerned.

[26] See http://acto-russia.org

[27] Confidentiality is the norm in the clinical trials sector, which complicated this research significantly. Guarantees of anonymity did not enable us to obtain more information.

[28] It was not Evgeni Evdochenko himself who communicated this, but he does not deny the facts.

[29] www.clinicaltrials.gov

[30] The trials in question were CLCZ696A2117 (phase II), CLCZ696B2214 (phase II) and CLCZ696B2314 (phase III) of the drug LCZ696 (combination of Valsartan and AHU-377); also: CSPP100A2255 (phase II) et CSPP100A2368 (phase III), trials of the drug Aliskiren.

[31] See Appendix V