Clinical Drug Trials in Ukraine: Myths and Realities

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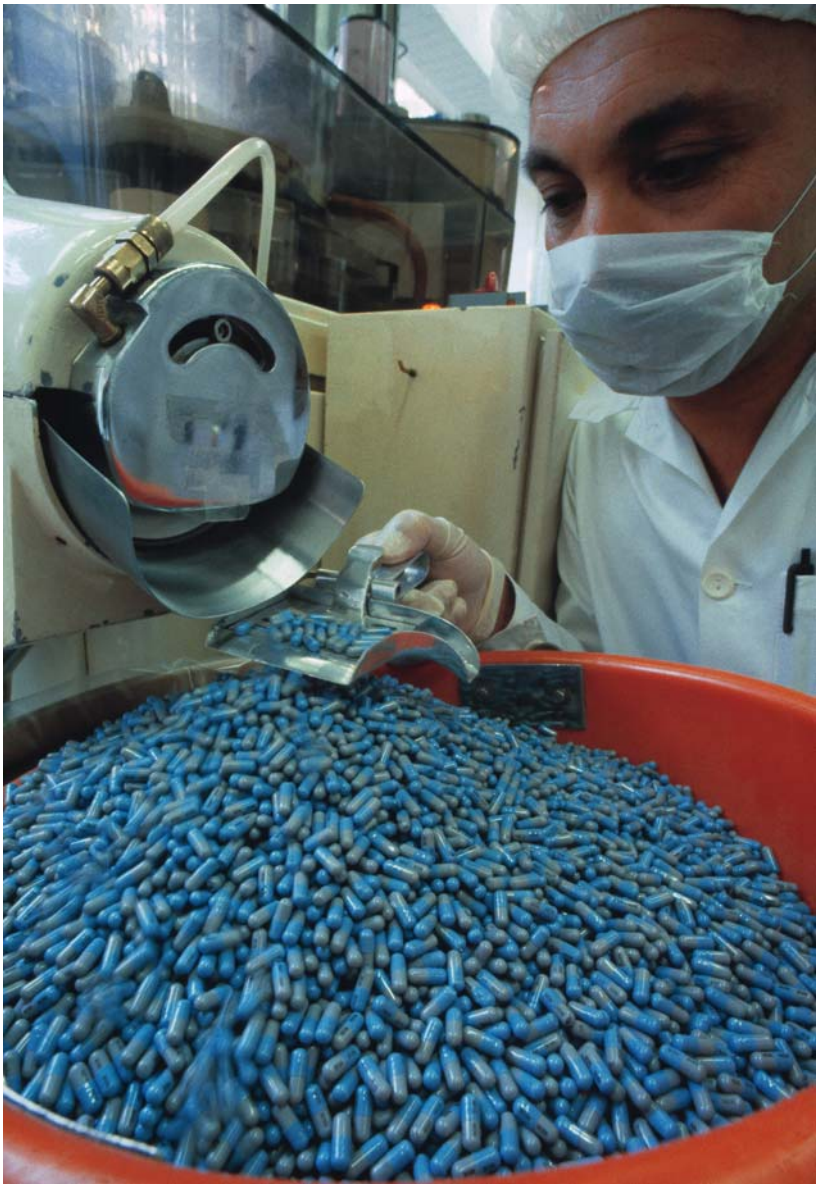

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For strategic reasons and to maximise profits, industry-sponsored clinical drug trials on human subjects are increasingly offshored in developing and emerging countries. In those countries, pharmaceutical companies can find a large pool of vulnerable 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 done by **a Ukrainian** investigative journalist.

List of abbreviations

CRO	Contract Research Organisation
CT	Clinical trial
EBA	European Business Association
FDA	Food & Drug Administration
LEC	Local Ethics Committee
MoH	Ministry of Health
SEC	State Expert Centre

Some background information

The first authorisation to conduct an international clinical drug trial in Ukraine dates back to 1996. The State Expert Centre (SEC) of the Ministry of Health[1] reviews and regulates all clinical trials (CTs) in the country.

Since 1996, the number of multicentre international CTs has been constantly growing in Ukraine, according to official figures. Whereas in 1998 20 international CTs were conducted in the country, the number reached 466 CTs in 2008[2]. According to one Contract research organisation (CRO), more than 500 CTs were initiated in 2011 alone in Ukraine, suggesting an upward trend[3]. The number of approved CT sites has followed a similar trend, from 175 in 2001 to more than 1300 in 2009.

Other figures – including statistics on the type of trials being conducted by December 2012 – can be found in the Scrip Ukraine country profile[4].

The majority of CTs in Ukraine are Phase III trials (66% of all CTs in Ukraine in 2006), followed by Phase II trials (30%) and a minority of Phase I and IV trials (1% and 3% respectively)[5].

Recent amendments in the legislation have tried to bring the regulatory environment in Ukraine in conformity with the one of the European Union. The most important legislative orders for those who conduct CTs in Ukraine are:

- MOH of Ukraine 23.09.2009 № 690 "On Approval of the Procedure for Conducting Clinical Trials of Medicinal Products and Expert Evaluation of Materials Pertinent to Clinical Trials and Model Regulations of the Ethics Committee." (Amended by Decree of Ministry of Health of 12.07.2012 № 523)
- MOH of Ukraine of 11.04.2012 № 255 "On regulating the ethical aspects of clinical trials of medicinal products"[6]

Despite the fact that many actors involved in clinical trials depict the Ukrainian regulatory environment as quite favourable, we have come across many problems and issues related to the conduct of clinical trials during our investigations. Through interviews with officials, researchers and participants involved in CTs, through analysis of statistics, speeches and statements made by representatives of the medical community and pharmaceutical companies, through exchanges with various actors and through monitoring of media reports, our investigator has gathered elements that dispel some myths surrounding clinical trials in Ukraine.

Myth number 1: Clinical trials are an open business

Clinical drug trials (CTs) are one of the most restricted and secretive areas of medicine. Despite the fact that CTs were first conducted over 15 years ago in Ukraine, information about them is extremely scarce and difficult to find. The organisers of CTs usually refer to medical confidentiality and the desire of pharmaceutical companies to maintain trade secrets.

At all scientific conferences, in congresses, in interviews and in official statements, CT organisers – including sponsoring companies, officials from the Ministry of Health, and medical researchers – state the following: CTs in Ukraine are conducted under strict governmental control, in strict accordance with the standards and regulations of Ukraine. CTs bring huge benefits to patients and to volunteers who participate in clinical trials. Medical institutions gain access to the latest information and technology; CTs thus pave the way for progress in medicine.

Several legislative changes were recently made in order to bring the regulation of clinical trials in Ukraine in line with international standards[7].

What really happens? Does society have access to information on CTs? Does society have the right to know and to scrutinise compliance with CT regulations? Are there violations of the rights of CT patient-participants?

First of all, it should be said that freedom of speech in Ukraine is restricted and limited in comparison with West European countries[8]. Very little information on CTs can be found in the public domain and in local medical literature. When a journalist tries to investigate the subject, he/she faces many hindrances and difficulties as he/she searches for information. In general, on the request of a journalist, a government agency should respond within 5 days. However, by law, if an issue is rather complex, a reply may be given in 30 days, or even longer. Government officials often use the maximum term. Once a reply is given, it does not respond to the questions raised, but gives a general outline on how plans and programmes are carried out, etc. In Ukraine this is called a "formal reply", without the requested content. Most journalists are not interested in investigating the topic of clinical trials, because it may take more than a month, even a year, to gather information. And once the official "formal replies" are obtained, it often appears that there is nothing to write about. If critical articles are published on certain topics, officials go to great lengths to prove that they are acting entirely according to the letter of the law.

Numerous formal interviews and conversations[9] – most of which were not recorded, as otherwise the person was not willing to talk – show that all key stakeholders in the organisation of CTs are reluctant to answer questions about them. These include pharmaceutical companies (sponsors), organisations that conduct CTs on their behalf (contract research organisations or CROs), managers of medical facilities, universities or departments (sites) where CTs take place, as well as the personnel that perform them. All their answers are limited to stating that CTs are held for the sake of the patients, who are now benefiting from new drugs that will save the health and lives of millions of people in the future. No one wants to go into details. One of the advantages put forward by them is the fact that during CTs not only the efficacy but also the side effects (safety) of new drugs can be tested. These can thus be eliminated in the drug development process before they are commercialised.

All in all, any information related to clinical trials is considered strictly confidential by physicians and officials. They refuse to provide information, explaining, firstly, that their patients have not given their consent, and secondly, that their sponsors do not allow the disclosure of confidential business information. None of the interlocutors agreed to provide us with the informational consent form that should be studied and signed by a CT participant.

Several discussions were also held with the companies Roche and Pfizer (at the European Business Association, EBA)[10]. They promised to take up the issue with their head office. Finally, a refusal to share documents such as the consent form was once again issued on the grounds that the pharmaceutical companies fear that their competitors would receive the information supplied.

A similar situation arose with regard to contacting CT patient-participants. During an interview at the EBA, several attempts were made to arrange a meeting with a principal investigator and patients. The request was denied on the grounds that it violates the rights of the patients and the "Law on the Protection of Personal Data". The request to communicate with CT participants, at least on the phone, was also rejected, even when offered to interview them in the presence of their physician.

Roche provided contact details of a physician who agreed to answer questions. Despite all requests the physician did not give a single opportunity to meet or talk over the phone with patients that have participated in CTs.

Freedom of speech in Ukraine is limited. Journalists' requests are often ignored or receive a formal response. Another method of gathering information was tried through NGOs that protect the rights of patients. V. Serdyuk, the president of the Ukrainian Council for Patients' Rights and Safety, agreed to assist. He used his position as a representative of the patients' organisation and held several meetings with officials from the Ministry of Health and other stakeholders to gather information about CTs.

Since 10 January, when the New Year holidays ended in Ukraine, we have been actively working with V. Serdyuk to gain access to clinical sites and to meet CT participants. Being a journalist, our investigator was refused access. However, the president of the patients' organisation did not achieve anything either. At the Ministry of Health and at the MoH State Expert Centre, he was promised the meetings, but they were put off until "tomorrow" and never took place. He talked about this in his interview.

Interview with Viktor Serdyuk, president of the All-Ukrainian Council for Patients' Rights and Safety

Journalist: As a defender of patients' rights do you have the right to go to any hospital and talk to people?

V. Serdyuk*: Yes I do. It is allowed by law and it is laid down in the charter of our organisation. However, the hospitals' rules are the following: without the permission of a chief physician the medical staff will not answer any questions, especially questions about CT patient-participants.*

J: Due to the nature of your job, you are acquainted with many hospital chiefs. Why did you not apply to them?

V.S*: A chief physician of a hospital will answer my questions only after he has been allowed to do so by the officials of the corresponding department of the MoH. At the Ministry I was not refused, but I only received promises. My appointments, however, were always postponed indefinitely.*
Finally, my patience ran out and I went to the Kiev Regional Hospital, which is in the list of CT sites, without calling in advance to make an appointment. A chief physician was forced to meet me because I was asking about the activities of the Local Ethics Committee (LEC). This is an important question, and he could not refuse to give me the information. The chief physician called for the physician in charge of the LEC. During a conversation with the LEC head it turned out that no meetings had been held and that the committee had not yet been set up. Firstly, it is impossible to carry out CTs without an LEC. Secondly, almost 10 months had passed since the dissolution of the MoH Central Ethics Committee. In this period, every hospital should have set up an LEC and held regular meetings. There had not been a single meeting at the regional hospital!

J: According to the law, many situations that arise during CTs are required to be resolved in a week. For example, if a patient-participant in a CT suffers from side effects, a prompt decision must be made as to whether or not he/she should be taken out of the CT. There are many similar situations in which a decision has to be made not by a physician, but by the LEC.

V.S: *It was not possible to get answers from the LEC chairman. He promised to find time for a meeting, but then suddenly backtracked. Later on, he said on the telephone that at first he had made a mistake: that the committee had been set up and that minutes of the LEC meetings did exist. He promised to show me the document, but then stopped answering his telephone.*

Information gathering has become more difficult after the CT scandals broke in Kiev and Poltava (see chapter 2). Officials, physicians and representatives of pharmaceutical companies refused to meet or talk in March. We thought that the CT scandal involving children would soon be forgotten, and that it would be easier to obtain the necessary information. However, a new scandal broke, the epicentre of which was the Kiev Psychiatric Hospital. This time it was not about CTs – although this institution does also conduct CTs, including trials sponsored by Swiss pharmaceutical companies[11] – but about the rules that apply to physicians treating patients (see 2.2).

Myth number 2: Clinical trials comply with Ukrainian legislation

2.1. Recent controversies in Ukrainian clinical trials involving children

In early March 2013, a CT controversy broke out in Ukraine. It was the first time such a "scandal" had been discussed in public since our investigator has been working on the CT issue – that is, for many years. Monitoring of the media reports showed that many journalists did not pay close attention to the details and did not elaborate further on the issue. It was difficult for them to understand the kind of violations that had occurred as no one reads or knows the laws, given the scarcity of publicly available information about CTs.

It all began with a statement made in early March 2013 by Valery Golovko, a deputy from the opposition party "Batjkivshyna" ("Fatherland"), at the Parliament of Ukraine. According to media reports[12], he stated that a medicine had been tested at the regional hospital of Poltava incurring numerous violations, including the fact that the trial had been carried out on orphan children without due informed consent and that the hospital did not have the accreditation certificate necessary for conducting such studies.

Later on, 14 deputies from various opposition parties released a joint statement indicating that violations in drug trials in which children, including orphans, were involved, occurred not only in Poltava, but also in Kiev. They accused the Ministry of Health of Ukraine of covering up unlawful practices in clinical drug trials involving children, based on what they call "numerous facts"[13]. These trials involved the following medicines at different locations:

- Doripenem (Doribax®), a broad-spectrum antibiotic used to treat complicated urinary tract or intra-abdominal infections, marketed by the UK company Janssen-Cilag (a subsidiary of Johnson & Johnson). The CT under investigation took place at the Poltava Oblast Children's Hospital.
- Bosentan (Tracleer®), used in the treatment of pulmonary artery hypertension (PAH), licensed by the Swiss company Actelion Pharmaceuticals. The CT under investigation took place at the Medical Centre of Paediatric Cardiology and Cardiac Surgery in Kiev.
- Somatropin (Jintropin®), a synthetic hormone used to treat Growth Hormone Deficiency, produced by the Chinese company GeneScience Pharmaceuticals. The CT under investigation took place at the Institute of Endocrinology and Metabolism – Academy of Medical Sciences of the Ukraine in Kiev.

Deputies in Ukraine have parliamentary immunity, i.e. they cannot be prosecuted for their actions, speeches and statements. They can only be brought to trial for criminal cases in which they are directly involved. Therefore, the deputies may not only receive and examine any documents, but also disclose violations, report cases of corruption, breaches of law, etc. The deputies handed their statement about CTs to the General Prosecutor of Ukraine.

Following the deputies' statement, the Ministry of Health (MoH) issued a formal press release announcing that a request for clarification had been made to the accused institutions and that, after receiving their replies and after verification of all the relevant documentation, the allegations were proven to be unfounded, since all the clinical trials were carried out in accordance with Ukrainian regulations. Additionally, it states that

> *"having considered the information on violations at CTs, the Ministry of Health will set up a special commission to examine the procedures of clinical trials in accordance with MoH Ukraine Order number 690. Results of the examination will be made public"[14].*

The Ministry of Health has also announced that, after studying the case, it reserves the right to file a legal action against the deputies should it be proven that they have spread false information.

Since that press release, more than two months have passed. The Ministry of Health has not yet reported the results of the commission's work, which was supposed to study the issue of clinical trials involving children. It is not known whether such a commission has been formed and which experts have been involved.

2.1.1. Analysis of Actelion's bosentan clinical trial

The MoH press release mentioned the following about this case:

> *"Research into the drug "bosentan" was conducted with the participation of one child at the Scientific and Applied Medical Centre of Paediatric Cardiology and Cardiac Surgery of MoH Ukraine in Kiev. The clinical trial was approved at a meeting of the Scientific Expert Council of the State Expert Centre of MoH Ukraine (Minutes Item 01 dated 27.01.2011). A confidential official letter was sent to the Office of the Vinnytsya City Council Child Care Services to inform them that the patient was taking part*

> *in the clinical trial. The clinical trial accreditation certificate was available at the hospital"*[15].

The statement made by the group of opposition deputies, however, says the following:

> *"In the Department of Paediatric Cardiology of the Scientific and Applied Medical Centre of Paediatric Cardiology and Cardiac Surgery of MoH Ukraine, cases were found during research on the drug "bosentan" in which the Child Care Services had not been informed about the fact that children were taking part in the clinical trial. The clinical trials were conducted without a proper accreditation certificate from the health institution"*[16].

Mention of the Child Care Services[17] in the press release of the MoH is evidence that an orphan child was not only under treatment, but took part in a CT. Usually the Child Care Services should only be informed when a child does not have one or both parents. If a child has both parents, they are asked to sign an informed consent form. As a rule, medical researchers do not report such cases to any institution, especially the guardianship services, as they have nothing to do with it. But if an orphan or semi-orphan child is involved in a clinical trial, a social service official or the director of the corresponding orphanage must sign the relevant documents and take responsibility for the consequences. According to key informants, signing an informed consent form for an orphan to take part in clinical trials is a mere formality and it is easy to obtain from an official or the director of an orphanage[18].

By law, the guardianship services do not have any leverage over the hospital. There is no available information showing that the guardianship services have ever intervened in the process of administering treatment to children, and the same is true of clinical trials involving children. By law, Child Care Services must make sure that the rights of children living without their parents are not violated. However, not a single case has been reported in which the Child Care Services monitored how orphans were treated and how clinical trials involving these children were conducted. It seems everything is in the hands of physician-researchers.

The fact that the Child Care Services in Vinnytsya were contacted indicates that the child lived in this city and that he/she was an orphan.

Ukraine has long rejected proposals to conduct clinical trials involving children[19]. Two years ago, amendments were made to legislation and CT operators are now allowed to involve child participants in CTs. However, the law permits the participation of orphans in CTs only in very exceptional cases, when the product is vital to the child and can save his or her life. On the question of benefit-harm assessment there should be absolutely no doubt that the CT will benefit the child's health. In this way, the law is intended to protect the rights of children whose parents are no longer there to do so.

Another point in the MoH statement raises questions: the fact that only one child was involved in the trial. Conducting a CT on only one participant seems inefficient and pointless. However, pulmonary artery hypertension (PAH) is a rare disease. According to a recent search of an international database[20], 104 studies on bosentan are listed, of which 2 are active in Ukraine at the aforementioned institute in Kiev, and are sponsored by Actelion. Both are Phase III international trials studying PAH in children, one being an extension of the other. A total number of 64 children have been enrolled, spread over 48 trial sites located in 19 countries (including 3 sites in Ukraine). It may well be, therefore, that only one child has participated in the controversial trial – but this kind of information is not available from the database record.

Another troubling fact is that the paediatric formulation of bosentan is not allowed in the United States, whereas it has been authorised in the European Union (July 2009) and in Switzerland (July 2010), although in the latter case only implicitly. The FDA medication guide for bosentan, which was revised in October 2012, says: "*It is not known if Tracleer is safe and works in children below 12 years of age*"[21]. Whether this trial was intended to further document the efficacy and safety of the paediatric formulation of bosentan in order for it to be re-submitted to the FDA, or whether the organisers took an excessive risk involving children to test this drug, including in Ukraine, is not clear.

In their statement, the deputies suggest that not only one but several children participated in the Ukrainian bosentan trial. This is also disturbing. However, it will be difficult to find compromising evidence from the Ukrainian records, if any. Since the trial started in 2011, the clinical records could easily have been filed away and subsequently changed, as is customary in Ukraine. At the 4th Ukrainian Pharmaceutical Forum, which took place in Kiev in October 2011, representatives of Local Ethics Committees proposed that CT documents should be stored for 10-15 years. However, hospitals do not have the facilities for storing a large number of documents over the years. It was difficult to get an answer to questions regarding where and how these documents are stored. This clearly suggests that CT documents are not properly stored. There are alleged cases in which a patient's medical record has been rewritten, either in its entirety or on a few selected pages, in order to

hide physicians' mistakes. Therefore, the CT documents for 2011 may have been thrown away or rewritten as needed.

Finally, the fact that the deputies alleged that the institution where the trial took place had no due authorisation to do so is also a concern.

2.1.2. Analysis of the Jintropin trial

The second allegedly unethical trial took place at the children's department of the Institute of Endocrinology and Metabolism in Kiev.

According to the deputies, the CT under investigation was violating the law. Here is their statement[22]:

> *"In the Paediatric Endocrinology Department of the Public Institute of Endocrinology and Metabolism, 26 patients have participated in a clinical trial of the Chinese drug "Jintropin" beyond the period specified by the insurance contract. The information consent procedures of 9 patients were contrary to the requirements of the law, as the forms were only signed by one of the parents rather than the mandatory two".*

The official position of the Ministry of Health mentioned the following[23]:

> *"According to the conclusions of the Central Ethics Committee of MoH Ukraine dated 02.03.2011 (№ 5.12-228/KE) and of the MoH Ukraine State Expert Centre dated 09.03.2011 (№ 193/KD), post-registration clinical trials of the drug "Jintropin" were conducted in the Department of Paediatric Endocrinology of the Institute of Endocrinology and Metabolism in the period from 10.03.2011 to 10.03.2012, within 6 months, on 30 patients with growth hormone deficiency. The drug has been registered in Ukraine since 21.04.2009 (registration certificate number 259). Since that time it has been centrally purchased by MoH Ukraine and is used on children with growth hormone deficiency in Ukraine.*
>
> *During treatment, no side effects or negative consequences, or indeed deaths, were recorded. All children completed treatment with a positive clinical outcome (satisfactory gain in growth). Regarding the patients' informational consent: in 26 cases it was signed by both parents and by the patient, and in 4 cases it was signed by one of the parents".*

The MoH statement raises several questionable points. Firstly, after using the term "clinical trial" in the first paragraph, it mentions only "treatment". Clinical trials are no longer mentioned. Secondly, the deputies mainly claimed in their statement that there had been irregularities in the informed consent procedure. The MoH noted, for its part, that there had been no fatal cases. However there was no mention of any child deaths by the deputies. Why did the officials have to justify themselves?

As has already been mentioned, an informed consent form must be signed by both parents when children take part in clinical trials. If it is signed by only one parent when both are alive, it is considered a violation of the law. And if it is signed by a grandmother or a guardian, or a director of an orphanage, it proves that the child is an orphan. By law, the participation of orphans in CTs is permitted only in cases in which a drug is vital to save the life of a child.

Finally, the MoH officials admit that the informed consent procedure had breached the law in 4 cases (9 according to the deputies), as consent had been given by only one of the parents. The law requires the signature of both parents, even if they are divorced or separated. The MoH did not explain why this had happened. They did not even mention the fact that one had been signed by a grandmother, as the supervisor of this CT told a TV channel. This fact indicates that the child lives without parents. No explanations were given as to why an orphan child was included in the CT group.

Neither was there any mention, in the MoH statement, of the supervisor sending a letter to the Office of the Child Care Services regarding this trial. In contrast, the MoH did give this information for the bosentan trial. Why?

The answers to the above-mentioned issues could not be obtained from the Ministry of Health. Officials refer to the fact that the position of the MoH is fully explained in their press release.

2.1.3. Analysis of the Doripenem trial

The alleged unethical trials in Poltava are those that have the greatest resonance.

Deputy Valery Golovko accused physicians from Poltava Regional Hospital of, firstly, conducting "illegal trials of dubious drugs on children", and secondly, of enrolling "orphans in clinical trials".

The deputy's statement says[24]:

> *"In Ukraine, clinical trials of drugs that have been recently submitted for registration have been conducted with numerous procedural violations. A striking fact is that orphans are involved in the trials beyond the expiration of the*

> *insurance policy or without the permission of one of the parents and, even worse, with violations of the informed consent procedure for the child patients. These elements are observed in many health care institutions. There are cases of clinical trials involving children in the Paediatric Department of the Poltava Regional Children's Hospital, in particular the multicentre clinical trial of the drug "doripenem". It is known that the accreditation certificate for this hospital was missing for almost a year and a half (from 20.11.2010 to 17.02.2012)".*

The Ministry of Health has denied all the deputy's accusations through an official statement that says, in reference to this specific case[25]:

> *"Conducting clinical trials is a procedure carried out by numerous medical and scientific research institutions in Ukraine, under the control of the MoH Ukraine State Expert Centre, to evaluate the efficacy of a drug. This medicinal product is already registered, has passed extensive testing, and is permitted to be used in Ukraine. This procedure is governed by the current of MoH Ukraine order № 690 dated 23.09.2009.*
>
> *The Ministry of Health immediately responded to the published statement and requested that the […] Department of Health of the Poltava Regional State Administration confirm or deny the claims. The following replies were received.*
>
> *Poltava Regional Children's Hospital is the clinical base of the chair of the Department of Paediatrics number 2 of the higher state educational institution of Ukraine, "The Ukrainian Medical Stomatologic Academy". The Academy, in turn, is the clinical base of the MoH Ukraine State Pharmacological Centre and, as a clinical centre, has all the permits to conduct clinical trials of drugs.*
>
> *In the period of June to September 2012, during clinical trials of the drug "doripenem", two children were treated. This medicine is an antibacterial agent and is used to treat urinary tract infections. It is authorised for use in Ukraine (registration certificate number UA/9213/01/01, valid from 17.12.2008 to 17.12.2013).*
>
> *In the patients' medical records there is an informed consent form signed by both parents, which is a requirement for the inclusion of a child in clinical research monitored by the Ethics Committee of Poltava Regional Children's Hospital. Today these children are in sustained remission of the disease".*

By law, participants have to be provided, by the CT sponsors, with insurance that guarantees them compensation in the event that the study harms their health or is fatal. This is standard procedure for all participants, including orphans. Previously, CT sponsors were able to avoid having to provide CT participants with insurance, but after the recent legislative changes it has now become obligatory. The Ministry of Health has stated that CTs cannot begin until all participants are insured. The statement of the deputies, however, suggests that insurance coverage was not provided during the whole duration of the trial, which is a violation of the existing law.

The involvement of children in CTs falls under the authority of Yuri Pavlenko, Presidential Commissioner for Children's Affairs in Ukraine. He promised to investigate the situation and find out whether violations during CTs in Poltava Regional Hospital had occurred or not. However, according to informed sources, he visited the hospital in Lubny – located halfway between Kiev and Poltava – and had a talk there with the physicians during his field visit in March, but did not go to Poltava.

Afterwards, he told journalists:

> *"The Prosecutor's Office, the Regional Health Administration of Poltava Regional State Administration and the Ministry of Health carried out an investigation and concluded that no clinical trials or testing of any drug or vaccine in the Poltava region, or in the whole of Ukraine, were performed. Firstly, it is forbidden by law. Secondly, in this period, which was mentioned in the deputy's statement, the vaccines in question were not available in the region. In Poltava, the medical records of all orphans and children deprived of parental care, who were in hospitals in the years 2011-2012, were reviewed. As a result, no trace or reference that trials or testing had occurred in the region of Poltava were brought to light"[26].*

Experts from patients' organisations have stated that the investigation of the Presidential Commissioner for Children's Affairs was that in appearance only. He did not study the situation in the field and did not even go to the Poltava Regional Hospital. There were no reports confirming that he had met with the children and their parents mentioned in the deputy's statement. Moreover, the Commissioner got the type of product being tested mixed

up: the CT was not conducted on a vaccine, but on an antibiotic. His statement reveals his incompetence in this area.

The Presidential Commissioner for Children's Affairs does not know whether the law permits clinical trials involving children to be conducted or not. The Ministry of Health confirms that the CTs have been carried out and names the drug, but Yuri Pavlenko states that the CTs have neither been conducted in the Poltava region, nor in Ukraine in general. How can he identify violations, if he does not know the regulations, CT standards, etc.?

All the above confirms that government officials avoid the topic, are not interested in how CTs are carried out and do not know the regulations.

Further investigation revealed some interesting facts.

The Poltava Hospital management states that "*until 17.02.2012 the drug "Doribax" ("doripenem") had not been used in the Regional Children's Hospital*", but it does specify when it was actually used. The Ministry of Health reported that the CTs were conducted in the period from June to September 2012. However, in early January 2012, the US Agency for Food and Drug Administration (FDA) published information on the early termination of a clinical trial of Doribax (doripenem) due to safety concerns. The manufacturers of the antibiotic decided to expand its field of application and organised CTs during which the efficacy of the drug in the treatment of patients with various forms of pneumonia was tested. However, the result was not as expected. Patient clinical recovery numbers were too low and the death rate in the group receiving doripenem was higher than in the control group, in which a different drug was used.

> *"It turned out that the mortality rate of patients is higher, and the clinical cure rate is too low, compared with the group of patients receiving imipenem-cilastatin"*[27].

The FDA, whose verdict is binding and must be respected, reminded the experts that in the USA "Doribax" is not approved for the treatment of any type of pneumonia and is contraindicated in a dosage over 500 mg every 8 hours.

How, then, is this antibiotic recommended for use in Ukraine? The product is registered in Ukraine and the instructions contain all the necessary information. Firstly, Doribax is recommended for the treatment of adults – people over the age of 18. Secondly, the list of diseases comprises pneumonia, intra-abdominal infections, complicated urinary tract infections and pyelonephritis. The dosage is the same for all diseases: 500 mg every 8 hours, the course of treatment from 7 to 14 days.

The prescribing information also states that "*there is no experience of using this drug for children under 12 years old*". Why is this age mentioned? Is there any data on use of the drug for the 12 to 18 age group? This is not specified.

Can this be considered a violation of the treatment process? It should be considered that Doribax is not recommended for patients under 18 years of age. It was therefore clearly a CT and not treatment, according to standards approved by the Ministry of Health. Taking into account the information from the FDA, it can be concluded that the health of children was exposed to risks. But neither the physicians nor the officials recognise this.

The prescribing information indicates that the drug can cause side effects, and recommends consulting a doctor immediately if the following occurs when taking Doribax: severe allergic reaction, hives, difficulty breathing, swelling of the mouth, tongue or face, chest pain, bloody stools, fatigue, severe diarrhoea, severe cramps, etc. The dose and administration details include the threat of serious side effects, including "lethal hypersensitivity reactions – anaphylaxis". It is not excluded that such kinds of complications arose during the CTs of the drug in the treatment of pneumonia, as a result of which the FDA ordered their early termination. The fact that children were treated in cases of urologic diseases, not in cases of pneumonia, did not mean that they were protected from the side effects that might have occurred at any time.

Did the physicians know about this? They must have known. Did the parents know? It is unknown. Most probably they did not know what kind of drug their children were injected with and they did not read the prescribing information.

One of the reasons that could influence the decision of parents to involve their children in CTs is the poor state of the health system and their low income. According to the Constitution of Ukraine, medical assistance should be publicly funded. However, patients have to buy everything at their own expense, including drugs, syringes etc. Perhaps this is why almost 90% of drugs in Ukraine are sold freely in pharmacies without any need for a prescription. This includes antibiotics.

The cost of a pack of "doripenem" (10 vials) is more than 4 thousand hryvnia (about 450 euros). For a course of treatment a minimum of three packs, as well as syringes, droppers, etc., need to be bought. Taking into account the low wages in Ukraine, as well as the low living standards in general, it is understandable that some parents accept offers for their child to take part in clinical trials. The physicians very often do not even pronounce the words "clinical trial".

2.1.4. Conclusions and unanswered questions

The contradictions of the doripenem case reflect how government officials, namely the MoH and the Presidential Commissioner for Children's Affairs, dealt with communications. First they wrote on their official website that there had been no clinical trials involving children at all. Then they wrote that there had been CTs with children but without violations. They even named hospitals which were not mentioned in the deputy's statement. The MoH stated that all the CTs had taken place without incurring violations, but it did not grant permission to talk to the children, their parents or guardians.

Many questions are thus left unanswered.

For example, what was really done to the children in Poltava Regional Children's Hospital: were they treated according to a treatment protocol approved by the Ministry of Health or were they participants of a CT? The same question arises for the other controversial trials of bosentan and Jintropin.

Pharmaceutical companies affirm that children in Ukraine are being given the opportunity to be treated with the latest drugs. Experts from patients' organisations believe that adults are using children as a resource for carrying out clinical trials. In so doing, they do not really care about children's health and rights.

Hospital executives in Poltava state that no violations occurred. They also say that there have been no CTs. This was a treatment procedure in which two children were injected with an antibiotic prescribed for urologic diseases. The consent form to use the medication had been signed by both parents. However, the response of the Ministry of Health clearly states that "*during the clinical trials of the "doripenem" drug two children were treated*". Who is lying then: the head physicians or the Ministry of Health?

According to the law, there is no need for any signed permission from the parents in the routine treatment of children. If an informed consent form has been registered by the hospital, then it was a CT rather than standard treatment. The hospital categorically refused to give any information about the children, the contact details of their parents or their general practitioner. As always, patient-doctor confidentiality and the Law on the Protection of Personal Data were referred to.

Researchers have informally reported[28] that the above-mentioned clinics, where CTs with children were conducted, did not have accreditation at that time. This means that violations of the law have occurred. The reason is simple: at that time the Ministry of Health was not issuing the relevant documents. There was an ongoing management change in the Ministry of Health, many committees were not working. That is why applications were not considered.

The scandal was eventually silenced. State officials declared that there had never been, nor are there now, any problems with CTs involving children. All the deputies' statements were declared to be political provocations from the opposition[29].

2.2. The problematic doctor-patient relationship

Ukraine has a long-established tradition according to which a patient fully trusts his/her doctor and follows his/her recommendations. Typically, a doctor's advice does not cause concern to the majority of patients.

Doctors frequently abuse this position of power over their patients. According to testimonies of the relatives of those who took part in CTs, physicians, in order to recruit participants from their pool of patients, sometimes tell them that new drugs have been received as humanitarian aid. "They are very expensive, but we could make an exception for you and you will get it for free. Please sign the form to show that you agree to receive them. And that you will not pay for them", they say. People agree to this. Parents of child patients also sign all the documents, because the treatment of chronic diseases is very expensive, they have no insurance, their wages are low. In addition, patients and their families understand how dependent they are on their doctor. In Ukraine, given the prevailing conditions, it is very difficult, if not impossible, to refuse a doctor and to go and see another for treatment. This is pointed out by patients themselves, by experts from NGOs and by lawyers.

A dramatic recent example of patient abuse: the Kiev Psychiatric Hospital

The Kiev Psychiatric Hospital, named after Pavlov, is the main medical institution in the mental health service system. Our investigator has visited it several times, including with a TV crew reporting on the preparation of the Ukrainian law on psychiatric care and patients' rights as well as with international organisations in 2011 and 2012. All the visitors were shocked by what they saw there.

This hospital has special status and outsiders are not allowed to visit it. Having a press card does not help gain access. Medical buildings are locked, windows are barred, and patients only go for a walk accompanied by nurses. Communicating with them is prohibited.

In March 2013, a TV programme that specialises in investigative journalism conducted an experiment to investigate the way patients are treated there. A young man asked one of the doctors at this institution to hospitalise a middle-aged woman. His version of events was that "the woman is the mother of his wife, has a very difficult character and disturbs the life of the young family". The request was to isolate the woman, to punish her for

interfering in the family matters of her daughter, to scare her, to make her quiet. The media reported that the doctor agreed to hospitalise the healthy women for 1000 hryvnia (approximately 95 euros). The doctor promised to make her life hell. The conversation with the doctor was recorded with a hidden camera[30].

The doctor said:

> *"She will be tormented; the woman patients will beat her. Her head will be hit against a toilet bowl in the bathroom. A drunken nurse will beat her at night. This will be hell! I assure you that there are people in the hospital under false pretence and good money is paid for it! The money is not spent in vain. The woman will not receive any treatment there, no sedation, nothing! She will suffer! You will pay every month. And who knows how long your relative will live. She could live for five years and she could live for only two months".*

At first, the hospital refused to comment on the case in question, then it was said that this case was slander. Later on it was revealed that the doctor mentioned in this case had been fired from the psychiatric hospital[31].

In late March, it was reported that the psychiatric hospital had no money for medicine and food for the patients. However, under the law, this should all be funded by the State and by the municipality of Kiev.

Then information came out revealing that some patients in the hospital do not receive food or even water. Some are given only porridge, bread and tea. There are rooms there in which people live out their lives in terrible suffering. According to information made available on the Internet, the prosecutor's office began an investigation into this psychiatric hospital. The reason given for this was a statement claiming that mentally sick people were being forced to sign documents giving away their apartments and other property to their relatives[32].

The patients without relatives are also put at risk. Inadequate treatment leads to rapid deterioration of their health, sometimes even to loss of life. Their property is also given away to others. The prosecutor's office is still investigating the issue. No additional information has appeared because of the secrecy of the investigation.

It is well known that psychiatric hospitals have special status. In the Soviet era the psychiatric service was part of the penal system: people who were against the state were often sent there. Obviously, some features of the old system still continue to be in force today.

The above-mentioned journalistic investigation has shown that patients' rights in the hospital are promised but not observed.

Myth number 3: Clinical trial sites meet international standards.

What guides CT organisers in selecting clinical trial sites? Officials claim that they are guided by legal requirements, which strictly regulate this issue. The government, through the Ministry of Health and the State Expert Centre (HEC), considers all proposals, analyses the capabilities of each hospital or centre and, only after careful checking, makes a decision. The CT sites should theoretically be located only in higher-level hospitals, where medical schools are based and where health care is provided not only by regular physicians but also by university professors.

Municipal (i.e. ordinary city) hospitals, which are not teaching hospitals, cannot and should not be CT sites. The main reasons for this are: poor resource infrastructure, a lack of modern diagnostic and laboratory facilities, and the lower professional qualifications of the medical staff. Many drug CTs involve critically ill patients, e.g. patients with a myocardial infarction, stroke, lung diseases, cancer and other complex diseases. In such cases, intensive care and emergency units, modern equipment, tools and medicines are needed, but are either not available at municipal hospitals or are in poor condition. Physicians in such hospitals do not have the appropriate qualifications or experience of running a CT. All these factors can have a significant impact on the progress and results of the CT. Therefore, these municipal hospitals are not officially included in the list of CT sites.

However, recently, CT participants have asserted that the sites are only selected by CT sponsors, which are pharmaceutical companies. If they name a hospital that they are comfortable with, it is included in the list of CT sites. The law also leaves room for the sponsor to select the CT site[33]. The State Expert Centre states that the list is compiled in compliance with all legal requirements governing CTs, but that may be seriously questioned. Officials claim that all hospitals in which CTs are held have advanced equipment, diagnostic facilities, certified laboratories, and well-trained medical staff. These are the arguments used to attract foreign pharmaceutical companies interested in conducting CTs in Ukraine.

However, it is evident that health care in Ukraine is lagging behind world standards. The health system has been gradually destroyed by years of underfunding, corruption and the incompetence of its managers. According to Article 49 of the Constitution of Ukraine, medical care is free of charge for citizens. This means that it should be funded through the State budget. As there is no social security (insurance) system, the State budget is the only source of financing for the country's health system.

These facts are known by the managers of multinational pharmaceutical companies that are planning to conduct CTs in Ukraine. Companies from many different countries have representative offices in Ukraine; they have been doing business here for a long time, monitoring changes in legislation, analysing media reports, etc.

Those that work in the field of medicine know very well that, since the Declaration of Independence of Ukraine in 1991, the Ministry of Health has replaced 16 or 17 of its ministers. Some of them held the post for only 4 to 8 months. Naturally, this has had a huge impact on the health care industry, leading to its deterioration, poverty and lack of qualified human resources. For the last three years, all the attention of the MoH has been devoted to putting out tenders to determine which companies will supply medical equipment, medicines, vaccines, medical materials, etc., all funded by the State. On average, over the last few years, the Ministry of Health has had an annual budget of about 7 billion hryvnia (roughly 650 million euros), spent on medical staff salaries, payment of the running costs of health facilities, as well as on the implementation of government public health programmes such as tuberculosis control, HIV/ AIDS, immunisation of children, etc. According to the Ministry of Health, in 2013, the Ministry received only 19% of the funding needed from the central government.

Officials do not like to recall these data. They are taken from official sources, in particular, from the Supreme Council's Health Committee, articles of the Law applying to the 2013 State Budget, and from the 5th report of the Government of Ukraine on the implementation of the European Social Charter for the period from 1 January 2008 to 31 December 2011[34].

In Kiev, numerous CTs are constantly being carried out. Do Kiev hospitals match international standards? According to the Kiev Statistics Office, the debt of Kiev hospitals reached 170 million hryvnia in the first 4 months of 2013 (about 16 million euros). Medical institutions do not receive financing for development, for new equipment, tools, repair works and so on. More than 50% of the X-ray equipment was purchased over 15 years ago. Ultrasound equipment, electrocardiographs and other diagnostic equipment are in an equally poor state. Equipment often breaks down and there is no money for repairs, hence it is difficult to do the necessary tests on schedule, essential during both regular treatment of patients and in CTs.

The above-mentioned facts lead us to conclude that hospitals equipped with outdated equipment as well as poor laboratory and diagnostic departments can barely serve as appropriate sites for clinical trials of new drugs. It often occurs that patients need to go through additional diagnostics and tests while looking for treatment, not in the state and municipal hospitals' laboratories but in private

ones, to verify the accuracy of a diagnosis. They do this because of a lack of trust: they doubt that the equipment has been correctly monitored and configured, and they do not believe that the reagents in public laboratories are of good quality. Those who participate in CTs do not have a choice; they have to undergo all the examinations at the hospital in which the CT is being conducted. Do they obtain accurate results? Is it possible to trust 100% the reports of physicians who conduct clinical trials?

Journalists, together with patients' organisations, conducted an experiment: a diluted solution of tea was sent to laboratories in Kiev and Kharkov. In their analyses, only one (!) of the 6 laboratories identified the solution as tea and noted this in its record. The other 5 laboratories stated in their records that it was urine, and even indicated a protein level and the presence of glucose and minerals.

In 2010-2012 our investigator also participated in another experiment together with the patients' organisation "Health of the Nation". Volunteers sent blood samples to several laboratories (observing all necessary requirements) for blood glucose testing. The results were catastrophic. The laboratories came back with a level of glucose for the same person that varied between 4 and 20 units.

These results were shown to experts from the State Pharmacological Centre and they were asked for comments. They replied that it was not an experiment, but a provocation.

A conversation with V. Chumak (former director of the MoH State Pharmacological Centre) turned out to be very interesting. He is considered a highly competent person in the pharmaceutical industry, an experienced manager. The initial questions that were put to him were: *is it possible, in such conditions, to trust the quality of the CT? And how is it possible to identify the effects and side-effects of a drug on the body of a CT participant if the majority of laboratories in Ukraine do not guarantee the quality of their research?*

Interview with Viktor Chumak, former Director of the State Pharmacological Centre MoH

V. Chumak: *Why is it not possible to trust? An experienced physician determines, without laboratory tests, whether a medicine helps a patient or not.*

Journalist: However, a physician-researcher must keep a record of all the results of a trial and a record of the laboratory diagnostics of a CT patient-participant. What does he record?

V.C.: *He records the data given by the laboratory. There is no reason not to trust its results if the laboratory is certified and has a work permit.*

J: A base/site in a poor state and problems with laboratory services may lead to results of CTs in Ukraine differing from those obtained in other European countries. Do the sponsoring companies pay attention to this fact?

V.C.: *Why should they differ? In fact, all CTs are conducted according to the same rules. And if a sponsoring company is alerted to something, a physician who conducts a CT can always be asked to check everything again. Usually, the results of CTs conducted in Ukraine are beyond doubt, the indicators are the same as in other countries.*

Discussions were also held with the pharmaceutical experts from the Ministry of Health, who said almost the same thing.

The previously mentioned scandal at the Kiev Psychiatric Hospital (see 2.2) is also very worrying as this institution also conducts clinical trials, including Swiss ones[35].

The Ukrainian Psychiatric Association has confirmed that clinical trials of mental health drugs are carried out in this hospital. How are the CTs conducted there? The hospital authorities state that everything is done according to the law. Informed consent forms are signed by the patients themselves or by their relatives or trustees.

But does a hospital of this kind meet the requirements of the health care institutions in which CTs are conducted? Can the informed consent forms of CT participants be trusted? Have they been signed according to all the rules? Do patients understand what they are signing? If the informed consent form is signed by relatives, are they really interested in a positive outcome from the patient's treatment or are they just interested in receiving the patient's house or other property?

As she was looking for information about CTs in the hospital in question, our investigator contacted the associations of psychiatrists (there are several of them in Ukraine). None of the physicians agreed using his/her name. Even those who are considered to be leading experts asked not to broach the subject of CTs in psychiatric hospitals, claiming that – since there is no money for the necessary medicine – CTs provide free treatment and a chance for these patients, if not to be saved, then at least to have their suffering eased.

To the question "Do the patients receive medicine or placebos?" our investigator was assured that they are given medicine and that no one is left without help. None of the physicians showed an informational consent form.

Myth number 4: CTs in Ukraine are unbiased

Independent observers and experts are increasingly talking about the fact that drug companies are finding ways to "programme" the results they need. Members of the CT subcommittee of the European Business Association (EBA)[36], which includes local representatives of the multinationals Pfizer and Roche, were asked to comment on this issue.

All of them stated that pharmaceutical companies conduct CTs exclusively to obtain objective information in order to determine the effect of a drug on the human body. The pharmaceutical industry spends a lot of time and millions of dollars producing a safe and effective drug.

Independent experts consider that, for the sake of profit, pharmaceutical companies are seeking ways to reduce the cost of the CT process. This is why they choose developing and emerging countries, including the post-Soviet countries, with low salaries and very low insurance costs for CT participants compared with Western countries. They are also interested in reducing the time of CTs, in particular the period of recruitment of CT participants. This may even lead to a situation in which physicians recruit more participants than necessary for a CT. All these violations are caused by a desire to beat the competitors and bring a drug to the market as quickly as possible.

An "industry bias" in CT results was confirmed by researchers from Toronto and Harvard Universities in 2010[37]. They studied CT results in relation to funding sources for five groups of drugs, including antidepressants and oncology drugs. Data from 500 CTs showed that 85% of the industry-sponsored trials gave positive results. The other government-funded trials showed more modest results – only 50% of the products received a positive evaluation. In a similar 2007 study of statins (cholesterol treatment)[38], researchers concluded that trials funded by the pharmaceutical industry were 20 times more likely to give results favouring the tested drug.

In Ukraine it is alleged that pharmaceutical companies suggest to physicians and researchers what indicators should be used for a successful CT. In this case, they refer to the fact that CTs have already been completed in some countries and obtained positive results. Hence the same results should come from Ukraine. Such advice is "considered" by physicians and influences their work. The reason is simple: the salary of a doctor is very low, on average 2-3 thousand hryvnia (200 to 300 euros). It is legally permitted to earn more money through CTs, to take part in scientific conferences abroad, etc. Working in conditions such as those that prevail in Ukraine, it is very difficult for a doctor to be independent and to keep his/her own point of view. For this reason they mostly follow the "advice" of the sponsors.

Myth number 5: Sponsoring companies are in total control of CTs

Following the CT controversies involving children, the European Business Association (EBA) sent out a press release on 18 March entitled "Safety of clinical trials in Ukraine" that basically said the following:

> *"Members of the European Business Association, represented by leading international companies and conducting clinical trials in Ukraine, are extremely concerned about the interpretation of clinical trials as a result of the statement of the group of deputies dated 11 March 2013.*
> *We consider that the information given in the statement and presented as "fact" should be carefully checked to avoid possible unfounded accusations, which can affect the reputation of medical institutions and their staff. Therefore, in our view, Ukrainian society is not well enough informed about clinical research and the benefits it undoubtedly brings to the country. CTs provide severely ill people with free-of-charge, high-quality treatment using modern highly innovative drugs. Taking into account the critical situation of the health care system and the low income of the majority of Ukrainians, they are extremely important".*[39]

The CT system is organised in such a way that pharmaceutical manufacturers often have no direct relation to the CT process. The responsibility of carrying out the CT usually falls to an intermediary, a company which organises clinical trials called a Contract Research Organisation (CRO). Everything ends up in the hands of physician-researchers. How CTs are conducted depends a great deal on their professional and ethical skills. Surely there are physicians who do their best to meet all the requirements of the law. However, there are others who permit violations and do not see it as a problem. For example, when our investigator travelled to Lviv, Kharkiv and Poltava, she often heard that it is not that important if an informed consent form cannot be signed by a patient; a family member can do it. If a patient is not capable of deciding by himself/ herself, the rules allow that an "outsider" – a so-called "witness" – sign the form instead of the patient. Experts believe that this is a direct way for violations to occur. A hospital employee can become an "outsider", and the patient's relatives will not even know that he/she is involved in a CT.

In Kharkov, some students and teachers told our investigator off the record that students participate in CTs. This fact was also mentioned during a congress on CTs in Kiev. There are many higher educational institutions in Kharkov, among them the National University of Pharmacy, where CTs are conducted. Surely, it is much faster to recruit a group of volunteers if they are students, who are highly dependent on their teachers and the dean to succeed. Documentary evidence could not be obtained to back up the claims. Students claimed that they were asked to take part in clinical trials, and that if they refused they could be given low scores in their exams. They could not tell more because they were afraid of being expelled from the university. This issue should be investigated further.

Human rights workers claim that a great number of violations occur during the CT participant recruitment process. This is the opinion of the paediatrician N. Kolomiets, a representative of the NGO "League for the Protection of Civil Rights".

> *"It is hard to quickly bring together a group of volunteers to participate in a CT. Not all parents give their consent to involving their children in experiments. That is why they look for boarding schools, orphanages and orphans living with guardians. Including these children in CTs is simple: managers of orphanages and boarding schools sign informational consent forms without asking questions.*
> *Mentally ill people, single old men, vulnerable people, who are not protected by anyone, are involved in CTs. I know of such cases".*

Organisers of CTs and physician-researchers deny these facts. They consider the words of the human rights worker to be slander.

All physicians who conduct CTs state that they adhere strictly to the requirements of the law.

Yaroslav Shparik, PhD, an oncologist at Lviv National Medical University[40], gave the following answers:

Interview with Yaroslav Shparik, oncologist, Lviv National Medical University

Journalist: How do you form a group (how long does it take, what are the criteria, etc.)?

Y. Shparik: *A group of patients is formed according to the type of disease. Each CT has 30 to 50 criteria that need to be analysed. The duration depends on the kind of group that is formed. If for example, we need patients with breast cancer that require postoperative chemotherapy, then ten patients can participate every month. If the CT is related to a rare type of tumour, with rare characteristics (e.g.*

mutation), it may take many years, with potentially no results at the end.

J: To what should patients pay attention when signing an informational consent form?

Y.S.: *They should read it carefully, consult those whom they trust and ask the physician all the necessary questions. Issues related to the safety of the treatment, and to patients' rights and duties, are especially important.*

J: Have you experienced cases, in your practice, in which people have refused to continue their participation in a CT?

Y.S.: *Refusals once treatment has begun happen rarely. A patient quickly becomes convinced that he/she is receiving high-quality (often the best possible) treatment. Very careful (more accurate than in routine practice) observation of a patient is carried out. Tests are often conducted in leading laboratories in Europe and the U.S., additional monitoring methods are used, etc.*
Sometimes even the transport costs are covered by sponsor companies (in a recent study our patients, together with a guide, were brought by train to Kiev, travelling business class, and from the railway station to the clinical trial by taxi). A lot of patients quickly learn the value of the therapy, the cost of which may be hundreds of thousands of hryvnia, and which they receive free of charge. Is it logical to refuse it?
Sometimes the patient is not allowed to participate in a CT by the physicians, who consider that he/she will not follow protocol. We have to work with unpunctual, "forgetful", irresponsible people. During a CT, these characteristics may create additional risks for the patients.

J: The Chairman of the National Commission on Bioethics criticised our CT system for its insurance scheme, which is very different from its European equivalent. Insurance payouts are miserable compared to other countries. What is your opinion about this?

Y.S.: *Unfortunately, researchers do not have an influence on the policy of insurance companies. At the end of the day, this is an issue that concerns not only CTs, but also health insurance (particularly for travel abroad), car insurance, etc. After all, these insurance payments have a correlation with the income of our citizens. Can we have an influence on this? It is not the fault of the sponsors, but more of the insurance companies.*

J: What is the most difficult aspect of working with CT participants?

Y.S.: *The most difficult aspect is dispelling myths created by the media, like "Ukraine is a testing ground for foreign pharmaceutical companies" or "patients are experimental guinea pigs", etc.*

Myth number 6: Independent ethical control of CTs is guaranteed

It is essential that all participants are protected during a CT. In 2012, the Ministry of Health introduced fundamental changes to the set-up of the Ethics Committee. An Order was issued (11.04.2012 № 255)[41] abolishing the Central Ethics Committee, which had operated under the Ministry of Health. Since then, in hospitals where CTs are conducted, a local ethics committee (LEC) has had to be created. This is a long and complex process. For Ukraine it is a new experience; there is no clear information on how to do it. There are many organisational issues relating to where the LEC members have to work and store documents.

Whereas CTs continued to be conducted at all sites, local ethics committees were not in place and the central committee was not operational anymore. Moreover, changes were introduced in the summer of 2012, when many researchers and directors of clinics were on holiday.

Our investigator managed to talk with several LEC representatives from clinics in Kiev. Not officially, but on condition of anonymity. Even by the end of 2012, LECs had not yet been set up or become fully functional everywhere. One of the reasons is that LEC members are volunteers, i.e. they have to work in their free time and are not remunerated. The average salary of a doctor, equivalent to 250-500 euros, is much lower than in the industrial sector. Health professionals are interested in earning extra money. Nobody wants to spend time on those activities that do not generate financial income. Hence, LECs are not really active.

In official interviews, doctors and lawyers say there are no problems, and LEC meetings are held on schedule. As there are many documents to review and approve within 7 days, LECs should meet at least four times a month. But many LEC members say they meet only once a month.

Maryana Kotsyba-Suvalo, Lviv Regional Hospital lawyer and LEC Secretary, gave the following answers[42]:

Interview with Marina Kotsyba-Suvalo, lawyer, Lviv Regional Hospital and secretary of the Local Ethics Committee (LEC)

Journalist: What does the LEC do?

***M. Kotsyba-Suvalo**: The LEC evaluates the ethical and legal aspects of each CT, including the patient enrolment procedure. Its conclusions can be positive or negative. Particular attention is given to those patients who are incapable of discernment and to minors.*

J: Who are the members of the LEC?

***M.K.:** It has 5 members: the head of the LEC is the deputy chief physician of the regional hospital. The deputy head is a Professor of Neurology from the Medical University. The LEC also comprises the head of the obstetric division and the deputy chief surgeon. The secretary of the LEC is a lawyer-consultant, namely me.*

J: How frequently does the LEC meet?

***M.K.:** The law (MoH Order) already exists, but the implementation procedure, with precise instructions, is not yet in place. So the LEC meets according to the needs as there are many documents to review.*

J: How many CTs are held in your hospital?

***M.K.:** It is a big clinical trial site, many CTs are held here. Sometimes there are 40 of them or even more.*

J: Which pharmaceutical companies from what countries apply for a CT? What drugs are being tested here: cardiology, cancer or some others?

***M.K.:** Different manufacturers choose our hospital, from many countries within and outside Europe. But I cannot give you more information, as it is a commercial confidentiality issue.*

J: Has the LEC received any complaints from patients or from their relatives when problems have arisen during a CT?

***M.K.:** As a lawyer, I have a duty to protect the rights of our patients. And I do. Since the establishment of the LEC there have never been any such complaints.*

J: What kind of complaints might patients have while participating in a CT? What problems might arise during the CT, in your opinion?

***M.K.:** There have been no complaints and no problems. We are working to explain everything about CTs to our patients. Doctors use a terminology that is difficult for the patient to understand, the language in the informed consent forms is too complicated; it is easier for a lawyer to explain everything to the patient in a way that is easy to understand.*

J: Who drafts the informed consent forms? Can you give us an example of how you explain the difficult terms and conditions of CTs to the patients?

M.K.: *We use the forms we are provided with. They are prepared by the pharmaceutical companies and are validated by the central authorities. But showing them to people who are not part of the CT is strictly prohibited. This is confidential information, and the sponsor companies categorically prohibit it. I can only say that everything is presented in such a way that the interests of the patients and doctors involved in a CT are taken into consideration.*

J: As a lawyer, you probably know what financial compensation is foreseen in cases in which the CT has caused the health of your patient to deteriorate?

M.K.: *This is confidential information as well. Nobody has the right to disclose it, only the sponsor companies.*

J: The law foresees that the payment should not be less than a certain limit. Recently amendments were introduced to the legislation: what is the minimum amount now? Do you have to say this to patients who participate in a CT?

M.K.: *Why are you always interested in confidential information? All those of us who are connected with CTs sign a confidentiality form and we are not allowed to disclose information. So I cannot say.*

J: What do you have to do when a medicine provokes side effects? To whom do you report?

M.K.: *Researchers report to the ethics committee and to the sponsor companies.*

J: Does it often happen?

M.K.: *Sometimes it happens, but not often. The ethics committee considers the case and decides what to do next.*

Traditionally, many clinical trials are held in Dnepropetrovsk, where the population is more than 1 million inhabitants. Here, future doctors are trained at Dnepropetrovsk Medical Academy, in the Medical Institute of Postgraduate Studies and the Institutes and Clinics of the Academy of Medical Sciences. All this is taken into consideration by sponsoring firms and they organise clinical trials here. One of the largest clinical trial sites is the Dnipropetrovsk City Hospital. Here the LEC was created and is headed by Nikolaï Shinkarenko, whom was also interviewed[43].

Interview with Nikolaï Shinkarenko, head of the LEC, Dnepropetrovsk City Hospital

Journalist: For how long have CTs been held in your hospital?

N. Shinkarenko: *The hospital has participated in clinical trials since 1991. Since that time, we have signed 156 contracts for clinical trials.*
It is a municipal institution with 800 hospital beds; we also have a clinical-diagnostic department. There are a total of 17 divisions, of which 7 are therapeutic and 10 surgical, as well as many laboratory facilities. Every year we treat 24000 patients and perform 8000 surgical operations. The main division is oncology, where about 3500 patients are being treated. Therefore, one of the areas of clinical trials here is oncology.
We also have medical school departments: oncology, nuclear medicine, internal medicine, cardiology, and pathology. All except the last one do CTs. For clinical trials the fact that the clinic has a Department of Pathological Anatomy, employing high-class specialists, is of great importance.
Up to 10% of our patients participate in CTs. The number of cancer patients is more than 350 - 400 a year, which is a lot.

J: How does the LEC work in your hospital?

N.S.: *The LEC has a lot of work and great authority. By law it is impossible to conduct clinical trials in a clinic where no LEC has been established. CTs are not held in those cases in which the LEC does not agree. A sponsor may then apply to another medical institution, where there is an LEC, and work there.*

J: Who are the members of the LEC?

N.S.: *At present our LEC consists of 8 people: five doctors from various specialties, a priest, a lawyer and one engineer. All candidatures were approved by the hospital administration.*
Members of ethics committees cannot know everything about the drugs that are tested. The LEC has the right to turn to experts for advice to help to evaluate all the information about the drug and its characteristics.

J: When does the LEC meet?

N.S.: *The LEC must meet after business hours. It's hard. There are no stipulations in the Ministry of Health Order concerning how often we should gather. It is recommended that we meet no less than once a month. How to do this?*

The meetings are long; we need to study all the documents, understand everything. We cannot rely on doctors for explanations as they are on duty and busy with patients.
We are a public organisation, and we have a serious responsibility. It was much easier to work when there was a Central Ethics Committee at the Ministry of Health.
We need facilities for the LEC meetings, for meetings with researchers and participants of CTs, as well as for storage of numerous documents. The clinic cannot provide enough free space. This is a big problem.

J: Who approves the members of the LEC?

N.S: *The members are approved by the head physician of the hospital.*
We study the history of the disease, talk to patients and their relatives and consider their opinion. We learn how the informed consent form was signed. We always remind them that we have a "Data Protection Act" and a "Law on the Protection of Personal Data". Everything concerning the CT is confidential, it is not for outsiders. All the issues are discussed only with the participants of the CT.

For the different reasons mentioned above, it can be said that the ethical supervision/control of CTs – although stipulated and regulated by law – is not guaranteed and/or is influenced by conflicts of interests on the part of doctors/researchers or hospital managers.

Conclusion

The issue of CTs is complex and secretive: only very little information can be obtained from public sources. If a journalist tries to investigate the issues of CTs, he/she faces many hindrances and difficulties in the search for information. This is why journalists rarely write about this topic.

The scandal which broke because of deputy Golovko's statement made the topic of CTs a top news item. However, only the statement of the deputy and the answers of the Ministry of Health were reported. No journalistic investigation or analytical articles followed. The reason for this is obvious: it is almost impossible to get any information.

Consequently, some people became aware that the CT system is not as correct and accurate as it is claimed to be by those who finance and conduct clinical trials. Some people started to find out what myths prevail in the CT system and what the realities and facts are. The main conclusion to be drawn is that not only patients, but also pharmaceutical manufacturers, should thoroughly analyse whether or not the legislative regulations are being properly met. From a corporate behaviour perspective, carrying out studies on one or more children, including orphans – who need even more protection as vulnerable subjects – in a context of weak ethical supervision and regulatory mechanisms, is irresponsible.

It is difficult to judge clinical trials conducted in Ukraine. The number of CTs increases every year, but there is a lack of information about them. Since Ukraine has a high level of corruption – and medicine is no exception – public trust in officials and the health system is low; it is very doubtful that clinical trials are conducted in strict compliance with the law.

The legal framework in Ukraine meets international standards; the rules of CTs are equivalent to those in West European countries. However, there are many ways to incur violations in the implementation of the rules governing CTs, especially as clinical trials are turned into an exercise of financial gain for some of those involved. International organisations like the World Health Organisation and the Parliamentary Assembly of the Council of Europe have repeatedly pointed out that the health care system in Ukraine is insufficiently financed. There is still no social security (insurance) for medicine in Ukraine. The infrastructure of hospitals and laboratories is lagging behind modern requirements. The outdated equipment affects the accuracy of diagnosis and the suitability of the prescribed treatment. Under these conditions, it is very difficult to conduct clinical trials according to all the rules and to achieve accurate results.

Every year, more and more European pharmaceutical companies apply to conduct clinical trials in Ukraine. Swiss companies have been carrying out CTs in Ukraine for years. During the investigation our investigator managed to talk to representatives of Roche Ukraine. She was not able to visit the clinical site: the interviews took place in the office. She was not allowed to meet the patients who took part in the clinical trials. At Novartis, a meeting did not take place at all: several arrangements were made over the phone for a meeting, but it was repeatedly postponed and never took place.

The recent CT controversies have drawn public attention to those hospitals where CTs are conducted, including those where Swiss companies operate. Another scandal is linked to the Kiev Psychiatric Hospital, where CTs have been conducted for many years. The list of clinical trials sponsored by Swiss companies includes the testing of drugs on schizophrenic patients. Pharmaceutical manufacturers have refused to answer where (site) these are taking place and which drugs are being tested. However, in Kiev there is only one clinical site where such trials are conducted. This is the hospital where TV journalists filmed the story about the mishandling of patients by doctors. How can the CT be carried out in such conditions and with such specialists? Are the results of these clinical trials really reliable?

Experts from patients' organisations claim the sponsor companies have a special interest in conducting clinical trials in Ukraine as it is much cheaper than in other European countries. For example, the maximum insurance payout to a CT participant was, for a long time, between one and two thousand dollars. After the 2012 amendment to the legislation, the minimum payment should not be less than 10 thousand dollars.

CTs should not be an issue only for business, medical, patients' rights and ethics specialists. CTs concern everyone. After all, when buying a medicine, each of us believes that it will have the positive effect described in the leaflet. Therefore, we should all be concerned that clinical trials are being conducted in accordance with legal regulations and ethical requirements, and that they are not biased so as to favour an exaggerated positive result.

Annex: list of interviews

1. M. Sereda, medical director of Roche Ukraine
2. S. Mikhailov, head of the Clinical Trials Subcommittee of the European Business Association
3. V. Chumak , former director of the State Pharmacological Center of the Ministry of Health
4. V. Serdyuk, president of the All-Ukrainian Council of patients' rights
5. O. Skorina, head of the legal service of the All-Ukrainian Council of patients' rights
6. N. Kolomiets, leader of the public organization "League of the protection of civil rights"
7. Y. Shparik, oncologist, Lviv National Medical University (recommended by Roche Ukraine)
8. A. Morozov, vice director at State Expert Center of the ministry of Health of Ukraine, professor
9. A. Bazilevich, professor at Lviv National Medical University after D. Galitsky
10. M. Gzhegotsky, deputy of the general doctor at Lviv Regional Hospital
11. I. Zakalyuzhniy, lawyer at Lviv Regional Hospital, member of the local ethical committee
12. M. Kotsyba-Suvalo, lawyer at the Lviv Regional Hospital, secretary of the local ethics committee
13. S. Rasputnyak, Deputy Director of the Department of Pre-Clinical and Clinical Studies, The State Expert Center of the Ministry of Health of Ukraine
14. N. Shinkarenko, head of the local ethic commission in Dnipropetrovsk State Hospital
15. G. Legeza, representative of the NGO protecting patients (Dnipropetrovsk)
16. V. Kornatsky, former director of the Central Ethics Committee of the Ministry of Health
17. V. Ocheretenko, Director of the NGO "Health of the Nation"
18. N. Polischuk, ex-Minister of Health

Interviews (without recorder) were also made with staff members of the Kharkiv National Pharmaceutical University, of the Dnepropetrovsk Medical Academy, and of the National Medical University Bogomolets.

[1] Previously called State Pharmacological Center (SPC), http://pharma-center.kiev.ua
[2] All the figures cited in this introduction are taken from : Clinical Trials Market in Ukraine (Part 2), Journal of Clinical Studies, Vol 3 Issue 6, December 2011 (http://jforcs.com/jcs/downloads/clinical-trials-market-in-ukraine-part-2/)
[3] OCT Quarterly Newsletter Issue 2 (www.oct-clinicaltrials.com)
[4] http://marketing.scripintelligence.com/files/2013/01/UkraineProfileSampleNov2012.pdf
[5] The Journal of Clinical Studies, ibid.
[6] All legislative texts in Ukrainian can be found at http://zakon.rada.gov.ua
[7] See Introduction, http://zakon.rada.gov.ua and http://arzinger.ua/en/press/publications/42613/
[8] http://glavnoe.ua/news/n135826: "Ukraine in terms of press freedom for 2012 divided the 131-134th place with Zambia and South Sudan among 197 surveyed countries and territories and barely restrained in the category of "partly free," said the human rights organization Freedom House from the U.S. to the report released today. These three states are the latest in this category with a rating of 60 points, the next category being "not free" countries." (unofficial translation)
[9] See annex 1 for a complete list of interviewees
[10] European Business Association. EBA is a non-profit organization, which unites over 950 foreign and domestic companies operating in Ukraine. At present EBA is a leading organization of foreign business in Ukraine (http://www.eba.com.ua/)
[11] According to our investigations, both Roche and Novartis are or were recently conducting Phase II and Phase III trials on schizophrenia drugs in this hospital.
[12] See among others (in Ukrainian and Russian): http://www.pravda.com.ua/news/2013/03/11/6985223/ , http://www.unian.net/news/558321-oppozitsiya-trebuet-rassledovat-ispytanie-lekarstv-na-detyah.html, texty.org.ua/pg/news/movchun/read/44127/Opozycija_zvynuvachuje_vladu_v_doslidah_nad_ditmysyrotamy, http://magnolia-tv.com/text-news/2013-03-12/22169-m-l-ts-ya-poltavshchini-perev-rit-nformats-yu-shchodo-viprobuvannya-vakts, http://www.poltava.pl.ua/news/21015/, http://ukranews.com/ru/news/ukraine/2013/03/11/91717), http://www.privivok.net.ua/smf/index.php?topic=1235.0;wap2,
[13] ibid
[14] For the original MOH press statement in Ukrainian, see http://www.moz.gov.ua/ua/portal/pre_20130312_a.html (last accessed on 18/07/2013)
[15] Ibid
[16] See media reports fn 10
[17] The Child Care Services are the State's social services for orphans and semi-orphans in Ukraine. Also called guardianship services, these do not only deal with children who have lost their parents. If the parents lead an antisocial lifestyle – e.g. alcohol or drug abuse, neglect of children – they could be deprived of their parental rights. In Ukraine, children whose parents have been deprived of these rights are also called orphans or social orphans. Either their relatives look after them and become their guardians, or the social services for children and children's orphanages take care of them.
[18] http://www.privivok.net.ua/smf/index.php?topic=1235.0;wap2
[19] In Ukraine, according to the law, citizens below 18 years of age are considered minors
[20] www.clinicaltrials.gov (last accessed on 18/07/2013)
[21] http://www.fda.gov/downloads/Drugs/DrugSafety/ucm089801.pdf
[22] See media reports fn 10
[23] See official MOH press statement fn 12
[24] see media reports fn 10
[25] see official MoH press statement fn 12
[26] See http://np.pl.ua/2013/03/yurij-pavlenko-zhodnyh-vyprobuvan-vaktsyn-na-dityah-syrotah-na-poltavschyni-ne-provodyly/
[27] http://www.rusmed.info/cont/osobennosti_glaukomy.html
[28] On the condition of anonymity
[29] In Ukraine, after the parliamentary elections in October 2012, the confrontation between the government and the opposition escalated dramatically
[30] http://news.liga.net/news/capital/845861-skandal_v_psikhlechebnitse_kieva_prodazhnyy_vrach_otstranen_ot_raboty.htm#, http://ru.sn.ua/ukrayina/v-kievskoy-durdome-vrachi-ustroili-konclager-kormyat-tolko-kashey-i-sozdali-palaty-smertnikov-301430.html, http://glavnoe.ua/news/n134607
[31] http://www.aif.ua/society/news/57819
[32] Ibid
[33] See art 3.4 of the MOH Order № 690 of 23.09.2009: "The selection of researchers and health care facilities (health care institutions - hospitals) relies on the sponsor. Requirements for researchers and health care facilities are listed in Section V of this Order. Sponsors may delegate any or all of its functions to a contract research organization (…)". (http://zakon.rada.gov.ua, unofficial translation)
[34] http://www.coe.int/t/dghl/monitoring/socialcharter/Reporting/StateReports/CommentsAllUkrainianCouncil2013_en.pdf http://www.coe.int/t/dghl/monitoring/socialcharter/Conclusions/State/Ukraine2009_en.pdf http://www.coe.int/t/dghl/monitoring/socialcharter/Reporting/StateReports/Ukraine1_en.pdf
[35] See fn 10
[36] http://www.eba.com.ua/
[37] http://www.stcharlesresearch.org/images/RepDrugTrialOutcomes%20AnnIntMed%208-3-10.pdf
[38] http://www.plosmedicine.org/article/fetchObject.action?uri=info%3Adoi%2F10.1371%2Fjournal.pmed.0040184&representation=PDF
[39] http://www.eba.com.ua/static/press-releases/PR_HCC_18_03_2013_ukr.doc (Original text in Ukrainian, last accessed on 18/07/2013)
[40] He was recommended to our investigator by Roche Ukraine
[41] All legislative texts in Ukrainian can be found at http://zakon.rada.gov.ua
[42] The interview took place at the end of 2012
[43] The interview took place at the end of 2012