RISK MANAGEMENT ASPECTS, WAR AND FURTHER PERSPECTIVES IN CLINICAL TRIALS IN UKRAINE

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Abstract. *There is a first time for everything, including a crisis, which often comes unexpectedly and brings with it uncertainty and complexity. It rarely happens that politicians, government or managers are able to assess appropriately the impending danger, anticipate and take the necessary measures to avoid negative consequences. And it does not matter what kind of crisis it is: pandemic, financial and economic one, extreme weather events and associated natural disasters, or war. The crisis almost always contains unusual challenges and tasks, requires non-standard solutions. In addition, it is really important to act quickly. On the other hand, although any crisis has negative consequences, it often can cause the creating of the value for the society, can bring positive changes. Especially it concerns for the crises that continue for months or years. Such a crisis is changing and evolving all the time, and these are characterized by an abrupt development, there are spark and halt over the time. On the over hand, for the industry like clinical trials when the participation/adequate input of each stakeholder is obligatory, it is really necessary to develop overall strategy, ensure synchronicity of actions of all participants. Moreover, not all the stakeholders have direct link/communication among themselves, which adds a level of complexity into the resolution of the risk(s) under such circumstances. Any well-planned strategy cannot be successful without great motivation, clear instructions, good communication among all the parts, appropriate monitoring of the processes, the deliverables and the noncompliance with the following re-training, if necessary. It is fairly much relevant for Ukraine that is subjected to violence and aggression from Russia last 10 years. All group of the industry involved was not prepared for the disaster first, still started understanding, analyzing and reacting appropriately to constantly changing circumstances. That is why the purpose of the article is to research risk management strategies for the risks originating from modern crises, which make ineffective the traditional approaches, without paying attention to new non-traditional, constantly changing, unsustainable, sophisticated threats. At the same time, the purpose is to research new paradigms in multi-agency collaboration to resolve such challenges. The methods which are being used in this article are Empirical/Quantitative Researches, including Observation, Measurement and Comparison ones, Graphic images, outlines, tables have been provided to illustrate the logical sequence of the research. As a result of the study, the main risks affecting clinical trials in Ukraine due to the war and other events were established.*

Keywords: *risk, management, crisis, strategic, communication.*
JEL Classification: D80, D81, D79, D22
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Introduction. Geography of clinical trials on humans is constantly expanding, cover all new countries around the world. When choosing participating countries for clinical trials of a potential drug, large and small pharmaceutical companies are guided by similar criteria: «Each Sponsor has its own research strategy, as well as strategy for further expanding the successfully tested drug into the International Market. Before selecting country for the clinical trial, the Sponsor considers

numerous factors such as the desired country population, epidemiological data, experience in similar trials, competitive landscape in the country, scientific societies, regulatory/ ethic committees' approval process, including regulatory timelines, having naïve to the certain treatment patients and so one. » [1]

Ukraine is a non-EU, but still European country that became particularly attractive for the Sponsors over last 20 years. Together with key criteria listed above there are several significant advantages while conducting clinical studies in the country:

- Clinical trials in Ukraine almost always cost effective;
- Submission process to Regulatory authorities (RA) and Local Ethic Committees (LECs) can go in parallel, which allows to save the time;
- No special license for exporting biological specimens;
- Ukrainian sites can quickly enroll patients;
- Ukrainian sites usually provide high quality of the research;
- Ukrainian investigators can easily adapt to the changes, regardless of the type of the factor that cause the given change.

Along with the benefits and opportunities, that can provide the country every sponsor considers danger for its business. Unfortunately, Ukraine is still on the list of riskiest countries in the industry, as it was attacked by its neighbors 2 times over last 10 years, and the last aggression is still going on.

Literature review. In this article the analysis of status of Clinical trials in Ukraine during last 10 years mainly based on Dr. David Rubens researches of crisis/risk management in 21th century. «Beyond 'Command & Control" Developing a New Paradigm for Incident Command Systems, Critical Decision-Making and 21st Century Crisis Response", David Rubens, 2015 [14].

In order to highlight the practical data to illustrate challenges, as well as deliverables in the industry in Ukraine materials of the sixth scientific-practical conference with international participation «Clinical trials of medicinal products in Ukraine: new challenges and responses to them» of MoH of Ukraine, October 2020, as well as information from the website of MoH of Ukraine from September, 2022 and November 2022 about clinical trails' status in Ukraine have been used. [3, 4, 6, 9, 11].

Ukrainian Clinical Studies at Risk due to Russian Invasion, Zahraa Chorghay, PhD, Mar 01, 2022, As Russia's clinical trials sector falls, Ukraine rebuilds, August 23, 2022, Priya Nair – expresses mainly deliver the forecasts and warnings. [2, 3]. International standard of the industry ICH GCP E6R12, as well as local Procedure for Conducting Clinical Trials of Medicinal Products and Expert Evaluation of Materials Pertinent to Clinical Trials and Model Regulations of the Ethics Committees approved by MoH Ukraine Order of 23.09.2009 № 690 provides specific rules that should be followed by all stockholders [13].

Aim. The purpose of the article is to research risk management strategies for the risks originating from modern crises, which make ineffective the traditional approaches, without paying attention to new non-traditional, constantly changing, unsustainable, sophisticated threats. At the same time, the purpose is to research new paradigms in multi-agency collaboration to resolve such challenges.

Methodology. The methods which are being used in this article are Empirical/Quantitative Researches, including Observation, Measurement and Comparison ones. Graphic images, outlines, tables have been provided to illustrate logical sequence of the research.

Results. Let us to have a look at trends in the industry of the clinical trial since 2013 till 2022, when the risk started becoming obvious, when Russia started actively intervened in internal affairs of Ukraine, while Ukraine chose the European vector of development. It is necessary to answer the question of whether or not international pharmaceutical companies think Ukraine still has great prospects in the industry despite ongoing threats to conducting studies.

First some statistics related to clinical trial in the country since 2013 according to data provided by Ministry of Health of Ukraine (MoH). The number of clinical trials approved by the State Expert Center of the MoH in Ukraine for 2010-2020 (data provided as of 02 Oct 2020) is provided in table 1 [4]

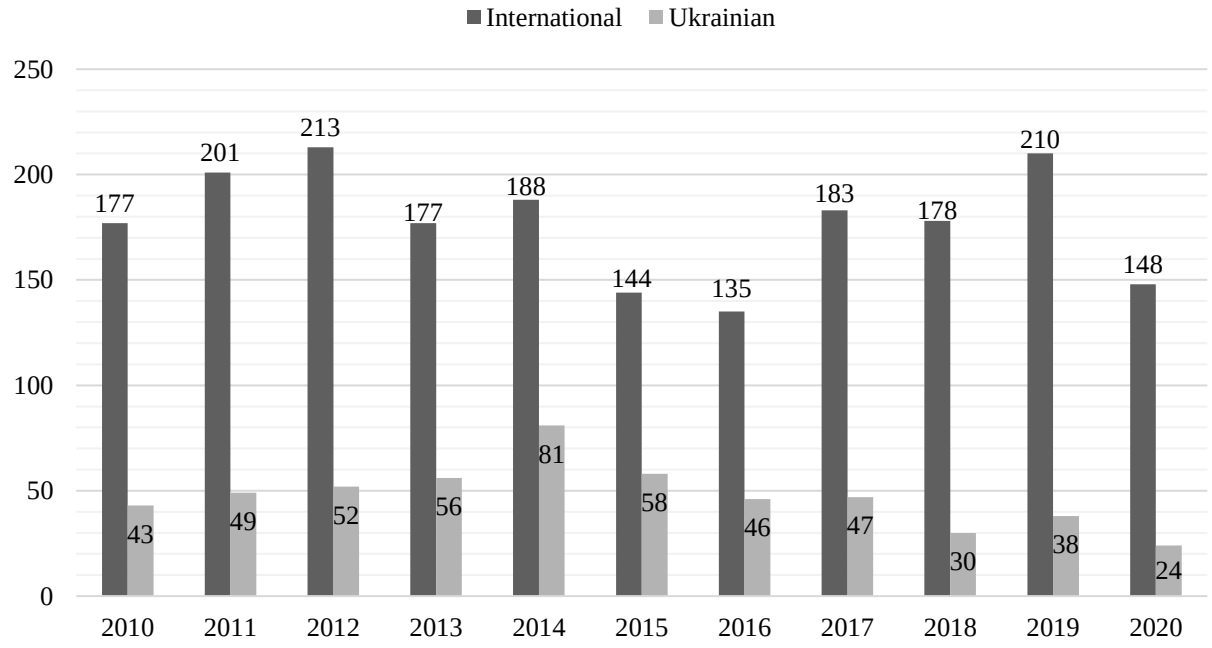

Table 1. Number of clinical trials 2010-2020

According to statistical data of the State Expert Center of the Ministry of Health of Ukraine (Tabl. 1) in 2012 RA approved the largest number of international clinical trials 213. The average between 2010 and 2014 was 191,2. One can be indicative of the number of submitted studies, as well as an indirect indicator of

interest of international investors in the capacity of Ukrainian clinical sites of conducting Clinical Trials there.

However, as a result of aggression, as well as annexation of the significant part of Ukraine the number of studies gradually decreased on 29,4% to 135 trials till the end of 2016. It may be explained that many sponsors decided to put on hold Ukrainian sites in international sponsors' upcoming and expected projects. This is also true for regions that have not been affected by the war. The sponsors were rather monitoring the risks arising as a result of it. Table 2 provides details on the number of audits in Ukraine [4].

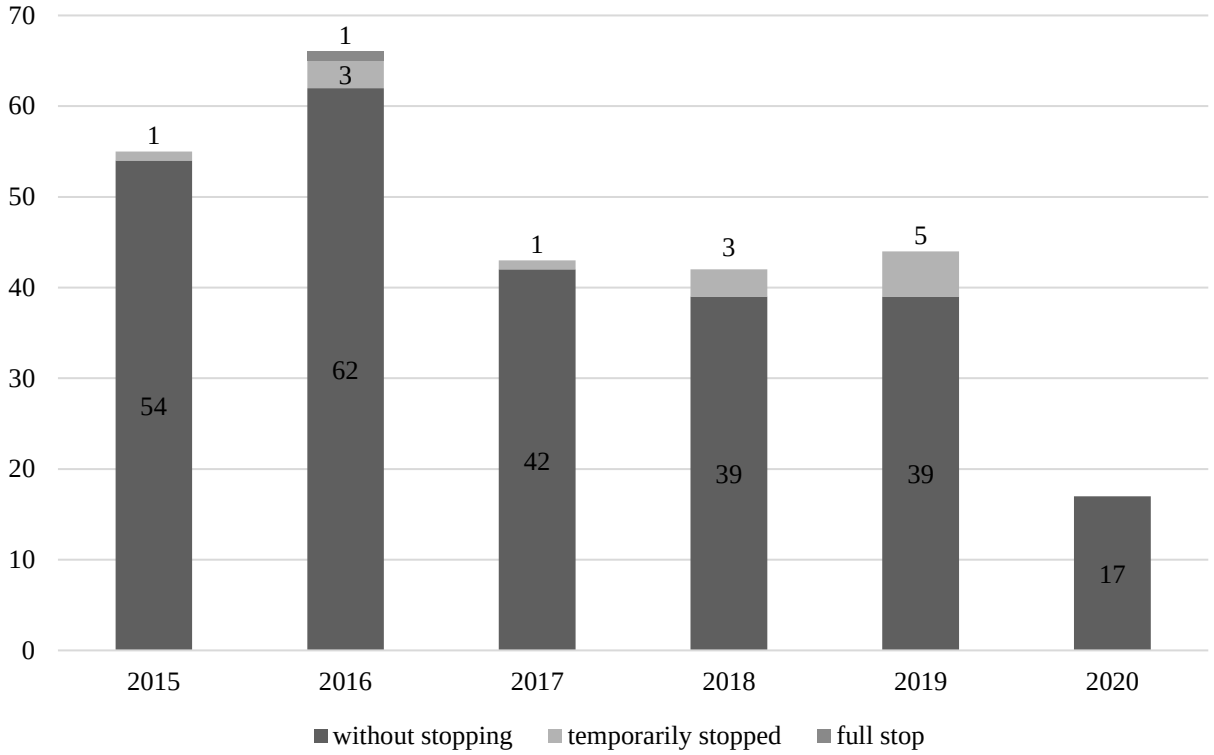

Table 2. Number of audits since January 2015 till October 2019 data provided as of 02 Oct 2020

Thus, comparing the data of tables 1 and 2 it is easy to notice that in 2015 and 2016 number of clinical trials approved by MOH in Ukraine is decreasing, while the number of audits is increasing over the same time period. The increased number of audits is usually a clear sign of extra attention to the quality by the sponsors, RA, various agencies.

In 2017 the picture is different, number of audits was reduced on 32%, while number of approved international trials was increased on 23% compared to the previous year. In general, it could be seen as the Ukrainian community of clinical trials managed to quickly increase its capacities, as well as confidence of international sponsors in the country by 2017.

The average between 2017 and 2019 was 191,3 approved by RA studies per year, and in 2017 was achieved appropriate 183 approved studies. This is particularly

surprising, because as a result of Russian aggression the industry in Ukraine lost 3 very important research cities as Donetsk, Lugansk and Simferopol, which required recovery of resources. This is especially true for Donetsk which was one of the top 5 of the Ukrainian research cities.

Here are some of the statistics according to MoH which indicates how fast the industry in Ukraine has been growing over the period 2015-2019:

Another indicator that indirectly shows the scale of the study is the phase of the study. There are 3 core phases on the path to approval for any new drug. And the largest/wide-scale clinical study is phase 3 - that goes for every aspect of the trial – number of countries, number of sites, number of patients and of cause amount of investment. Number of international clinical trials in Ukraine for period from 2015 till 9 months of 2020 is depicted in Table 3, provided by the State Expert Center [4].

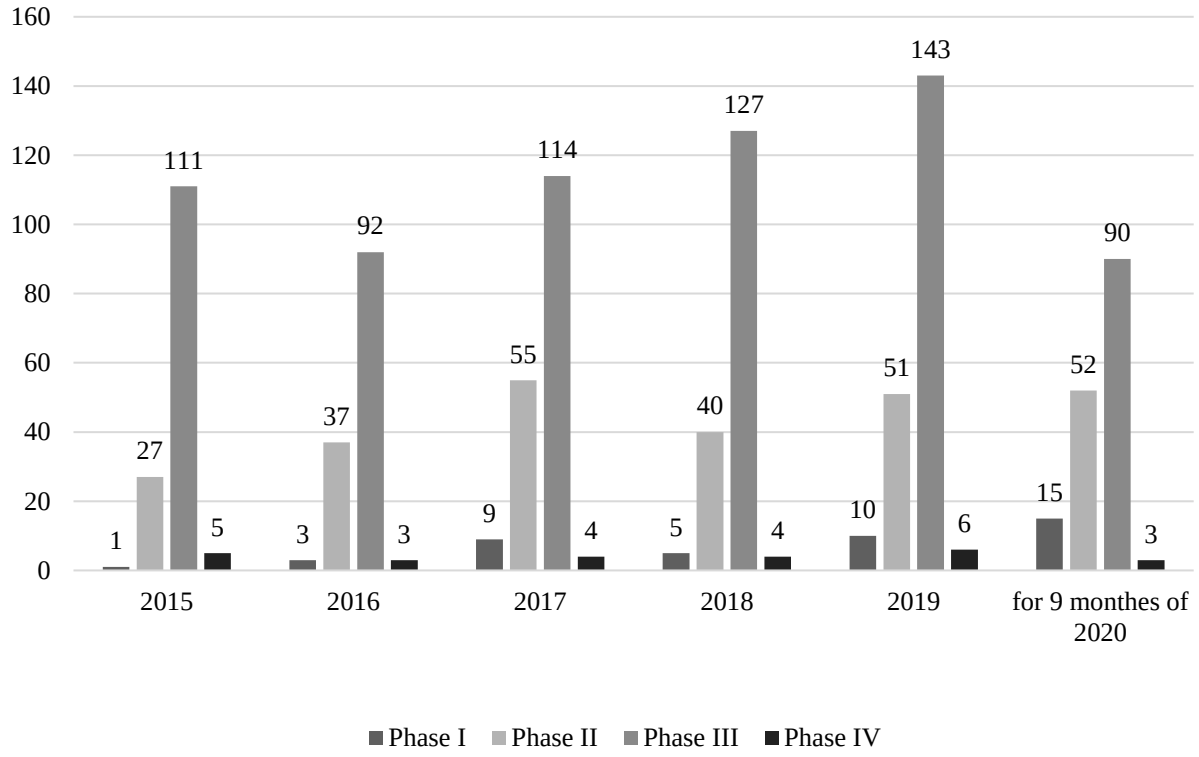

Table 3. Number of Clinical trials by phase in Ukraine

Phase 3 studies number increases on 22%.

Therefore, increase in the number of both sites and patients can be indirectly shown based on the data provided in the table above [7].

The comparative data of number of clinical trials per 100.000 population is another indicator of the development of the industry. Number of Number of clinical trials per 100,000 populations as of October 2, 2020 is shown in Table 4. And Number of clinical trials per 100,000 populations as of July, 2015 is presented in Table 5 [4]. So that we can compare amounts and evaluate it growth.

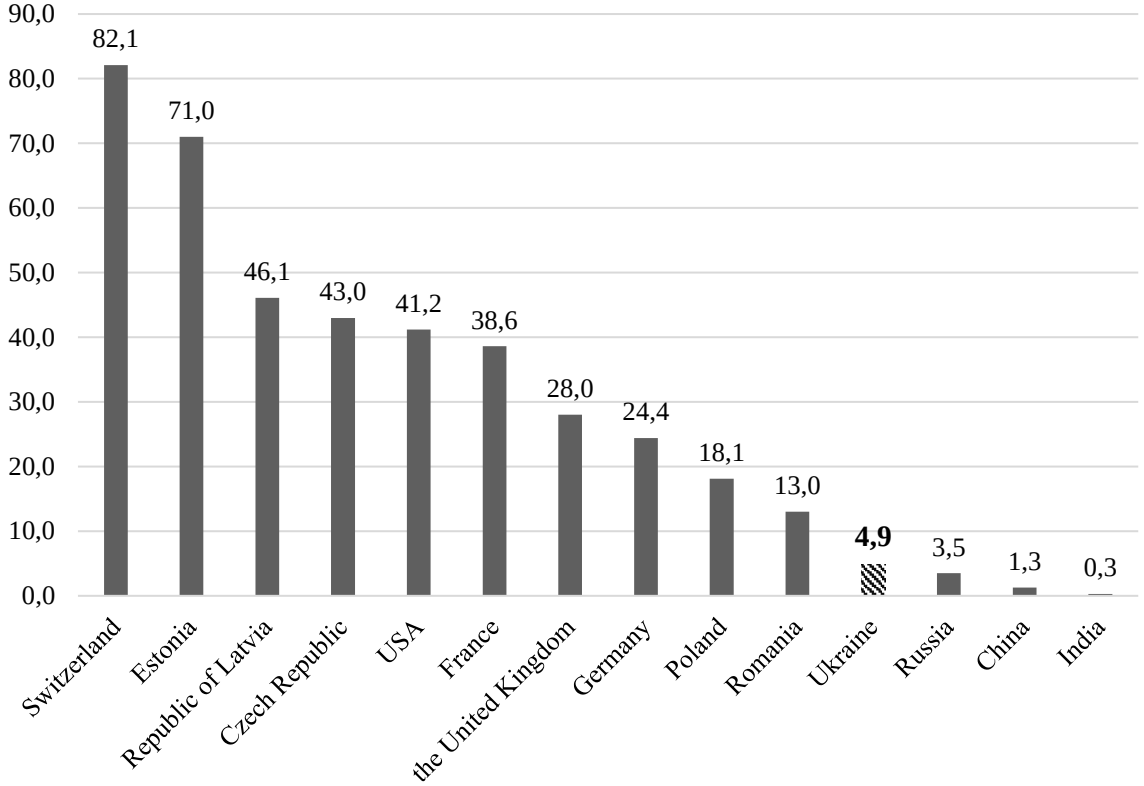

Table 4. Number of clinical trials per 100,000 populations as of October 2, 2020

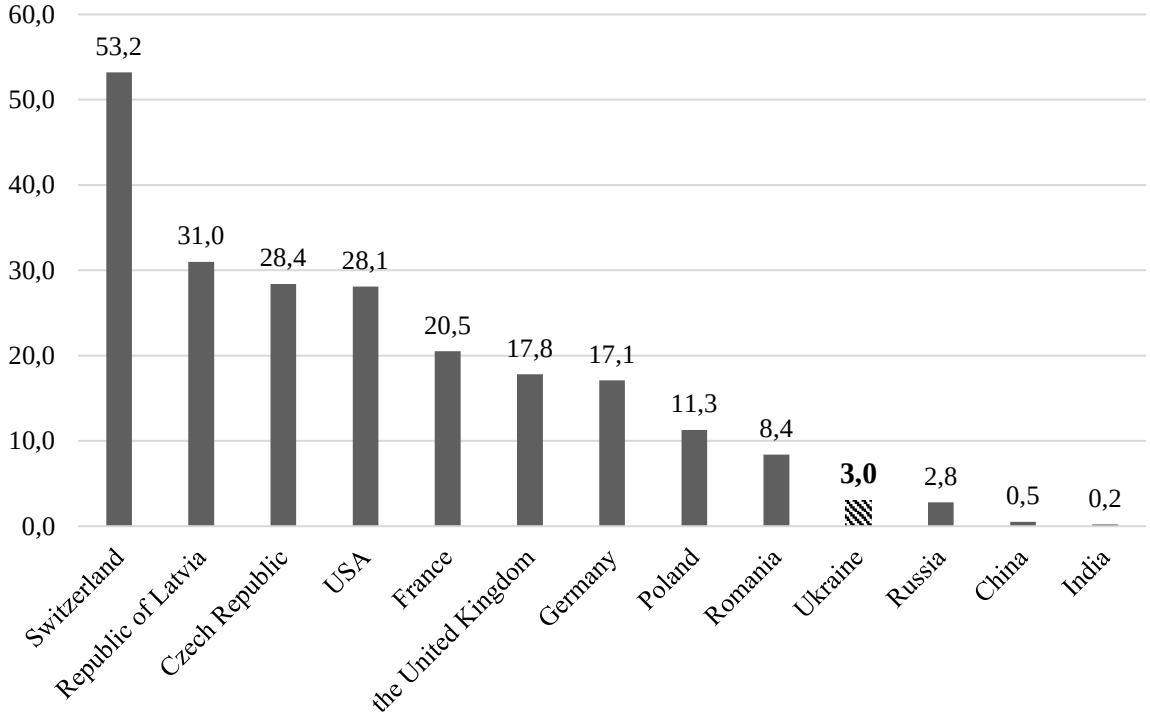

Table 5. Number of clinical trials per 100,000 populations as of July, 2015

The number of clinical trials per 100.000 population increased on 39% by 2020 over last 5 years.

The statistic provided by the State Expert Center of MoH above reflects the latest trends in the industry over last 10 years both negatives and positives, as well as divides the period into 3 periods:

- 2014 till 2016 – a drop in the amount of researches in Ukraine due to first Russian aggression;
- 2016 till February 2022 – despite both Ukrainian territory and population have been reduced, the international pharmacy companies did not loss the interest to the opportunities which can provide the industry. The number of studies has been going up;
- February 24, 2022 – October 2022 - a drop in the amount of researches in Ukraine due to first Russian aggression.

In order to understand transformational changes within industry it is necessary to define the core stakeholders of any clinical study in Ukraine and consequently the decision maker(s), and who is ultimately the risk owner(s) "The person, organization, or entity accountable and with authority to manage a risk." [1]

Every research is initiated by a pharmaceutical company/the sponsor. As it well known the core value of any research is the information, which is being received in the experiment. Thus, the pharmaceutical company/the sponsor is first core stakeholder who take care of all the aspects of the study financial, organizational, quality ones.

An international clinical trial is a human experiments which is being conducted according to an international ethical and scientific quality standard ICH GCP, the current version is ICH GCP E6(R2). Below are first 3 out of 13 principles of the standard:

2.1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

2.2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

2.3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society. [7]

Thus, the subject of the clinical trial/the patient is also core stakeholder of the clinical trial.

A contract research organization (further CRO) is another stakeholder that can be involved in the study in certain country, it is a sponsor's representative in the country. Sponsor can delegate to CRO as many responsibilities as it wants.

Almost all sponsors in Ukraine currently prefers to delegate to/to outsoars different CROs by 2023, which indirectly proves that CROs are able to react to risk in a timely manner.

There are 2 more core stakeholders of any clinical trial MoH and LEC – these bodies regulate, provide their either expert opinion or approval/rejection either in country and in the given hospital respectively in accordance with ICH GCP and local regulations (Order of 23.09.2009 № 690 of MoH Ukraine) [13].

Finally, investigators/clinical sites – "A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator." [8]

Now when all core stakeholders are identified, let us have a look at the greatest difficulties the industry in Ukraine has faced since 2014, what exactly were done to mitigate the problems/improve the situation, and save the industry, to get it restarted for the further development.

1. The most significant risks caused by Russian invasion?
2. Who owns the problem? The core decision makers? The risk owner(s)?
3. Risk response strategy which was chosen in 2014 – 2016 in comparison with 2022? What is the difference/ what was changed?

1. In December 2022 one of the biggest worldwide CRO PPD carried out a survey on top 5 Challenges and Opportunities Drug Developers Face in Executing Clinical Trials (Tabl. 6) [15].

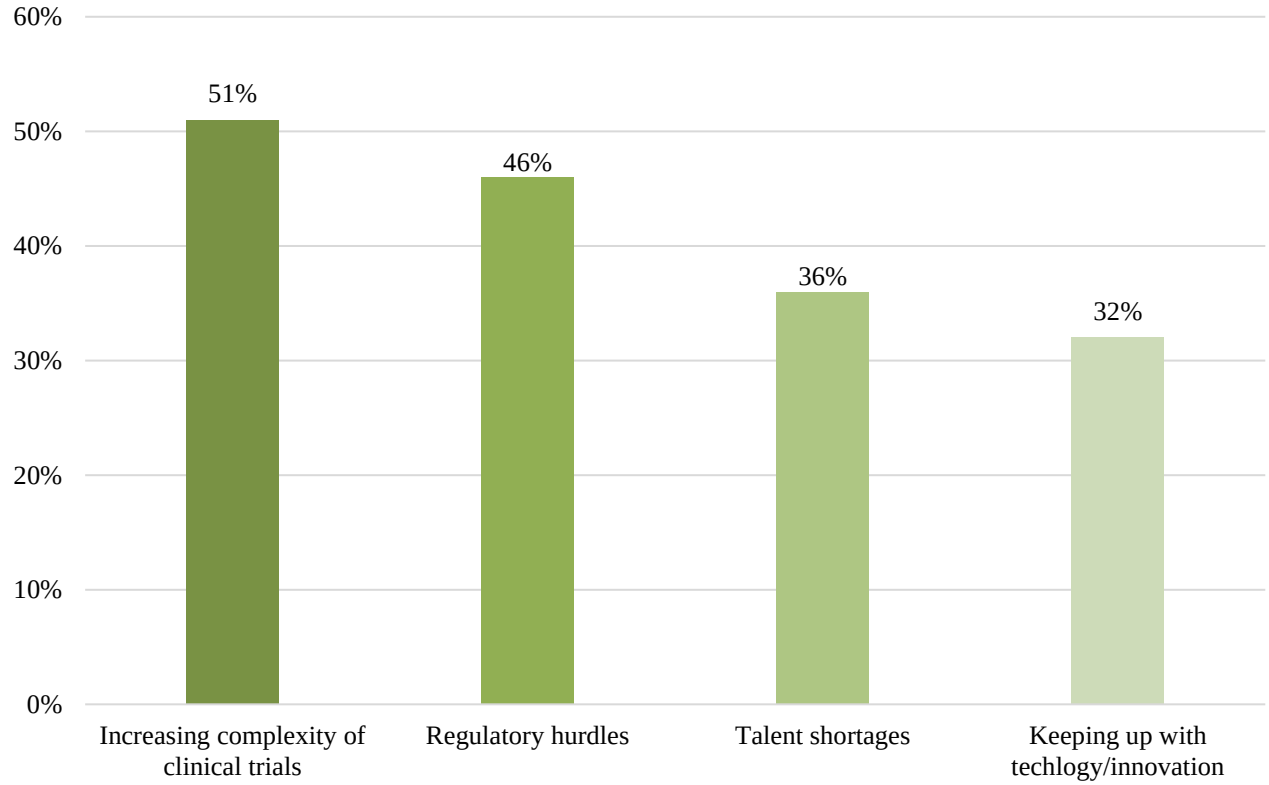

Table 6. Top 5 Challenges and Opportunities Drug Developers Face in Executing Clinical Trials

Almost all challenges (with the exception of Increasing complexity of clinical trials) are applicable for both periods. In the meantime, first and fourth-most reported

challenges are applicable to damages to clinical trials in Ukraine due to the occupation by Russia. In addition, patient's recruitment includes also patients' retention and diversity.

2 Both the clinical trials sponsors'/ CROs and MoH Ukraine should be considered owner of the problem in the current situation: both of them no longer ensure neither quality/data integrity of the study, nor both patients' safety and well-being. In addition, the sponsors were not able to ensure logistics of drug and lab supplies. It goes without saying, the sponsors ran the risk of losing data for patients, who has been already enrolled, but not supposed to complete the clinical trial. In the meantime, the sponsors' and MoH Ukraine definitely are core decision makers.

3 In 2014 – 2016 it was a new risk - nobody anywhere knew how to take care of it, how to mitigate the damage to patients who were being treated in Donetsk, Lugansk or Simferopol, who lost both free and effective medication and medical care, as well as to the sponsors - it was the damage of the equipment, investigational drug, the data received by the sites over the study, and the most significant loss was the time wasting.

Therefore, looking ahead, it should be noted that risk management strategies were not the same in 2014-2016 and since 24 Feb 2022.

Unfortunately, the risk of Russian intervention was identified too late - nobody expected Russia Federation to violate international agreements and actually annexes part of the territory of Ukraine. However, at some stage it became obvious that there are a lot of issues to resolve and nobody knows how to do it – as there is no possibility to attend the sites in Donetsk, Lugansk or Simferopol to monitor sites' activities, deliver study drug to the site and ship biological specimens from the sites to the central Lab. Both Sponsors' and CROs' project managers should have evaluated the risk properly as soon as possible to identify resources either to save patients in the study or to accept the risks and as a result to lose the data. Although many sponsors and CROs have been eagerly following the crisis since November 2023, almost no sponsor was prepared to a moment when the situation got worse and became uncontrolled. No action has been taken before this moment, as well as no mechanisms were created to mitigate the risk. Some CROs were trying to keep monitoring, find a little detour on the way to get the sites, to deliver drugs, re-supply sites with accompanying materials. Many attempts have been made to relocate patients to Ukraine-controlled territory. However, the clinical trials demand transparency, it is hard to do this if there are no real mechanisms. Thus, someday MoH of Ukraine make a decision to accept the risk – RA recommended to sponsors not to start new clinical studies, to stop patients' enrollment and to discontinue these patients who are already in the study in Donetsk, Lugansk, and Crimea.

David Rubens investigating the modern trends in the development of risks notes propensity for mutation which require the change in the risk management approach: "Developing a New Paradigm for Incident Command Systems, Critical

Decision-Making and 21st Century Crisis Response «Similar to a virus that mutates so much from its original form that it not only refuses to respond to traditional approaches, but redefines the parameters of the threat… so the new threat must be seen in terms of a completely new and distinct threat topology, rather than merely being a sub-set of previously modelled problems, or anomalies that fall outside of the parameters of crisis response. If classical risk management was the domain of the statistician, predicting future possibilities based on an analysis of an aggregate of the masses, the threat set by the new paradigm is predicated on the criticality of the singularity, the outlier – the unknowable and inconceivable" [14].

Unknowable and inconceivable risk does not mean resolved and non-refundable, especially considering the fact that tension on the line of contact between Russian and Ukraine has not much decreased. The logical solution in the current situation was to get stronger the core stakeholders' interaction, to keep in mind key takeaways, to search the right strategy, to make sure the risk is being controlled/to reduce the possible negative consequences in case of recurrence.

Here are some measures taken by the MoH of Ukraine, CROs, Investigators.

MoH of Ukraine – the Regulatory Authority must have had the most difficult challenges after 2015, as it was necessary properly identify the basic directions of development, mobilize resources:

1. to keep pace with the industry to make sure both compliance with the modern trends of the clinical trials in terms of changes in European legislation, as well as in ICH GCP E6(R12).
2. every effort had to be made to boost the investigators', as well as clinical center growth/to provide a qualitative training
3. to facilitate the process of the submission of the documents
4. to get ready for Russian intervention reoccurrence

Over the time period 2015-2020 Ukrainian RA successfully handled the tasks – changes in ICH GCP E6(R12) has been implemented, local low was harmonized with European legislation, implemented electronic forms, electronic register of clinical trials, as well as electronic on-line services. MoH of Ukraine has been conducting numerous seminars and workshops for investigators – many new specialists were engaged.

In fact, Investigators' number increases on 30% over 2015-2019 [9]. The amount of investigators, who work in Ukraine (according to MOH of Ukraine), is presented in Tabl.7 [9].

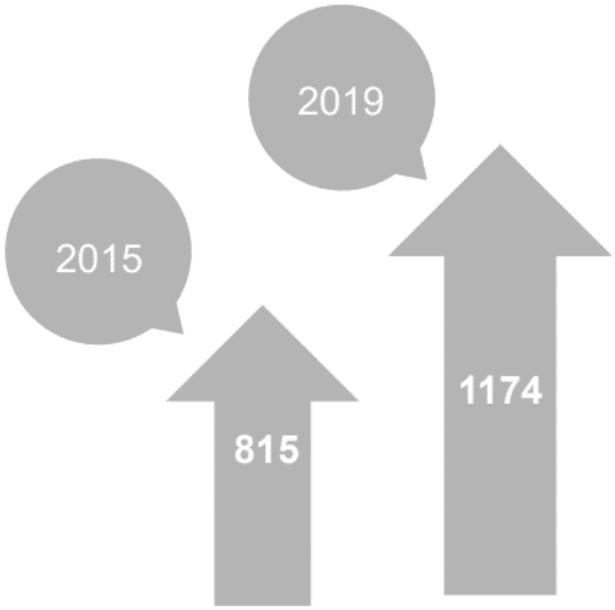

Table 7. Number of investigators in Ukraine

Number of clinical sites in Ukraine (approved by MOH of Ukraine) is provided in the Table 8 [9].

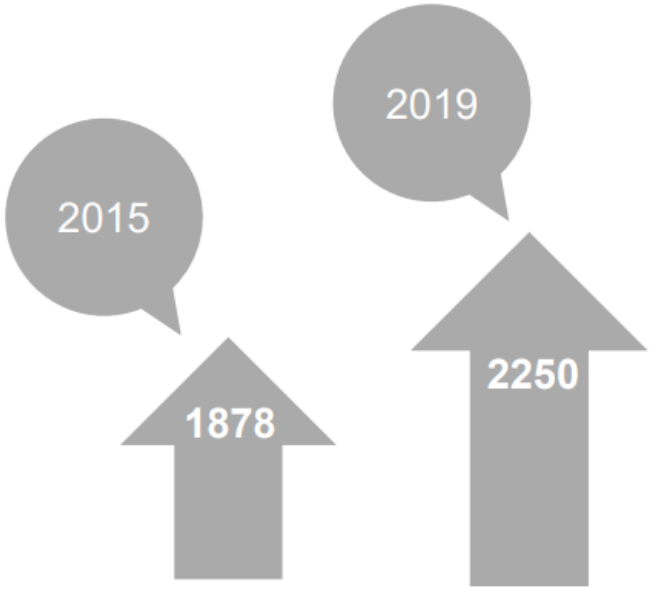

Table 8. Number of clinical sites in Ukraine

Clinical sites` number increases on 16,5%.

Looking ahead, it should be noticed that Ukrainian RA was well-prepared to face Russia's full-scale military invasion to Ukraine in February 2022. Let us consider the last third of the period we are talking about. According to Information-memo about the state of clinical trials in Ukraine for the period from 01.01.2022 to 08.31.2022 which has been released by State Expert Center of the MoH Ukraine we

can observe the following trends in number of submissions of protocols over first 8 months January-September in each year - in 2020, 2021, and 2022 (Tabl.9) [6].

Table 9. Number of submissions of protocols by State Expert Center

Month	**2020**	**2021**	**2022**
1-January	15	14	22
2-February	20	18	12
3-March	14	27	0
4-April	20	33	1
5-May	20	21	3
6- June	19	39	0
7-Jul	30	33	4
8-September	16	24	0
	154	**209**	**42**

According to the table the number of submitted protocols in January decreased on 35% in 2021 in compare to previous year, and clearly shows how much war in Ukraine in 2022 affected the local market of the clinical trials.

The table 10 illustrates the number of terminated because of sponsors decision studies since March till August of 2022 [6].

T**able 10. The number of terminated because of sponsors decision studies**

Month	**In total**
March	16
April	16
May	4
June	2
July	2
August	2
In total	**42**

There are approximately 20% of all active studies at that time. Most of terminated studies either were in the initial stage of the trial or just began the patients' enrollment.

Almost all studies terminated enrollment, which is can be perfectly well understood, as it would be irresponsible from sponsor's side to get involved new patients in conditions of uncertainty. Number of studies in which treatment was stopped is provided in Table 11 [6].

Table 11. Number of studies in which treatment was stopped

Month	**In total**
March	182
April	11
May	4
June	2
July	3
August	0
In total	**202**

In the meantime, above mentioned metrics (20% of terminated studies, as well as stop treatment for 202 studies) demonstrate rather the readiness to face the risk. 80% clinical trials continue conducting in Ukraine. More other, although in 2022 Russian Federation attack was much larger and affected almost 1/3 of the territory of Ukraine, core stockholders - RA, sponsors, CROs, LECs were able to mitigate the risk adequately.

MoH of Ukraine turned out to be quite ready for "the circumstances of military aggression and martial law." On 12Mar2022 Ukrainian RA provided detailed recommendations how to proceed with the patients, drug, laboratory. Here are some recommendations [12]:

- In case it is not possible to continue clinical trial at the approved site, to implement the procedure of patient withdrawal from clinical trial, or should this be possible –transfer such patients to other clinical trial sites since under current circumstances it is difficult to safeguard their rights, safety and health to the full extent.
- It is recommended to take all possible actions regarding uninterrupted provision of patient IMP (Investigational medical product – drug Author) at site and compliance with study protocol by all parties to ensure patients safety under conditions of Martial Law
- Sponsor should evaluate IMP related risks and consider any alternative methods of organizing IMP delivery with complying to storage conditions set by manufacturer.
- IMP may be delivered to subjects by independent distributor, contracted by Sponsor, in those cases when it is possible as per study protocol and with detailed instructions from Sponsor to subjects available
- To consider an option to use site laboratories for patient examination, provided there are necessary contractual agreements and required technical possibility
- In case it is not possible to continue clinical trial at the approved site, to implement the procedure of patient withdrawal from clinical trial, or should this be possible –transfer such patients to other clinical trial sites since under current circumstances it is difficult to safeguard their rights, safety and health to the full extent.

Here are Number of patients, who were relocated from original Ukrainian clinical site due to war (Table 12) [6].

The last table give us the information that the risk management strategy has been chosen in 2022, either risk mitigation or avoidance, wherever possible. The core stakeholders turned out to be prepared to make possible to transfer patients to other sites not only within the country but also to other countries' sites.

Table 12. Number of subjects transferred to other Clinical Trial Sites

	March	**April**	**May**	**June**	**July**	**August**	**Total**
Ukraine	0	43	41	24	44	4	156
Poland	4	34	34	24	5	6	107
Germany	1	3	15	14	4	9	46
France	0	1	3	2	1	0	7
Spain	0	6	2	3	1	2	14
Italy	0	4	0	1	0	3	8
Hungary	0	5	0	0	0	0	5
Moldova	0	7	3	0	1	0	11
Czech	0	3	3	6	2	2	16
Belgium	0	1	2	1	0	0	4
Switzerland	0	1	1	0	0	0	2
Romania	0	1	0	1	1	0	3
Estonia	0	2	0	0	0	0	2
Slovakia	0	1	0	1	0	1	3
Israel	0	0	1	2	0	0	3
Lithuania	0	0	0	3	0	0	3
Netherlands	0	1	0	0	0	0	1
Great Britain	0	1	0	0	1	0	2
Portugal	0	1	0	0	0	0	1
Canada	0	0	2	0	0	0	2
Greece	0	0	2	0	0	0	2
Bulgaria	0	0	1	0	0	0	1
Georgia	0	0	0	1	0	0	1
RF	0	0	0	1	0	1	2
Total	5	112	110	87	60	27	**401**

Undoubtedly, such advances wouldn't be possible without close communication/collaboration among all core stakeholders.

Let us have look at the typical scheme of communication among core stakeholders in clinical trials (Fig.1).

It should be noted that not all kind of the communication are happening in a regular basis, some of them are being occurred quite rare, especially between RA and clinical sites or between the sponsor and the clinical sites (for example the audits when either MoH or Sponsor can conduct at the clinical site with quality check purpose, or investigational meeting with the training purpose which conducts the sponsor before the study start).

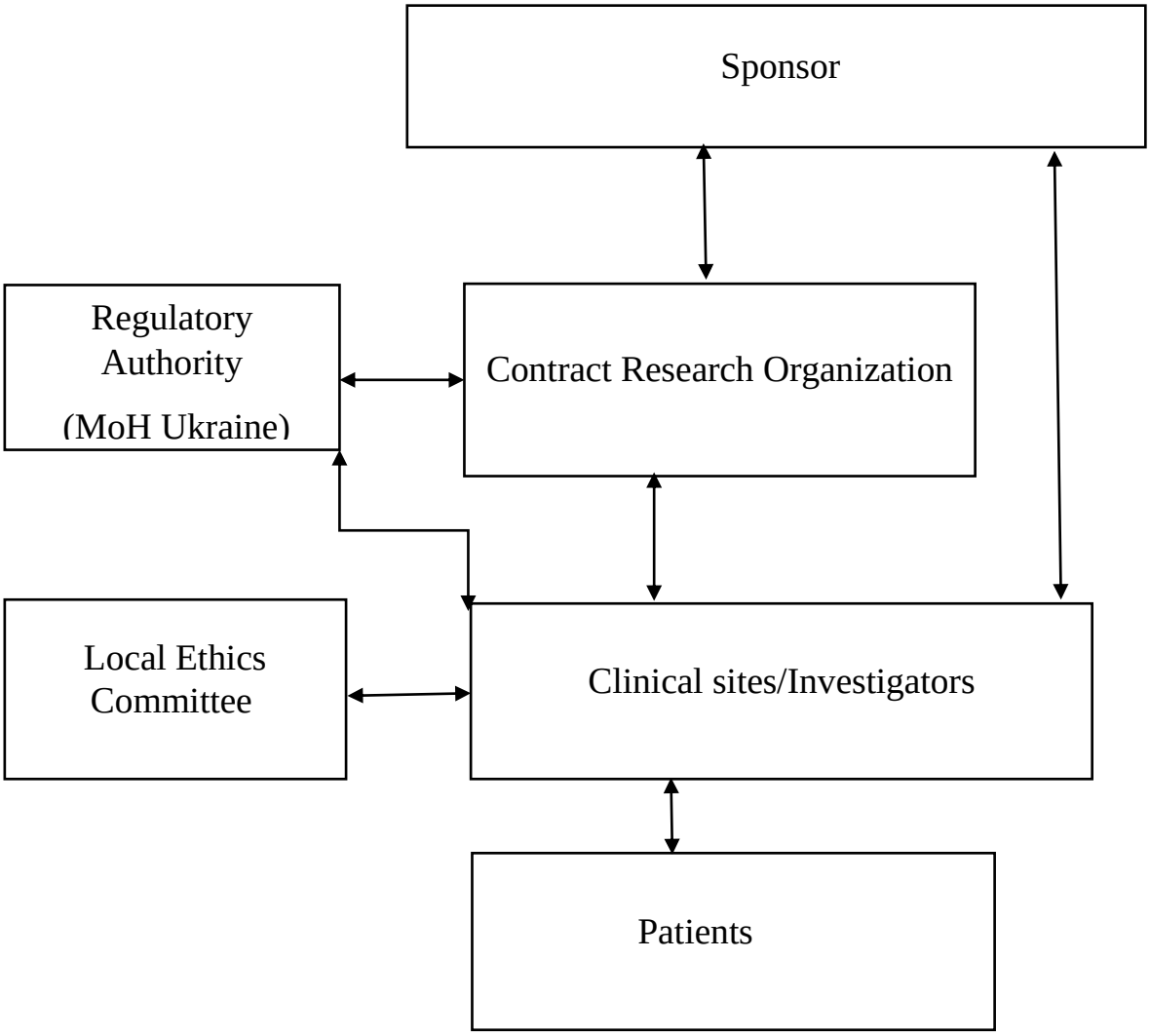

Figure 1. Typical scheme of communication among core stakeholders in clinical trials*

Sources: developed by the author

The liveliest communication happens regularly in the following couples:

- Sponsor-CRO
- MoH-CRO (MoH-CRO if the sponsor is conducting the clinical trial without CRO)
- CRO-clinical site
- Sponsor – clinical site
- Clinical site-patient

Thus, to make the patients' transfer possible it is necessary to provide multiple communication, to make sure the patient's transfer will be beneficial to both the patient and study integrity.

- MoH of Ukraine make a decision to allow patients' transfer
- Both MoH of Ukraine and site's LEC should be notified
- Sponsor make a decision to transfer patient, delegate CRO to start discussing with sites, identify list of patients who wants to be relocated

- CRO start discussing list of patients with both patient's original site and new one, which is about to receive a patient/keep conducting further procedures within the study with the patient
- Original site discussing with the patient, identify possible issues/difficulties, address them to CRO
- CRO discuss with sponsor the budget of the relocation including patients logistic, accommodation, any other supports. As soon as the sponsor approves the budget CRO gets back to the original site
- Both original site and the new site are being instructed by the CRO, all the communications/instruction are being documented, including emails, minutes of the teleconferences, sponsor's/CROs clarifications
- Original site makes a copy of the patient's medical records, certify it, hand over to patient he/she to provide it personally to the new site
- Original site notifies its LEC about patient's transfer
- CRO make sure that patients inform consent form translated into Ukrainian/certified/approved by Ethic committee/RA (applicable for patients who are being transferred to the foreign site)
- Before re-starting the study at the new site the patient should be re-consented, the process should be documented in patient's medical chart appropriately
- CRO should check that all the procedures have been performed/documented in accordance with both ICH GCP E6(R12) and local low.
- CRO/sponsor should make sure respective coordination among all accompanying vendors – logistic, drug delivery, accommodation etc.

Furthermore, according to website of MoH of Ukraine there are some positive trends has been identified by the November 2022 despite the ongoing war in the country:

- 55 clinical trials started,
- 10 clinical trials restarted,
- 8 studies restarted patients' enrollment.
- RA audits restarted

Discussion. The war has taken a heavy toll on the clinical trial system in Ukraine. There were a lot of experts who be treated with doubt that clinical trials industry in Ukraine can handle it. "Most of the industry-sponsored clinical trials are part of multi-country investigations. In these cases, the trials could likely pivot to other countries, especially for US drug approval, which can be easier to obtain with US-based data. However, the largest impact will be for studies being conducted entirely in Ukraine or in earlier clinical stages, since it can be time-consuming and difficult to start from scratch elsewhere to secure trial approval, begin recruitment, and actually carry out the study." [3].

Given the scale of the breakdown, as well as difficulties that the industry originally faced in 2014 some sponsors rushed to part both the benefits and the results already achieved, accepted the risk and went to other countries.

"When the Ukraine war started, clinical trial activity in the country was frozen, Vyshnyvetskyy recollects. While some overseas-sponsored studies with recruited patients managed to continue, investigations with a small number of participants or ones that are yet to recruit had local sites scrapped or put on hold, he adds. "Nobody knew what to do next because players did not know when the full-scale aggression would stop.""[2].

"After months of hard work, there is now a sense of returning to normalcy in Ukraine-based study sites. New trials have started locally in the past several weeks, Vyshnyvetskyy notes. In the past six months, two single-country studies were initiated, as well as 44 multinational investigations with a site in Ukraine, according to GlobalData's clinical trials intelligence." [2].

Conclusion. These sponsors that make decisions to leave in Ukraine, to mitigate the risk, to be acting in collaboration with one another - did not regret it. The main reason is that, although the risk has been transformed significantly since 2014 and suddenly acquired a new shape, in 2022 all core stakeholders turned out to be ready for facing the risk based on the previous experience, had a good mitigation, as well as contingency plan. These 10 years for the industry in Ukraine have shown that to achieve sustainability of the system it is necessary to learn to find new non-standard methods in the face of crisis, as well as in associated with it uncertainty and time pressure. In the meantime, to be able to ensure the stable operation clinical trials as an industry with extremely complex communicative relationships among core stakeholders it is necessary to make sure the excellent quality of relationships and trusting collaboration.

"Management, based on the concepts associated with organizational resilience, that would allow multiagency operations to main their functionality in high-volatile crisis environments, and the lessons that can be learned from high reliability organizations in terms of recognizing the importance of reliability over efficiency… the acceptance by all levels of the crisis management community of their responsibility to create and maintain 'organizations that work' could lead to a rapid improvement in the rates of success" [14].

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