Web-based symposium

A Symposium on Clinical Trials in Ukraine and Bioethics*1, 2

Invited lecturers

Viktoriia Dobrova, Professor of Department of Clinical Pharmacology & Clinical Pharmacy & Vice-chairperson, Research Ethics Committee of Clinical and Diagnostics Centre, National University of Pharmacy, Kharkov, Ukraine

Evgeny Levenko, Arensia Exploratory Medicine, Kyiv, Ukraine

Veronika Patsko, Clinical oncologist, National Cancer Institute, Kyiv, Ukraine

Moderator

Chieko Kurihara, Specially-appointed Professor, Kanagawa Dental University, Kanagawa, Japan

Commentators

Chiaki Kagawa, Professor Emeritus, Yamanashi University; Representative Director, Japan Association for Bioethics, Japan

Courtney A. Granville, Director Scientific Affairs, Drug Information Association, Washington DC, USA

Sandor Kerpel-Fronius, Professor of Clinical Pharmacology, Semmelweis University, Department of Pharmacology and Pharmacotherapy, Budapest, Hungary

Kotone Matsuyama, Professor, Department of Health Policy and Management, Nippon Medical School, Tokyo, Japan

Francis P. Crawley, Ukraine Clinical Research Support Initiative (UCRSI); Executive Director, Good Clinical Practice Alliance – Europe (GCPA) & Strategic Initiative for Developing Capacity in Ethical Review (SIDCER), Leuven, Belgium

Jerry Menikoff*3, Director, Office for Human Research Protections (OHRP), Department of Health & Human Services (DHHS), United States

Monday, October 10, 2022
Time: Kyiv (EEST) 14:00-17:00; Europe (CEST) 13:00-16:00
US Washington DC (EDT) 7:00-10:00; Japan (JST) 20:00-23:00

Online (Zoom) webinar

Organized as a part of the 34th Annual meeting of the Japan Association for Bioethics (JAB) with the support of members of the Ethics Working Group of the International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP)

*1 This web-based international symposium was held as a part of the Japan Society for Bioethics the 34th Annual Conference on 19-20 November, 2022, under the Presidency of Professor Kenji Doi, Kwansei Gakuin University. Video recordings was made available on demand to annual conference participants, and now open to public at: https://www.youtube.com/watch?v=TLLJP2pLTnQ
Short report on this symposium was published in IFAPP TODAY: Kurihara C, Matsuyama K, Crawley FP, Kerpel-Fronius S, Dobrova V, Levenko E, Patsko V. Clinical trials in Ukraine and bioethics: IFAPP collaborating with JAB. IFAPP TODAY 2022. Nov/Dec (29): 9-12.
https://ifapp.org/static/uploads/2022/11/IFAPP-TODAY-29-2022.pdf

*2 This symposium was held in October 2022, when Russian attack was becoming more disruptive, however, we could find Ukrainian clinical trial infrastructure kept well with the support of global society. Now at the time of publication in July 2023, the lecturers informed that their technical capabilities have become much better than it was in the beginning of war and even in October 2022, keeping the level in peaceful time.

*3 Given that this web-based symposium was delivered at a time when he was speaking on behalf of the U.S. government, since he is no longer employed by that government, nor empowered to speak on behalf of it, Dr. Menikoff chose to not have his remarks published.

Abstract

This is a record of a web-based Symposium on Clinical Trials in Ukraine and Bioethics, held on October 10, 2022, around the eighth month after the start of the Russian invasion of Ukraine, organized as a part of the 34th Annual meeting of the Japan Association for Bioethics (JAB), with the support of members of the Ethics Working Group of the IFAPP.

The Japanese Constitution has a paragraph of eternal renunciation of war and many of the Japanese bioethicists recognize peace and “do no harm” (against war) to be among the core principles of bioethics. The objective of this symposium is to strengthen the structure to support Ukrainian Clinical Research as this represents an integral part of the scientific and healthcare systems of the country as well as being integral to the continued development of the Ukrainian society.

This is a right of a sovereign state and national and international community of bioethicists and researchers have an obligation to strengthen solidarity to provide ongoing support to the importance of clinical research and the expansion of awareness regarding the situation of research, medicines, and health in Ukraine.

Three Ukrainian speakers have conveyed the real status of current situation.

We should learn how we can support Ukrainian researchers and patients and the public, while also considering development of international guidelines for research in war/conflict setting and other disruptive situations, based on reflection in depth of bioethical implications.

Key words

Ukraine, war, clinical trial, ethical principles of research involving humans, bioethics

Rinsho Hyoka（*Clinical Evaluation*）. 2023；51(1)：103-52.

Opening Remarks

Opening Remarks and instructions

Chieko Kurihara

Specially-appointed Professor, Kanagawa Dental University, Kanagawa, Japan

Welcome Address

Chiaki Kagawa

Professor Emeritus, Yamanashi University
Representative Director, Japan Association for Bioethics (JAB), Japan

Remarks from Drug Information Association

Courtney A. Granville

Director, Scientific Affairs, Drug Information Association, Washington DC, USA

Opening Remarks and instructions

Chieko Kurihara

Thank you very much for your participation. This symposium on Clinical Trials in Ukraine and Bioethics is organized as a part of the 34th Annual Meeting of the Japan Association for Bioethics with the support of members of the Ethics Working Group of the International Federation of Association for Pharmaceutical Physicians and Pharmaceutical and Medicine (IFAPP). There is no financial support to this meeting, and all the speakers and participants are voluntarily and willingly participating.

I am Chieko Kurihara, moderator of this symposium as a member of Japan Association for Bioethics and Ethics Working Group of IFAPP.

The primary objective of this symposium is described here (Table 1). The Japanese constitution has a paragraph of eternal renunciation of war and many of the Japanese bioethicists recognize “peace” and “do no harm”, including “against war” to be among the core principles of bioethics. We wish to strengthen the structure to support Ukrainian clinical research as this represents an integral part of the scientific and healthcare system of the country, as well as being integral to the continued development of the society. This is a right of sovereign state, and we as a community of bioethicists and researchers have an obligation to strengthen solidarity to provide ongoing support to Ukrainian researchers and patients and the public. Today, we are grateful

Table 1　The primary objectives of the symposium

- The Japanese Constitution has a paragraph of **eternal renunciation of war** and many of the Japanese bioethicists recognize peace and "do no harm" (against war) to be among the core principles of bioethics.
- This symposium wishes to strengthen the structure to support Ukrainian Clinical Research as this represents an integral part of the scientific and healthcare systems of the country as well as being integral to the continued development of the Ukrainian society.
- This is a **right of a sovereign state** and we as a national and international community of bioethicists and researchers have an obligation to strengthen solidarity to provide ongoing support to the importance of clinical research and the expansion of awareness regarding the situation of research, medicines, and health in Ukraine.
- To day we are grateful to have the Ukrainian speakers to convey the real status of current situation.
- We wish to learn how we can support Ukrainian researchers and patients/public, while also considering development of international guidelines for research in war/conflict and other disruptive situations, based on reflection in depth of bioethical implications.

Table 2　The secondary objectives

- The Japanese participants will take this symposium as a precious opportunity for reflection on a more in-depth analysis of the bioethical implications of the current situation, framing it in their own historical experience of both of aggression in other countries as well as being attacked by weapons of mass destruction during World War II.
- The international participants will expand our ongoing considerations for publication of scientific papers considering international guideline development and outputs based on this symposium and other for addressing research and ethics in conflict and other disruptive situations.

to have the Ukrainian speakers to convey the real status of their situations.

This is the secondary objectives (Table 2). The Japanese bioethicists will take this precious opportunity for reflection on the bioethical implications of the current situation considering our own historical experience of both of aggression in other countries, as well as being attacked by weapons of mass destruction during World War II. The international participants will expand our ongoing discussions for publication of scientific papers considering international guideline development, addressing research and ethics in conflict, and other disruptive situations.

This is the profile of participants (Table 3). There are participants from these countries, and many are medical professionals and researchers, but most of them are bioethicists and others are bioethicists of non-medical professionals.

For the opening, Chiaki Kagawa, Professor Emeritus, Yamanashi University and Representative Director of the Japan Association for Bioethics will have Welcome Address. After one commentator from Drug Information Association (DIA), Courtney Granville will provide a message bridging the previous webinar organized by DIA to this one, three Ukrainian speakers will give presentations, and then four commentators will make comments. We hope that all the participants could learn from this precious opportunity.

Table 3 Profile of participants

Country	Detailed profile	
Japan	Bioethicists: 2 Medical professional: 2	4 (Later shared among bioethicists (members of JAB) in Japan.)
Ukraine	Medical professional/research specialists (speakers): 3 Medical professional/research specialists (participants): 4	7
Europe	Bioethicist, Belgium: 1 Medical professional/research specialists, Hungary, Switzerland, France, Poland: 4	5
USA	Medical professional/research specialists: 3 Bioethicists: 2 Regulator (bioethicist): 1	6
Australia	Medical professional/research specialists: 1	1
Liberia	Bioethicist: 1	1
India	Bioethicist: 1	1
Total	Medical professional/research specialists: 17 Bioethicists: 7 Regulator (bioethicist): 1	25

* This categorization is not based of the agreement of each participant.
Most/many of medical/research specialists seem to be bioethicist.

Welcome Address

Chiaki Kagawa

As the Representative Director of the Japan Association for Bioethics (JAB), I am pleased that JAB will host this important international workshop under the title 'A Symposium on Clinical Trials in Ukraine and Bioethics.'

The Russian attack on Ukraine has not only shocked people around the world, but it continues to have a dismal effect on many aspects of people's lives. Around the world, people have been shocked and dismayed by this war. Scientists, public health officials, ethicists, and people generally are becoming increasingly aware of issues in clinical research that have become more challenging and urgent than previously thought.

Ukraine and Russia still hold large positions internationally as places where clinical researches are conducted. Big pharmaceutical companies with global activities are conducting large number of clinical studies in both countries as are too smaller and equally important investigator-driven studies. The international community as well as the national and local communities have benefited from the valuable work in clinical trials conducted in Ukraine and Russia. However, the recent military conflict has made it extremely difficult to continue clinical studies in both countries. The current changes will have a direct impact not only on Ukraine, but also on the international community. First and foremost, we need to understand the situational challenges of research in this disruptive situation. This includes the ethical challenges, as well as the challenges arising in trial conduct and logistics.

In this symposium, we will explore the current situation of clinical research in Ukraine from the perspective of ethics. We will ask what this new situation of conflict means for the ethics of clinical research internationally and what we need to learn from it. Furthermore, we need to think about how clinical research should be conducted scientifically and ethically in the limited situation of war, based on an appreciation of the current situation. It is not just the special issues related to extreme situations such as war that needs to be considered. Considering the universal conditions required for clinical research itself, regardless of the situation, it should be indispensable even when we are in the extreme situation of war.

In an exceptionally fluid situation fraught with many new problems, it is difficult to find the direction that the international community should take in response to the clinical research situation in Ukraine today. However, in order to grasp such a difficult perspective, we should be able to provide solid clues based on both the recognition of the current state of clinical research in Ukraine and a broader consideration of the role the clinical research enterprise plays in our societies today.

It is our hope that this symposium on 'Clinical Research in Ukraine' will help us to have a better understanding of the role of ethics in research during conflict situations as well as the responsibility of the international science and ethics communities in providing adequate responses.

On behalf of my colleagues at the JAB, I look forward to welcoming you to this symposium.

Remarks from Drug Information Association

Courtney A. Granville

I am here from Drug Information Association (DIA), a neutral, multidisciplinary membership organization. We use our neutral platform to educate and convene stakeholders to solve problems and ensure the integration of innovation into our clinical trials and clinical research continuum.

Back in March of 2022, I was at our Europe annual meeting where our stakeholders talked to us about bringing forward the conversation around the impact of the war in Ukraine. So beginning in May, we started to organize a webinar series, recognizing that the war brought with it an unprecedented crisis in clinical trials and research. We saw that we could use our platform to share experiences and up-to-date information and also to unite the international clinical research community around what they needed to do to develop local, regional, and global responses, and going beyond that, also about preparedness for disruptive events and to create a lasting output and impact that could guide response in the future.

Starting those webinars back in May enabled a connection to the Ukraine Clinical Research Support Initiative (UCRSI). Working with this group, which is led by Francis Crawley, Viktoriia Dobrova, Mark Turner, and Beata Aurich, names that are not unfamiliar to this group, we were able to bring this important discussion forward through another six webinars with many, many expert speakers, and about 600 different registrants and participants in the webinars. We covered the regulatory response to the war, the needs that exist for streamlining future guidance and good clinical practice guidelines to apply in conflict situations, ethical considerations to prioritize support and protect study participants who have been impacted, and spe-

cifically also the impact of the war on cancer clinical trials and on patients living with what is rare disease. So we covered quite a breadth.

The webinars highlighted not just the resilience of the clinical research enterprise in the region, but also highlighted the need to think differently about clinical trials and research in our current ecosystem, so we can preserve its ability to innovate and bring solutions forward to patients even in times of crisis. In fact, the conflict has highlighted the critical societal importance of research and its role in maintaining both health and economic prosperity.

We are now working as a team with IFAPP and the UCRSI and many, many experts to publish the findings and recommendations that emerged from our conversations in publications including our magazine called the Global Forum (Fig. 1), which anyone can access, and we will be continuing to have follow-up conversations and discussions. Thank you again, for having me in this symposium. I look forward to a robust morning of discussion.

Fig. 1 DIA Global Forum

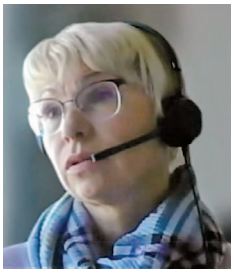
Special section in March 2023 Global Forum
https://globalforum.diaglobal.org/issue/march-2023/

- SPECIAL SECTION: CLINICAL RESEARCH IN UKRAINE
  Special Section Introduction: Protecting Clinical Research, Researchers, and Research Participants in Ukraine
  Cancer Trial Continuity in Ukraine Is a Shared Responsibility and a Global Imperative
  Responding to the Wartime Needs of Ukraine's Patients with Rare Diseases
  Ethical Considerations: Clinical Research in Wartime Ukraine and Beyond
  Giving Voice to the Unheard
  Part 1: Ethical Considerations for Research with War-Affected Populations
  Part 2: Ethical Consideration for Children in Wartime
  Ethical Considerations on Clinical Trial Participation and Management in Wartime Conditions: Perspective from the IFAPP Ethics Working Group
  From COVID-19 Pandemic to War: Clinical Trial Industry Powers On Under Extreme Conditions

Special section in April 2023 Global Forum
https://globalforum.diaglobal.org/issue/april-2023/

- SPECIAL SECTION: CLINICAL RESEARCH IN UKRAINE – PART 2
  The Lessons of War Inform Good Clinical Practice Guidelines
  Three Perspectives: Maintaining Good Clinical Practice (GCP) During War
  GCP in the Context of Global Regulatory Reliance and the Situation in Ukraine
  Clinical Trials Continuity: Ukraine State Expert Center Perspective and Recommendations
  Maintaining Safety While Relocating Ukrainian Clinical Trial Participants

The current issues of the ethical review system in Ukraine in the context of Russian invasion



Viktoriia Dobrova, PhD, DSci (Pharmacy)

Professor of Department of Clinical Pharmacology & Clinical Pharmacy & Vice-chairperson, Research Ethics Committee of Clinical and Diagnostics Centre, National University of Pharmacy, Kharkov, Ukraine
University of Heidelberg, Germany
Ukrainian Clinical Research Support Initiative

1. Introduction

I am grateful, first of all, to the Japan Association of Bioethics, its representative Director Professor Chiaki Kagawa, and personally Professor Chieko Kurihara for such a great opportunity to present information about the ethical review system of Ukraine and the influence of war on our system. In addition, I am grateful to Francis Crawley for his willingness and initiative to support clinical trials in Ukraine during this devastating time, and his great energy, spent time, and brilliant ideas. I want to note and say my warmest greetings to the DIA team, especially Courtney Granville, for the opportunity to use the DIA platform during all of the summer of 2022. We can share and discuss different issues in clinical trials which arise during Russian aggression in Ukraine.

2. Regulatory authority of clinical trials in Ukraine

Ukraine is a huge European country (Fig. 1). The population is more than 41 million, but Ukraine is a low middle income country. It is GDP per capita in 2021 was only $2,500. It is not bigger GDP, so it is very important to spend this money in a proper way for health care support and development. If we find some good ways to involve other finances for our healthcare system for supporting our patients to give them some new medicines and modern treatment, it is very good, because current health expenditure as a share of GDP in 2019 was only 7% according to WHO publications. This 7% includes out-of-

Fig. 1　Ukraine snapshot - some facts about country and health care system

pocket money and government budget money for different medical provision. Therefore, we need additional support for our healthcare system and for the treatment of our patients. That is why clinical trials as one of such additional sources of proper support for our Ukrainian healthcare system are very important.

If we speak about the regulatory authority of Ukrainian clinical trials, it is the Ministry of Health of Ukraine. The state enterprise, "State Expert Center of the Ministry of Health of Ukraine", performing expertise assessment, approving all protocols of clinical trials in Ukraine.

3. Clinical trial status in Ukraine before the active invasion

How were clinical trials before this active war invasion in Ukraine? At the beginning of the active invasion of Russia on 24th February 2022, there were 794 clinical trials in the Ukrainian clinical trials enterprise, and all these clinical trials had been approved by the State Expert Center of the Ministry of Health of Ukraine and our Research Ethics Committees. Then, they were approved by our regulatory authority – Ministry of Health. 584 clinical trials had started and were being conducted in different phases: first, second, and third phase. Nearly 85-90% of these clinical trials were from international organizations and international sponsors, so they were multicenter clinical trials, and their sponsors were international companies. As of 24th February, 210 clinical trials had been approved by the Ministry of Health and were being prepared for their launch. The launching of clinical trials is a time-consuming process. So, all these clinical trials were prepared, clinical sites were ready, contract research organizations were prepared to conduct these clinical trials at that moment.

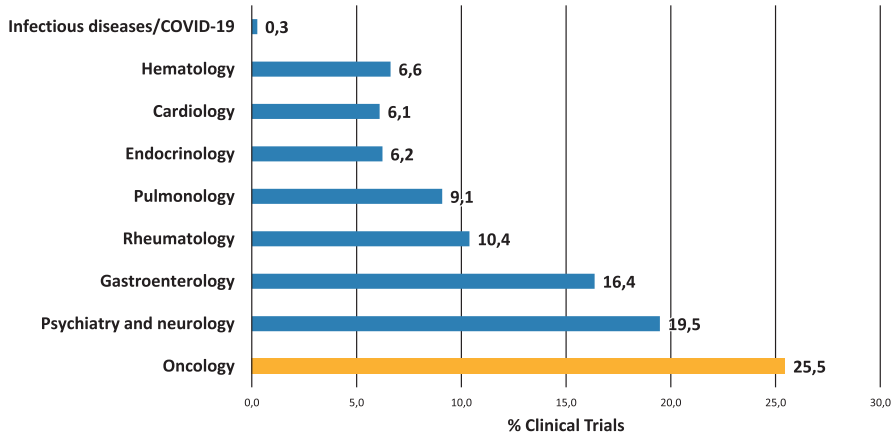
I want to emphasize that our State Expert Center has been very active since the first day of the war. Persons who have participated in the DIA webinars know that Dr. Taisa Herasymchuk, Director of the Department of expertise of materials for preclinical and clinical trials, presented these data, and presented the work of our State Expert Center. On the first day of this devastating situation, we did not know what to do with researches, patients, documentation, etc., but from the first week of March, our State Expert Center started finding solutions to support our clinical trials, to help our investigators, to help our sponsors, contract research organization, and offered different important decisions for clinical trial research subjects.

4. Distribution of clinical trials

Today, I will not speak about investigator-initiated clinical trials, but I will speak most of all about clinical trials, which are sponsored by pharmaceutical and biomedical companies like commercial clinical trials (Fig. 2). Investigator-initiated clinical trials are called "clinical research", not "clinical trial". It means that these researches are not interventional research. In such investigator-initiated clinical trials in Ukraine, we do not study non-registered, non-approved medicines. We will not speak today about such research. This is another topic for discussion, and it is much more about how medical science in Ukraine works. This topic needs other materials.

Today, I will draw your attention to only clinical trials which are sponsored by pharmaceutical and biomedical companies. The reason why we speak so carefully and why we pay huge attention to clinical trials in Ukraine is that 25% of these clinical trials are oncological clinical trials. During these clinical trials, drugs that are very important for humanity are studied, and this information is very important in terms of the activ-

Fig. 2　Distribution of clinical trials to nosology (2021) *



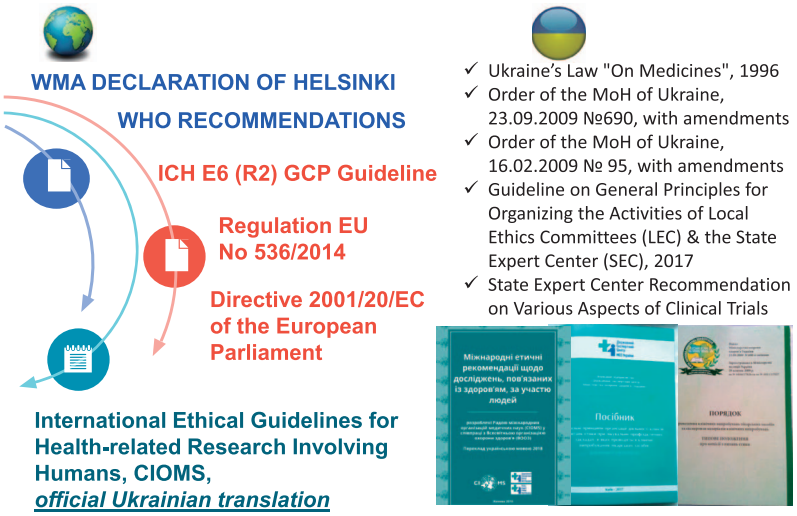
* according to data of State Expert Center Ministry of Health of Ukraine (https://www.dec.gov.ua/materials/aktualna-informacziya/?role=applicant)

ity, efficacy, and safety of these drugs. Therefore, you see how clinical trials in Ukraine are distributed according to nosology: psychological, neurological, gastroenterology, rheumatology, pulmonology, endocrinology, cardiology, and hematology diseases. This is the main field of our clinical trials in Ukraine. So, data from these researches are very important not only for Ukrainian patients but also for many patients who are enrolled and for many pharmaceutical companies and for healthcare professionals.

5. Normative and legislative documents

In Ukraine we work with all important basic normative documents of the European Union and world documents such as the Declaration of Helsinki, WHO recommendations, and CIOMS guidelines (Fig. 3). We use all these documents for the review of clinical trials in Ukraine. We have used these documents for the last

Fig. 3　Basic normative and legislative documents for Ukrainian clinical trial system



two decades. During the last two decades, our system of clinical trials has developed, and many new documents were added or some of these documents were changed. So, there are a lot of documents that are completely harmonized with European Union documents and with world documents for approval for assessment of clinical trials. So, Ukraine completely goes in the way of the European Union and the whole world according to the protection of human rights, and the quality of clinical trials is very important for us, for researchers: for sponsors, ethics committees, and our Ministry of Health and State Expert Center.

Therefore, we have, first of all, Ukraine's Law "On Medicines" (1996) and two main orders: Order of the Ministry of Health of Ukraine №690 with amendments (since 23.09.2009), Order of the Ministry of Health of Ukraine №. 95 (2009). These orders are amended, and these orders completely involve all topics in the ICH-GCP. Since 2021 , our State Expert Center has been included as an Observer (official status) in ICH and obtained the status of an Associate Member of the ICMRA (International Coalition of Medicines Regulatory Authorities). It is very important for collaboration and future harmonization of our system.

Again, I am presenting you information, which was designed by Sergii Rasputniak, head of GCP and GLP Audit Department of State Expert Center. Our Ukrainian Law of Medicines includes two articles, Article 7 and 8, about clinical trials of medicines and the protection of patient and volunteer's rights, who want to participate in clinical trials. Our main orders which regulate our clinical trials are the same. They include main topics and procedures which are in Directive 2001/20, so they are oriented with this document. ICH Good Clinical Practice Guidelines in Ukraine are all amended according to the R2 of the ICH GCP (E6).

I want to emphasize that in Ukraine the clinical studies approval process is a parallel process. The State Expert Center and local REC make a review and take decisions independently and approximately at the same time. So, our authority makes its own review of clinical trials, and our local REC makes its own review of these clinical trials. When both of them give their approvals, only then the clinical trial is started.

6. Research ethics review system in Ukraine

In general, the research ethics system in Ukraine can be described as a decentralized system with a lot of local RECs (Table 1). More than 400 local RECs exist in Ukraine. For participation in clinical trials as Research Center, each clinical trial site must have a working Research Ethics Committee. The US calls them the Institutional Review Board, but we call them Research Ethics Committees (RECs). Ukraine does not have central ethics committee. Therefore, local RECs are completely independent and have self-management. This is neither good nor bad. This is our local situation. A very interesting and very important point is that par-

Table 1 Research Ethics Review system in Ukraine

DECENTRALIZED SYSTEM:
•More than **400** local Research Ethics Committees at each trial site
•NO central ethics committee
•Most of REC's members are employees of institutions that have clinical trial sites
•Participation in REC is voluntary and non-payment duty
•Regulatory recommendation for researchers and sponsors from the **State Expert Center of the Ministry of Health of Ukraine** is a main informational source for RECs

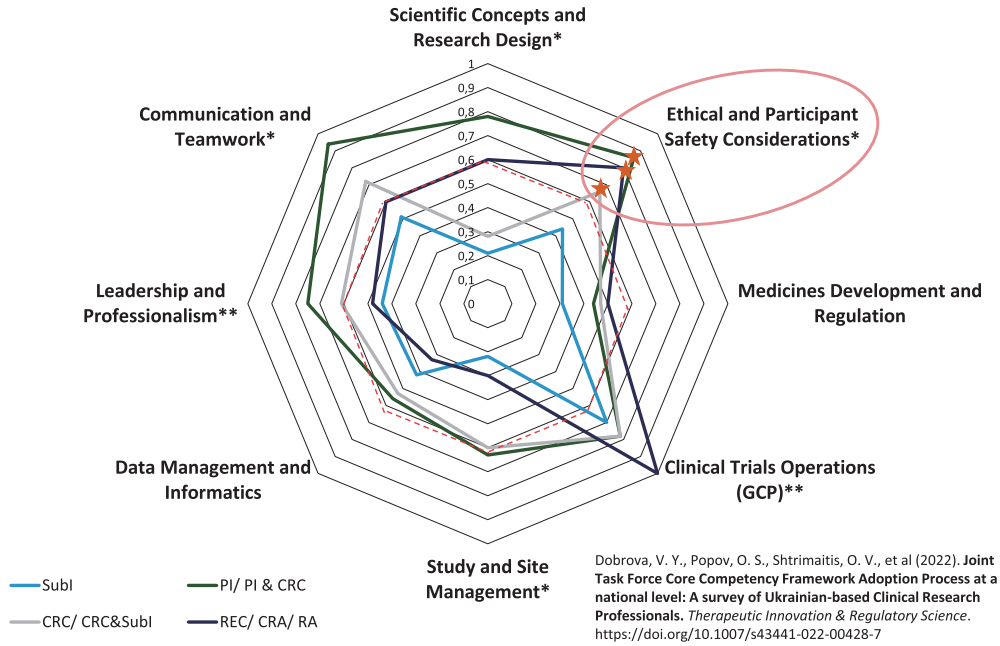
ticipation in REC is voluntary and a non-payment duty for the members. The membership of RECs is completely according to the ICH-GCP norms, a minimum of five people, one of them non-employee, one of them non-research, and a non-medical person. Our RECs have very good support from State Expert Center, and sometimes we have a weak interaction between different RECs, but we have a perfect interaction with State Expert Center. So, each REC can call the special department and ask questions and get help and support from specialists from State Expert Center.

Our research ethics protection system has four capstones. The sponsor is responsible for protection of study subjects. The researcher is responsible for the willingness, well-being, and health of the study subjects. The State Expert Center controls the situation and controls all data of our research. The local REC gets all information about all situations in the trial site and adverse events, different transfers of patients, and many other information. These are the four important capstones for protection of trial subjects.

7. Master's education program

I want to present to you some small research data about our education, because in Ukraine we pay attention not only to how we can get money from sponsors, but we want to conduct clinical trials in our clinical centers at a correspondingly high level of research quality and ensure research subjects (patients) protection (Fig. 4). Long time in Ukraine we had different short-term programs for the training of research personal of clinical trials, clinical associates, monitors, etc. Four years ago, we opened a master educational program "Clinical research", and during this process of opening, my team and I studied a lot of curriculums. We studied curriculum for clinical research professionals, and we did surveys of our researchers, that included our principal

Fig. 4　Self-perceived level of competence in base competence domains by role in clinical trials (Master's educational program "Clinical Research")



Dobrova, V. Y., Popov, O. S., Shtrimaitis, O. V., et al (2022). **Joint Task Force Core Competency Framework Adoption Process at a national level: A survey of Ukrainian-based Clinical Research Professionals.** *Therapeutic Innovation & Regulatory Science*. https://doi.org/10.1007/s43441-022-00428-7

investigators, members of REC, clinical research coordinators, and many other persons who are involved in conducting clinical trials.

You see the data of some assessments of their competency in different questions, and you see that most of them have good competency, more than 60%, according to ethical questions. They want to study these questions and pay attention to get new knowledge and to study it during additional educational programs for clinical research professionals, master's degree educational programs. We designed this curriculum. For us, it is very important to protect first of all our subjects and then get good data and good information for sponsors for future assessment of the efficacy and quality of new medicines and for the healthcare system.

8. Science projects for Ukrainian research ethics system development

The other one that I wanted to show you is that we worked as practical professionals during all this time together with State Expert Center, with Dr. Sergii Rasputniak, together with some of our contract research organizations' members, and together with our friends from different countries: from the United States, from Lithuania, from Latvia. We participated in two big science projects. One is "Identifying and Addressing Challenges of Effective Functioning in the Ukrainian Research Ethics System (2015-2017)". We estimated and assessed how our ethics system worked at that time. As a result of this project, there was an improvement of our State Expert Center and new recommendations, which I showed you before.

The second project "Developing Recommendations for Ethics Committees and Policy Guidance for Eastern European / Central Asian Countries to Support Public Health Emergency Preparedness and Response (2020-2021)" started during COVID-19. I am grateful to Francis Crawley for involving me in this project. We did a good assessment of how our Review Ethics System transformed and worked during COVID time when we saw this pandemic situation, when we get such challenges. This project helped our research community to understand how we can prepare to work online through electronic documents. This project and this time helped us understand how we can work in such a situation in which we are now.

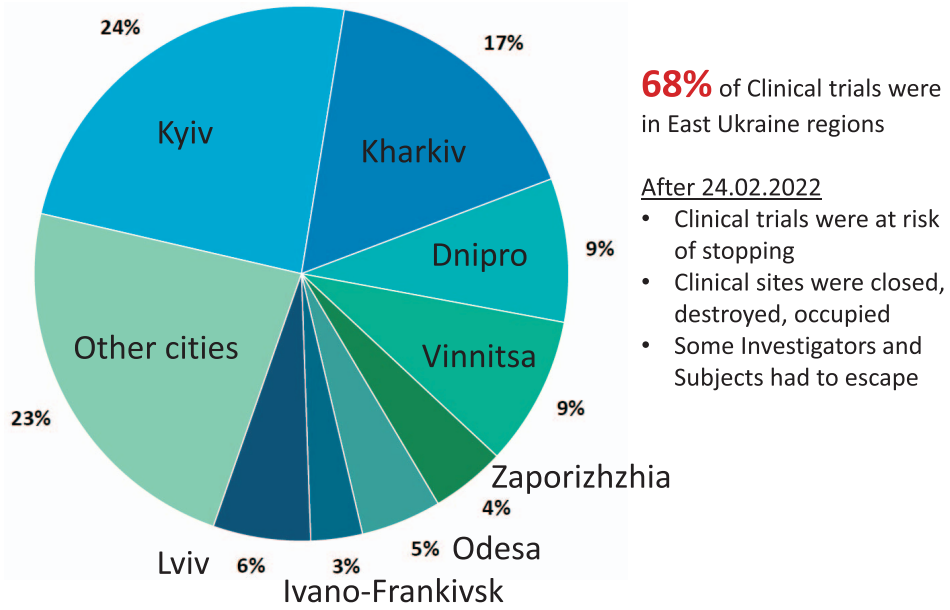
9. Distribution of clinical trials in Ukraine cities

If we come back to our topic of how this war influenced our clinical trial and research ethics system in Ukraine, I want to show you the distribution of clinical trials in Ukrainian sites before the war (Fig. 5). More than 68% of clinical trials were in eastern Ukrainian regions. From the first days, these were the sites that saw Russian aggression, so they needed to take some steps to react to this situation. In fact, after the 24th of February, many clinical trials which were being conducted in these regions were at risk of stopping. Many clinical sites were closed, some were destroyed, and some are occupied even now. Some investigators and subjects had to escape, and our system had to quickly react to this situation and try to come up with the best decision on how to manage such a situation.

10. Transfer of clinical trial subjects

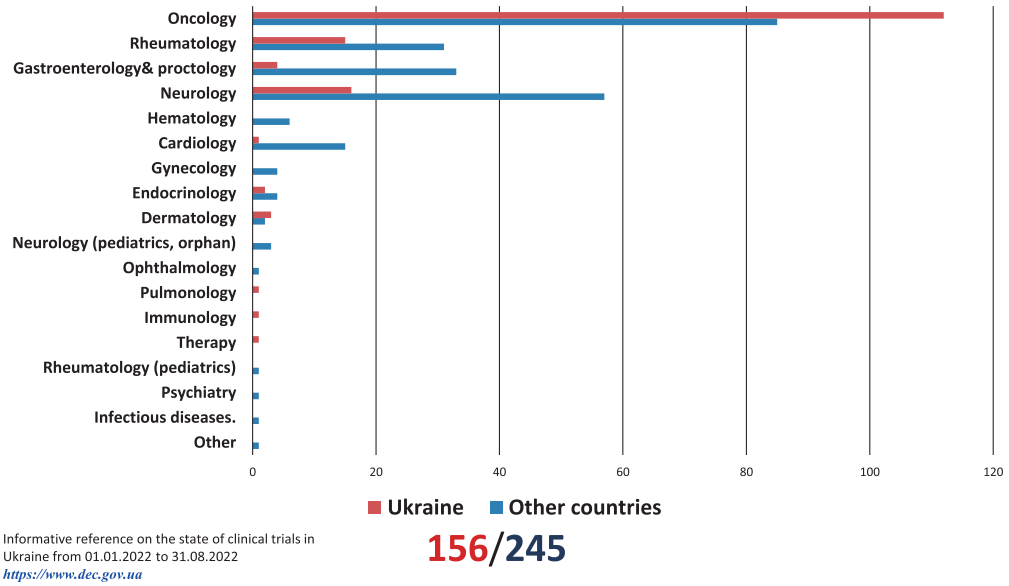
The most important task at this time is how to protect our trial subjects (Fig. 6). First, there was a transfer

Fig. 5　Distribution of clinical trials sites in Ukraine *



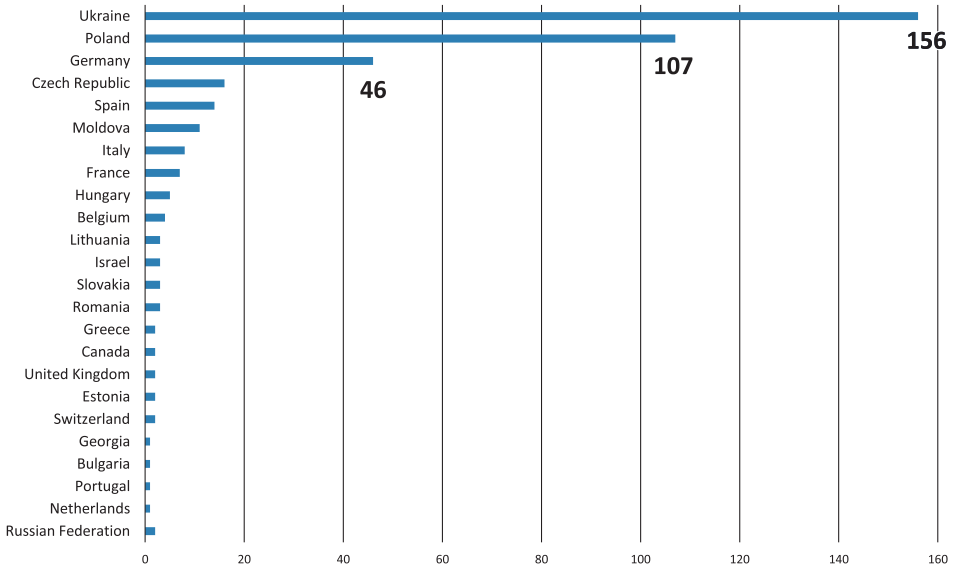
* according to data of State Expert Center Ministry of Health of Ukraine (https://www.dec.gov.ua/materials/aktualna-informacziya/?role=applicant)

Fig. 6　Transfer of clinical trials subjects after 24.02.2022: Nosology



of clinical trial subjects. You can see how this transfer was distributed according to nosology. Most of the oncology patients were moved from the eastern regions of Ukraine as well as to other countries. In fact, neurology, rheumatology, gastroenterology, hematology, and cardiology patients were also moved from the eastern part of Ukraine and to different countries. The number of patients that moved to eastern part of

Fig. 7 Transfer of clinical trials subjects after 24.02.2022: Country



Informative reference on the state of clinical trials in Ukraine from 01.01.2022 to 31.08.2022
https://www.dec.gov.ua

Ukraine is 156 and to other European Union countries is 245.

In terms of the transfer of these patients to different countries, our nearest neighbor, Poland actively started to move these patients to give them an opportunity to continue their participation in clinical trials (Fig. 7). The GCPpl Association in Poland signed new recommendations. They reacted very quickly. Germany also took an active part to move our participants. Some of the participants got an opportunity to participate in clinical trials in German research centers or to prolong their participation in their own clinical trials but in centers in Germany. You see this distribution in other countries like Czech Republic, Spain, Moldova, Italy, France, and others.

11. Clinical trials during the war in Ukraine

When we speak about how in a philosophical or existential way this war influenced our research system and what we need to decide now, all research ethics systems not only of Ukraine but the whole world faced unprecedented challenges by this war. We see clearly what we should do. This is a typical organizational issue experienced by Ukrainian clinical trial research ethics community. This challenge has a lot of uncertainty, complexity, and ethical dilemmas. We clearly see that the assessment of risks and benefits for research subjects should be implemented first. This is that part of the iceberg that we see. We need this instrument of risk-benefit assessment, but what we do not clearly see, and we have some difficulties in clarifying by ourselves but we need to clarify are strategic consequences. How will we feel the long-term impact of this situation of war in Ukraine for all clinical trials system in the world? What strategic ethics consequences and long-time ethical impact should we consider and predict and perhaps prevent them in the future?

12. Issues for research ethics review during war

These are our thoughts about issues of research ethics review during the war (Table 2). The issues experienced by Research Ethics Committee were those related to the process of ethics review and monitoring. First of all, it is a lack of experience. Our members of the RECs, that are working under bombs and missiles, do not have such criteria how to assess the minimal risk for research subjects in these conditions. No one in the world has criteria on how to work and conduct clinical trials in such devastating situations. For example, today, our civilian infrastructures in different cities again were bombed and were under missile attacks by Russian troops. Our RECs do not have criteria for assessment of patients' risk for research procedures and estimations of thier ability to continue such studies.

Another major problem is organizing REC meetings and members' communications. Many members of RECs are employees of these hospitals where clinical trial sites were, and they may be in other countries. They need procedures and need regulations on how to work and how to guarantee assuring transparency and how to do remote work. So, Research Ethics Committee needs to develop procedures that ensure REC member's safety and data confidentiality and conditions of electronic data flow, transparency in conditions of remote work, and compliance with review deadlines. All these tasks are big challenges for volunteer work which research ethics review is.

Table 2　Issues for research ethics review during war: Novel challenges for RECs

- **Protocol review**
  - Risk assessment (study participants)
  - Assuring study personal safety
  - Risk minimization procedures (related to active war)
- **Organization of REC meetings**
  - REC member's safety
  - Data confidentiality (lack of electronic dataflow)
  - Regulation and assuring transparency in conditions of remote work
  - Interaction with others RECs
  - Compliance with review deadlines

Table 3　Issues for research ethics review during war: Ethical monitoring of studies

- Onsite vs remote
  - Risks to safety (REC members, study participants, site personnel)
  - Risks to data confidentiality (paper vs electronic dataflow)
  - Ensuring adequate human subjects protection
  - Impossible to monitor the safety of research subjects in trial sites temporary occupied by Russia
  - Interaction with REC of host clinical trial sites where researched subjects were removed from Ukraine or from some regions of the country

Now, the RECs of Ukraine need to consider special ways for ethical monitoring applying mostly remote methods by constantly evaluating possible risk to the safety for their members, study participants, and ensuring proper human subjects' protection in such a difficult circumstance (Table 3). A very critical question is how to monitor and protect research subjects' rights in this situation when some research subjects are in different countries and

on different site. We need coordination between such sites interchanged by this information. One very difficult and critical question is how to monitor and protect research subject rights on their trial sites that are occupied by Russia and how to manage the interaction between these clinical sites. Taking this into account, it is pretty hard to avoid an excessive burden on Ukrainian RECs, which has not conceded any recommendations. Effective organization of research ethics committee work is still a big question now in Ukraine's research ethics system.

13. Informed consent

Last but not the least is the informed consent problem (Table 4). Some of the potential subjects cannot give consent in the usual way. Some subjects cannot get new information about a change of informed consent. Some of the subjects who were transferred to different countries got informed consent subjects in different languages. How should we organize the translation of these informed consents? How can we organize to support understanding of this informed consent in this situation? In such cases, the witness is obliged to sign and indicate the data on the document, and the researcher must indicate in the primary recommendations how the impartial witness was selected.

Many investigators used calls and remote technologies to obtain consent for the setting and for signing as the first possibility. We do not have clear rules on how to do according to electronic signing, but it is important to mention that investigators were provided these apparently flexible frameworks which were huge barriers for ongoing and new trials. On the other hand, the risk of violation of informed consent quality must be avoided. Therefore, we see a different question, how to work with surrogate informed consent, and how to work with delayed informed consent, how our research ethics committee should assess these types of informed consent. I want to say very trustfully that our Research Ethics Committees do not have a huge experience in working with surrogate informed consent or with delayed informed consent and reviewing of such informed consent. So, it is a very delicate and very important question of how to clarify these topics for our research ethics committee members and also for the clinical trials review system. In this situation, all our investigators try to do it in the best way to avoid additional visits of subjects in clinical sites for the additional signing of informed consent or of data checking. Our investigators do the best way for our patients to protect them to get this data in a remote way, but it is a very big ethical control issue whether it is a good way or not a good way, and the quality of such data is very important and a very big issue for all review systems.

Table 4 Informed consent procedures during war time

- It is necessary to look for alternative procedures to obtain the IC
- The potential subject may give oral consent in the presence of an impartial witness.
- The potential subject and the researcher who responsible for IC process sign and date certain forms of the IC
- Surrogate IC
- Delayed IC
- It is necessary to avoid the supplemental visit of subject to clinical site for IC sign and date

14. Recommendations

I want to say again that from the first day of the active war our state authority and State Expert Center gave recommendations for sponsors on how to work in this situation and some recommendations for ethics committees [1, 2]. If clever and responsible ethics committee member opens sponsor recommendations, they should understand that they are the same participants of the protection of human rights as a sponsor and they are responsible for this protection, so they can use these recommendations for sponsors and can ask for clarifications from State Expert Center on how to work in this situation and use past recommendations and get new recommendations.

Our State Expert Center also gave recommendations for sponsors. They presented it in an open space in their internet site. They clearly recommended using European Union Medicine Agency recommendations (Fig. 8), and they gave a link on their site so everyone can open these recommendations and work according to these recommendations, and conduct reviews according to these recommendations.

Fig. 8　Basic recommendations on the management of clinical trials during active hostilities from the State Expert Center of the Ministry of Health of Ukraine and the EMA (screenshots of web-sites)

1) Recommendations “For sponsors of clinical trials/sponsors’ representatives, investigators, heads of enterprises, institutions and organizations involved in conducting clinical trials” (as of June 1, 2022)

2) Recommendations “For ethics committees, heads of enterprises, institutions and organizations involved in conducting clinical trials”

I would like to draw your attention to these main topics, the responsibility of sponsors for assessing the feasibility of new clinical trials, patient recruitment, provision of the possibility of patient transfer to another trial site in Ukraine or in other countries, measureing and ensuring the provision of investigational medical product - is it possible to do it or not possible (Table 5). Of course, RECs, if they want to do assessments of new protocol or amendments of protocols, can use these recommendations, these algorithms, and optimize their work according to them.

Table 5 Recommendations from State Expert Center

Main topics:

- ❖ Sponsor's responsibility for assessing the feasibility of a new clinical trial; patients' recruitment
- ❖ Provision for the possibility of the patient's transfer to another trial site in Ukraine and/or in other countries
- ❖ Taking all possible measures to ensure the continuous provision of IMPs to patients at the trial site;
- ❖ Reporting all protocol violations related to patient safety and other trial aspects
- ❖ Optimizing the communication process with patients:
  - ▪ Replacement of physical site visits by telephone contacts or video visits (telemedicine methods),
  - ▪ Rescheduling or canceling visits;
  - ▪ Specifying peculiarities of providing patient's informed consent etc.

Table 6 Research ethics review during war

State authority recommendation:

Apply all possible measures to assure continuous REC functioning according to REC's procedures and requirements, consider measures of individual protection of REC members

Adaptation of RECs Procedures:

•SOPs updating and development

- Remote work of REC members
- The use of online applications (training, funding)
- Risk assessment related to war (criteria for study protocols review, a special check-list)
- Assure effective and safe communication between different RECs, including from foreign countries

Optimization of communication process Research Ethics Committee can use, and we recommend to use of such recommendations as the first basic step to do a review in a good way. In this situation when we do not have a lot of resources, when we are under the pressure of bombing, it is very important to get some recommendations. If we have these recommendations, we can start from these and move forward to do new guidelines exactly for ethics committee, but now it is very important to organize our work and use these proper recommendations.

What main questions are taken into account for these national recommendations (Table 6)? We need to urgently adapt our procedures, particularly related to the remote work of REC members, the use of online applications, criteria for study protocols, new special checklist, new SOPs for effective communication, and all these aspects that requires training, support, funding, and communications between RECs not only of Ukraine but also RECs of different countries. It is very important to get such support and to do this communication.

15. Risks of ethical review during war

What are the global risks of ethical review during war (Table 7)? These are risks of acceleration, and risks of inappropriate ethical review that we have in global way. Despite the public health emergency in these

situations and despite these disaster situations, the RECs should keep in mind and be very careful about the huge risk of accelerated or inappropriate ethical review that involves a range of possible problems such as conflict of interest and therapeutic misconception. We want to look after our patients and help them, but sometimes it is very close to therapeutic misconception. The lack of RECs' members training in reviewing such studies doesn't help to do this review in a good way. In this situation, possible pressure on RECs and their decision grows and intensifies, because the potential benefit for society becomes decisive. It is very easy to take a wrong decision due to urgency of consideration, taking in mind only the potential benefits for society, which can prevail under risk for this study subject, not some unknown participant, but exactly for this person.

Table 7　Risks of accelerated/inappropriate ethical review during war

- Conflict of interest
- Therapeutic misconception
- Insufficient level of knowledge and competence of REC member
- Influence of different restrictions on REC work
- Possible pressure of global problems significance on local REC decision
- Errors and imperfections of the process due to the urgency of consideration
- Reassessment of benefits for society
- Insufficient communication with other stakeholders
- Insufficient transparency and public involvement

A very big problem is the low cooperation between different RECs inside Ukraine. When participants move to another site, the RECs from two sides should interact and change information about this participant, but low cooperation between them is still a great problem in Ukraine. Another connected problem is poor communication and insufficient transparency. Today, we do not have a clear roadmap of how to take into account all mentioned issues and how to improve our research ethics system, but we need to think about it and it is very important to make decisions for such issues.

16. Conclusion

Victoria Naumova presented through the face of women the different Ukrainian cities such as Kharkiv, Mariupol completed crushed, Zaporizhia today is under the new bomb attack, Dnipro, Luhansk, Lviv. These cities were the big clinical research centers before 24.02.2022. Why we are speaking about clinical trials not in the Ukraine, not in the past, and why we are thinking about clinical trials in the future? Because all our community, all our society, all our people of Ukraine, are fighting for our future generations, and we think that our future is so bright, and independent that our freedom is very important for us and for all the world because now we are protecting our society, our country. Our people are protecting not only the democracy and choice of Ukraine, but we area also protecting the democracy and choice and independence and liberty of all the world. I believe that in the near future, I can present you information about our new clinical trials, and about rebuilding our research ethics system. I believe that in the near future, we will get this win, and we can present new clinical trials in our country.

As a last note, I want to state the word of Spanish philosopher George Santayana, "Those who do not learn history are doomed to repeat it." So in this situation, it is very important that we learn our history and do our best to not repeat this history again.

Discussion

Q Thank you so much for your brilliant presentation. Every time you present during this war, it gets even better and better. It was so clear. You made it so evident, and you gave us real direction. Could you say like a summary of what you said what should we be doing now?

Dobrova For me, it is a very philosophical question. What we should do now for our research community, we are doing now the very important thing that we discuss this topic for all the world, not only inside Ukraine or not only between Ukrainian people, and we try to find a decision on how to manage it in the best way. For the ethics review system, for clinical trials system, all that we do is very important and this information that we give to people all over the world is very important, but if we speak about how to manage this situation, I want to ask all people involved. I know that many people now say: "We are tired, we have some problems, we are afraid of the nearest winter, we are afraid of the nearest heating season, for example, in Western Europe, we are afraid that our economy will crash, we are afraid that it is not a good way to continue the fight". I want to repeat the words of Joe Bayden: "If Russia stops its invasion, the war will end right now. If Ukrainians stop defending themselves, it will be the end of Ukraine." So, Ukraine cannot stop fighting if the community and the world find the power to support us, not protect us, because we protect ourselves and we fight for our future. Therefore, in a more philosophical way, do not be tired but believe in Ukraine, believe in our army, believe in our people, and you will see we can manage in a good way. We will meet each other in the next year or in the next to next year in Kyiv, at a big conference, similar to what we participated with Francis from State Expert Center. We will discuss how to improve our system, how to drive our system in European Union according to Regulation 536, so believe us and support us.

Q I would like to ask you that under such a stressful situation, would it not it be better to have one national ethics committee in Ukraine? In Hungary, we have one national ethics committee for all the clinical trials in which new non-registered drugs are used.

Dobrova About 15 years ago, we had one central ethics committee, but our Ukrainian law on medicine contains articles according to which the rights and safety of research subjects must be protected by local ethics committees. Therefore, in this situation, to make one ethics committee which will work I do not think is the best way today. Maybe in the future when the war is over, it will be good to find a coordination center as we started to do with Sergii Rasputniak and State Expert Center. In 2018, we started to do this work after our research which founds some challenges and issues within our research ethics system. But now it is not very good, because according to our legislation, the Ukrainian RECs are not a paid organization. For people who are independent, for people who are working at this local place, it is much easy to understand whether this center is good for clinical trials because the local people are able to see inside these clinical trials site and see their own patients. Now, it is much more important to just give them help and to just give them support, and if research ethics committees have questions, they can easily send them to State Expert Center and get qualified help and explanation.

ARENSIA Research Clinic in Kyiv: Operation from Day 0 of War

Evgeny Levenko, MD
ARENSIA Exploratory Medicine, Kyiv, Ukraine

1. Introduction

Thank you so much for organizing to the Japanese Association for Bioethics and for inviting me to such an important conference. The morning was really horrible in Kyiv. I am currently in Kyiv, the capital of Ukraine. We have a very long and significant attack by Russians. Unfortunately, we have some victims here in Kyiv, and some buildings were destroyed, but our power and our spirits became stronger. In fact, we now have the next alert, and it just started, and in fact, we should be going into the shelter. It was a special recommendation not to ignore any of these, but I will continue and see that life during the war. We are trying to create some recommendations to find a way to do business, how to manage our patients, and how to proceed with studies, but every day, we have some corrections, and today, we have such examples. In our clinic, for example, we had around 10 patient visits, some of which we did in the shelter, and some visits have been cancelled. Thus, we see that during the war, the recommendations are very good, but life is not that easy. In any case, I would like to share my experience from the very beginning of the war until today.

2. About ARENSIA

A few words about our company, ARENSIA is a German-based company with a network of research clinics in eastern and central Europe (Fig. 1). We have operations in Romania, Moldova, Georgia, and Ukraine, and now we have opened some units in Bulgaria and the United States. Our main focus was early development; therefore, 90% of our studies were phase one and phase two studies.

In Ukraine, we have been present since 2017 (Fig. 2). We had three research clinics at the very beginning of the war: oncology clinic and multi-therapeutic research clinic - I am right now in this clinic, and since 2020, we have opened one more clinic, especially for the COVID trials. Before the war, we had 86 employees, including 28 physicians, 12 nurses, and five pharmacists (Table 1). At that time, we had been conducting approximately 50 studies, 20 of which were recruiting. We managed to have almost 300 patients, and on

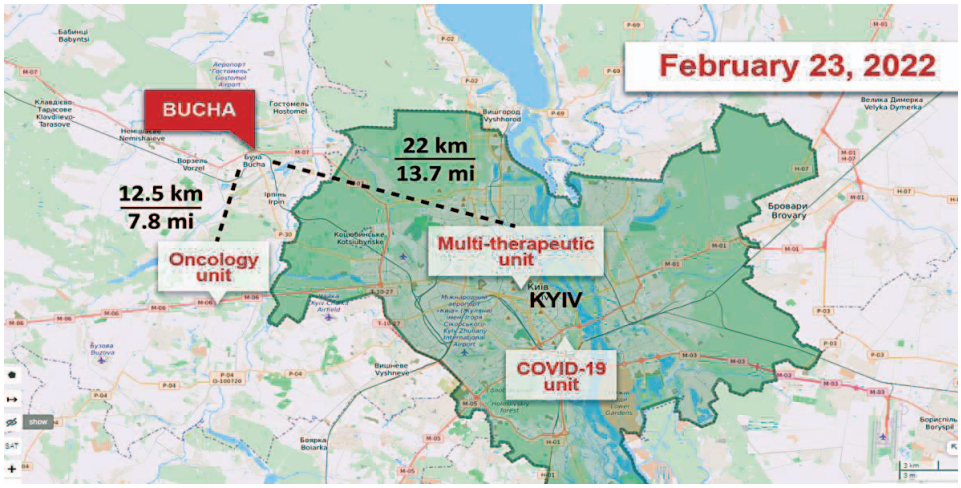
Fig. 1 ARENSIA locations

Fig. 2 ARENSIA Research Clinics, Ukraine

Table 1 Day 0 = February 23rd, 2022

Team	86 Employees, including 28 Study physicians 12 Research nurses 5 Pharmacists
Research pipeline	44 Ongoing studies, 20+ Recruiting
Patients	297 Active form overall Ukraine 30+ Patient visits per day

Fig. 3　Location ARENSIA Clinics Ukraine



average, we had 30-patient visits per day.

This is to show you the map of where we are and where we have been before the war (Fig. 3). Our oncology clinic is located slightly outside of Kyiv. I linked it to Bucha, because everybody in the world now knows this city. It was a resort-like city outside Kyiv, with very nice forests and many lakes. This is a horrible story about civilian victims after liberation. Our oncology unit is located only 12 km from the city. Multi-therapeutic and COVID clinics are in the downtown area of Kyiv, 15 kilometers from Bucha.

3. Day 1 of War

All of us woke up on the 24th of February, and we were indirectly in the epicenter of the start of the war. We had been attacked. Many ideas have come to mind. Our company had prepared somehow for the war. We created a business continuation plan, but how does it apply because when you are hearing those explosions, you are thinking about your family, children, and your personal things? All the businesses collapsed immediately. All local laboratories stopped operations with no couriers or transportation. Even pharmacy shops were closed, and it was a full disaster. All sponsors we used to work at the time stopped the studies, but how to stop patient care?

Normally, my working day starts at seven o'clock, and it takes me only 30 min to get to the clinic from home. However, on the morning of the 24th, it took me around four hours to get to the clinic. We had a meeting and decided to continue our patient care because, at that time, we had hundreds of patients with the question, will you continue with us, will you look after us and support us? Therefore, we decided to continue research and patient care.

4. Guidance from Healthcare Authorities

Our regulatory authority, the State Expert Center of the Ministry of Health, provided full support for clin-

Table 2 Guidance from Health Authorities

March 1st, 2022

State Expert Committee (SEC) issued recommendations regarding conducting of clinical research during war

- Safety of the patients first!
- Shifting of patients to other locations
- Consenting of the patients
- Phone contacts instead of visits
- Ethics considerations

ics, and issued recommendations on what to do during the war (Table 2). The first version of the recommendation was published on 1st March, and for us, this was a very important point. We have been in full contact with the regulator and coordinated our steps.

To briefly explain what has been published, first, the safety of the patient should be maintained. Therefore, for everybody, sponsors and investigators, the first priority is patient safety. According to this regulation, shifting of the patients to other locations was approved, and we used this point very well. Consenting of the patients, even remote consenting, had been approved, and before the war, I was thinking about it, but after the breakdown of the war, it became a reality. In addition, phone contacts instead of visits, if patients cannot come to the center, have also been made possible, and, of course, everything should be considered from an ethical point of view.

5. The situation with the clinics

This is the situation on the 24th of March, just to show you how Russians have been close to Kyiv, green is the territory of Kyiv, and red is the closest distance Russians came to Kyiv (Fig. 4). Our oncology clinic is located in the occupied territory.

Fig. 4 March 24, 2022

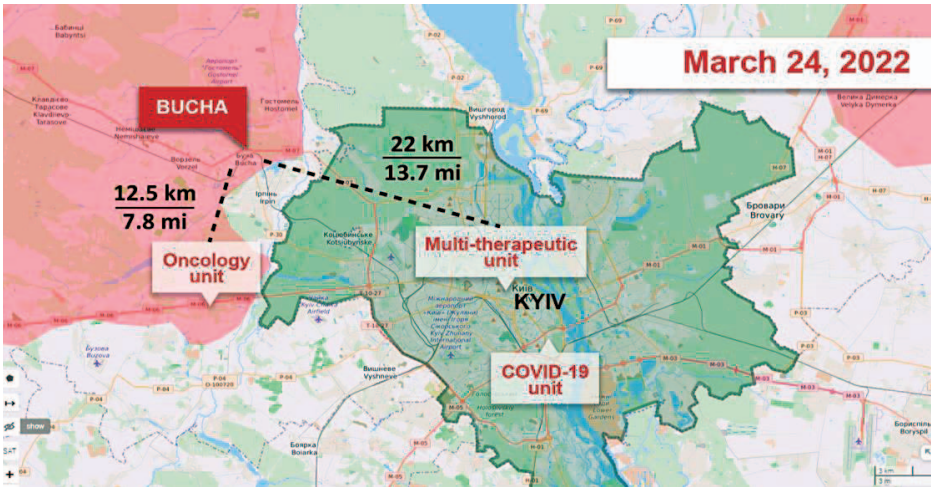


Table 3　ARENSIA Oncology Clinic: March-May 2022

- Area of severe battles
- Occupation ~ 3 weeks
- No electricity ~ 4 weeks
- No road infrastructure
- No mobile phone
- No internet connection

- ARENSIA staff could not come to clinic
- Source documentation*, PK samples, IMP not accessible
- Local Ethics Committee – no meeting, no electronic submission

The source documentation remained fully safe.

What happened in our clinics (Table 3)? There were 12 patients in our main clinic, but the oncologic units appeared in the area of severe battles, and they had been occupied for 3 weeks. There was no electricity for almost one month. The road was destroyed completely, with no internet connection and no mobile phones. In fact, we lost our connections with our unit. Our staff had no opportunity to temporarily access the clinic. We had no access to source documentation, case samples, investigator medical procedures, and meetings of the local ethics committee because they did not have electronic submission. Fortunately, after liberation on 15th of April, I and several members of our team visited our clinic, and we recovered all source documentation. It was not touched by the Russians. These are some pictures from our clinic (Fig. 5). There are some signs of severe attacks and broken windows, but in general, the building itself survived. This is the part of the missile directly on the backside of the clinic, and this is the door to our unit closed by a chair.

In our downtown area, our main clinic, this part was never occupied by Russians (Table 4). We had no

Fig. 5　ARENSIA Oncology Clinic: March-May 2022

Table 4 ARENSIA Multi-Therapeutic Clinic: March-May 2022

- Area downtown Kyiv city
- Never occupied
- No interruption of electricity/water/heating
- Mobile phones & internet running

- No stop: ARENSIA Clinic operating 24 H / 7 Days
- 12 Medics in unit, 10 supportive staff distantly
- Source documentation, PK samples, IMP under control
- Local labs active (Incl. at the places of patients' concurrent location)
- On-going shipments by local and later international couriers
- Local Ethics Committee – all meetings performed, electronic submission
- HA/SEC – fully operational, 4 new studies approved

single day or a single minute of electricity interruption. I have also been surprised by that, but this is a reality, so there are no blackouts in our clinics. Same with water supply and central heating. Everything is fine, with mobile connections and the Internet. Therefore, we have been in full contact with authorities and with our sponsor and have had many discussions about what to do and how to continue. It was really a hard day and full of work.

We have not stopped the operations. Nearly 12 doctors, pharmacists, nurses, myself, and our medical director stayed for two months. We stayed in our basements. During the night, we went down into the basement, and in the morning, we started our work at our clinic. Therefore, nothing happened with source documentation, PK samples, and everything is fine with IMP. At some point, local labs restarted their operations. This was a day-to-day change in order. We received some support from local laboratories, and at some point, couriers restarted their operations. For us, we were able to receive and ship goods out of Ukraine and receive medications and supplies to our hospital. The local ethics committee approved the study. We have changed from face-to-face meetings to online meetings. Fortunately, in our SOPs, we also have the option of an elec-

Fig. 6 ARENSIA Multi-Therapeutic Clinic: March-May 2022

Table 5　ARENSIA COVID-19 Research Clinic: March-May 2022

- Area downtown Kyiv city
- Never occupied
- No interruption of electricity/Water/Heating
- Mobile phones & internet running

- No stop: ARENSIA Clinic functioning 24 H / 7 Days
- Hospital temporarily transformed into back-up military hospital
- 1 Ongoing study on COVID-19 prevention, 100+ HVS
- Source documentation, PK Samples, IMP under control
- Local labs (including at the locations of patients' concurrent location)
- Ongoing shipments by local and later international couriers
- REC – all meetings performed, no electronic submission

tronic submission.

Therefore, the sponsors used this option very well. Again, our regulator, State Expert Center, was also fully operational, and we got four approvals for the studies we submitted before the war.

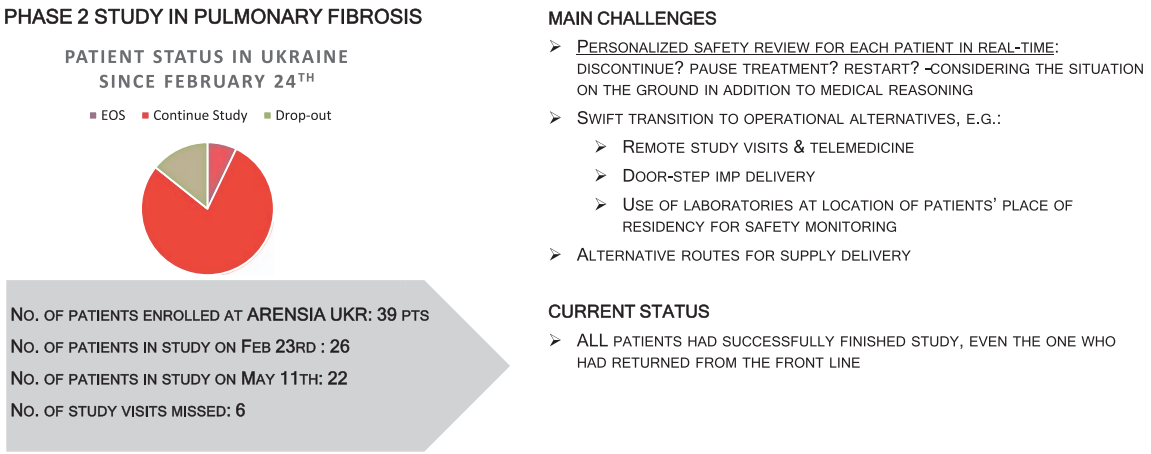
These are some examples (Fig. 6). This is our shelter downstairs for cleaning, so we have been sleeping directly on the floor. This is the preparation training for potential chemical attacks. Here you see that during an air alert, we stay inside our clinic, but without a window in the safest place. This is also the case during the night in our shelter on the floor of our clinic.

At our COVID site also situated in downtown Kyiv, nothing happened, so we continued our studies (Table 5). At the time, we had only one ongoing study involving 100 healthy volunteers. It was a COVID prevention study. Nothing happened to the source recommendations, PK samples, and in general, the clinic continued their work, but temporarily, this hospital switched to military service. However, we continued with everything, and the situation with the local ethics committee was fine, so they continued with their meeting clinic.

6. Case studies

I would like to show you several examples of how and what we did (Fig. 7). So one of the examples, this

Fig. 7　Case study: Pulmonary fibrosis



is a phase two study of post-COVID pulmonary fibrosis. Before the war, we randomized almost 40 patients in this study, with our site being the top recruiter in this study, and on the 23rd of February, we included 26 patients. Until May, only four patients had discontinued, but 22 completed the study completely, and out of all the studies we did, we missed only six visits.

What adjustments were made after approval by the ethics committee and sponsor? In some cases, phone contact was used instead of patient visits. In addition, we switched to local laboratories as we had patients from different centers of Ukraine, so they sent us lab reports from their cities and the same option was with MRI. Therefore, they electronically sent us the results and uploaded them to the sponsors. In addition, we used alternatives for the delivery of IMP to patients and as an alternative to shipments to our site. Therefore, the current status of the study is that all patients successfully completed the study, including one patient who returned from the frontline.

For example, it is not one study, but in our Oncology Clinic, we have been running six oncology phase one studies (Table 6). As mentioned previously, this clinic was closed, and the territory had been occupied. We relocated all our patients, first to our clinic downtown, and 15 patients were transferred from Ukraine to Moldova. Therefore, the decision to transfer the patient was made by the sponsor on March 4th and the first dose was administered on March 23rd. You can ask why it took so long, but this is not in fact long, because it was first of all a lot of things to discuss, find the way to deliver patients from Ukraine to Moldova, and to do a lot of regulatory things behind that, to get approval in Moldova by their regulatory authority, also by ethics committees, the same things to be done here in Ukraine, just to announce to our regulator and also the ethics committee and also to prepare a new Russian informed consent, also to take care of insurance for the patients, and to organize transportation and allot accommodation for the patients, so it was really hard work.

From the point of view of the sponsor, it is also not easy to do so because they need to change everything in the IWRS system and also to change source documentation. We needed to copy everything and deliver this patient together to another site, so it was really difficult work. The current state is that the patient would like to go back to Ukraine, and now we are working in another direction, so we are now shifting the patient from Moldova to Ukraine. It is again the same work all over, to inform about that regulatory authority, also to

Table 6 Case Study: Oncology

- 6 Oncology studies
- Decision to transfer patients made on: Mar 4th
- 15 Patients transferred from UKR to MOL
- Dosing re-started: March 23rd

Main challenges

- Set regulatory framework for an unprecedented situation
- Communication and rapid decision making across all levels and chains of command at pharma companies
- Logistical re-arrangements: EDC, IWRS, source documentation, medical history, delivery of additional supplies to the receiving site, etc.
- Accommodation and transportation arrangements for the patients

Current status

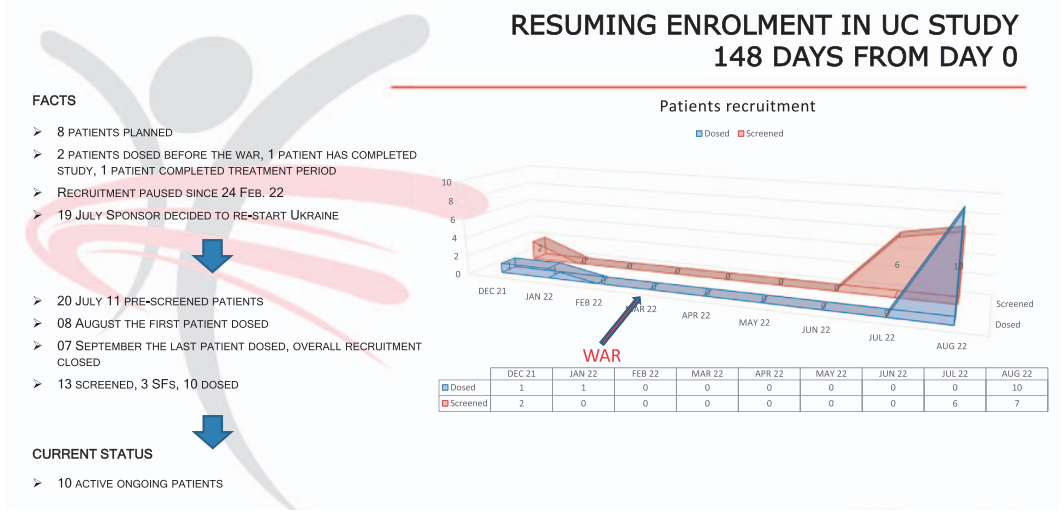
- 6 Patients have returned back from MOL to UKR and continue study participation

continue with patients, to get medication, to change all the systems we used in the studies.

7. Resuming enrolment in ulcerative colitis studies

This is a recent example (Fig. 8). Some sponsors have decided to restart their studies in Ukraine. One study was a phase 2 ulcerative colitis study. Initially, we planned to obtain eight patients. This study was approved by the sponsors. Two patients were recruited prior to the war. The sponsor paused recruitment at the beginning of the war. On the 19th of July, the sponsor decided to restart recruitment in Ukraine. It is a biotech company in the United States. The next day, we screened 11 patients. At that time, there were a few open sites. Patient needed some medical service, which is why we have been quite lucky to have so many patients. Dosing was started in August. At the beginning of September, we closed dosing and study recruitment in the study. Now, we have 10 active patients, and according to the protocol, scheduling of even shipments of Ambien samples to central labs in Europe is not a problem, although it is longer, but not that difficult.

Fig. 8　Resuming enrolment in UC study: 148 days from Day 0



8. Current status

Table 7　Today status

Team	42 Employees, including
Research pipeline	19 Ongoing studies, **3 New studies in start-up** **2 Studies to resume enrolment**
Patients	256 Active form overall Ukraine 5-15 Patient visits per day

So far, the company has a clinic with 42 people on our team (Table 7). Unfortunately, out of 50% of our staff, some moved to another country, some decided not to continue in ARENSIA, and some stayed in other cities of Ukraine, but half of the team worked and continued the medical service here. We now have 19 ongoing studies, two of which are recruiting. Two studies seemed to resume enrollment soon. In total, we have 256 ongoing patients, who are not only from Kyiv, but from different cities in Ukraine, and we have 5-15 patient visits per day.

9. Future of research in Ukraine

In general, I would like to mention what President Volodymyr Zelensky said several times that Russia had brought such problems to Ukraine and Europe that could not have been imagined a few months ago. This is the complete absence of oncological treatment or problems with access to insulin for patients with diabetes. Surgery could not be performed. He said this in May. Currently, the situation is improving, but it is still quite difficult. Since the beginning of the full-scale invasion of the Russian Federation into Ukraine, the military of the aggressor country destroyed 570 healthcare facilities, with 101 hospitals completely destroyed. This is also information from the beginning of summer; now I guess it is even more. Therefore, clinical trials have played an increasing role in helping fight the humanitarian crisis and provide continued treatment access and patient care in Ukraine.

These are a few pictures we clicked during the summer when we had some stabilization here (Fig. 9). It can be observed that the team is located here. We are working. We have routine meetings. We have patient visits. In addition, we visited the German Ambassador to our clinic, and she was also astonished to see how we did what we did, that we are not stopping during the war. You can see that our physicians are doing their conferences and examining patients, so we are almost back to normal business life.

We are almost back to our own private lives (Fig. 10). We have our physician deliver a nice lady, and we celebrate, also made gifts. We celebrated the birthday of one of our employees, and our medical director received a charity diploma. Life is almost back to normal life, but you can see that this morning again shows us that this war is continuing and the enemy is near our borders and in our country, but I am pretty sure that Ukraine will survive, and everything will be fine.

Fig. 9 Business as usual...

Fig. 10　...And life as usual

Discussion

Q　I noticed that you started clinical studies, and it broke down during the war, and then you started the clinical studies again. I am curious, what is the transition when you want to bring people back to start studying again?

Levenko　The situation is like this: some sponsors decided to fully stop clinical trials. This also means that active patients have unfortunately stopped participating. This is a disaster, because in some cases, in oncology studies, patients had no access to modern medications at all, to modern services, but some sponsors simply put on hold screening of new patients and randomization dosing of new patients. Half of the sponsors decided to continue with active patients. Therefore, it was not like the full stop of the research, so we continued seeing that Ukraine is a really big country, and war is ongoing. This is a fact, but we are relatively far from the front line. This distance is approximately 500 km. Life in Kyiv until this morning was normal. For this reason, many sponsors decided to restart their activities, because Ukraine is well known as a high recruiter, and some studies cannot even move forward without our support and recruitment. This is why sponsors seem more likely to restart operations in Ukraine.

We organized everything together with couriers, local laboratories, and our research society. We did a lot of work with our regulator, and we are improving the situation for the research. Initially, we had no chance to send out anything from Ukraine. Couriers deliver Ambien samples to central labs within 48 to 72 hours. It is okay. It is not air delivery but ground transportation that works well. So, I cannot say about stopping operations; we continue with the patients' top of the research, and now the situation is improving and better.

Q　If we start a clinical study, we normally start it, and we go through a process by sticking to the process.

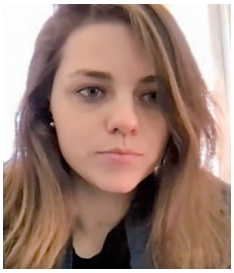
In a situation of war, what seems to happen is that patients leave, lose momentum, cannot get drugs, or move them to other situations. It interferes with the protocol; therefore, something for us to learn from changing the protocol in an interim period when the protocol changes or shifts.

Levenko Decision has been studied case by case. In some cases, for example, we started to use local safety labs instead of a central lab. Our clinic is mainly concentrated in phase one; therefore, we only froze these PK samples. They survived here in our clinic, so we sent them out later on, and in general, the majority of our studies in our clinic have not been interrupted. Therefore, we are receiving everything directly from our site, so we do not have any warehouse in Ukraine. This is why we had all the policies before the war. After one month, we re-started receiving medications. In fact, there were few protocol violations or deviations. Therefore, we tried to keep procedures visits by visits according to schedule. In some cases, we used phone contacts instead of patient visits, but there were not many visits. Sometimes, we have not been the windows allowed by the timeframe of protocol visits. We kept safety first, and tried to do so in line with the protocol as much as possible.

Q Suppose there may be some kind of intention of the sponsor company, not only their wish to continue the clinical trial or provide experimental therapy for the patient but also there may be some kind of intention to maintain the infrastructure of clinical trials in Ukraine. What is your impression based on the actual situation?

Levenko In fact, in the majority of cases, all sponsors clearly understand the situation here, and they try to support it in many different ways. We had several cases where patients emigrated from Ukraine by themselves, without our directions, or when they decided to move in the very first days of the war. Sponsors were informed about this, and we found a solution on how to shift patients to hospitals that are not participating in the trial. It was just to take care of the patients, to provide medical services to them, and we received financial support from the sponsors. Therefore, they ask us what we need, and maybe we need some equipment. So it is a lot of different ways of support, and in fact, here in Kyiv, almost all clinics are fully operational including laboratories, MRI centers, and big institutional hospitals. Therefore, here, we have everything as usual. We also have sponsors providing additional medications to us, not only those for clinical trials, but also other medications that we need. There was no shortage of medication. This is my experience. This may be a different situation in other clinics. Again, we are conducting our studies almost like before the war.

Clinical trials under the Air Raid Alert accompaniment[*1]



Veronika Patsko, MD
National Cancer Institute, Kyiv, Ukraine

1. Introduction

My name is Veronika Patsko, who is a clinical oncologist at the National Cancer Institute. The National Cancer Institute is the largest governmental oncological center in Ukraine. We consulted more than 100,000 patients annually. There are 20 surgical rooms where thousands of surgeries are performed.

2. Before 24th of February

Before 24th of February, Ukraine had many clinical trials in different spheres, mainly oncology, rheumatology, therapy, and so on (Fig. 1). On the moment of 24th of February, Ukraine, there were 120 ongoing oncological studies, and over 80 of them were ongoing at the National Cancer Institute in different departments.

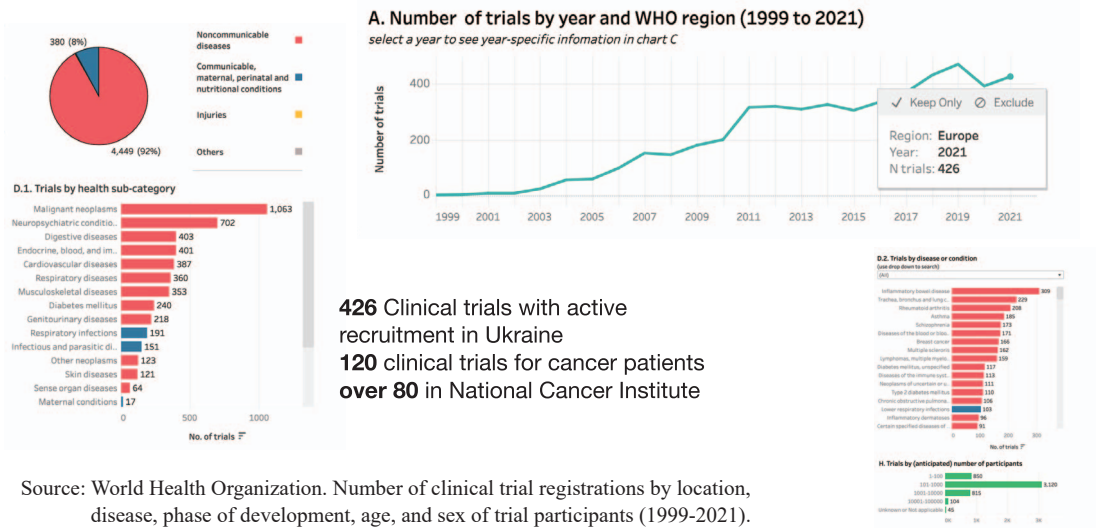
On 24th of February, terrible events began. People moved west, and some moved abroad. Many people are afraid.

3. New phase of clinical trials

Therefore, that day, we had to start a new “phase” of clinical trial during the war. This came together with the medical care. In addition, clinical trials are part of treatment, so especially in oncology, many patients require new types of treatment, so we need to start something new. There were issues that I tried to combine

[*1] This presentation was provided on October 10, 2022, when our world saw terrible Russian attacks on the city center of Kyiv, with an increasing number of civil victims even during this talk. According to the lecturer, at the time of publication in July 2023: bombing, their capabilities of conducting clinical trials become much better, keeping the level in peaceful time, with substantial global support; Ukrainian oncological patients desperately need clinical trials for them to be able to receive effective new treatments for severe diseases, and Ukrainian infrastructure of clinical trials have been kept responding to the people who most in need.

Fig. 1　Before 24th of February



426 Clinical trials with active recruitment in Ukraine
120 clinical trials for cancer patients
over 80 in National Cancer Institute

Source: World Health Organization. Number of clinical trial registrations by location, disease, phase of development, age, and sex of trial participants (1999-2021). https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/number-of-trial-registrations-by-year-location-disease-and-phase-of-development

into groups that was very important in the decision. First is information. Therefore, we need to assess the capacity of our staff. They needed to save their families and children, so some of the staff moved. There was a need for supplies, the need to save data, because it is very important in clinical trials, and everything was about safety: safety of personnel, safety of patients, and safety of data.

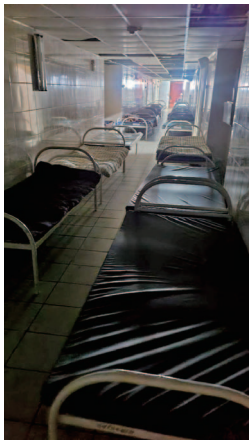
4. Information

Information: I called it a period of letters and calls. It was very important for doctors to know where patients were, whether they were safe, whether they could get to the clinic, whether they could receive medical care, and to inform them what to do next. Therefore, if they are safe, they can visit the clinic where we informed them whether we can continue their treatments. The second was to inform all team members. We needed to know where all were, to whom we can rely in this period, who were staying in Ukraine, who were moving abroad or moving to the western part, because for a few months, half of our team moved to the western part of Ukraine, so we could only have calls from them, but they could continue care of patients who also moved to the western part. As part of our patients, they moved and our doctors moved there, they could continue, and also inform sponsors that we are continually working. We can provide them with information and we can provide them supplies. So, it was a period when we had this bombing, and in the corridor, I was working with a laptop writing many letters. We need to do many jobs like this.

5. Capacities

During the entire period starting from 24th of February, the National Cancer Institute did not stop its work (Fig. 2).

Fig. 2　Capacities



National Cancer Institute
didn't stop its work

We worked everyday 24/7, and in these photos, you can see the basement. It was supplied by water. The beds were moved on the basement of National Cancer Institute. On the first days, we continued treatment under- ground for patient to be safe, and also one bone marrow transplant was performed underground because patient was already planned for this procedure. This procedure was planned for 24th, so we could not post- pone it. Moreover, there was a problem in that a lot of clinics in Kyiv District were closed due to occupation of that area, due to problems with roads, and a lot of patients who were treated there before the work required oncological help in this period, and they were looking for an oncology clinic who can continue this work. Starting from the beginning of the March, we just moved from the basement to our floors, in rooms without windows. So we continued our work at the beginning, not as normal, but we tried to come back to normal.

6. Staff

This was a big problem because many medical staff, especially nurses, lived in the Kyiv region, and they could not work because of bombing, tanks, and troops on the roads. Thus, Kyiv was mostly isolated, with only one road left to leave Kyiv or to come to there in the first month. Other areas were very dangerous to go inside. You can see the doctors who were giving drugs to continue the treatment of patients. As a doctor, I needed to examine the patients, take blood tests, make the drug for them, and then control the infusion. Thus, a lot of work has been done. Most doctors performed the entire treatment cycle.

7. Supplies

Talking about supplies, I would like to remind me that I am not talking only about the general work of the National Cancer Institute as an oncological clinic, but also about clinical trials. So, everything like that was done. All clinical trials were performed because we needed to collect biological samples and to work with them, and we needed to provide patients with drugs from clinical trials. We had a pharmacist, me, and other

doctors from other departments who continued this clinical trial. We continued to perform this procedure according to the protocol and avoid protocol deviations. Our local laboratory performed all the required tests, as well as an MRI machine and CT, and we could continue it according to the schedule.

As for supplies, we are lucky enough to be the biggest center, so there were a lot of supplies in our local depots that we had enough to share with patients from other sites. Therefore, some sponsors decided that patients, for example, from Kharkiv, which was and is continually and severely bombed, were moved to Kyiv, and they just told us which medication we can give them in this clinical trial, because clinical trials are ongoing in 5, 6, or 10 cities of Ukraine, so we have different sites, and we can move patients from site to site in one clinical trial. From some parts of Kyiv, the patients, for example, were moved to the western part of Ukraine, and some from the eastern part of Ukraine were moved to Kyiv, and we could continue their treatment because we had enough supplies. This was a big problem for the first month because there was a problem with couriers. Nobody can bring this to us. Fortunately, we had sufficient drugs, so we only covered this period. Then, when courier companies started to work again and when central depots started to work again, we could obtain new deliveries of drugs.

In addition, on 24th of February, all civil flights stopped, and there was a problem with delivery because it took more time. Essentially, it was difficult in Kyiv, as there was only one road left that could be used for civil transportation for the first period. It was difficult for sponsors to deliver the drug and also to deliver back biological samples from sites to the central laboratories. In addition, many men went into the army, so there were not enough workers, but now we are working almost as it was before the war.

8. Data

It was very important for us to have access to the Internet, source, documentation, and safety of source documentation on sites, because some sites in Ukraine were bombed. However, at the National Cancer Institute, there was no problem with electricity, there was no problem with access to source documentation, and there were enough doctors to put this information into the eCRFs. Talking about the National Cancer Institute is safe. The building was not directly bombed.

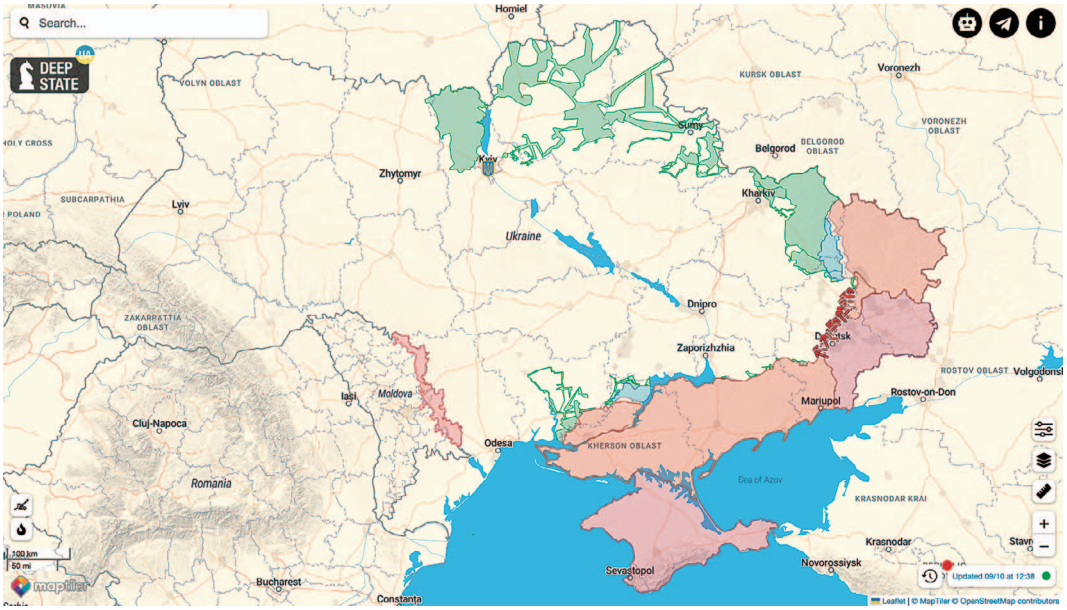
As for the biological samples, we were lucky enough to have uninterrupted power supplies all the time. Therefore, there were no problems with electricity. All samples survived this period until courier companies worked again, so everything was safe. There were no protocol deviations even during the hardest period, but there was a problem with kit supply for the first few months, but now it is also absolutely fine, almost as it was before the war.

9. New reality of clinical trials in Ukraine

This is a map of the attacks on Ukraine (Fig. 3). Data is till yesterday. Ukraine is quite a large country, and there is a large distance between the battlefield and other cities in which many clinics have participated in clinical trials, including oncological trials. Therefore, the distance is quite large, and we can continue to perform clinical trials almost as before the war.

We are in great demand from the patients who require this help (Table 1). I can provide you with a simple

Fig. 3　Clinical trials in Ukraine – new reality: map of attacks (as of October 9, 2022)



https://deepstatemap.live/en#6.5/48.573/31.474

This map was copied from the data provided in "DeepStateMap. Live" on October 9, 2022. The situation is changing every day, and you can find the latest map on the website of "DeepStateMap. Live." Its update is not secured; thus, it is cautioned not to use it for actual needs, for example, evacuation.

example from Oncology. For example, for people with melanoma, we have immunotherapy, but in the case they progressed, we had no treatment for them, and only conducted clinical trials. There are many patients who require new treatment, which has not yet been registered, because they used all their probabilities of treatment that we have in this study. Some of them cannot move abroad because they have children, they probably have old parents, and they cannot move abroad for treatment, but they need it here. Often, patients ask me about this. They called our center and asked me whether we had clinical trials. Therefore, statistically from the Cancer Institute, 10% of our patients in clinical trials were moved abroad to other sites with the same protocol and continued treatment in the clinical trial. Now, we have high requests from patients because patients from territories that were occupied come to the west, so Kyiv, Lviv, or in cities where it is more peaceful currently, they are asking about treatment, so we need to treat even more patients, and so there is high demand.

As it was during the COVID period, now also there is a big gap in diagnostics and treatment and many patients who could be treated at earlier stages. In addition, for advanced diseases, according to

Table 1　Clinical trials in Ukraine – new reality: demand from patients

Nearly 10% of patients were moved on sites abroad and continuing their treatment there
Now the quantity of patients 30% higher than on 23rd of February
More advanced diseases due to gap in accessibility of medical care
High demand on clinical trials among Ukrainians
But recruitment that was stopped on 24th of February still not opened

Fig. 4 UPD: morning of 10th of October, 2022

international guidelines, we need to include these patients in clinical trials to have more opportunities to live longer.

Our workforces are almost the same as before the war. We are working in our general routine, and it is relatively safe for both patients and staff to continue working as we used to. In addition, patients are moving, and they require this help, so there is a high demand, and there is a possibility from our side to continue treatment like this. We can also continue to provide shipment of biological samples, and sponsors can deliver drugs with temperature control, so it is absolutely possible as it was before.

10. Present situation in Kyiv

Here is a phrase like a military joke, "Being a Ukrainian is to be ready for the end of the world but also have plans for the future." However, today, I would like to make some updates regarding the situation in Kyiv and just to remind us that the war is still ongoing. Today, these are photos taken a few hours ago (Fig. 4). It is similar to the city center of Kyiv. Eighty rockets were fired in many cities in Ukraine, and they bombed the entire country. I would also like to show you several videos. You can see a kindergarten ground in the city center. The consequences of the bombing are evident. It was our morning today.

So please stay with Ukraine and support Ukraine. Thank you for your attention.

Discussion

Q I am thinking about where the rest of the world today? They watched these presentations. This war was not simply a military action. These are not simply armies or weapons. However, it is also people fighting for their lives, and you people here are on the front lines. You are fighting for your country and your lives because the soldiers are there. The final video was terrible. If I refer correctly, that is, to the bridge to the

peace monuments between Russia and Ukraine. It is an absurdity. It is very important what you are doing, and the work you do is heroic. Thank you for coming here today sharing this information with us.

Patsko　Thank you for your support and attention. You are correct about this monument, but there is no further friendship between our people. They are just terrorizing civil cities. Today, there were 10 bomb attacks, which came into the city, 10 dead people, and while we were talking, it is already 11, so one person died in the hospital during our talk, and there were kids among them. Thus, it was just civilian people who were going to work in the city center with no military objects at all. The Central Ukrainian University has museums in this region. We only had a hole on the road and 10 dead bodies. We continue to live and discuss our main topic in this talk. My colleagues, who have presented before, agree with this. Today, until five in the morning, the situation is slightly different. Therefore, it is almost calm in the city. There was a problem in the eastern Ukraine. We have our soldiers dying there for our freedom, for our democracy, but we continue to develop science, we continue to develop. During the war, for example, at the National Cancer Institute, we put a new linear accelerator and opened a new neurosurgical department, so we continue to develop and live here. We cannot simply freeze or stop doing things.

Comments from International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP) and Ukraine Clinical Research Support Initiative (UCRSI)[*1]

Sandor Kerpel-Fronius, M.D., D.Sc., FFPM

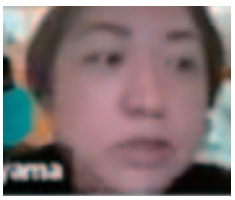
Professor of Clinical Pharmacology, Semmelweis University, Department of Pharmacology and Pharmacotherapy, Budapest, Hungary

Kotone Matsuyama

Professor, Department of Health Policy and Management, Nippon Medical School, Tokyo, Japan

Francis P. Crawley

Ukraine Clinical Research Support Initiative (UCRSI); Executive Director, Good Clinical Practice Alliance – Europe (GCPA) & Strategic Initiative for Developing Capacity in Ethical Review (SIDCER), Leuven, Belgium



The effect of Ukraine war on international drug development

Sandor Kerpel-Fronius, M.D., D.Sc., FFPM

1. Introduction

We all agree that the most horrible interaction in human society is a war. This war is exceptional from a scientific point of view because it destroyed healthcare facilities and caused the disruption of many international clinical trials. People working in drug development should now look very carefully at the effects of the Ukraine war, what can we learn from that to manage clinical trials better in catastrophic situations? This is the subject of my presentation.

[*1] After the three commentators from the two organizations, Dr. Jerry Menikoff provided his comment which is not published but the summary is described by Chieko Kurihara at the last part of this section.

2. Fate of clinical studies in Ukraine and Russian Federation

During the war, we have many clinical trials that were stopped both in Ukraine because of the war and in Russia due to the economic sanctions, which were introduced as an answer to the savage attack of Russia on Ukraine. But the situation became very different in the two countries. In Ukraine, during the war, many of these trials were interrupted only just for a very short time. The enormous resilience we just have heard in the lectures given by Ukraine colleagues resulted in the rapid resumption of trial activity. Many clinics continue to accrue patients. Unfortunately, in the departments which were destroyed, or the physician and patient had been killed, they had to stop trial activity, but many of the patients could be transferred to other Ukrainian centers. Now we see that most of the trial activities are resumed and carried further.

In Russia, the situation is different. The trials were stopped due to economic sanctions, because in the economic sanctions, all large pharmaceutical companies were asked to stop marketing interaction with Russia and also to stop trial activities. Practically, all large companies followed this request and the trials and the accrual of patients were immediately stopped. Neither the hospitals, nor the patient or physicians were destroyed or killed, so actually, medical activities could continue to go on. Nevertheless, most of the international trials stopped very rapidly because of the lack of further investigational medical drug supply, the stopping of the international transport of biosamples, and finally the contacts with the sponsors were also severed.

It seems that the stopping of international clinical trials in Russia will have a much longer effect on the community, because due to the distrust which develops during the war, it will take a very long time until the trials could be resumed, when there will be a peace again. So the development will be different in the two countries. Ubnfortunately, many trials are lost forever, which is a loss for the international community developing drugs.

3. Statement of IFAPP Ethics Working Group

The Ethics Working Group of IFAPP, which is the International Federation of Associations of Pharmaceutical Physicians, very early, already in March, began to discuss the problems related to clinical trials in Ukraine and also in Russia [1]. We concluded that the most serious danger for trial participants might be the abrupt closing of trials by the sponsors and possibly abandoning seriously sick patients who already receive treatment. We actually heard in the comments that several companies did exactly this and rapidly stopped their trials, even ongoing treatment of patients. According to our opinion, this is one of the most serious problems at the start of a disaster when the investigators try to understand the size and the effect of a catastrophe.

In this chaotic situation, pharmaceutical physicians performing clinical trials in these locations are left

1) Kerpel-Fronius S, Baroutsou V, Franke-Bray, B Kurihara C, Mutsuyama K, Naseem S, Schenk J, Members of the IFAPP Working Group of Ethics. Investigational drug supply for seriously ill patients in time of war. *IFAPP TODAY*. 2022. Number 23 (April); 1-2.
https://ifapp.org/static/uploads/2022/04/IFAPP-TODAY-23-2022.pdf

alone. Mostly their contacts with the companies are severed. They have to make their own decision according to their understanding of GCP and for the benefit of patients. In the Ethics Working Group of IFAPP we came up with a recommendation regarding how to manage trial patients in the early phase of human-made or natural catastrophes. I would like to emphasize here that we included natural catastrophes into our discussions because war and natural catastrophes cause similarly great effect on the population on the environment and on the society.

4. Recommendations of IFAPP Ethics Working Group

So our recommendation of the IFAPP Ethics Working Group is that participants already receiving trial treatment during a disaster should be considered as a vulnerable patient group [2]. This suggestion is based on a CIOMS recommendation, which essentially states that a vulnerable patient population is defined according to the circumstances in which the patient population is at that time. We think that at the start of the war, the patients who already committed to participate in a clinical trial constitute a vulnerable patient population. Sponsors and clinicians have a great responsibility toward these patients, because the patients especially those who have serious diseases have all their hope in the ongoing clinical trials to which they gave their informed consent.

So our recommendation is that if possible, the continuation of already initiated trial treatments for the benefit of the patients is a primary obligation of clinical investigators in case of war, economic sanctions and during natural catastrophes [2]. We think that this short recommendation is for the benefit of the patients and is primarily relevant at the early phases of disaster when the situation is chaotic, the extent of the damage is not yet known, and also the contact with the sponsors are mostly disrupted. So, the pharmaceutical physician has to make his/her own decision in case of each individual patient according to their best scientific knowledge and ethical understanding. We hope that this recommendation will be used in later catastrophes affecting clinical trials.

2) Kerpel-Fronius S, Kurihara C, Crawley FP, Baroutsou V, Becker S, Franke-Bray B, Matsuyama K, Naseem S and Schenk J. The ethical responsibility to continue investigational treatments of research participants in situation of armed conflicts, economic sanctions or natural catastrophes. *Front. Med*. 2022; 9:950409. doi: 10.3389/fmed.2022.950409
https://www.frontiersin.org/articles/10.3389/fmed.2022.950409/full

Introduction of the collaborative activities with IFAPP Ethics WG

Kotone Matsuyama

I am a clinical pharmacologist, in charge of research governance at Nippon Medical School, which is a private medical university in Tokyo. I would like to give a brief introduction about the IFAPP, The International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine.

IFAPP was founded in 1975 and promotes pharmaceutical medicines in various countries. Currently 27 countries from all over the world, including Europe, Asia, America, and African countries are participating in IFAPP. Chieko, Sandor, and Francis who are participating today belong to the Ethics Working Group. We are collaborating with CIOMS, WMA, and also Ukrainian Clinical Research Support Initiative (UCRSI).

The Ethics Working Group has contributed three articles to our newsletter *IFAPP TODAY*[1, 3, 4], on the issue of clinical trials in Ukraine. Also, we have published two papers on ethical issues in clinical trials in the conflict situations in Ukraine[2, 5]. We will also have a session on the Ukrainian conflict within DIA and Japan Association for Bioethics (Table 1), and then we will have the annual meeting next week in Athens, Greece. Here is the session name titled, “Ukrainian war crisis impact on clinical trials (Table 2).” Hope that some of you could join.

Table 1　Continuous participation/organization of meetings of IFAPP, to support Ukrainian clinical trials and discussion in depth for publications

- Repeated participations in the web-meetings organized by the Ukrainian Clinical Research Support Initiative (UCRSI) since April 2022
- Presentations, chairing of the series of webinars (weekly) produced by the Drug Information Association (DIA), starting the end of July to the end of August
- Collaboration with the Japan Association for Bioethics for this webinar and a Conference in Japan in November 19.
- A session at the annual meeting of IFAPP: ICPM 2022 in October

3) IFAPP deplores Russia’s aggression in Ukraine. *IFAPP TODAY*. 22 (March 2022): 1. https://ifapp.org/static/uploads/2022/03/IFAPP-TODAY-22-2022.pdf

4) Crawley FP, Aurich B, Kurihara C, Matsuyama K. Perspectives on Clinical Trials During Times of War The Situation of Ukraine. *IFAPP TODAY*. 24 (May 2022): 1-4. https://ifapp.org/static/uploads/2022/05/IFAPP-TODAY-24-2022.pdf

5) Kurihara C, Crawley FP, Baroutsou V, Becker S, Franke-Bray B, Granville CA, Matsuyama K, Naseem S, Schenk J and Kerpel-Fronius S. The continuation of clinical trials in times of war: A need to develop ethics and situationally adaptive clinical research guidelines. *Front. Med*. 2022; 9.966220. doi: 10.3389/fmed.2002.966220.

Table 2 Session on Ukrainian clinical trials at the annual meeting of IFAPP, International Conference on Pharmaceutical Medicine (ICPM)

October 19, 2022 – Day 1
PARALELL HALL – ONLY VIRTUAL
11:00 – 12:00 Session: "Ukrainian war crisis impact on clinical trials: Ethical aspects and patient rights"
Chair:
Sandor Kerpel-Fronius, MD, DSc, FFPM, Semmelweis University, Department of Pharmacology and Pharmacotherapy, Budapest, Hunbary
Speakers:
Francis P. Crawley, Bphil, Executive Director, Good Clinical Practice Alliance (GCPA) & SIDCER
Chieko Kurihara, BSocSc, specially-appointed Professor, Kanagawa Dental University, and Member of the IFAPP Ethics Working Group

Ethics, clinical research, situationally adaptive clinical trials, and open science: Learning from the Ukraine crisis

Francis P. Crawley

1. Introduction

Because this is a meeting with members of the Japanese Association for Bioethics, I also want to say something specifically about ethics and clinical research, and I will say something too about situationally adaptive trials, and then I want to talk about open science because open science is a bit of a buzzword today. It is very popular, but I also think it is very important.

2. The Ukraine Clinical Research Support Initiative (UCRSI)

I start with just by saying something about the Ukraine Clinical Research Support Initiative. It is because of Viktoriia that we started this, and we are still small. We never got organized, have not done enough. We wanted to respond to the situation in Ukraine, and we wanted it specifically around clinical research. As it turns out, we are the only group and that is all of us who are meeting today and those who come together in other meetings who have focused on clinical research and what is happening with clinical research during this terribly destructive period.

So we wanted to bring communication, and I have to say IFAPP has been absolutely incredible with this, DIA has been incredible with this, but mostly it is all our colleagues from Ukraine who were so generous to take the time to try to instruct us on this to try to ensure and we learned so much from what they are doing. We think what is most important is to support this clinic research enterprise, and I will try to discuss why as we go on.

3. What is medical research enterprise?

What we learned from Ukraine is that research is not something extra. It is not something we do as a luxury. It is an essential part of society. It is important for medicine. It is important for science. It is important for education. It is a profession, as we see today, and as we have heard from real professionals, who are really dedicated to what they do. It is an essential part of public health. A lot of us think that we can do without clinical research, that clinical research, clinical trials are just some kind of luxury that we have in our societies. It is not true. If we do not have clinical research in our societies, we do not have good functioning of public health systems. It is surely a fact, and it has been shown over and over again. The clinical research industry contributes so much to society and it is so important to society. I spent last week in Munich with clinical trials conference in Europe, and you can see the countries fight to have clinical trials. They want to have clinical trials because it is so important for the well-being of the country. I think it is impossible to imagine a healthy society without a healthy medical research enterprise.

4. UN Universal Declaration of Human Rights

I want to say something about the Universal Declaration of Human Rights, because I think human rights have been so abused and misused by people with regard to research and what is going on in Ukraine and with what is going on in the entire war situation that I wanted to counter it. This is the preamble of the UN Universal Declaration of Human Rights 1948, 'Whereas the recognition of the inherent dignity and of the equal and inalienable rights of all members of the human family is the foundation of freedom, justice, and peace in the world.' Disregard and contempt for human rights, even by people who advocate for human rights results in barbarous acts, and this freedom is so critically important and that freedom includes science. So everyone is entitled to all the rights and freedoms, and we cannot abandon people because of the situation that they find themselves in without distinction of any kind, and you can go back and read the Universal Declaration. Everyone has the right freely to participate in the cultural life, which includes science and the benefits of science.

5. The ethical justification of research

So these are the justifications we give for clinical research. Normally, we say there are two things which we need to justify clinical research. Originally, we said coming out of the Nuremberg situation where we saw that research was done in a barbarous way, as part of war, not as part of something that is integral to society. We said informed consent was needed. Then, we went until 1960s to say no, informed consent is not sufficient. We need something more. We need also to have external review, so ethics review, but there is more.

As the Declaration of Helsinki says, there is a requirement to continually improve our knowledge and tools for responding to disease, suffering, and health care. This is a requirement we do not do just because it is a luxury, or we can do it in a peaceful stable environment. We need to do science even in disruptive environments. We need to do it today in Kyiv, and the assurances that the results of the research will be used to improve the medical community's response to disease and that is what we heard in each of the presentations today, that that is why we are doing the research, because patients need it, because the community needs it. Ethics must consider the needs of and the needs for research and science with regard to populations and their situations.

6. Ukraine's clinical research enterprise

Just to say, what is going on in Kyiv today is just unacceptable. What is going on since March is completely unacceptable. Ukraine has been 25 years building a clinical research infrastructure. It is part of the country. They built excellent ethics committee. Viktoriia spoke about it today. They have excellent regulatory environment. Both Viktoriia and Evgeny responded to that, and we saw that in Veronika's presentation as well. The clinical trials enterprise has contributed significantly to the wealth and prosperity of Ukraine. Nobody is going to deny that. It is part of Ukraine's self identity. It is part of their understanding of them being part of this European enterprise. It is essential for them, and the clinical research enterprise is vital to

Ukraine. It is not something in addition. It is not something extra, and it is vital to the patients that are in most trials today, and I think it is simply worthy of support.

7. Adaptive design in clinical trials

In a our paper [5] we discussed the need for situationally adaptive clinical trials. We have this idea that clinical trials should be adaptive. We want clinical trials to be adaptive and that is where the design allows for modifications after the initiation of the trial without undermining the validity and integrity of trial.

What is the purpose of this? The purpose of this is to be more flexible within the clinical trial and more efficient. But what we have always talked about with regard to adaptive design is adaptive within the clinical trial, what we learn as we do the clinical trial we adjust the clinical trial. I think what Ukraine teaches us is that we also need to be adaptive to the situation in which the clinical trial appears. So now we need to rethink and redesign our adaptive design models for clinical trials that are also fit for purpose. We need to be adaptive to the changing situation of the trial. We need to respond to disruptions as Eugeny and Veronika are doing now as we speak and their colleagues are doing now on the frontlines of these clinical trials in these disruptive situations. So really, health science needs to prepare for, learn from, and respond to disruptions, crisis, and disaster situations.

8. Clinical research, data, and responding to disruptions

Health threats, natural disasters, and geopolitical disruptions, like we are talking about today, can lead and do lead to significant clinical trials disruptions. So we need, as we say in these two important reports, one from TransCelerate that came about during COVID 2021, 'The Clinical Report Considerations,' and the other ACRO and TransCelerate which was just published in September show us in a certain way, especially the one from the TransCelerate in 2021, how we can adapt our clinical research, how we can report our clinical research, have oversight to the clinical trials, and the State Expert Committee is demonstrating that that is possible in Ukraine through the war and care for the safety of the participants, care for the care of the participants, and also protect the integrity of the data and the data itself.

9. UNESCO's Recommendation on Open Science

I just want to say something here about UNESCO's Recommendation on Open Science which came at the end of last year. This is really interesting because this is the preamble, and again, this is the very opening of this recommendation on open science and why do we have open science. It says because we recognize the urgency of addressing complex and interconnected environmental, social, and economic challenges for people, including in this spiraling and that is what we are seeing today situations. This is why we need open science, and this is why we need science, period. This is the second paragraph. It talks about the vital importance of science to respond to these challenges and to promote democracy and peace. We do not stop doing science because there is conflict, and we leave no one behind with regard to access to science and benefits from scientific progress. I have seen too much war rattling coming out of bioethicists and people like this in

the West, saying we have to exclude people from science. This is crazy. This is just absolutely wrong. This is, we have to participate in science. We have to allow people to participate in science and scientific knowledge because by ensuring that the scientific knowledge, data methods, and processes needed to respond to the present and future global health and other crises, and where is there are larger crises than in Kyiv today, are openly available for all countries, including Ukraine.

I want to say in one of our earlier meetings a representative from WHO said, the disruption of clinical trials in Ukraine is not only a disruption of scientific knowledge and healthcare in Ukraine, it is a disruption of scientific knowledge across the world. Thus, for the purposes of this recommendation, open science is defined as an inclusive construct, and this is what we want. This is where we are going in science. Every country now is talking about open science and how to do it, and the purpose is to increase scientific collaborations and sharing of information for the benefits of science, but also for the benefits of societies.

10. The duty of bioethics vis-à-vis science

So just to close during this very important discussion on bioethics, and Japan understands this as well as anybody understands this, and I am also very happy that Gloria is here today with us. They have gone through terrible situations in war too. It is so important here, the fundamental duty of bioethics with respect to health-related research is to promote the integrity and practice of the scientific enterprise - that is why we do bioethics - in an environment that is universally open, without prejudice, and contributes to the public good.

*　　*　　*

Additional comment by organizer, Chieko Kurihara

Following the presentations by three commentators, Dr. Jerry Menikoff, M.D., J.D., then Director, Office for Human Research Protections, Department of Health & Human Services, United States, provided significantly important comment and Chieko Kurihara provided closing remarks to express her wish to continue following discussion, but these are not included in this publication of proceedings. As in the footnote 2 of cover page, Dr. Menikoff spoke on behalf of US government but at the time of publication he is not employed by that government thus he chose to not have his remarks published, but permitted organizer's summary.

First of all, Dr. Menikoff expressed his pleasure at seeing the excellent presentations by Ukrainian researchers during the wartime environment. He also expressed his supporting evaluation on two papers by Ethics Working Group of IFAPP [2, 5] that they suggested important points of ethical considerations regarding continuation of clinical trials in wartime.

He talked about the need for case-by-case based flexibility of regulations for human subject protection, making clinical trials be adaptive. He stressed that ethical responsibility to continue investigational treatments will depend a great deal on the nature of the clinical trial, as they are "investigational" in terms of

efficacy and safety. All the relevant stakeholders have to make right decision considering a very difficult, complexed wartime circumstance. Our experience with COVID-19 pandemic could be a good example, where we dramatically reshaped our clinical trial system across the world. It meant actually stopping a lot of clinical trials that probably again involve new risks, where the new risks outweighed the possible benefits, both to the information that we would learn from the trial and the possible direct benefits to the trial participants. Two types of distinct interests (among others): interest of current participants in continued participation in a clinical trial, and interest of society from continuing the trial. We need to balance safety of patients, caregivers, other health personnel versus possible direct benefits to patients as well as benefits to Ukraine economy, and benefits to society in general from continuation – weighing of alternative options in complex wartime circumstances. Both are context dependent and involve evaluating complex obligations.

After the talk of Dr. Menikoff, Chieko Kurihara expressed to extend discussion to the next web meeting with people participating in this symposium and new people coming in. She expressed her wish especially for Ukrainian participants to keep health and keep on providing care for patients and keep up the democracy of their country.