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

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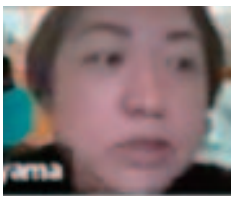

The effect of Ukraine war on international drug development

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.

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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.