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

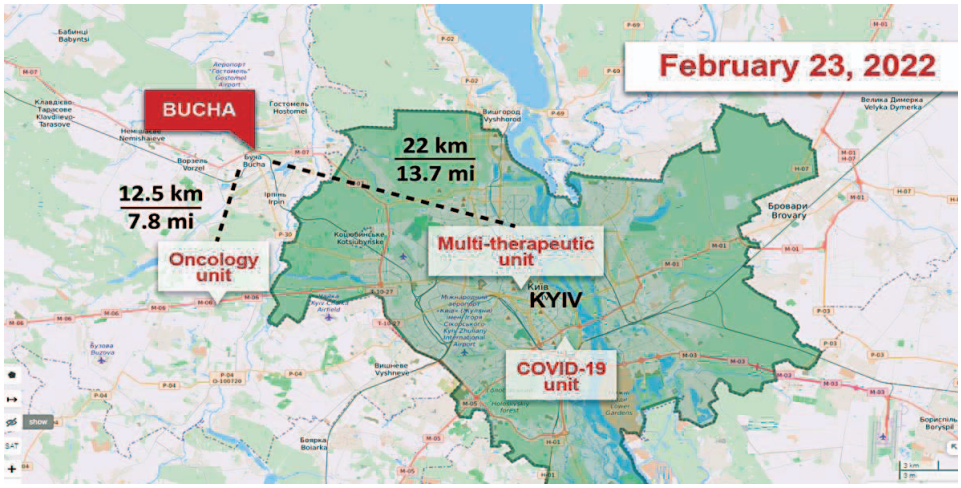
Fig. 1 ARENSIA locations

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

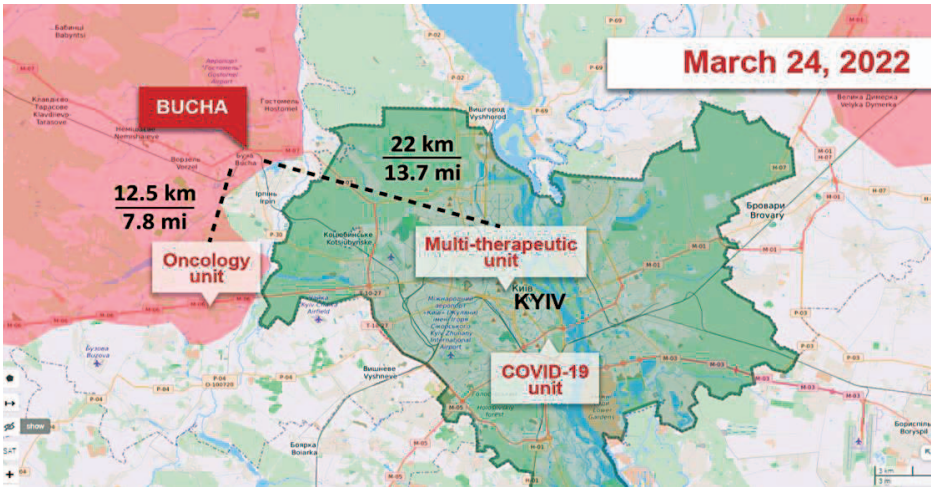


Table 3　ARENSIA Oncology Clinic: March-May 2022

- 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.

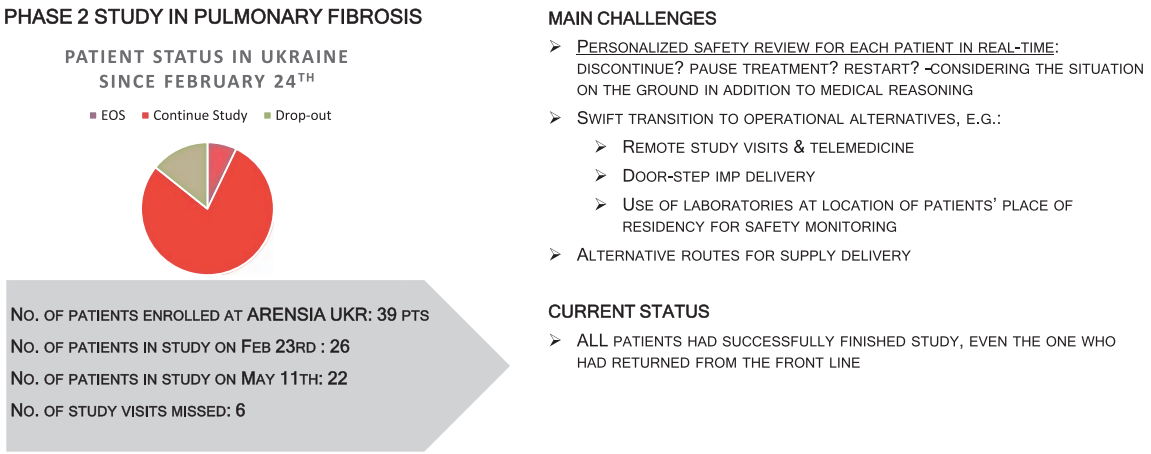
These are some examples (Fig. 6). This is our shelter downstairs for cleaning, so we have been sleeping directly on the floor. This is the preparation training for potential chemical attacks. Here you see that during an air alert, we stay inside our clinic, but without a window in the safest place. This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

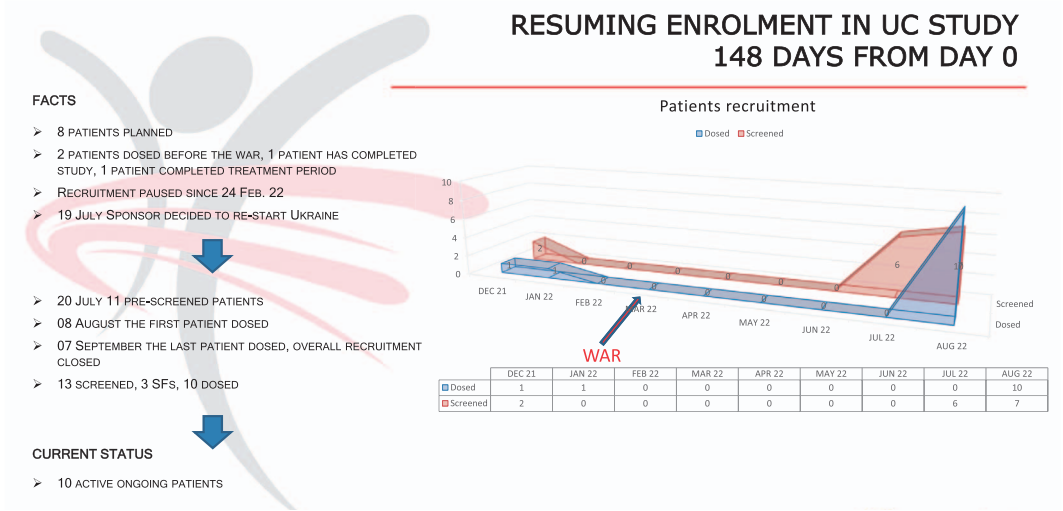
- 6 Patients have returned back from MOL to UKR and continue study participation

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.