

STERLING

THE BATTLE FOR MEDICAL PROGRESS
THE IMPACT OF THE WAR
IN UKRAINE ON THE CONDUCT
OF CLINICAL TRIALS

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Introduction

We have all seen the scale of the human tragedy that is unfolding in Ukraine. The eyes of the world are justifiably focused on what is happening, both in the country and across the globe, as the broader economic impact bites.

While nothing should divert attention from finding an end to the conflict and helping those who have fled or lost their homes and livelihoods, it's also important to understand the potential consequences for the pharmaceutical industry and patients around the world.

We also need to understand that the sanctions placed on Russia will have a compounding effect.

This paper first explores how the situation on the ground in Ukraine is impacting the conduct of clinical trials and the maintenance of access to trial medication for patients. Second, it discusses the broader impact of the invasion of Ukraine in combination with sanctions against Russia.





On the ground in Ukraine

Ukraine has become a major centre for clinical research in the post-Soviet era. Significant investment, including a centralised digital healthcare records system that covers about two thirds of the population, has modernised its healthcare infrastructure. Ukrainian clinical trial investigators have a reputation for delivering reliable data^{1,2,3} and there is a relatively large treatment-naïve population. These factors have combined to make Ukraine attractive as a location for multinational, multi-centre clinical trials.

Estimates vary, but prior to the invasion it is likely that there were between 500-700 ongoing or planned trials in Ukraine^{1,2}, with most major pharmaceutical companies running trials. The majority were multinational trials that were still recruiting patients when the war started.

Many are critical “Phase III” trials, run late in the development of a new medicine, and for some multinational trials the bulk of the trial sites were in Ukraine. In terms of therapeutic

areas, oncology trials represented the majority^{2,3}, with lung and breast cancer being the most numerous.

The number of trials in Ukraine represents only a small percentage of the global total, but the country features prominently in regulatory submissions. As many as 50% of recent EU new drug applications have included trial data from Ukraine, although the figure is likely to have been around 20% for US applications.

The early impacts

Very quickly after the conflict started, the destruction of healthcare infrastructure began³. In the first 100 days there were more than 260 artillery and missile strikes on healthcare facilities. Medical resources in the most impacted areas were diverted to front-line medicine. Logistics became a challenge, not just for patients trying to see their physicians, but also for the import of trial medication, export of blood samples or other biological material to analytical laboratories, and for the movement of materials within Ukraine. The World Health Organisation (WHO), other non-governmental organisations (NGOs), and governments deployed people and resources into Ukraine and neighbouring countries as part of a huge humanitarian effort.

Recruitment to ongoing clinical trials stopped. While some trial sites were initially able to continue treatment of patients, many trial investigators were unable to work. The risk of patients being lost to follow-up and therefore excluded from trial analysis increased³.

Following guidance from the Ukraine Ministry of Healthcare, the Ukrainian Association for Clinical Research initially tried to relocate trial patients from badly affected regions to trial sites in unaffected locations³ (see footnote). But this became much harder as the conflict spread. Approximately 25% of the population has been displaced (5m to neighbouring countries and 7m within Ukraine). Consequently, even in areas where infrastructure has not been directly impacted by the conflict, healthcare systems have been stressed by refugees from elsewhere in the country. Maintaining contact with large numbers of patients that became refugees in other countries was challenging.

The initial clinical response

Early on, observers drew parallels with the impact of the COVID-19 pandemic on clinical research. The European Medicines Agency (EMA) initially advised companies to fall back on regulatory guidance issued at that time⁴ and many implemented measures developed during the pandemic. However, the challenges presented by the two situations are very different. Remote monitoring, “direct-to-patient” supply of clinical trial medication, and other contingencies worked well during the pandemic, when hospital access was restricted and patients were locked down at home. However, these measures are much less feasible when hospitals have been rendered unusable and patients are no longer in their homes or even their country.

The conflict shifts

Over time, the focus of the conflict has moved to Eastern and Southern regions of Ukraine. While this has allowed some relaxation of pressure on healthcare systems in other areas, sporadic missile attacks and air raids continue. Perhaps as a result of this uncertainty, acute stress points persist, and there is some contradiction between opinion regarding the broader healthcare system challenges and the status of clinical trials.

At the time of writing, the WHO and other organisations operating at the macro-level continue to paint a picture of stressed healthcare infrastructure and workers, with shortages of surgical and medical supplies. Conversely, intelligence from albeit a small number of pharmaceutical companies indicates that some previously displaced patients are returning to their original trial sites and that enrolment of new patients in trials may even have resumed at some sites. However, information from

logistics providers involved in clinical trials indicates that volumes remain significantly depressed (perhaps by as much as 90%) which would seem to support the view that material impact on trial activity continues

Notwithstanding this uncertainty, the situation on the ground in Ukraine has consequences both for the patients involved in the trials and for patients more broadly. For patients in ongoing trials, particularly for those involved in studies of life-threatening or life-limiting indications, losing access to trial medication is potentially catastrophic.





Maintaining access to trial medication for Ukrainian patients

To mitigate the impact of anticipated interruptions to supply routes, many pharmaceutical companies had already taken proactive steps in the weeks leading up to the commencement of hostilities. Volumes of trial medication and laboratory sample kits were shipped to sites to allow the continued treatment of trial patients for as long as possible.

Nevertheless, as noted earlier, patient enrolment into ongoing trials was stopped shortly after the war began. Regulatory guidance was issued⁴ regarding the handling of refugees

who had been clinical trial subjects prior to their displacement, so that they could continue to receive medication and potentially continue their involvement in the relevant trial at a site in their destination country.

Defining the route forward

Initially, it was not clear exactly how transfers of individual patients would work in practice. Then, on April 4th, the European Clinical Trials Coordination Group (CTCG) issued definitive guidance for the transfer of displaced Ukrainian trial patients to sites participating in the same multinational trial in other countries within the EU/EEA⁵.

This was quickly followed by country-specific guidance in a number of countries including Austria and Denmark^{6,7}. The guidance states that, where possible, patients should be transferred to the care of alternative trial sites in their destination country. If such sites do not exist, or if it is not practicable for patients to be treated by those sites, then the guidance allows for “compassionate use” (see footnote) of trial medication in order that the patient’s treatment can continue outside of the relevant trial.

Footnote: The w defines “compassionate use” as a treatment option that allows the use of an unauthorised medicine. Under strict conditions, products in development can be made available to groups of patients who have a disease with no satisfactory authorised therapies and who cannot enter clinical trials.

Challenges remain

The CTCG guidance provides extensive technical detail regarding accountabilities, process and the pre-requisites associated with transferring patients. While this clarity will have been welcomed by trial sponsors, it should be recognised that there will be significant practical challenges in fulfilling the requirements. The process requires patients to be managed on an individual, case-by-case, basis. Almost all the process steps require open lines of communication with trial sites in Ukraine, functioning communications infrastructure and access to intelligence regarding the situation at Ukrainian trial sites. None of which can be guaranteed given the volatile situation on the ground in many areas of Ukraine.

Notwithstanding the potential absence of intelligence regarding the situation on the ground, the trial sponsor is in the best position to coordinate the transfer of patients from one trial site to another. However, under the regulations governing the conduct of clinical trials, the trial sponsor should not know the identity of individual patients. The scope for sponsor involvement is therefore limited.

The guidance also allows for displaced patients to contact the regulatory authority in their destination country, in order that they can connect with alternative trial sites. However, it is not clear how displaced patients who no longer

have access to the physicians that were treating them at the Ukrainian trial site would be able to contact the authorities in the country to which they have fled.

Even in circumstances where a patient can be linked to a destination site, administrative hurdles remain.

For example, patients must undergo a further informed consent procedure at the new site which may not have staff that speak Ukrainian.

Finally, the guidance assumes that the destination country has capacity in its healthcare system to accommodate refugees and that individual trial sites can cope with additional patients. Given that some adjacent countries have accepted two million or more refugees already, this cannot be guaranteed.

A positive foundation for future progress

While practical challenges exist, the regulatory authorities, together with trial investigators and sponsors, should be applauded. Regulation has quickly provided a procedural framework under which displaced Ukrainian trial patients can continue, at least theoretically, to access their medication, while investigators and sponsors have played their part in implementing practical measures to make it happen.





Impact of Russian sanctions

For similar reasons to Ukraine, Russia has become a major hub for clinical trials. Estimates of the number of ongoing or planned clinical trials in Russia vary, but there may have been as many as 1,500¹, with oncology again the most prevalent therapy area.

While most of these trials are sponsored by domestic Russian companies, Russia is nevertheless the sixth largest ex-US location for studies sponsored by international companies.^{8,9} The majority of these internationally-sponsored trials are multinational studies with significant numbers of trial sites in Russia.

The implementation of international sanctions against Russia appears to have had no impact on trials sponsored by domestic Russian companies.⁹ However, all major international pharmaceutical companies quickly ceased patient admissions to ongoing trials in Russia. They also stopped preparations for planned trials, with no intention to re-start activities in the foreseeable future.

Ethical and practical issues around trial activities in Russia

The practical question over how to handle patients already admitted to ongoing trials represents something of an ethical dilemma for trial sponsors, particularly given the number of ongoing trials of new oncology medicines.

The pharmaceutical industry exists to improve patients' lives, meaning there is an ethical obligation to continue treatment of a patient in a trial unless treatment needs to be withdrawn for safety reasons

As a result, at the time of writing, internationally-sponsored trials in Russia have not been stopped completely and patients admitted to trials prior to sanctions continue to be treated.

Initially at least, there were significant logistical challenges to this position. When Moscow State University announced that recruitment to trials sponsored by international companies had stopped, it was noted that the closure of Russian airspace to most international airlines was making the shipping of blood and other trial samples difficult. Most internationally-sponsored trials were using central laboratory facilities outside Russia⁹. If the analysis of trial samples is pivotal to the outcome of the trial, then continuing the trial may not be feasible. While some alternative logistical solutions have now been implemented, intelligence from logistics providers to clinical trials indicates that the impact on volumes is similar to that noted earlier for Ukraine.



Significant risk of delayed or failed clinical trials

The situation on the ground in Ukraine, combined with the effect of sanctions against Russia, have created a perfect storm to hamper the development of trial medicines in both countries.

Admissibility of data from clinical trials is tightly controlled. Each trial requires a predetermined number of patients for the trial to have the necessary statistical power to show whether a treatment has worked. Continuity of both treatment with the trial medication and assessment by the trial investigator is critical. While some gaps in data of individual patients can be managed through statistical methods, extensive gaps where patients have been “lost to follow-up” may mean that those patients are excluded from analysis entirely.

Given the number of trial sites in Ukraine, the risk of significant numbers of patients being excluded from the analysis of trials is acute.

The cessation of admission of new patients at trial sites in Russia and Ukraine compounds matters further, as the overall effect on the trials concerned may be exaggerated due to the nature of the trials and the number of trial sites in those countries vs. those in other countries. Collectively, trials in Ukraine and Russia may represent a small percentage of total global activity, but in many trials the geographical distribution of trial sites is skewed towards the two countries. For example, the author is aware of one proof-of-concept trial with sites in Russia, Ukraine and only two other countries – it is not a big trial, but it is critical for the drug and the company. There will be many others like this.

The solutions are complicated – and incomplete

To compensate for the loss of trial sites and patients in Ukraine and Russia, trial sponsors can, within certain regulatory constraints, increase the

number of patients admitted at sites in other countries or open additional sites in those countries. However, both approaches will result in the trial taking longer, with the potential to delay regulatory approval and availability of medicines for patients.

Given the number of sites originally located in Ukraine and Russia, there is a further risk that patient admissions at other sites cannot be increased sufficiently, or that additional sites cannot be identified. The tightly defined patient population for trials may require a particular mix of ethnicity, phenotype or genotype and the geographic distribution of sites will have been designed to accommodate this.

Some trials may therefore never admit the predetermined number of patients, and so will fail, directly impacting approvals and the availability of new medicines.



Conclusions and references

While some trial sites in Ukraine are beginning to re-start activities, there is no question that the combined effects of the war in Ukraine and sanctions against Russia are disrupting clinical trials in both countries. It is not yet clear if the sponsors of those trials will be able to offset the loss of patient numbers by implementing mitigating actions in other countries. There is therefore a significant risk that trials will need to be prolonged, ultimately

delaying or perhaps preventing regulatory approvals for the medicines concerned.

The extent to which these risks materialise in a sustained way will of course be dependent on how long the conflict continues. Reconstruction of infrastructure in Ukraine will take time and it seems highly likely that sanctions against Russia will remain in place for the foreseeable future.

Hundreds of thousands or even millions of patients across the globe may be deprived of the opportunity to benefit from new medicines which they would otherwise have had access to. For many, their lives will be diminished as a result. For others, their lives will be shortened, further expanding the human tragedy that this war has created.

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