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Drug development hit by war

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ABSTRACT

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Introduction: Drug development is the process by which academic, pharmaceutical or, government laboratories identify or screen new chemical entities to find potentially active pharmacological compounds and bring them to the market. This process is undoubtedly the heart and soul of modern medicine. War is an incidental condition that can disrupt the drug development pipeline and clinical research. During the current Russia-Ukraine war, multiple sanctions are being imposed on Russia which is disrupting the supply chain and slowing down the process of drug development.
Objective: This review was done to understand how war and international conflicts affect the global drug development process.
Methods: Information was obtained by reviewing the data from previously published news material. We used PubMed, Google Scholar, Web of Science, Medline, and Embase as our search engines and keywords like (Ukraine, Russia, clinical trial, pharmaceutical industry, war, and drug development). In total, we reviewed 74 articles, and the obtained information was interpreted, compiled, evaluated, reassembled, deconstructed and conclusions were reached.
Conclusion: In the past despite multiple wars, mankind has not learned from their past mistakes. The pharmaceutical industry should form mitigation plans so that in the time of crisis other options are available for drug discovery and clinical research.

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Introduction

Drug discovery and clinical research are the heart and soul of modern medicine. Unmet clinical need is the driving force for initiation of a drug discovery programme (Hughes *et al*., 2011). Living through a pandemic has forced mankind to watch out for stories of positivity. The power of recalling ancestors is innate and strong, back in 2014 when Crimea was taken over and the war in east Ukraine started (Fishchuk R, 2022) it hindered biomedical clinical research and development. Beauty lies in the eyes of the beholder, an optimist grabs opportunity even in the most challenging circumstances. Back in 1941, when the Russian army was captured by the Germans, being an optimist, Cochrane, father of evidence-based medicine conducted the first and most successful clinical trial in the most incredible and inhuman of circumstances (Browne G, 2022a).

There are multiple steps in a clinical trial which includes screening of volunteers, recruitment of participants and follow-up to monitor the efficacy and safety of the medications in participants. Based on the clinical trial data recorded, regulatory agencies issue the approval. With the ongoing war there are various factors hampering this system (Khan T, 2022).

For instance, Ukraine is pretty attractive due to its big treatment-naive population and centralized healthcare infrastructure (Castaneda R, 2022a). Whereas Russia is among one of the top destinations for conducting clinical trials due to cost effective operations, quicker recruitment from a larger population and a centralized system of healthcare (Castaneda R, 2022b).

Multiple clinical trials have been shattered by the war. The only possibility to get treatment for rare and life threatening diseases for patients is by enrolling themselves for clinical trials (Fishchuk R, 2022). Thousands of patients are at the verge of losing their last option of survival (Browne G, 2022a). As the war in Ukraine is escalating and has flipped up millions of lives, people had to flee outside which also includes patients with severe disease who were devastated by the double edged sword of severe illness and displacement.

When the Russians bombed cancer treatment centres in eastern Ukraine civilians started fleeing, including those enrolled in existing cancer trials, forgoing their planned therapy. Although western Ukraine is not yet invaded by Russians, the health clinics here are overburdened by displaced people fleeing from the war torn east Ukraine. Other European countries are welcoming cancer patients from Ukraine but oncologists are overwhelmed, by not only the lack of available drugs in their countries but also from an apparent lack in timely and adequate coordination with Ukraine as usual mechanisms of diplomacy are preoccupied with warfare (Russia's war in Ukraine is killing cancer care in both countries, 2022).

Current scenario in Ukraine

Healthcare system in Ukraine is most likely to be stretched, there will be a great ripple effect on its local clinical trials industry. With the recent war, pharmaceutical industry sponsors might need to relook at their strategy keeping in mind geopolitical tensions. There are at least 621 pharmaceutical industry sponsored clinical trials in ukraine, out of these 117 are in oncology therapy area, as per FDA (Browne G, 2022a) and a large proportion of these studies are multi-centric in nature (Castaneda R, 2022a). The Ukraine clinical trial distribution has been presented in **Figure 1**.

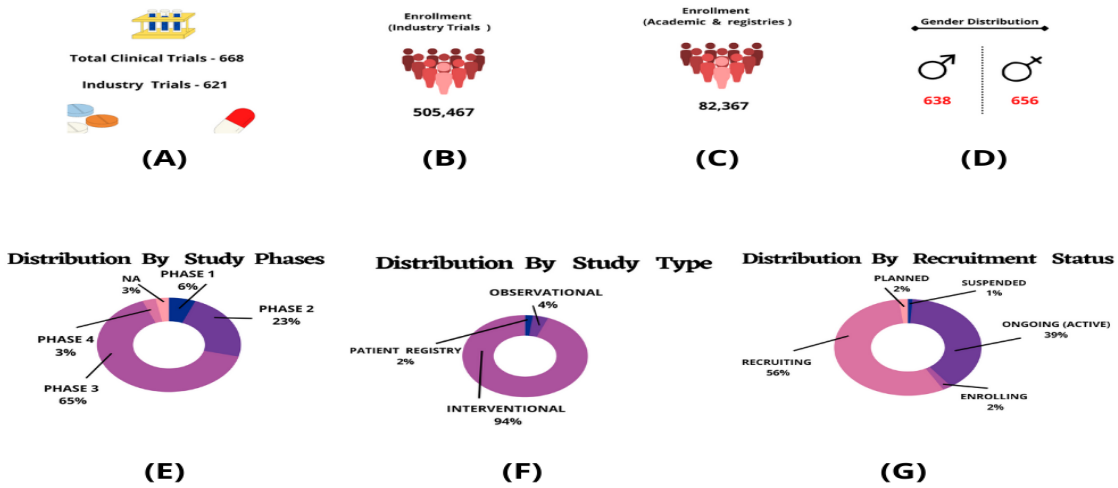


Figure 1 . Ukraine clinical trial distribution: 1(A) Trial numbers 1(B) Enrollment based on industry trials 1(C) Enrollment based on academic and registries 1(D) Gender distribution in clinical trials 1(E) Distribution by study phase 1(F) Distribution by study type 1(G) Distribution by recruitment status (Home- Clinical Trials.gov, 2022).

Current situation of Russia

While healthcare in Ukraine is impacted due to invasion by Russia, patients in Russia are affected by inflation and sanctions crippling the Russian healthcare industry. Russia has a lot of clinical trial sites specializing in early phase research and has emerged as a top host for phase 1 clinical trials globally. As sanctions escalate these clinical trials will undergo delay unless pharmaceutical companies contemplate building new health infrastructure elsewhere or recruiting volunteers to complete the ongoing trials (Castaneda R, 2022b).

Further with the fall of the Russian ruble and cost of imported drugs reaching the sky, state hospitals struggle even more to cover the cost of treatment. This has led to cost cutting from other innovative treatments and genetic research (Russia's war in Ukraine is killing cancer care in both countries, 2022).

With the ongoing war there are numerous conditions and situations which have hampered the complete system of clinical trials (Castaneda R, 2022b).

Due to the unstable geopolitical situation there is unavailability of willing participants for clinical trials, both new and ongoing (Castaneda R, 2022a). There is also disruption in the supply chain which has affected the pharmaceutical industry. Currently there can be two different solutions to this situation.

- Firstly, select and recruit new volunteers and participants in other countries, but this will increase the burden on the pharmaceutical companies. This will also need financial investments and further delay the final results. Further, there is a big question which will happen to the participants who were recruited into the trials and medicated but lost to follow up (Khan T, 2022).
- The second solution is for the pharmaceutical industry to wait till the disputes are resolved but nobody really knows when it will happen . In addition, there could be a possibility of psychological impact of war on participants which might lead to unrelated adverse impacts. So there are numerous questions for which there are no correct answers but only ripple effects (Khan T, 2022).

Response of Pharmaceutical Companies

Medicines that are meant to treat fatal diseases are essential as they may be the last hope for the needy patients and any impact on the supply chain of such medicines would render patients helpless and may increase the war's ongoing toll on people. This has put pharmaceutical companies in an awkward situation. This is an ethical boundary no company is willing to breach. Holding back these drugs would lead to grossly inadequate resources and injustice by directing those limited supplies to people in power (Browne G, 2022b) .

- There are 27 clinical trial sites in Ukraine by GlaxoSmithKline which also includes the trial of otilimab in patients with rheumatoid arthritis.
- KarXT a drug under phase 3 clinical trial for schizophrenia, developed by Karuna therapeutics could also be delayed.
- 11 of 195 study locations of phase 3 trials of the drug Keytruda developed by Merck are in Ukraine.

It is not only the pharmaceutical industry which is affected due to the war, biotech companies are getting affected as well (How Russia's invasion of Ukraine could affect 200+ clinical trials, 2022).With the war and invasion happening, CEOs of leading biotech and pharmaceutical companies have had to ask their global counterparts to distance themselves from Russian industry.

- Companies like Sanofi, Astrazeneca, GSK are prioritizing safety of their people, attempting to maintain access to vaccines, medicines and consumer healthcare products for their trial participants (LaHucik *et al*., 2022).
- Johnson & Johnson, Merck, GSK and Eli Lilly have stopped conducting any new clinical trials and enrolling new patients for ongoing clinical trials in Ukraine, Russia and Belarus.
- On the other hand, 20 active trials sites are functional of Astrazeneca, the largest pharmaceutical company of Britain. They are weighing up whether to stop trials. This includes their trial on combination dose of its Covid-19 vaccine with Russian sputnik lite vaccine involving 100 volunteers from Russia (GlaxoSmithKline says it will not start any new clinical trials in Russia, 2022).
- Bayer has prospectively halted all advertising, promotions, capital investment projects and resolved to not pursue new business opportunities in Russia.
- Roche's Russian colleagues play a role in accessing medicine, therefore they will keep running their operations in Russia (Ellis R, 2022).
- Pfizer is one of the rare pharmaceutical companies which has taken a clear position for Russia. It has made a public release, defining that all medicines supplied to Russia and Ukraine will be maintained based on patient-spirited grounds. Pfizer has a principle of putting patients first. Pfizer will be donating all profits made from their subsidiary in Russia to provide direct humanitarian aid to the citizens of Ukraine. There will be no new clinical trials in Russia from Pfizer but will stop recruitment of volunteers in ongoing clinical trials

(Pfizer Updates company position in Russia Pfizer, 2022).

As per a senior research fellow at the Oxford institute for ethics, law and armed conflict, companies can stop supplying life-saving drugs anytime and they won't be legally bound to answer because it's at their disposal with whom they want to trade (Browne G, 2022b).

Pharmaceutical companies stand in concord with Ukraine and from a moral standpoint it's not a viable choice for drug manufacturing companies to suspend all operations in Russia unlike other business sectors (Liu *et al*., 2022). The humanitarian support extended by various pharmaceutical companies has been presented in **Table 1**.

Table 1: Table summarizes the humanitarian support extended by various pharmaceutical companies (Pharmaceutical industry response to the war in Ukraine, 2022).

Sr. No	Company Name	Humanitarian Support
1	Novo Nordisk Foundation	7.4 million Euros
2	Novartis	2.6 million Euros & 600 thousand packs of essential medicines
3	Astellas	73 thousand Euros
4	Bayer	3 million Euros
5	Astrazeneca	890 thousand Euros & Drugs worth 2.6 million Euros
6	Boehringer Ingelheim	2.5 million Euros
7	Bristol Myer Squibb	>890 thousand Euros
8	Merck	2 million Euros
9	Teva	9.8 million Euros
10	Otsuka	100 thousand Euros

Data is the new oil of the modern era, health records are something like that. Restarting a trial is challenging, sometimes it is like conducting two trials. Due to war situations in multiple clinical trial sites, the collected data is often destroyed. Restarting or suspending clinical trials alone potentially produces really bad quality data, not to mention it can be very disturbing for the trial volunteers (Browne G, 2022a). If Russia remains an unstable trial host, queries as to where these trials should relocate and whether the new place would have enough health infrastructure or volunteers to complete the requirements for the trials are to be raised. Most of the innovation drug industry in Russia is in institutions or companies with links to the government (Castaneda R, 2022b).

Ukrainian companies such as Enamine and Medchemica teamed up on an endeavor -'Covid Moonshot' which is a generic drug that could be used as a therapy for patients affected with Covid without the obstacles of intellectual property and patent licensing. Due to war its trial is also hampered and clinical trial sponsors are looking for other alternatives for CRO's in India, China and other potential countries to fill in this gap (Stewart A, 2022).

With every crisis there comes an opportunity. The current geopolitical and international relations of these war-torn countries are in favor of Indian and Chinese companies, which may seek to replace western pharmaceutical MNCs in these regions.

Sputnik V Covid-19 vaccine has been developed by Dr. Reddy's in partnership with the Russian government. Indian pharmaceutical companies are continuing to run their functionalities in Russia. Nearly $600 million of the annual revenues of Indian companies comes from Russia. Western MNCs are scaling down their supplies and business in order to comply with the global sanctions on Russia (Rajgopal D, 2022) .

Discussions

Research and development of new drugs and therapies is important for survival of many patients worldwide and the ongoing war has hampered this process overall. This is affecting the people of those countries by disrupting the supply chain, imposing sanctions and biased supply of limited resources. Going forward the people in other parts of the world will also get affected in the long run due to delay in research and development of potential life saving drugs. Although the pharmaceutical companies are not bound by any law to continue supplying essential medicines and their potential life-saver drugs to the patients, they have taken humanitarian and patient centered decisions in these difficult international and geopolitical situations despite suffering huge financial losses. Wars bring a lot of hardships so it should always be the last resort and peacekeeping dialogues should be the way forward in cases of conflicts and tensions. Most importantly, there should be a treaty at a global platform ensuring that in adverse circumstances like war, things related to humanity should be least affected.

Conclusions

Life is a matter of choices and mankind has both options available. Optimistic people like Cochrane took wartime in a constructive manner and conducted clinical trials, whereas in 2014 when Crimea was taken over and the war in east Ukraine started, people suffered due to war and it badly impacted all major industries including the pharmaceutical industry. Despite this, pharmaceutical companies did not mitigate the future crisis and we can see what is happening today in Ukraine and Russia. Humankind should learn from past mistakes and plan for the future accordingly.

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Competing interests

Authors declare that they have no competing interests.

References

Browne, G. (2022)[a]. The War Puts Ukraine's Clinical Trials—and Patients—in Jeopardy. Retrieved 3 April 2022, from https://www.wired.co.uk/article/war-ukraine-clinical-trials-jeopardy

Browne, G. (2022)[b]. Big Pharma's Ethical Dilemma: Should They Keep Selling to Russia?. Retrieved 3 April 2022, from https://www.wired.co.uk/article/big-pharma-faces-an-ethical-dilemma-should-they-keep-selling-to-russia#intcid=_wired-uk-bottom-recirc_918fa474-c358-40ef-b249-193b66276644_entity-topic-similarity-v2

Castaneda, R. (2022)[a]. Ukraine: Industry-sponsored clinical development at risk. Retrieved 3 April 2022, from https://www.clinicaltrialsarena.com/analysis/ukraine-industry-sponsored-clinical-trial-development-at-risk/

Castaneda, R. (2022)[b]. Clinical trials in Russia: drug development pipeline at risk. Retrieved 3 April 2022, from https://www.clinicaltrialsarena.com/special-focus/ukraine-crisis/clinical-trials-in-russia-at-risk/

Ellis, R. (2022). Pharmaceutical Companies Cutting Ties With Russia. Retrieved 3 April 2022, from https://www.webmd.com/drug-medication/news/20220315/pharmaceutical-companies-cutting-ties-with-russia

Fishchuk, R. (2022). 'He will die': Russia-Ukraine war's unseen medical horrors. Retrieved 3 April 2022, from https://www.aljazeera.com/features/2022/3/16/ukraine-if-they-move-her-son-from-intensive-care-he-will-die

GlaxoSmithKline says it will not start any new clinical trials in Russia. (2022). Retrieved 3 April 2022, from https://www.theguardian.com/business/2022/mar/17/glaxosmithkline-says-it-will-not-start-any-new-clinical-trials-in-russia

Hughes, J. P., Rees, S., Kalindjian, S. B., & Philpott, K. L. (2011). Principles of early drug discovery. *British journal of pharmacology*, *162*(6), 1239–1249.

How Russia's invasion of Ukraine could affect 200+ clinical trials. (2022). Retrieved 3 April 2022, from https://www.advisory.com/daily-briefing/2022/02/25/russia-ukraine

Home - ClinicalTrials.gov. (2022). Retrieved 10 April 2022, from https://www.clinicaltrials.gov/

Khan, T. (2022). After Effects of Russia - Ukraine Conflict Over Pharma and Life Sciences Industry. Retrieved 3 April 2022, from https://pharmashots.com/7033/after-effects-of-russia-ukraine-conflict-over-pharma-and-life-sciences-industry

LaHucik, K., Armstrong, A., Bayer, M., Sagonowsky, E., & Dunleavy, K. (2022). UPDATED: Biotech leaders call on industry to cut ties with Russia amid Ukraine invasion. Retrieved 3 April 2022, from. https://www.fiercebiotech.com/biotech/russian-invasion-ukraine-could-impact-more-200-clinical-trials-sites-european-country

Liu, A., Sagonowsky, E., & Kansteiner, F. (2022). AbbVie, Eli Lilly, Novartis and more cut back in Russia amid corporate exodus over Ukraine war. Retrieved 3 April 2022, from https://www.fiercepharma.com/pharma/abbvie-eli-lilly-novartis-and-more-cut-back-russia-amid-corporate-exodus-over-ukraine-crisis

Pfizer Updates Company Position in Russia | Pfizer. (2022). Retrieved 3 April 2022, from https://www.pfizer.com/news/press-release/press-release-detail/pfizer-updates-company-position-russia.

Pharmaceutical industry response to the war in Ukraine. (2022). Retrieved 3 April 2022, from https://www.efpia.eu/news-events/the-efpia-view/efpia-news/pharmaceutical-industry-response-to-the-war-in-ukraine/

Rajgopal, D. (2022). Biz as usual for Indian pharma cos despite Russia-Ukraine war. Retrieved 3 April 2022, from https://www.livemint.com/companies/biz-as-usual-for-indian-pharma-cos-despite-russia-ukraine-war-11647889982207.html

Russia's war in Ukraine is killing cancer care in both countries. (2022). *BMJ*. 376.

Stewart, A. (2022). "We Want to Return to the Lab": How the Russian Invasion Has Disrupted Drug Discovery in Ukraine. Retrieved 3 April 2022, from https://themedicinemaker.com/discovery-development/we-want-to-return-to-the-lab-how-the-russian-invasion-has-disrupted-drug-discovery-in-ukraine