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Abstract

Since the invasion of Ukraine in February 2022, clinical trial conduct has become extremely challenging due to damage to the healthcare infrastructure and patient displacement. This current study aimed to estimate the number of cancer clinical trials at risk of impact from the conflict. A descriptive analysis and narrative review were completed using data from cancer clinical trials with sites in Russia or Ukraine using the ‘clinical trials.gov’ online database between February 2022 and May 2022. There were 508 clinical trials involving sites in Ukraine or Russia. Most were multinational studies (470 of 508; 93%). The majority of studies were phase 3 (344 of 508; 68%) and these also had the largest sample sizes (median 624, range 12–5637). The most common tumour types were lung (128 of 508; 25%), urogenital (94 of 508; 19%) and breast (78 of 508; 15%). A meaningful number of trials had curative intent (129 of 508; 25%). The most common intervention was immunotherapy-related (218 of 508; 43%), followed by other targeted therapy (185 of 508; 36%). Ukraine and Russia are both large centres for global clinical trial activity. The invasion of Ukraine may result in underpowering of international clinical trial results with loss of future recruitment sites for both countries.

Keywords

Cancer, clinical trial, conflict, Russia, Ukraine

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Introduction

The disruption and chaos caused by military conflict has a profound impact on healthcare including cancer care and clinical trials. Clinical trials have become an essential part of the therapeutic model for all oncology patients.¹ Barriers to onsite cancer care and resultant increases in mortality have been seen in previous war-torn countries including Bosnia, Syria, the Lebanon and Iraq.^{2–5} These countries have struggled for years to rebuild healthcare systems amid continuous civil unrest. Forced migration and lack of medical resources during the conflict in Syria resulted in a 50% decrease in the number of practicing physicians from 2008 to 2017.⁵ These factors likely contribute to the indirect increase in mortality during times of war.⁶ The barriers to clinical trial conduction in Syria were identified by healthcare staff as a lack of funding, lack of electronic computer systems and patient displacement.⁷ Unsafe travel routes to hospitals also meant huge loss to follow up. Cancer care in these countries has suffered due to the lack of prioritization in resources and availability of staff.

Following the invasion of Ukraine on 24 February 2022, the feasibility of maintaining active cancer trial sites in Ukraine became extremely challenging. In order to ensure validity of clinical trial outcomes, a controlled and consistent environment must be in place across international sites. Ukraine and Russia make significant contributions to multinational cancer clinical trials.⁸ The impact of the conflict in Ukraine on conducting clinical trials will be variable but primarily relates to loss of treatment centres, internal displacement and forced migration.^{8,9} The contribution of clinical trial sites located in Russia is also likely to be impacted by the conflict. All clinical trials operate around specific time-points to allow for clear and standardized

data collection and analysis. Loss of study subjects may therefore result in studies being underpowered. There are limited collated data on the volume of domestic and international clinical trials that may be at risk in the two nations (Ukraine and Russia) currently directly involved in this conflict. The aim of this narrative review was to describe the current landscape of systemic cancer clinical trials in Ukraine and Russia and estimate the number of cancer clinical trials at risk as a result of this conflict.

Materials and methods

Study methods

A descriptive analysis and narrative review of cancer clinical trial data collected contemporaneously from the online database ‘clinical-trials.gov’ was undertaken. Data collection was undertaken between February 2022 and May 2022.

Search strategy and data collection

The search strategy included ‘cancer’ or ‘neoplasm’ or ‘tumour’ searched for both ‘Ukraine’ and ‘Russian Federation’. Inclusion criteria for the study were interventional solid tumour trials with clinical sites in Ukraine or Russia that were active, active but not yet recruiting, currently recruiting or enrolling by invitation at the time of data collection. Haematological malignancies were manually excluded. Data on clinical trials for therapies for solid organ malignancies in both adult and paediatric patient cohorts were included. Data collected included clinical trial name, phase, recruiting status, tumour type, site(s) involved, intervention aim, intervention type and sponsorship type. The search did not access Ukrainian or Russian clinical trial registries due to language barriers.

All data reviewed in this study were public data from an online database. No medical records were accessed and no patients were contacted as part of this study. Therefore, no consent process was involved in this study. Ethical approval was received from St John of God Healthcare Ethics Committee (no. 1952).

Statistical analyses

Statistical analyses were completed using the R statistical package (R version 4.1.3 for macOS®; R Foundation for Statistical Computing, Vienna, Austria). Demographic and clinical characteristics were summarized using standard descriptive summaries such as mean for continuous variables and percentages for nominal and ordinal data.

Results

There were 508 studies recorded that met the inclusion criteria. Most of these trials were multinational ($n=470$) with a small number of clinical trials that were solely based in Russia ($n=36$). Only two clinical trials were located solely in Ukraine. There were 192 Ukrainian clinical trial sites and 474 Russian trial sites, with 150 clinical trials involving both Ukraine and Russia. Most clinical trials in this cohort were commercially sponsored trials (454 of 508; 89%) with only 36 non-commercial trial sponsors recorded between Russia and Ukraine (Table 1).

Of the 508 studies, 498 studies involved adults only (98%) with five clinical trials including paediatric patients and five including both paediatric and adult patients. The most commonly listed phase of study was 3 (344 of 508; 68%), followed by 2 (106 of 508; 21%), 1 (22 of 508; 4%) and 4 (12 of 508; 2%). Twenty-four studies had a phase listed as not applicable. Almost all studies (497 of 508; 98%) were either recruiting or active but not recruiting.

Of the recruiting studies (246 of 508), 62% (153 of 246) were phase 3, 11% (56 of 246) were phase 2, 4% (nine of 246) were phase 1, 2% (five of 246) were phase 4 and 9% (23 of 246) listed the phase as not applicable. As expected, sample sizes were largest in multinational phase 3 studies (median 624, range 12–5637). Median sample sizes for phase 1, 2 and 4 trials were 104, 200 and 280 patients, respectively. It was not possible to determine the number of individual trial participants involved in Ukrainian and Russian trial sites from the publicly available data.

The most common tumour types documented were lung (128 of 508; 25%), urogenital (94 of 508; 19%) and breast (78 of 508; 15%). Other tumour types included upper gastrointestinal (gastric, hepatobiliary, pancreatic) (52 of 508; 10%), gynaecological (39 of 508; 8%), colorectal (22 of 508; 4%), head and neck (23 of 508; 5%), skin (17 of 508; 3%), central nervous system (nine of 508; 2%), bone (three of 508; 1%), sarcoma (five of 508; 1%) or solid tumours not otherwise specified (38 of 508; 7%) (Figure 1). Most clinical trials were for advanced disease (379 of 508; 75%) with a meaningful number of trials in the early stage/curative intent treatment setting (129 of 508; 25%). The most common intervention was immunotherapy-related (218 of 508; 43%), followed by other targeted therapy (185 of 508; 36%), antibody drug conjugates (25 of 508; 5%), hormonal therapy (27 of 508; 5%), chemotherapy (20 of 508; 4%), surgical treatment (22 of 508; 4%) and radiotherapy (five of 508; 1%).

Discussion

War has a profound impact on all aspects of healthcare including non-communicable diseases such as cancer. Since the invasion of Ukraine in February 2022, there has been significant disruption to the care of people with cancer as with almost every

Table 1. Characteristics of the cancer clinical trials ($n = 508$) identified by a systematic search of the online database 'clinicaltrials.gov' between February 2022 and May 2022 in a study that aimed to determine the current landscape of cancer clinical trials in Ukraine and Russia and estimate the number of cancer clinical trials at risk as a result of the conflict.

Characteristics	Total study cohort	Trial sites	
		Russia	Ukraine
Study site	508	474 (93)	192 (38)
Phase of study			
Phase 1	22 (4)	17 (4)	10 (5)
Phase 2	106 (21)	93 (20)	34 (18)
Phase 3	344 (68)	330 (70)	143 (75)
Phase 4	12 (2)	12 (3)	3 (2)
Recruiting status			
Not yet recruiting	4 (1)	2 (<1)	2 (1)
Recruiting	246 (48)	229 (48)	99 (52)
Enrolling by invitation	7 (1)	7 (1)	0 (0)
Active, not recruiting	251 (49)	236 (50)	91 (47)
Sample size			
Phase 1	104 (30–500)	104 (30–500)	138 (30–500)
Phase 2	200 (4–1595)	200 (8–1595)	168 (4–1000)
Phase 3	624 (12–5637)	644 (12–5637)	682 (60–5637)
Phase 4	280 (81–1036)	334 (81–1036)	387 (160–1000)
Sponsorship type			
Commercial only	454 (89)	426 (90)	178 (93)
Non-commercial only	36 (7)	32 (7)	5 (3)
Both	18 (4)	16 (3)	9 (5)
Treatment intention			
Advanced/palliative	379 (75)	353 (74)	145 (76)
Curative	129 (25)	121 (26)	47 (24)

Data presented as n of studies (%) or median (range).

other aspect of daily life. This current study has described the significant contributions of Ukrainian and Russian patients and clinicians to oncology research as reflected in the number of active studies in solid malignancies listed on the 'clinicaltrials.gov' database. The conflict in Ukraine has led to the disruption of these trials both directly and indirectly.¹⁰ This has affected both patients and staff, which subsequently has effects on the research effort and the ability to answer important research questions.

In 2020, the global cancer observatory reported 162 000 new cases of cancer in

Ukraine with over 84 000 deaths.¹¹ Many of these patients diagnosed with cancer each year require pharmaceutical imports in the form of chemotherapy, immunotherapy or targeted therapy. These medications account for only a small portion of the total pharmaceuticals imported into Ukraine each year. In 2020, Germany, India and France were the strongest contributors to Ukrainian pharmaceuticals with 370 million, 222 million and 163 million US dollars' worth imported that year, respectively.¹² During the conflict, the supply of pharmaceuticals including trial drugs to clinical trial sites has been interrupted.¹³ Medications are

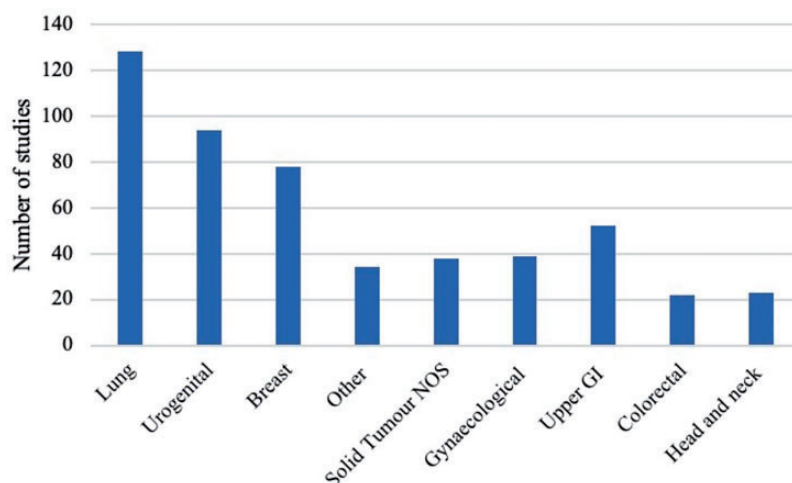


Figure 1. Number of cancer clinical trials ($n = 508$) identified by a systematic search of the online database 'clinicaltrials.gov' between February 2022 and May 2022 stratified by the tumour type that were included in a study that aimed to determine the current landscape of cancer clinical trials in Ukraine and Russia and estimate the number of cancer clinical trials at risk as a result of the conflict. NOS, not otherwise specified.

primarily transported to Ukraine by air, however all aerial flights to Ukraine have been suspended, leaving road delivery as the sole option for importing goods.⁹ Delays in the transport of clinical trial drugs have implications for their use at clinical trial sites. It is essential that these medications are stored in accordance with recommended guidelines in order to protect their anti-tumour efficacy and align with treatment protocols.¹⁴ There is also a risk of medication loss by the direct actions of armed conflict, as was the case in the shelling of oncology dispensaries in Melitopol and Chernihiv.^{15,16} It has been estimated by members of the global oncology community that diagnostic and therapeutic delays in Ukraine for even 4 months could result in an excess of 3600 deaths in coming years from the five most common cancer types.¹⁰ Four of these five (lung, breast, gynaecological, colorectal) are also the most common cancer types involved in clinical trials as demonstrated by this current study. For many of these patients, clinical trials offer

an important pathway to accessing the best available therapies.

A large number of oncology patients require on-site treatment either for standard of care chemotherapy or clinical trial treatment. Damage to healthcare infrastructure renders treatment continuation incredibly challenging. The five largest centres for oncology in Ukraine are in Kiev, which has been a concentrated site of conflict in the war to date.¹⁷ As of 7 April 2022, over 100 attacks on healthcare had been recorded by the World Health Organization including healthcare facilities and ambulances.¹⁸ Scheduled oncology care including oncology surgeries have been halted in Ukraine to allow for increased capacity for injured citizens.¹⁹ Due to the stringent monitoring systems and protocol-based treatment involved in clinical trials, completing scheduled treatments for many patients has been exceedingly difficult. For patients that have remained in Ukraine on clinical trials, amendments to patient visits have been made to continue treatment where possible, such as the use

of telephone consultations.¹³ In order to manage the disruption in clinical trials, the European Commission, the European Medicines Agency and the Heads of Medicines Agencies have advised the sponsors of clinical trials to adopt similar adaptations to those taken during the Covid-19 pandemic, including remote monitoring practises and allowance for increased protocol deviations.²⁰

Many Ukrainians have been internally and externally displaced due to the conflict. Clinical trial patients are subsequently detached from their trial sites.⁸ This presents difficulties with drug transport, patient monitoring and follow-up. Previous studies have shown higher mortality rates in internally displaced persons even compared with refugees, possibly related to the lack of structured support systems remaining in their country.^{21,22} The State Expert Centre of the Ministry of Health of Ukraine have advised clinical trial sponsors to follow participant withdrawal procedures if it is unlikely they will be able to continue on trial.²³ Where possible, they advise the transfer of care to another Ukrainian site or active international trial site to complete their treatment.²³ Many displaced patients have sought refuge outside of Ukraine with the subsequent burden placed on host nations to maintain their care. Over 7 million Ukrainian refugees have left Ukraine to seek safety in nearby countries such as Poland, Romania and Hungary and an estimated 13 million have been stranded in high risk areas due to damaged infrastructure and security constraints.^{24,25} The majority of these patients enter into an entirely new healthcare system with minimal details of medical history; and the language barrier presents significant difficulties to continuation of care. Resources, such as the 'oncohelp' website, have been implemented by the global oncology community to assist in the guidance of cancer patients from Ukraine.²⁶ This website, set

up by the American Society of Clinical Oncology and the European Cancer Organisation, provides information in Ukrainian about specific available oncology support in 22 different countries.²⁶ Continuity of care is even more difficult for displaced clinical trial patients given there are only a small number of specific locations where their trial will be in a position to continue their care.

The invasion of Ukraine may also have had a profound impact on Russian civilians, particularly those that are reliant on pharmaceutical imports.^{27,28} This includes a large cohort of cancer patients in Russia.²⁹ In 2020, 591 000 new cases of cancer were diagnosed in Russia with over 312 000 deaths.²⁹ Economic sanctions have been placed on many imported goods as a means of influencing the course of the conflict with sanctions also beginning to extend to the neighbouring country Belarus. This has yet to affect most pharmaceutical supplies due to humanitarian concerns over supplying life-saving medications including chemotherapy and clinical trial treatments.³⁰ Although drug shortages have been reported by doctors and patients in Russia, this may be related to patients purchasing extra supplies of medications over fears about future availability.³¹ Some pharmaceutical companies increased imports to Russia and Ukraine in the tense period leading up to the invasion, however the supply is not indefinite.¹⁴ Many of these companies have agreed not to sanction medications, however the wider sanctions in industry still affect medication provision.³² These include payment delays due to sanctioned financial messaging systems as well as limited air travel to Russia. This will affect importation of clinical trial drugs to the active clinical trial sites that have been recorded in this current study.

A large number of trials in this study were commercially sponsored (93%). In Russia, there were 442 trials involving

commercial sponsorship (93%). Despite continuing to supply trial drugs themselves, many major pharmaceutical companies such as Pfizer, Bayer, Roche, Merck, Novartis and Eli Lilly have paused recruitment to studies.³³ Some companies have also expressed that they will not be initiating new sites in Russia.³⁴ Sanctions may not impede the conduct of active clinical trials in Russia if pharmaceutical supply remains, however given the high number of commercially-sponsored trials, they are likely affect future recruitment.³⁵ The presence of sanctions may, however, make reimbursement to clinical trial sites more challenging thus hampering the ability of sites to take on new studies. Reluctance to initiate new trial sites will limit the available pool of patients for international clinical trials and may deprive Russian patients from access to clinical trials and novel therapies. Sanctions in previous wars that included diagnostic and therapeutic equipment as well as antineoplastic therapies were later associated with an increased incidence of cancer and cancer-related death.^{4,36} A recent open letter was published in the *British Medical Journal* with over 1000 signatures from Russian healthcare workers demanded an end to the war and the use of lethal weapons. The fears of these workers for the future of Russian healthcare and long-term impacts of this conflict were expressed as they wrote “for the moments of today’s war, we will pay for many years after”.³⁷

As the majority of trials in this cohort were multinational studies (93%), the global clinical trial network is likely to be affected. Studies may be underpowered by an inability to display statistical rigor due to lost data or patients being lost to follow-up in some clinical sites. The main impacts on international clinical trials with sites in Ukraine and Russia will be the premature withdrawal of participants and subsequent effect on study results. Future studies will

also be affected by the loss of both recruitment sites and commercial sponsorship in Ukraine and Russia. This current study recorded 246 clinical trials that were recruiting in Ukraine and Russia at the time of this study. The majority of these studies were phase 3 clinical trials (153 of 246; 62%). Without the validating results of phase 3 trials it becomes impossible for updated standard of care therapies to be implemented into global treatment plans.¹³ Phase 3 studies may be in some way protected from subject loss due to larger sample sizes but they also require longer recruitment times and larger power of investment to initiate trial sites. Furthermore, completed clinical trials that involve Ukrainian patients may be affected by loss of long-term follow-up data. Study sponsors may also look to make adjustments in order to compensate for loss of study subjects by seeking to recruit additional patients to studies in other countries.

This current study had several limitations. First, the study was unable to access Russian and Ukraine databases due to the language barrier. As a consequence, this current sample of clinical trials was likely to be an underrepresentation of the true number of clinical trials being undertaken in Ukraine and Russia, especially those that involve non-commercial sponsors. Secondly, the study has only produced an estimation of the potential risk for cancer clinical trials. As the war is still ongoing it was not possible to complete a comparative analysis of the impact compared with a historical control. This should be considered in future studies that address the outcome of the conflict following the passage of time. Furthermore, although the current study has estimated the impact of the conflict based on the current clinical trial landscape, the actual impact of this conflict on cancer care and clinical trials will be difficult to quantify in the immediate setting. As described in a recent article, the true

impact on certain areas of cancer care will be unquantifiable.³⁸ This may be due to ascertainment bias in screening and cancer underdiagnoses in years to come.³⁸ The current authors acknowledge the importance of involving both Ukrainian oncologists and those in adjacent countries in any future assessment of the real impact of this war in years to come.

In conclusion, patients and clinicians in Ukraine and Russia make significant contributions to international cancer clinical trials. This current study has documented the scale of potentially impacted clinical trials involving patients with solid organ malignancies as a result of this conflict. While the results of phase 3 clinical trials may be somewhat protected due to large sample sizes, these trials also make up the largest number of studies involved. The conflict particularly exposes commercial sponsors that collaborate significantly with investigators in both Ukraine and Russia.

Author contributions

All authors had substantial contribution to study design, manuscript drafting and editing. All authors reviewed and approved the final draft of the manuscript prior to submission for publication.

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Declaration of conflicting interests

The authors declare that there are no conflicts of interest.

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