Pharmaceutical Medicine (2022) 36:147–151
https://doi.org/10.1007/s40290-022-00431-1

EDITORIAL

Calling for Unity, Solidarity, Continuity, and Access-Oriented Action in Times of War

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Accepted: 19 April 2022 / Published online: 2 June 2022

War is an assault on health, and on life itself. War is an anathema to the profession of pharmaceutical physicians, and their vocation to *serve the health of people.* Pharmaceutical medicine is dedicated to the education, training, research, development, delivery, and oversight of medicines for the prevention and treatment of human disease, the reduction of suffering caused by ill health, and the improvement of the quality of life of individuals, communities, and populations. War divides. War is disruptive and generates discrimination. In the presence of the fault lines of armed conflict rippling through our medical and scientific research communities [1, 2], we call for unity and action; unity across the healthcare professions and the sciences, and action-oriented towards continued access to healthcare and medicines [3–5], including investigational medicines [6], peer-reviewed journals [7], scientific meetings [8], and online academic programs [9, 10]. Specifically, we argue for the continuity of non-clinical and clinical research, and tertiary education. We call for the protection of our colleagues and patients, the declarations and resolutions of the World Medical Association, the tenets of Good Clinical Practice, and the commitment to human rights in all places affected by armed conflict [11].

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Recent events remind us of imperatives that are relevant wherever and whenever conflict breaks out. We witness the unfolding of yet another war at a time when healthcare systems are critically stressed by the global pandemic. Conducting clinical research where additional needs arise from the physical and psychological trauma caused by war is challenging. Pre-existing disease burdens are worsened by disrupted healthcare [12, 13], weakened supply chains, inadequate disease surveillance, and compromised health measures; these all complicate the situation on the ground for research teams and study subjects [14]. Resource-deprived, dysfunctional clinical trial infrastructures, and the violence of armed conflict together force patients, researchers, and students to flee, searching for alternative venues for their treatments, work, and education.

We are struggling to counteract these deeply antagonistic, disturbing, and upsetting developments that impinge on development plans, research methodologies, and regulatory and ethical frameworks supporting clinical research [15]. And yet, precisely in transboundary public health emergencies, medicine and science can demonstrate their ability to respond, their character of innovation, and commitment to the principles and values they assert [16–19]. We pause our habitual clinical, bench, and desk work to highlight issues of acute concern for trial participants, researchers, regulators, and educators. We discuss these against the backdrop of the potential repercussions of simply "pulling the plug" [20].

Key issues for the continuation of non-clinical and clinical research are to ensure the continuity of clinical trials with special concern for patients' safety, well-being, and continued access to the same investigational medicines. The practical and logistical issues are study site changes and new systems for reliable and timely data collection. Medicines supply chains thus, must be sufficiently flexible to accommodate such unpredicted change. In addition, our well-functioning global research community can reach out to protect our colleagues, and advocate for the preservation of the *free* flow and exchange of knowledge, unrestricted scholarly travel, and international academic mobility for teachers, students, and their families. Robust online platforms for teaching and learning in the life sciences, including academic medicine, can be supported by a network of partner educational institutions, thus minimizing the disruption of higher education and research.

Addressing the needs of study participants in times of war requires us to move beyond our usual motivations and incentives. Thus, we pay attention to tangible support mechanisms, while acknowledging the difficulties this may cause for us, both as individuals and as citizens. We need to respect the needs, views, and capabilities of people in countries affected by war and other civil disturbances, many of whom cannot express their views freely [21, 22]. We also reject violations of basic human principles and norms [23, 24]. This balance needs honesty and respect particularly if consensus cannot be reached.

First, we advocate for continuing clinical trial participation as much as possible. We question halting the enrollment of new patients. For example, some study participants are children arriving in Poland; they were receiving investigational drugs in the Ukraine, but cannot continue dosing because the Polish site is not yet authorized to administer the study drug to the child [4, 6, 25, 26]. In some cases, the treatment cycles are shorter than the time it takes to open a study site. Thus, some sponsors refuse to act, while others are trying to recruit Ukrainian participants at Polish sites. And this is in the context that such investigative therapies in studies of oncology, heart disease, metabolic disease, and gene therapy might be life saving. Interruption of clinical supplies may therefore have severe consequences. If we view the situation of withholding medicines after successful trials as a serious violation of the ethical value of beneficence, then these Polish study subjects are having that inflicted upon them at an even earlier stage of the clinical trial. Principal investigators, regulators, and study sponsors ought to make additional efforts to guarantee that research participants can receive their treatment, regardless of the study site.

Data interpretation can still be possible when deviations from the study protocol are documented. We suggest the continuation of clinical trial dosing, while following the study protocol as closely as possible, until regulatory compliance to open a new study site catches up. The study participants are part of the intention-to-treat analysis or to a registry for efficacy and safety, regardless of their evacuation to another country. This approach, which we may call "protocol-driven compassionate use" meets the needs of participants to continue the medicines (that may be beneficial to them) and to receive appropriate safety monitoring for a new medicine, improves the data going into the intention-to-treat analysis, and is consistent with the responsibilities of the sponsor to provide support when a participant has volunteered for research. As the European Medicines Agency has recommended, missing data should be managed using appropriate statistical methods, well-documented assumptions, and relevant sensitivity analyses. This approach requires sponsors to go beyond supplying the medicines for the trial and to record the nature of, and reasons for, protocol deviations [27]. Preparedness for this, and other disturbances, should include sponsors creating opportunities to continue trials in neighboring countries (where, in any case, there may be sites already open for a large phase III study) and their ethical duty to continue with a trial medication once a trial has begun. We demand flexibility from sponsors, sites, and regulators until an international standardized approach to major disturbances is available.

Second, in disturbed settings, information about the nature, scale, and location of health needs and the

availability of medicines is essential [3]. Rapid and high-volume shifts in a population require a revision of the organization of supplies and humanitarian assistance, and contingency planning. Building on public health and research networks, therefore, is vital [4]. Mobile supply chains should be sufficiently versatile and adapt rapidly to changing conditions. This will require careful risk-proportionate attention to details such as pharmaceutical quality. For example, by finding a way to maintain a cold supply chain in the absence of a reliable electricity supply, there is scope for providing comedications for comorbidities because trial participants may also no longer have access to these through the usual healthcare system and the same supply chains could be used.

Third, of immediate concern and consternation is the threat to life and well-being amongst our displaced colleagues and their families; they are victims of war. We call for their protection and support as a non-negotiable human right, and the impact of armed conflict on their health and careers in exile must be mitigated. We deplore the mounting pressure from voices calling for the exclusion of scholars, researchers, academic institutions, and professional societies on the grounds of the passports they hold [1, 2, 7, 8], and that amounts to the boycotting of the work of our colleagues. Their exclusion is our loss. Silencing academics because they live (or lived) in societies that do not meet particular configurations epitomizes the hijack of rationality, empathy, and compassion by 'gut feelings' and personal bias [28]. The extrapolation from research integrity, research ethics, and research practice to such subjective concepts as civil society building, is farfetched, misguided, and perilous, especially where and when voicing dissent has legal consequences [21, 22]. Some voices have expected medical staff and research scientists to practice civil disobedience and stage protests in response to the current challenges [28]. This is particularly problematic in medically and materially deprived experimental research settings where the top priority is to treat and prevent ill health with improved diagnostic tools and therapeutics. These issues become especially pernicious when military engagement has no clear end, or becomes a perpetual stand-off. Such emotion-driven, politically charged biases can also lead to manuscript rejection based on the author's nationality, and editors are not exempted from our demands. We call for unity in our efforts at this time to prevent the suspension of science, medicine, and ethics development when the cascading effects of armed conflict create polarization with distressing consequences for generations to come.

Fourth, we feel compelled to ensure that tertiary education continues to sustain the generational renewal of the pharmaceutical medicine community. Increasingly, we have the benefit of online educational platforms [29], and the frontiers of tertiary education ecologies were already shifting before this new war. Tapping into the accelerating "platformization" of academia and capitalizing on the COVID-19 teaching and learning experience in the region [30–32] offers universities fresh opportunities to upgrade their competitive edge, and not solely during pandemics and wars [33]. A network of collaborating higher educational institutions to support displaced students and scholars could help students to continue their coursework and teachers to continue teaching and supervising their students even if they are not all physically in the same place.

In conclusion, we acknowledge the difficulties the current situation causes. The impact of modern communication strategies should not be underestimated. We can contribute to conflict resolution by continuing to exchange points of view and listening with particular attention to what we can learn from colleagues who differ in opinion. We highlight the importance of reinforcing the respect of the codes of conduct that lay out the obligations and responsibilities of scientists and scholars and identifying misconduct through established processes. We encourage trial sponsors to plan for major disasters, conserve versatility in their supply chains, exploit the latter when, inevitably, public health emergencies take place, and ensure trial participants continue to have access to study medication and the treatment of comorbidities. We demand the protection of our colleagues and their families in zones of armed conflict, providing individualized support as needed, including for displaced scientists and scholars. We reject the exclusion of researchers based on their origin or location. We call for the development of new techno-social networks of educational institutions around the globe willing and prepared to provide stopgap measures that minimize the disruption to education and the advancement of science, in places affected by conflict. As a community, we stand united in solidarity to continue to advance pharmaceutical medicine research in the interest of patients, their families, and their communities. These arguments apply in all countries involved with or affected by conflict. Trial participants and researchers are not directly responsible for conflict so deserve respect as far as possible without supporting aggression.

Declarations

Funding No funding was received for this editorial. The University of Liverpool generously provided the open access publication fee.

Conflicts of Interest/Competing Interests BRB, TA, FA, SLC, FPC, PEE, GH, CK, FL, NS, VS, MAT, and AW have no conflicts to report. BA has worked for GlaxoSmithKline and Novartis, but has no conflicts that are relevant to this editorial. JS has worked for Pfizer and was a government employee between 1980 and 2007.

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Availability of Data and Material Not applicable.

Code Availability Not applicable.

Authors' Contributions BRB drafted the initial text, coordinated the writing, and finalized the revisions of the manuscript. TA, FA, BA, SLC, FPC, PEE, GH, CK, FL, NS, JS, VS, MAT, and AW critically reviewed and revised the manuscript. All authors have read and approved the final submitted manuscript and agreed to be accountable for the work.

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