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## Points to consider on the impact of the war in Ukraine on methodological aspects of ongoing clinical trials

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# Points to consider on the impact of the war in Ukraine on methodological aspects of ongoing clinical trials

The war in Ukraine is expected to lead to disruptions in the conduct and planning of clinical trials. While more severe disruptions are expected in Ukraine, other countries are also affected in several ways, e.g. due to the arrival of refugees fleeing from Ukraine or due to impact of imposed sanctions. The direct or indirect impact of war-related events on trial participants, sites, logistics, etc. is likely to interfere with ongoing trials in several countries, not limited to the collection, analysis and interpretation of clinical trial data.

Most importantly, safety of study participants is the absolute priority and must be at the heart of every decision taken, regardless of any potential consequences for an ongoing trial. Secondly, whenever feasible and in the interest of their continuing care, patients should be offered to continue receiving treatment (even if this might require unblinding at individual patient level) and supported to stay in the trial as long as this does not imply a safety risk. Consequently, Sponsors should prioritise the interests of patients already enrolled in the trial while considering the future conduct and continued feasibility of the trial from an ethical, medical and methodological perspective.

At this point in time, it is not possible to provide general advice on how different aspects related to disruptions caused by the war in Ukraine should be handled, as implications on clinical trials are expected to be manifold. In general, ongoing clinical trials were logically planned to evaluate treatment effects (estimands) in the absence of such disruptions. In that sense, the goal of the trial remains valid since such treatment effects are of general regulatory interest. To this end, the emergence of the new unforeseen disruptive events may require the revision of the pre-specified estimand and/or the addition of estimands may be warranted. Substantial changes in the design and conduct of a trial should be appropriately documented, follow the local regulations and be approved by Ethics Committees and the relevant competent authority as substantial amendments under the Clinical Trials Directive (2001/20/EC) or substantial modifications under the Clinical Trials Regulation (EU)536/2014, unless directly mandated by the need to assure the safety of participants and personnel involved. Such urgent safety measures do not need prior notification, but the Sponsor, without undue delay, is expected to provide adequate information on the cause, measures taken and the plan for further actions in accordance with Art 3.9 of the CT-1 or Art 54 of the CTR.

Sponsors should use the estimands framework described in the [ICH E9 \(R1\) guideline](#) to deal with events related to the war impacting the trial. When such events meet the definition of *intercurrent event* as per the ICH E9(R1) guideline, i.e. they “*affect either the interpretation or the existence of the measurements associated with the clinical question of interest*”, they should be addressed accordingly at the estimand level. Sponsors should provide the rationale for the strategies chosen to handle those intercurrent events. War-related events leading to missing data (e.g. because of missing assessments) should be dealt with at the estimation level, using statistical methods that make appropriate missing data assumptions aligned with the estimand of interest. Additional sensitivity analyses may be required to assess the robustness of the results to missing data assumptions. In order to assist efficiently with the identification of data ‘affected’ and ‘unaffected’ by the war that are of major importance for interpretation of trial results, Sponsors should ensure that their systems are able to record protocol deviations accordingly and capture related reasons.

The war in Ukraine may impact ongoing clinical trials in aspects that are shared with the COVID-19 pandemic. In this regard, Sponsors are encouraged to consult the EMA [Points to consider on implications of Coronavirus disease \(COVID-19\) on methodological aspects of ongoing trials – Revision 1](#), and take into consideration other relevant points discussed there that are also applicable in this context. Likewise, it is recommended to seek Scientific Advice early in the process if substantial modifications to the current protocol and/or analysis plan are considered necessary. These aspects related to impact of the war on trial design elements, recruitment, data collection, analysis and interpretation of results will be thoroughly reflected upon during requests for EMA Scientific Advice and the assessment of affected clinical trial data submitted to the EMA for Marketing Authorisation Application.