BMJ Open

Regional variation in clinical-trial risks: a large-scale analysis of 585 clinical trials

Sylviane de Viron ,[1] Steve Young,[2] Laura Trotta,[1] Marc Buyse[1,3,4]

To cite: de Viron S, Young S, Trotta L, *et al*. Regional variation in clinical-trial risks: a large-scale analysis of 585 clinical trials. *BMJ Open* 2025;**15**:e094950. doi:10.1136/bmjopen-2024-094950

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-094950).

Received 11 October 2024
Accepted 23 September 2025

[1]CluePoints SA, Louvain-la-Neuve, Belgium
[2]CluePoints Inc, King of Prussia, Pennsylvania, USA
[3]IDDI, Louvain-la-Neuve, Belgium
[4]Interuniversity Institute for Biostatistics and statistical Bioinformatics (I-BioStat), Hasselt University, Hasselt, Belgium

Correspondence to
Dr Sylviane de Viron; sylviane.deviron@cluepoints.com

ABSTRACT

Objectives To assess 10 common indicators of clinical trial risks across regions.

Design Retrospective pooled analysis of routine central-monitoring outputs.

Data sources Data came from a central-monitoring platform (2015–2025), which contains data from clinical trials conducted worldwide by 46 different sponsors and contract research organisations acting on behalf of sponsors. Trial sites were grouped into seven geographic regions—North America, Central/South America, Western Europe, Eastern Europe, Africa/Middle East, Asia, Pacific—to assess regional differences in monitored clinical-trial risks.

Main outcome measures Primary outcome—Relative Key Risk Indicator (KRI) risk score, defined as the relative risk in the selected region in comparison to the expected risk computed using data across all regions globally for 10 common risks usually assessed in clinical trials.

Results A total of 585 studies involving 56 189 sites comprising data from all regions of the world were used in the analysis. No obvious concerns were identified regarding the conduct of reliable clinical research in any region. However, for some KRIs (eg, off-schedule visit rate, protocol deviation rate and screen failure rate), there was substantial variability observed of relative risks across regions. Conversely, some other KRIs (eg, visit-to-entry cycle time and adverse event reporting rate) had a very narrow distribution across all regions.

Conclusions These results highlight regional differences across some common risks that may help clinical trials sponsors to plan future trials and take prospective measures to reduce KRI-related risks in some regions of the world.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The analysis used a large dataset covering 585 trials and more than 56 000 sites.
⇒ Sites were grouped into predefined geographic regions to enable cross-region comparison.
⇒ Key Risk Indicators (KRIs) were selected because they are standardised and widely used across trials.
⇒ Heterogeneity was assessed using forest plots of relative KRI risk scores by phase, study size, therapeutic area and region.
⇒ The study relied on retrospective operational metadata rather than patient-level trial data.

INTRODUCTION

For years, regulatory agencies such as the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) have required monitoring of the conduct and the progress of clinical trials to ensure patient protection and the reliability of trial results.[1 2] Central monitoring, a core component of risk-based quality management (RBQM), proactively detects emerging quality-related risks (either pre-identified or unanticipated) during a clinical trial. This allows study teams to address confirmed issues and thereby drive higher quality outcomes.[2]

A variety of tools may be applied to support central monitoring, but the following two methods are most commonly used:

a. Key Risk Indicators (KRIs) are metrics for pre-identified risks in specific targeted areas of study conduct. Sites that deviate from the expected range of values (ie, based on pre-defined risk thresholds) for a given KRI are flagged as 'at risk'. The risk thresholds can be discrete values or set dynamically based on statistical methods.[2–7]
b. Statistical data monitoring (SDM) represents a more holistic approach to quality oversight, applying a number of statistical tests on all of the data collected during the conduct of a clinical trial. The goal of SDM is to identify atypical data patterns at sites that may represent various systemic issues or, in some rare cases, reveal fraud.[2–6 8–12]

Using KRIs or SDM, sponsors can detect a variety of emerging risks, including inadequate adverse-event reporting, protocol deviations or delays in data entry. Importantly, these risks can be flagged at different levels—site, country or region—providing a structured way to monitor and remediate data quality concerns.[7 8 11 13]

Clinical trials are now increasingly global, spanning diverse cultural, medical and regulatory environments. This diversity brings

benefits, such as broader representation of patients, but also creates challenges for consistent trial conduct. Regional differences in language, medical practice and experience with clinical research and good clinical practices (GCP) may influence trial processes and data quality. For example, patient-facing materials such as informed consent forms and patient questionnaires must not only be accurately translated but also adapted to the target culture.[14 15] The level of adverse event reporting varies significantly by region, largely driven by cultural differences.[16] Similarly, some countries display greater levels of patient compliance with doctor instructions than others, which may also be associated with higher rates of enrolment and retention.[17] Such variation can introduce heterogeneity in trial outcomes and complicate oversight.

The objective of this paper is to examine regional variation in commonly used KRIs—applied as markers of risk—across the world. By quantifying these differences, we aim to understand how regional factors may influence clinical-trial quality. In addition to these predefined regions, we performed two illustrative case analyses: Japan, to test the common perception of exceptionally high data quality, and Ukraine, to assess the impact of a crisis situation (the ongoing war) on trial conduct.

MATERIALS AND METHODS

Central monitoring solution

The CluePoints RBQM platform is a proprietary cloud-based solution that includes a central monitoring component among its suite of products, and served as the source of the data used in this analysis. The platform was launched in 2015 and enables and supports various types of RBQM analyses including risk assessment and planning, KRIs, SDM, quality tolerance limits, duplicate patients detection and data visualisation.[7–10 18–21]

Data are typically analysed multiple times (eg, monthly) within the central monitoring platform during the conduct of a study. Clinical and operational data collected from various sources may be analysed, including electronic case report forms, central laboratories, electronic patient reported outcome and electronic clinical outcome assessment systems, wearable technologies and clinical trial management system. When the SDM or KRI analysis identifies a site that exceeds a risk alert threshold (based on a P-value or a predefined threshold of clinical relevance), the system triggers the creation of a risk signal for review and follow-up by members of the study team. A risk signal typically remains open until the study team determines that it is either resolved or no longer applicable (eg, site or study closure, inability to remediate, etc.).[7]

Selection of data

The current analysis focused on 10 KRIs that are used across numerous clinical development organisations and trials in the central monitoring platform. These 10 KRIs, described in table 1 and online supplemental table S1, were considered representative as they are used in many clinical trials and cover a variety of risk categories (eg, safety, compliance, data quality and enrolment and retention) inherent to clinical trials.[7]

The analysis was performed using data collected in the platform as of 1 September 2015 and up to 1 August 2025. The trials contributing to this analysis spanned all study phases and therapeutic areas, with the majority being industry-led. The scope of the analysis includes site-level risk analyses created for the ten selected KRIs meeting the following criteria (figure 1):

1. The KRI used in the study meets the common definition as described in table 1.
2. The KRI used a statistical comparison method (vs a discrete risk threshold), so that a P-value is generated for each site for the KRI.
3. The country location of each site in the study is known (ie, assigned).

Table 1 Description of the 10 selected KRIs

Category	Label (code)	Description
Safety	Non-serious AE rate (AERATE)	Rate of non-serious adverse events per patient visit
	Serious AE rate (SAERATE)	Rate of serious adverse events per patient visit
Compliance	Missed assessment rate (MARATE)	Proportion of expected patient assessments that were not conducted (for identified assessments of interest)
	Off-schedule visit (OSVRATE)	Rate of patient visits conducted outside of allowable schedule
	Protocol deviation rate (PDRATE)	Rate of protocol deviations per patient visit
Data quality	Auto-query rate (AQRATE)	Rate of auto-queries generated per datapoint submitted
	Query response cycle time (QRESPCT)	Average time from query generation to query response
	Electronic case report form (eCRF) visit-to-entry cycle time (V2ECT)	Average time from patient visit to electronic case report form entry
Enrolment and retention	Early termination rate (ETRATE)	Rate of early-terminated patients per patient visit
	Screen failure rate (SFRATE)	Proportion of screen-failed patients out of total screened patients

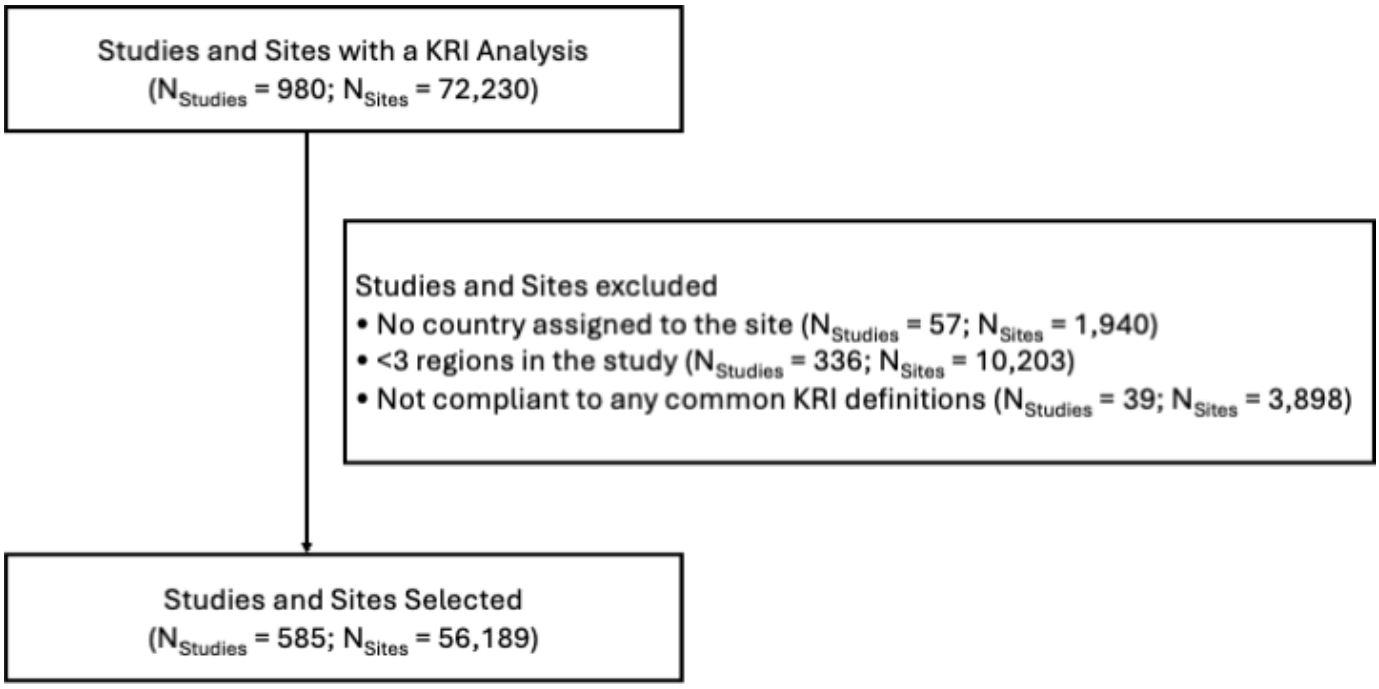

Figure 1 Study and site inclusion flowchart.
KRI, Key Risk Indicator.

4. Sites are located in a minimum of three regions for the given study.

Based on the assigned country, sites were mapped to one of the following regions: North America, Central/South America, Western Europe, Eastern Europe, Africa/Middle East, Asia, Pacific. In addition, we performed further analyses for Japan, to test the common perception of exceptionally high data quality,[17] and for Ukraine, to explore the impact of the ongoing war on trial conduct.

Statistical analysis

We computed a relative KRI risk score that assesses the relative likelihood of having a KRI-related risk in a specific region (or country) in comparison to the expected likelihood of risk computed using data across all regions (or countries). The following formula was applied:

Relative KRI risk score = $\frac{P_O - P_E}{P_E}$,

,P_O is the observed probability, that is, the number of significant P-values (<0.05) divided by the total number of P-values computed for the KRI in the region (or country). The higher this probability, the higher the relative risk in the selected region (or country).

P_E is the expected probability, that is, the number of significant P-values (<0.05) divided by the total number of P-values computed for the KRI in all regions (or countries).

A positive sign for the relative KRI risk score means that the region (or country) has a higher than average risk and a negative sign means that the region (or country) has a lower than average risk.

Let us illustrate the formula with an example. If in region X, 100 P-values were computed for 'non-serious AE rate' and 10 of them were significant, then P_O=10%, meaning that sites in region X were considered 'at risk' for this KRI 10% of the time. If looking across all regions, 1000 P-values were computed for 'non-serious AE rate' and 50 of them were significant, then P_E=5%, meaning that sites across all regions were considered 'at risk' for this KRI 5% of the time. In this example, the relative KRI risk score is $\frac{10\% - 5\%}{5\%}$ = 100%.

This means that region X has 100% more significant P-values than (ie, twice as many as) the average, which suggests that the region has twice the expected level of risk of having adverse events (AE) reporting issues (ie, either over- or under-reporting of AEs).

Additionally, for each relative KRI risk score, we calculated a 95% CI for binary variable using the Wilson Score method.

To assess potential sources of heterogeneity, we tested study phase, therapeutic area, study size (number of patients) as well as region as potential explanatory factors.

All statistical analyses were performed using R 4.2.2.[22]

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting or dissemination plans of this research. The study used only retrospective, fully de-identified, aggregate operational metadata derived from KRI analyses, and no direct patient or clinical data were accessed. Study findings will be disseminated to participating organisations through internal communications; no patient-facing dissemination is applicable.

RESULTS

In total, 4 189 913 KRI P-values were selected across 585 studies involving 56189 sites, contributed from 46

Table 2 Characteristics of the included studies

	Studies N (%)	Sites N (%)	P-values N (%)
Therapeutic area			
Cardiovascular	26 (4.4)	7156 (12.7)	586 149 (14.0)
Dermatology	65 (11.1)	6229 (11.1)	636 432 (15.2)
Endocrinology	33 (5.6)	4026 (7.2)	186 761 (4.5)
Gastroenterology	42 (7.2)	4596 (8.2)	354 638 (8.5)
Haematology	21 (3.6)	1040 (1.9)	52 108 (1.2)
Immunology	13 (2.2)	985 (1.8)	68 734 (1.6)
Infectious disease	47 (8.0)	4610 (8.2)	497 281 (11.9)
Musculoskeletal	28 (4.8)	2078 (3.7)	150 435 (3.6)
Neurology	53 (9.1)	5676 (10.1)	361 507 (8.6)
Oncology	168 (28.7)	12 914 (23.0)	915 724 (21.9)
Respiratory	39 (6.7)	3666 (6.5)	218 750 (5.2)
Other	50 (8.5)	3195 (5.7)	160 709 (3.8)
Study phase			
Phase 1	33 (5.6)	930 (1.7)	58 949 (1.4)
Phase 2	195 (33.3)	10 956 (19.5)	785 858 (18.8)
Phase 3	335 (57.3)	43 026 (76.6)	3 222 505 (76.9)
Other	22 (1.5)	1259 (2.2)	121 916 (2.9)
Region			
Africa and Middle East	279 (47.7)	2242 (4.0)	144 736 (3.5)
Asia	343 (70.1)	5562 (13.1)	358 895 (11.4)
Central and South America	329 (56.2)	5887 (10.5)	347 454 (8.3)
Eastern Europe	463 (79.1)	9973 (17.8)	758 484 (18.1)
North America	556 (95.0)	18 251 (32.5)	1 535 090 (36.6)
Pacific	272 (46.5)	1404 (2.5)	100 414 (2.4)
Western Europe	512 (87.5)	11 998 (21.4)	846 002 (20.2)

different sponsors and contract research organisations acting on behalf of sponsors (figure 1). The clinical trials landscape was fairly represented, with studies selected from a broad range of therapeutic areas and study phases. Oncology was the most common therapeutic area with 29% of studies (n=168), and phase 3 trials the most common study phase (n=335, 57%) (table 2). Additionally, studies covered fairly the different regions of the world with 48% of the studies with at least one site in Africa and the Middle East (n=279) up to 95% of the studies having at least one site in North America (n=556) (table 2).

The heterogeneity analysis indicated that study phase, therapeutic area and study size did not contribute meaningfully to between-study variation. In contrast, region emerged as the primary source of heterogeneity, consistent with the aim of our analysis (figure 2 and online supplemental figure S1).

Overall results

For a subset of the KRIs, we observe an important variability of relative risk across regions. 'Off-schedule visit rate', 'protocol deviation rate', 'screen failure rate' and 'serious AE rate' are the four risks with the largest distribution across regions. Conversely, some risks have a very narrow distribution such as 'visit-to-entry cycle time' and 'missed assessment rate' (table 3).

Case analysis: Japan—consistently high quality

Japan had a strikingly low relative KRI risk score for four different KRIs without any overlap with other regions: 'missed assessment rate', 'off-schedule visit rate', 'protocol deviation rate' and 'early-termination rate' (table 4).

Case analysis: Ukraine—impact of war on quality

In 2021, before the start of the war, Ukraine had a lower relative KRI risk score than the average across all countries (−55%, 95% CI −63 to −47%). However, after the beginning of the war, in 2022, the relative KRI risk score increased to 32% (95% CI 20 to 44%) higher than the average risk across all countries and it became even worse in 2023 with a KRI risk score of 121% (95% CI 104 to 137%) higher than the average across all countries (online supplemental figure S2). This is clear evidence

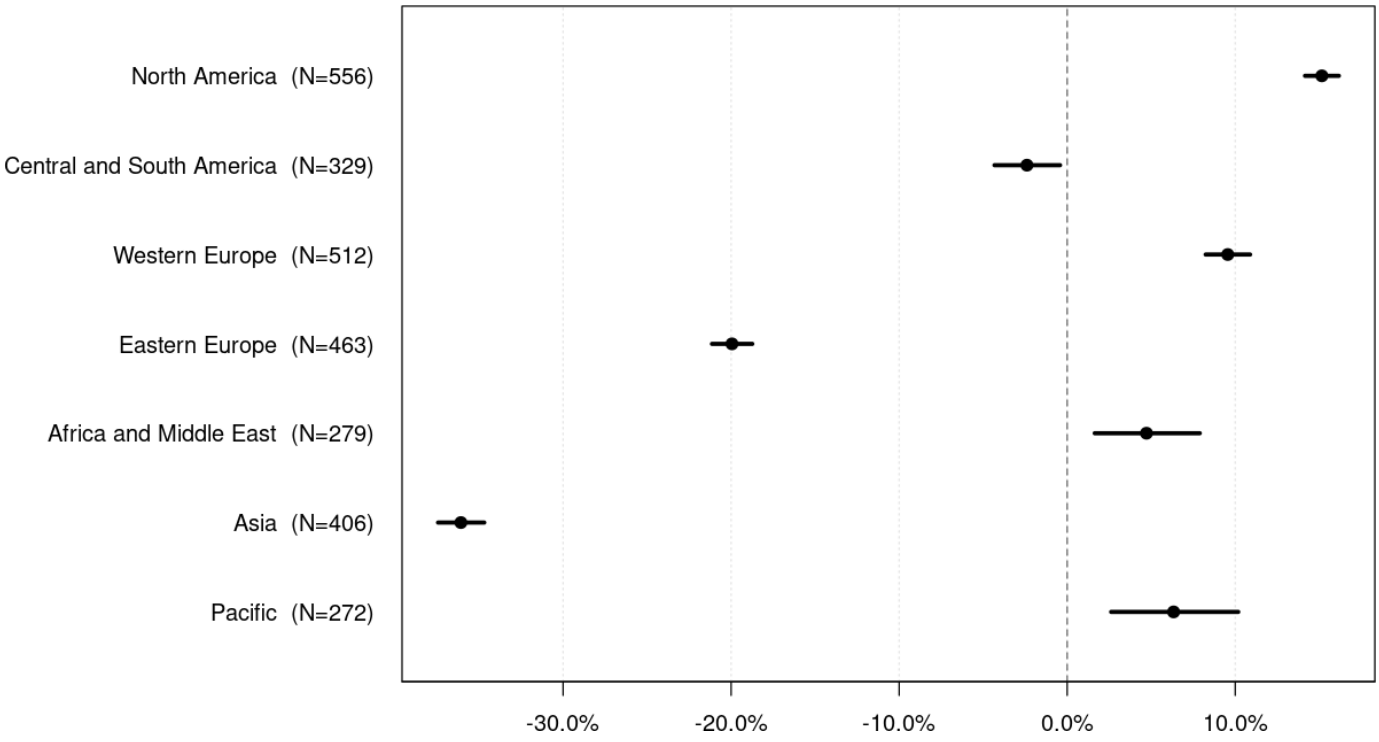

Figure 2 Heterogeneity analysis of relative Key Risk Indicator (KRI) risk score by country relative KRI risk scores by subgroup. A positive sign for the relative KRI risk score means that the region has a higher than average risk and a negative sign means that the region has a lower than average risk. Error bars show 95% Wilson CIs. Points represent the relative KRI risk score for the subgroup, and horizontal lines indicate 95% Wilson CIs. 'N' corresponds to the number of distinct clinical trials contributing data to that subgroup. The vertical dashed line at 0 denotes no difference relative to the overall baseline.

of a significant disruption to clinical trial operations in Ukraine since the start of the crisis in 2022.

Table 4 shows that the most significantly impacted KRIs in Ukraine focused on issues with missed assessments and delays in data reporting as one might expect. For example, the relative KRI risk score of 'missed assessment rate' moved from −98% (lower risk than the average) before the war to 249% (higher risk) since the start of the war, and the relative score of 'visit to entry cycle time' moved from −41% to 228%.

DISCUSSION

These results confirm the sensitivity and specificity of the tests used to detect differences in data from multicentre/multiregional clinical trials.[20] Of note, the detection of abnormal data patterns uses mixed effects statistical models that allow centres (or countries) to differ from each other, such that only deviations that exceed the natural (expected) variability in the data are flagged.[19 21] In this paper, we have focused on KRIs based on single variables, which are sufficient to detect regional variations, but for the detection of abnormal patterns in the data, the sensitivity and specificity of the detection vastly improve when a multivariate approach is used, that is, when many variables are tested at once rather than one at a time.[18]

The current analysis does not reveal any concerns with respect to conducting reliable research in any/all global regions. Rather, it highlights that even though sites received the same protocol as well as other study documentation at the start of the study, there are relative differences in commonly monitored risks that may help study teams to better understand what to expect and how to interpret the KRI results in each region.

Why does Japan have such a low relative risk score in multiple KRIs in comparison to other regions? This may be explained by cultural traits that are particular to Japan, including a greater emphasis on procedural compliance and precision. It has been observed, for example, that clinical trials conducted in Japan experience a lower patient drop-out rate than in other regions.[17] Prior analyses have also reported that compliance with protocol and GCP has been relatively high in Japan and that a lower number of electronic data capture queries were required than in other regions (though they were not able to report a statistical difference).[17] This is in line with the current analysis in which we observe that Japan has overall a statistically better performance across four compliance-related risks, including fewer issues with missed assessments, protocol deviations, early patient terminations and off-schedule site visits.

Crisis situations—taking the form of a pandemic or a regional war—may impact risk to trials as we have shown in the current analysis. As of 7 February 2024, the WHO has documented 1552 military attacks in Ukraine that have impacted health providers, supplies, facilities,

Table 3 Relative Key Risk Indicator (KRI) risk score and 95% CI by region

KRI	Africa and Middle East	Asia	Central and South America	Eastern Europe	North America	Pacific	Western Europe
Missed assessment rate	−5.2 (−14.2, 3.9)	−28.3 (−32.8, −23.8)	1.9 (−4.7, 8.5)	−13.4 (−16.9, −10.0)	12.0 (9.1, 15.0)	4.6 (−7.5, 16.7)	8.2 (4.3, 12.2)
Off-schedule visit	54.8 (40.0, 69.5)	−47.4 (−52.8, −42.0)	−5.0 (−13.0, 3.0)	3.4 (−1.8, 8.5)	12.5 (9.0, 16.0)	−43.3 (−54.5, −32.0)	−6.4 (−10.8, −1.9)
Protocol deviation rate	31.7 (22.1, 41.3)	−61.1 (−64.1, −58.1)	−14.2 (−19.3, −9.1)	−18.6 (−21.7, −15.5)	10.2 (7.6, 12.8)	53.3 (41.7, 64.9)	27.4 (23.8, 31.0)
Auto-query rate	42.7 (28.2, 57.3)	−33.1 (−40.4, −25.9)	−12.5 (−20.1, −5.0)	−21.7 (−26.5, −16.9)	17.0 (13.3, 20.7)	−5.0 (−17.6, 7.7)	−2.3 (−6.9, 2.4)
Query response cycle time	−58.1 (−65.0, −51.2)	11.4 (−19.1, −3.6)	−54.4 (−58.6, −50.3)	−17.8 (−22.1, −13.5)	39.0 (34.5, 43.6)	−48.8 (−58.4, −39.2)	11.2 (6.5, 16.0)
Electronic case report form (eCRF) visit-to-entry cycle time	−26.6 (−34.3, −19.0)	−36.6 (−41.5, −31.7)	−20.7 (−25.6, −15.8)	−4.6 (−8.7, −0.4)	16.5 (13.5, 19.5)	−33.6 (−42.9, −24.2)	9.2 (5.1, 13.2)
Early termination rate	−16.3 (−27.1, −5.5)	−30.7 (−37.0, −24.0)	−13.2 (−20.9, −5.5)	−12.7 (−17.5, −7.8)	13.0 (9.3, 16.7)	−8.4 (−22.7, 5.9)	9.2 (3.8, 14.6)
Screen failure rate	34.2 (21.4, 47.0)	−28.6 (−34.8, −22.4)	−20.6 (−26.2, −14.9)	−16.7 (−20.9, −12.4)	29.2 (25.3, 33.0)	−61.5 (−70.1, −52.8)	−12.6 (−17.3, −8.0)
Non-serious AE rate	−25.4 (−32.0, −18.8)	−34.0 (−37.6, −30.4)	72.0 (65.3, 78.6)	−40.6 (−43.3, −38.0)	7.3 (4.8, 9.8)	10.6 (1.1, 20.1)	18.6 (15.1, 22.1)
Serious AE rate	39.8 (29.8, 49.8)	−33.0 (−37.6, −28.4)	2.3 (−3.2, 7.8)	−35.8 (−39.0, −32.6)	15.8 (12.8, 18.9)	84.3 (70.8, 97.8)	1.2 (−2.4, 4.8)

Green boxes show that the region is at lower risk than the average for the specific KRI (CI do not overlap with −25% relative KRI risk score); red boxes show that the region is at higher risk than the average for the specific KRI (CI do not overlap with 25% relative KRI risk score).

warehouses and transport, including ambulances.[23] Therefore, clinical development organisations should develop strategies to deal with quality factors like missing data because of missed assessments, enrolment or study discontinuation. In some cases, modifications of the study protocols should be considered.[24 25] Not abandoning trials in those countries in crisis situations is key as clinical research is a necessity and protecting patients is the foundation of ethics.[26]

Strengths and limitations of this study

Our study has several strengths. This is the first study that provides a quantitative comparison of several clinical trial risk metrics across different regions in the world using data from a large number of clinical trials. Additionally, there are two advantages of using the relative KRI risk scores based on the proportion of significant P-values as a proxy of quality-risk in comparison to metrics based on absolute values. The first advantage is that it takes into account the nature of the trial. For example, the expected AE rate is different in each trial and therefore comparing the absolute values of each site across trials would be biased by studies for which a higher rate of AEs is expected. Second, the calculation of the P-value considers the sample size of the site, which avoids detecting false positive signals that would be flagged using absolute values.

The main limitation of the current analysis is that it includes a relatively small subset of the risk factors of any given trial. While our analyses did not identify study phase, therapeutic area or study size as contributors to heterogeneity, we cannot exclude the possibility that other unmeasured study or operational factors may also influence observed patterns. Nevertheless, the consistent finding that region accounted for most of the variation underscores the robustness of our conclusions. Additionally, it is limited to a description of study results as we did not examine the potential external factors driving the regional differences such as the health system quality, the standard of care or socioeconomic differences. The impact of those unmeasured factors may vary from one region to another.[27 28] In addition to that, regional factors related to clinical research infrastructure as well as the level of experience in conducting clinical trials may significantly impact the overall quality of research.[28] Finally, the methods used in this analysis detect very small differences that may not be important. We have therefore highlighted as meaningful only the region-KRIs for which the CI extends outside of the range from −25% to 25%.

Implications of findings

Providing KRI risk oversight at region or country level does not aim to exclude countries from participating in clinical research, but to take the corrective actions to ensure that risks remain controlled given the circumstances specific to each region or country. For instance, if a trial is planned in North America, table 3 highlights that there is a 29% higher risk related to the rate of screen failures. Control strategies should be considered to take

Table 4 Relative Key Risk Indicator (KRI) risk scores in illustrative case analyses for Japan and Ukraine before and after 2022

Category	KRI	Japan % (95% CI)	Ukraine Before 2022 % (95% CI)	Ukraine Since 2022 % (95% CI)
Safety				
	Non-serious AE rate	−36.4 (−41.1, −31.7)	−22.2 (−43.5, − 0.8)	−34.2 (−50.0, −18.4)
	Serious AE rate	−46.7 (−51.9, −41.4)	−58.4 (−72.7, −44.0)	−69.8 (−79.9, −59.6)
Compliance				
	Missed assessment rate	−48.9 (−54.3, −43.5)	−97.9 (−102.0, −93.7)	248.6 (222.1, 275.2)
	Off-schedule visit	−86.3 (−90.0, −82.7)	−57.3 (−83.6, −31.0)	60.2 (32.0, 88.5)
	Protocol deviation rate	−82.4 (−85.1, −79.6)	−30.9 (−50.9, −10.9)	99.5 (75.9, 123.2)
Data quality				
	Auto-query rate	−15.1 (−23.9, −6.4)	−64.2 (−79.1, −49.4)	−2.8 (−34.1, 28.4)
	Query response cycle time	−16.6 (−27.0, −6.2)	−46.4 (−66.8, −25.9)	53.9 (28.9, 78.9)
	Electronic case report form (eCRF) visit-to-entry cycle time	−47.6 (−53.0, −42.1)	−40.7 (−58.3, −23.2)	228.4 (189.0, 267.8)
Enrolment and retention				
	Early termination rate	−69.5 (−75.1, −64.0)	−81.4 (−99.6, −63.2)	121.7 (87.0, 156.5)
	Screen failure rate	−25.6 (−34.6, −16.7)	−18.4 (−41.8, 5.0)	101.2 (73.2, 129.2)

Green boxes show that Ukraine is at lower risk than the average for the specific KRI (CI do not overlap with −25% relative KRI risk score); red boxes show that Ukraine is at higher risk than the average for the specific KRI (CI do not overlap with 25% relative KRI risk score).

this risk into account. For example, if the observed risk is a high rate of screen failures, it may be appropriate to recruit additional sites to ensure that patient enrolment targets in the region are achieved, and/or to pro-actively monitor and assess the reasons for screen failures to assess their necessity. As another example, if an investigational product is new with a lack of prior safety knowledge, it will be key to balance sites from regions having fair safety reporting and other regions to ensure that diversity of the patient population as well as the quality of the reporting are both well controlled. Additionally, before and during the conduct of the study, other actions should be implemented like training and enhanced safety monitoring.

The other use case is the impact assessment of a crisis on KRI risks. Continuously assessing trends of KRI risks in a country or a region impacted by a severe crisis would help sponsor organisations to take corrective actions to continuously control the risks in the trial. In the example of the Ukraine war, most of the risk metrics except safety reporting deteriorated after the start of the war.

CONCLUSION

Successful conduct of clinical research is essential regardless of regional differences or presence of crises such as pandemic or war. Risk planning and risk control strategies should be implemented to ensure that patients get the care they need and that clinical trial data remain reliable.

Contributors All authors contributed to the design of this study and participated to the interpretation of the results. SdV performed the analyses. SdV drafted the manuscript. All authors revised and approved the final version of the paper and are accountable for all aspects of the work. SdV is the guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests SdV, SY and LT are employees of CluePoints. LT and MB hold stock in CluePoints.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study used retrospective, fully de-identified operational metadata derived from Key Risk Indicator (KRI) analyses. No patient-level data were accessed. For questions regarding research integrity at CluePoints, please contact: Sylviane de Viron, Data & Knowledge Manager, sylviane.deviron@cluepoints.com.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

Sylviane de Viron http://orcid.org/0000-0003-3890-557X

REFERENCES

1 EMA Guidance. Reflection paper on risk based quality management in clinical trials. 2013. Available: https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-risk-based-quality-management-clinical-trials_en.pdf [Accessed 30 Apr 2024].
2 US Department of Health and Human Services, Food and Drug Administration. Guidance for industry: oversight of clinical investigations – a risk-based approach to monitoring. 2013. Available: https://www.fda.gov/media/116754/download [Accessed 30 Apr 2024].
3 Wilson B, Provencher T, Gough J, *et al*. Defining a Central Monitoring Capability: Sharing the Experience of TransCelerate BioPharma's Approach, Part 1. *Ther Innov Regul Sci* 2014;48:529–35.
4 Gough J, Wilson B, Zerola M, *et al*. Defining a Central Monitoring Capability: Sharing the Experience of TransCelerate BioPharma's Approach, Part 2. *Ther Innov Regul Sci* 2016;50:8–14.
5 Barnes S, Katta N, Sanford N, *et al*. Technology Considerations to Enable the Risk-Based Monitoring Methodology. *Ther Innov Regul Sci* 2014;48:536–45.
6 TransCelerate. Position paper: risk-based monitoring methodology. 2013. Available: https://www.transceleratebiopharmainc.com/assets/risk-based-monitoring-solutions/ [Accessed 30 Apr 2024].
7 de Viron S, Trotta L, Steijn W, *et al*. Does Central Monitoring Lead to Higher Quality? An Analysis of Key Risk Indicator Outcomes. *Ther Innov Regul Sci* 2023;57:295–303.
8 de Viron S, Trotta L, Schumacher H, *et al*. Detection of Fraud in a Clinical Trial Using Unsupervised Statistical Monitoring. *Ther Innov Regul Sci* 2022;56:130–6.
9 Timmermans C, Venet D, Burzykowski T. Data-driven risk identification in phase III clinical trials using central statistical monitoring. *Int J Clin Oncol* 2016;21:38–45.
10 George SL, Buyse M. Data fraud in clinical trials. *Clin Investig (Lond)* 2015;5:161–73.
11 de Viron S, Trotta L, Steijn W, *et al*. Does Central Statistical Monitoring Improve Data Quality? An Analysis of 1,111 Sites in 159 Clinical Trials. *Ther Innov Regul Sci* 2024;58:483–94.
12 Buyse M, George SL, Evans S, *et al*. The role of biostatistics in the prevention, detection and treatment of fraud in clinical trials. *Stat Med* 1999;18:3435–51.
13 Bhatt A. Quality of clinical trials: A moving target. *Perspect Clin Res* 2011;2:124.
14 Kermani F, Politis Virk K. Language & culture in global clinical trials. *Appl Clin Trials* 2011;20.
15 U.S. Department of Health and Human Services FDA Center for Drug Evaluation and Research, U.S. Department of Health and Human Services FDA Center for Biologics Evaluation and Research, U.S. Department of Health and Human Services FDA Center for Devices and Radiological Health. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. *Health Qual Life Outcomes* 2006;4:79.
16 Im E-O, Liu Y, Kim YH, *et al*. Asian American Cancer Patients' Pain Experience. *Cancer Nurs* 2008;31:E17–23.
17 Tominaga T. Competitive Strategies for Japanese Clinical Trial Sites: A New Approach to Quality. *Ther Innov Regul Sci* 2014;48:702–8.
18 Venet D, Doffagne E, Burzykowski T, *et al*. A statistical approach to central monitoring of data quality in clinical trials. *Clin Trials* 2012;9:705–13.
19 Desmet L, Venet D, Doffagne E, *et al*. Linear mixed-effects models for central statistical monitoring of multicenter clinical trials. *Stat Med* 2014;33:5265–79.
20 Trotta L, Kabeya Y, Buyse M, *et al*. Detection of atypical data in multicenter clinical trials using unsupervised statistical monitoring. *Clin Trials* 2019;16:512–22.
21 Desmet L, Venet D, Doffagne E, *et al*. Use of the Beta-Binomial Model for Central Statistical Monitoring of Multicenter Clinical Trials. *Stat Biopharm Res* 2017;9:1–11.
22 R Core Team. R: a language and environment for statistical computing. 2021.
23 WHO. Ukraine witnessing increasing impact of attacks on health and education. Available: https://www.who.int/europe/news/item/07-02-2024-ukraine-witnessing-increasing-impact-of-attacks-on-health-and-education [Accessed 30 Apr 2024].
24 EMA Guidance. Points to consider on the impact of the war in Ukraine on methodological aspects of ongoing clinical trials, 2022. Available: https://www.ema.europa.eu/en/documents/scientific-guideline/points-consider-impact-war-ukraine-methodological-aspects-ongoing-clinical-trials_en.pdf [Accessed 30 Apr 2024].
25 Talbot A, Connor SG, Austin K, *et al*. The impact of the 2022 Ukraine/Russian conflict on cancer clinical trials. *J Int Med Res* 2022;50:03000605221143284:3000605221143284:.
26 Kurihara C, Crawley FP, Baroutsou V, *et al*. The continuation of clinical trials in times of war: A need to develop ethics and situationally adaptive clinical research guidelines. *Front Med* 2022;9:966220.
27 Keebler D, Teng E, Chia J, *et al*. Regional variations in adverse event reporting rates and ACR responses in placebo/standard-of-care arms of rheumatoid arthritis trials. *Rheumatology (Sunnyvale)* 2020;59:3023–31.
28 Ferreira JP, Girerd N, Rossignol P, *et al*. Geographic differences in heart failure trials. *Eur J Heart Fail* 2015;17:893–905.