New reporting items and recommendations for randomized trials impacted by COVID-19 and force majeure events: a targeted approach

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Background: Appropriate analyses and reporting are essential to the reproducibility and interpretation of clinical trials. However, the coronavirus disease 19 (COVID-19) pandemic and other force majeure events, like the war in Ukraine, have impacted the conduct of clinical trials.

Methods: The number of clinical trials potentially impacted were estimated from clinicaltrials.gov. To identify reporting items considered vital for assessing the impact of COVID-19, we reviewed 35 randomized phase III trials from three top oncology journals published between July and December 2020. For validation, we reviewed 29 phase III trials published between January and December 2021.

Results: Our results show that the number of clinical trials being potentially impacted in cancer, cardiovascular diseases, and diabetes is at least 1,484, 535, and 145, respectively. The magnitude of disruption is most significant in oncology trials. Based on the review of 35 trials, a modified checklist with ten new and four modified items covering pandemic's impact on trial conduct, protocol changes, delays, data capture, analysis and interpretation was developed to ensure comprehensive and transparent reporting. Our validation shows that six out of seven applicable reporting items were reported in less than 21% of the articles.

Conclusions: Our recommendations were proposed to improve the reporting of randomized clinical trials impacted by COVID-19 and force majeure events that are broadly applicable to different areas of medical research.

Keywords: Coronavirus disease 19 (COVID-19); randomized trials; reporting quality; research design; oncology

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Introduction

In early 2020, the World Health Organization (WHO) reported the first cases of pneumonia of unknown etiology, caused by a previously unknown coronavirus, in Wuhan, China. In March 2020, the WHO declared the coronavirus disease 19 (COVID-19), previously termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), outbreak a global pandemic. By the 17th of May, 2021, the pandemic has led to more than 162 million people being infected and has caused nearly 3.4 million deaths globally (1).

To mitigate the spread of COVID-19, strict social distancing and prolonged lockdown measures were implemented in many countries. During the ongoing pandemic crisis, despite adaptations such as remote data collection and monitoring (2), the willingness and ability to participate in cancer clinical trials have been adversely affected (3,4). Therefore, the conduct of clinical trials may be significantly impacted (5-7).

Moreover, during the ongoing COVID-19 pandemic, healthcare facilities are under intense pressure due to shortages in human resources, hospitalization of COVID-19 patients, and the disruption of the medical and personal protective equipment supply chains (8). This further presents an unprecedented challenge to the conduct of trials (5,9).

Accurate reporting and analyses can improve the reproducibility of published trials impacted by COVID-19. In addition to pandemics like the COVID-19 pandemic, other force majeure events, such as the war in Ukraine are not predictable, can also impact the conduct of trials. The CONSORT reporting guidelines for randomized controlled trials (RCTs) have been instrumental in upholding the integrity of trial reporting (10). Extensions of the CONSORT reporting guidelines have been proposed to cater to specific clinical situations (11). The pandemic has adversely affected the conduct of clinical trials, and the need to add new and modify reporting items to improve the quality of reporting is essential. Without such modifications, inadequate reporting of RCTs impacted by COVID-19 and other force majeure events may complicate the interpretation of study results, thereby negatively impacting future research and patient care. The purpose of this paper is to understand the deficiency for the reporting of randomized trials impacted by COVID-19, propose new or modified reporting items to address such deficiency, and to conduct a small validation on trials partially impacted by COVID-19.

Highlight box

Key findings:

- More than 2,100 clinical trials are potentially impacted by COVID-19.
- We identified reporting items that are important for assessing the impact of force majeure events not currently presented in the CONSORT reporting guideline for randomized trials.

What is known and what is new?

- Appropriate analyses and reporting are essential to the reproducibility and interpretation of clinical
- The COVID-19 pandemic and other force majeure events have impacted the conduct of clinical trials. Recommendations on statistical analysis and reporting practice were proposed for transparent reporting of randomized trials impacted by COVID-19 and other force majeure events.

What is the implication, and what should change now?

- Authors with to-be-published randomized trials impacted by force majeure events are encouraged to follow the proposed set of reporting items to enhance the quality of reporting.

Methods

Our search process is stratified into two parts: part one focused on understanding the number of trials potentially affected by COVID-19, and part two was directed at the effect of COVID-19 on the published articles. In part one, the search was based on the trial information reported in ClinicalTrials.gov to estimate the number of recently opened trials that could be affected by COVID-19. In part two, a comprehensive literature search was performed using PubMed to identify the recently published articles for information relevant to trials potentially affected by COVID-19. The reporting practice is expected to be similar for studies impacted by the pandemic. Therefore, an investigation of articles published recently should reflect the reporting inadequacy. By examining the current reporting practice, inadequately reported items can be highlighted for improvement.

Number of trials potentially impacted by COVID-19

In the search process on ClinicalTrials.gov, we examined phase III clinical trials conducted in all cancer types, cardiovascular diseases, and diabetes that commenced between January 2017 and December 2021. Specifically, only those trials with "Recruiting" status in February of 2021 for trials commenced between 2017 and 2020 and in June of 2022 for trials started in 2021 were included to obtain the number of trials that would be affected by COVID-19 at these two time snapshots for the corresponding years.

The search was conducted using the function "Advanced Search" with the following criteria being selected: (I) condition or disease, (II) status, (III) phase, and (IV) study commencement period of interests. While the second and third variables remained the same throughout the search process as "Recruiting" and "Phase 3", the rest varied. The

first search was as follows, "Cancer" was selected, and the study commencement period was set from "01/01/2017" to "12/31/2017" to collect the number of cancer trials in the specified period. Similarly, the search for later years "2018", "2019", "2020" and "2021" was performed accordingly. The above procedure was replicated for "Cardiovascular diseases" and "Diabetes". Trials with a recruitment status other than "Recruiting" were excluded from this study.

Reporting items for assessing the impact of COVID-19

We focused on published phase III RCTs in cancers because the results of the former section showed that the number of oncology trials potentially affected by COVID-19 was the highest. Non-original studies, such as meta-analysis or secondary data analysis, were excluded. Articles published between July and December 2020 in *JAMA Oncology*, *Journal of Clinical Oncology*, and *The Lancet Oncology* were examined. Original research articles meeting our eligibility criteria were included for data extraction. Essential study characteristics collected were: type(s) of cancers, number of treatment arms, number of patients enrolled, and the study locations (multinational versus single-country). The criteria for defining whether each reporting item was correctly reported or not are described below. In addition, a summary table is provided in the supplement (Table S1).

Reporting of study schedule

Reporting elements essential for assessing the impact of COVID-19 on the conducted clinical trial were captured. The months and years when the enrollment began and ended, the months and years when the treatment began and ended, and the last month and year of follow-up (usually defined as data cut-off) were extracted to assess whether the trial schedules were well-reported or not. Studies were classified as "Reported" if the data points discussed above were present in the main text. However, those that did not meet the criteria stated above were categorized as "Not reported".

Reporting of treatment design

The treatment duration was defined as either the number of chemotherapy or targeted treatment cycles delivered, including the length of each cycle or the radiotherapy treatment duration. This variable was classified as "Reported" if it was described as stated above. However, if studies failed to provide the number of cycles or cycle length, the reporting of this variable was classified as "Not reported". Trials reporting surgery as the only treatment modality would be labeled as "Reported".

Reporting of study locations

The reporting of study location was another item collected to understand the impact of the pandemic on clinical trials. The reporting of study locations was classified as "Not reported" if the information could not be extracted from the main text. However, if descriptions in the articles specified that study location could be obtained in the study appendix or online materials, the reporting was classified as "Reported in supplementary material". For those with study locations reported in the main text, they were first classified as "Reported in main text" and were further subclassified into "Region-level", "Country-Level", or "Site-level" according to the reported information.

Reporting of treatment-related events

The reporting of the occurrence of treatment-related events was our primary objective. The collected variables included the reasons for treatment discontinuation and treatment delay. The reporting of the reasons for treatment discontinuation was classified as "Reported" if the information was found in the main text. Otherwise, they were classified as "Not reported". Trials reporting treatment delays termed as "dose delay", "dose interruption", "treatment delay", or "treatment interruption" were labeled as "Reported". The absence of reporting in either the main text or supplementary material was labeled "Not reported". Trials reporting the percentage of patients experiencing treatment discontinuation or delay were further classified as "Reported with reasons", or "Reported without reasons".

Statistical methods

Descriptive statistics were used to illustrate the number of patients enrolled (the median, Q1, and Q3) and the length of the recruitment period (the mean and standard deviation). The other variables described in the methodology were presented as frequencies and percentages (in two decimal places). A bar plot was used to illustrate the number of trials recruiting participants in oncology, cardiovascular diseases, and diabetes per year between 2017 and 2021.

Results

Study selection and time trend

The total numbers of clinical trials posted between 2017 and

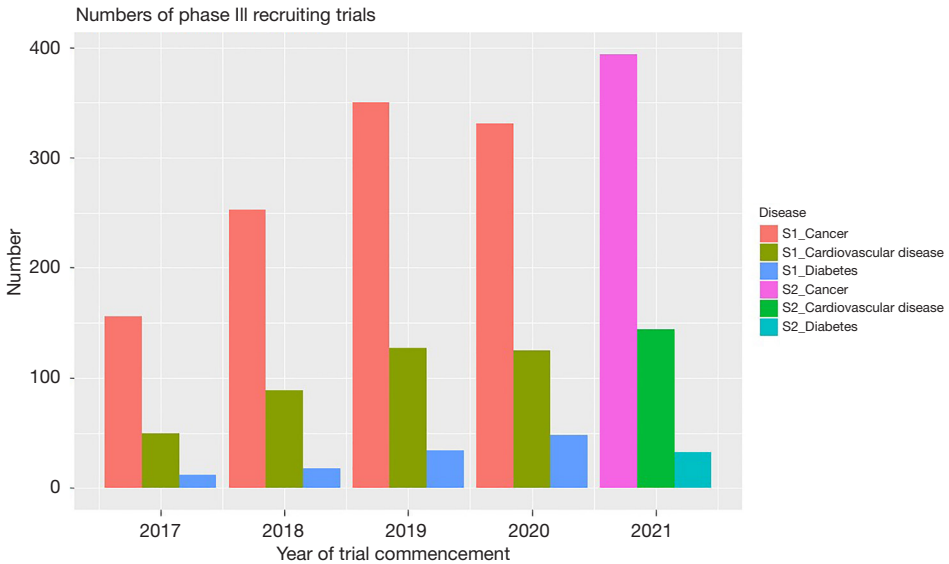

Figure 1 Numbers of phase III clinical trials with ongoing recruitment as of snapshot 1 (S1) on the 2nd of February 2021 (for trials registered between 2017 and 2020) and snapshot 2 (S2) on 24th June 2022 (for trials registered in 2021).

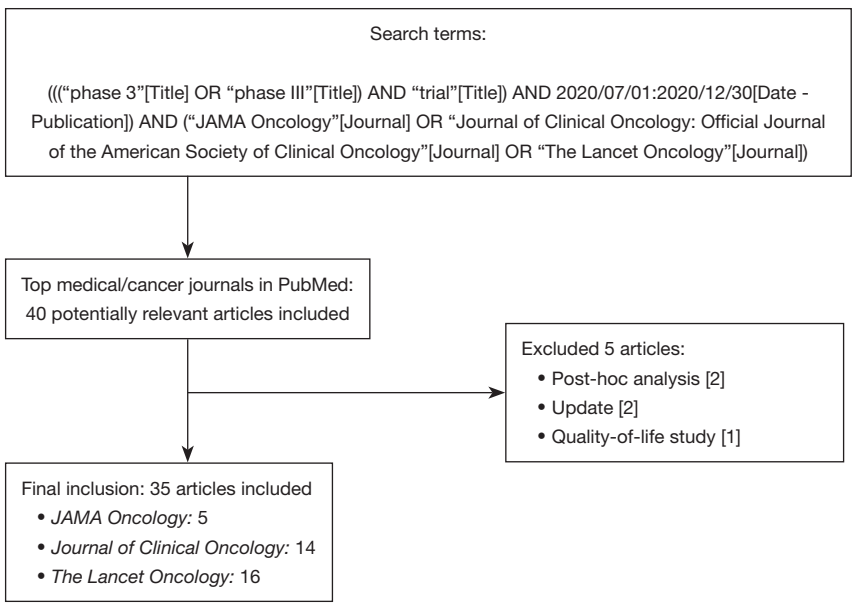

Figure 2 Process of literature search (Reporting Items for Assessing the Impact of COVID-19).

2021 and labeled as “Recruiting” in cancer, cardiovascular diseases, and diabetes were 1,484, 535, and 145 trials, respectively (*Figure 1*). Comparatively fewer oncology clinical trials commenced in 2020 relative to 2019. This can be the result of either a decrease in registration or a delay in the commencement of oncology clinical trials in 2020.

The literature search identified 40 potentially relevant articles. After a comprehensive examination, five articles were excluded. The articles excluded from the final analysis were post-hoc analysis (n=2), study updates (n=2), and quality of life (n=1) studies. Thirty-five original articles were included in this study, and five were published in *JAMA Oncology*, 14 in the *Journal of Clinical Oncology*, and 16 in *The Lancet Oncology* (*Figure 2*).

Table 1 Characteristics of the included articles

Characteristics	N=35	%
Cancer type		
GU cancer	7	20
Breast cancer	6	17
GI cancer	6	17
Hematologic cancer	5	14
Respiratory cancer	5	14
Multiple myeloma	3	9
Others	3	9
Treatment arms		
Two arms	30	86
Three and above arms	5	14
Number of patients enrolled		
Median	513	
Q1, Q3	301, 856	
Locations where the trial was conducted		
Multiple countries	25	71
Single country	10	29
Length of recruitment period (years)		
Mean (SD)	3.48 (2.25)	

GU, genitourinary; GI, gastrointestinal.

Characteristics of included articles

The characteristics of the 35 included articles can be found in *Table 1*. Among these 35 articles, 7 (20%) were genitourinary (GU)-related cancers, followed by breast cancer and gastrointestinal (GI)-related cancers, accounting for 6 (17%) articles each. Thirty (86%) of the studies were designed with two treatment arms, and 5 (14%) had three or more treatment arms. The median number of patients enrolled in the included trials was 513 (interquartile range 301 and 856). Twenty-five (71%) trials reported were multi-center, multinational studies. The remaining 10 (29%) trials were conducted in a single country, primarily in China (5, 14%). The average length of the recruitment period was 3.48 years.

Reporting items for assessing the impact of COVID-19

Table 2 illustrates the evaluation of reporting items for

Table 2 Reporting items for assessing the impact of COVID-19 in the included studies

Reporting items	N	%
MM-YY when the enrollment begins and ends		
Reported	33	94
Not reported	2	6
MM-YY when the treatment begins and ends		
Reported	0	0
Not reported	35	100
MM-YY of data cut-off		
Reported	20	57
Not reported	15	43
Length of treatment		
Reported	27	77
Not reported	8	23
Locations where patients were treated		
Reported in supplementary material	17	49
Reported in the main text		
Regional level	3	9
Country-level	4	11
Site-level	1	3
Not reported in the paper	10	29
Treatment discontinuation		
Reported		
With reasons	28	80
Assigned numbers of patients equaled the final numbers for analysis	4	11
Without reasons	2	6
Not reported		
Might be reported in a previous article	1	3
Treatment delay		
Reported		
With reasons	9	26
Without reasons	4	11
Supplement	3	9
Dose delays will not be allowed	1	3
Not reported		
Criteria were mentioned, but no result were provided	10	29
No relevant information found	6	17

MM-YY, month to year.

assessing the impact of COVID-19 in included studies. Thirty-three (94%) articles reported the months and years when they commenced and closed patient enrollments, and 20 (57%) articles reported the months and years of data cut-off. In addition, 27 (77%) articles provided information related to treatment lengths, such as the number of and length of chemotherapy cycle and total treatment length of radiotherapy. However, no trials reported the month and year when the first patient received the assigned treatment or the month and year when the last patient received his/her last treatment dose. Regarding the reporting of geographical region or site of recruitment, 8 (23%) trials reported this information in the main text and 17 (49%) in the supplementary materials (Appendix 1), while 10 (29%) did not provide any relevant information. In relation to the treatment effect-related factors, 28 (80%) articles reported the reasons for treatment discontinuation. Nonetheless, only 17 (49%) reported the number or the percentage of patients experiencing treatment delay, with explanations provided in only 9 (26%) trials.

Discussion

Our study demonstrated that more than 1,400 cancer-related clinical trials registered between 2017 and 2021 in the ClinicalTrials.gov database could be affected by COVID-19. In this study, we evaluated the quality of critical reporting items that could potentially be used to evaluate the impact of the COVID-19 pandemic on the conduct and interpretation of oncology clinical trials. Our study findings support the need for new reporting items and recommendations for clinical trials impacted by a pandemic.

For the essential reporting items already included in the current CONSORT guidelines, adequate reporting on these items was low among the existing articles. For example, items related to trial design and trial outcomes were partly reported, indicating the relatively low compliance to the existing guideline. The percentages of reporting the last month and year of follow-up, regions where patients were enrolled, and reasons of treatment delay were under-reported or not reported. Failure to report these items adequately could have consequences on both the reproducibility of clinical trials and the interpretation of results. These consequences are magnified under the impacts of COVID-19. Fifty-one percent of the articles reviewed did not report the proportion of patients experiencing treatment delays. Our results demonstrate that several of these reporting items were inadequately reported. Moreover, we also identified reporting items not currently present in the CONSORT reporting guidelines that are important for trials affected by the COVID-19 pandemic. This was achieved by reviewing existing CONSORT items by section/topic and thoroughly examining recent literature on the impact of the COVID-19 pandemic on trials that are generated by multiple stakeholders (see Table S2) (12-14).

Following the current version of the CONSORT guidelines for trials impacted by COVID-19 would result in inadequate reporting that could hamper result interpretation and reproducibility of clinical trials. Therefore, to ensure that the possible impacts of COVID-19 can be inclusively and clearly described, we propose a set of new reporting items and recommendations (*Table 3*, with an expanded version integrated with CONSORT in Table S3) for the reporting of clinical trials handled during a pandemic. *Table 3* contains the added ten new (Items 1c, 4c, 4d, 5b, 7c, 12c, 13c, 14c, 19b, and 19c) and four modified (items 12b, 14a, 18, and 22) reporting items. Notably, given that sensitivity analysis and missing data analysis were both important for assessing the impact of COVID-19 on the conduct of trials (15), we modified items 12b and 18 to reflect this. In addition, we would also like to highlight that the period of treatment was added to item 14a. As supported by the result in *Table 2*, this item is currently not routinely reported. However, this can help understand the potential impact of COVID-19 on trial conduct. Lastly, item 22 has been modified so that the authors are reminded to discuss how COVID-19 might have affected their trial interpretation. In particular, they are reminded to discuss the potential bias in interpreting the actual treatment effect.

To further demonstrate how trials may be impacted by COVID-19, a third literature search was conducted in PubMed to validate our proposed new reporting items and recommendations. Original research articles on phase III trials published between January and December 2021 in *JAMA Oncology*, *Journal of Clinical Oncology*, and *The Lancet Oncology* were examined. The literature search identified 81 potentially relevant articles. After excluding articles that did not meet the inclusion criteria that data collection should be completed no earlier than March 2020, 29 articles remained (Figure S1).

These 29 articles were examined using applicable reporting items in our new items and recommendations as these studies were impacted by COVID-19 during their follow-up periods (*Table 3*). Among these articles, the term "COVID-19" was found in eight articles, only one mentioned COVID-19 in the abstract (item 1c), and two

Table 3 New items and recommendations for reporting of randomized trials impacted by the force majeure event

Section/topic	No.	Recommendation
Title and abstract	1c	Indicate whether this study was conducted during the force majeure event in the abstract
Methods		
Participants	4c	Specify the study locations (such as community clinics and academic hospitals) in the supplement, including whether the study sites were affected by the force majeure event after trial commencement
	4d	If 4b includes remote data capture, describe the data collection process
Interventions	5b	Any changes to protocol interventions due to the force majeure event, with reasons
Sample size	7c	If yes to 6b and if 7b is applicable, did the changes to trial outcomes happen before or after a pre-planned interim analysis
Statistical methods	12b	Methods for additional analyses, such as subgroup analyses, adjusted analyses, and sensitivity analyses
	12c	Methods for addressing missing data
Results		
Participant flow (a diagram is strongly recommended)	13c	For each group, the numbers of participants experiencing treatment delay, with reasons
Recruitment	14a	Dates defining the periods of recruitment, treatment, and follow-up
	14c	Indicate whether the force majeure event impacted the study accrual rate
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses, adjusted analyses, and sensitivity analyses, distinguishing pre-specified from exploratory
Harms	19b	If applicable, are the adverse events associated with the force majeure event
	19c	If applicable, for each group, the numbers of participants experiencing laboratory test delays for assessing adverse events, with reasons
Discussion		
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence and the impact of the force majeure event

discussed the impacts of COVID-19 in the interpretation section (item 22). In addition, 15 articles mentioned that remote data capture is accepted in their supplementary (item 4d). Two described the modifications on the data cut-off date due to COVID-19 (item 5b) in the main text, and five reported adverse events caused by COVID-19 (item 19b) either in the main text or in the supplement. Among the five articles that reported changes to trial outcomes, only one failed to identify whether it happened before or after the pre-planned interim analysis. The reasons for the delay in treatment (item 13c), including whether they were attributed to COVID-19, were reported in six articles. Twenty-six out of 29 articles indicated that additional analyses were performed, 11 performed sensitivity analysis (item 12b; item 18), and 16 out of 29 articles addressed the issue of missing data (item 12c). However, as described earlier, only eight articles discussed COVID-19 in the text. Therefore, it remains unclear whether these additional analyses were conducted to evaluate the impact of COVID-19. In this brief assessment, six out of seven applicable reporting items that can be assessed were reported in less than 21% of the articles (*Table 4*). This indicates that the authors reporting trial results impacted by COVID-19 could greatly benefit from following our recommendations for transparent and clear reporting of clinical trial results.

This checklist should be considered as a tool to improve the reproducibility and consistency of reported trials impacted by COVID-19. A diagram has been created to help authors choose whether they should follow our new

Table 4 Reporting items for assessing the trials impacted by COVID-19

Reporting items	N	%
Indicated the study was conducted during the COVID-19 pandemic in the abstract		
Yes	1	3.4
No	28	96.6
If 4b includes remote data capture, describe the data collection process		
Reported	15	51.7
Not reported	14	48.3
Any changes to protocol interventions due to COVID-19		
Reported	2	6.9
Not reported	27	93.1
If yes to 6b and if 7b is applicable, did the changes to trial outcomes happen before or after a pre-planned interim analysis		
Changes to trial outcome		
Before a pre-planned interim analysis	3	10.3
After a pre-planned interim analysis	1	3.4
Not reported/no interim analysis	1	3.4
No changes to trial outcomes	24	82.8
For each group, the numbers of participants experiencing treatment delay		
Reported	6	20.7
Not reported	23	79.3
Any adverse events associated with COVID-19		
Reported	5	17.2
Not reported	24	82.8
Interpretation: considering other relevant evidence and the impact of COVID-19		
Reported	2	6.9
Not reported	27	93.1

recommendations (Figure S2). Authors are advised to check whether the new items and recommendations should be followed based on the following statements: (I) a clinical trial site closed to patient recruitment or under lockdown due to COVID-19 and (II) a COVID-19 outbreak occurring at any stage between the enrollment of the first patient and the time of data cut-off at the study location. If the answer is "yes" to either statement, authors are recommended to follow our recommendations for reporting trial findings. In addition, authors may consider using our new recommendations if the clinical trial was affected by a disruption in the drug supply chains due to the COVID-19 pandemic.

While transparent and comprehensive reporting of clinical trials was the primary focus of our study, we suggest suitable statistical analysis methods for clinical trials impacted by the COVID-19 pandemic. In light of the complexities of trial reporting during an ongoing pandemic, as addressed in this study, additional analyses, such as sensitivity analyses, should be performed (16). Regarding missing data, different methods (e.g., complete case analysis, single imputation, and multiple imputations) may be applied. Relevant descriptions and discussions on the utilization of these analytical methods can be found in the articles published by Molenberghs and Kenward (17) as well as O'Kelly and Ratitch (18). In addition, detailed analytical strategies targeting missing data under pandemic were also provided (19). For analysis of pandemic-related missing data and delayed assessments (e.g. scans and laboratory tests), the usage of interval censoring methods is recommended (7), with a more advanced analytical method for interval-censored data proposed in Fu and Simonoff's study (20). The addition of interim and sensitivity analysis or conducting a final analysis following early termination of trials are described further in the Food and Drug Administration guidelines (15).

Our recommendations may improve the overall quality of trial reporting during a pandemic. Another strength of this study is the applicability of the proposed recommendations to clinical trials, irrespective of the discipline. Furthermore, it is also expected that our work is applicable to not only trials that has been affected by COVID-19, but also other force majeure events, which includes the war in Ukraine and any pandemic that might happen in the future. Notably, we noticed that a relevant article was published recently. The guideline provided by Orkin *et al.* (21) focused on reporting the modifications to trial protocols and completed trials that were impacted by extenuating circumstances. Existing consort reporting items are judged by the authors based on three options: no change, impact, and mitigating strategy. Unlike the flexibility they provide, our approach is more targeted and provides recommendations focused on ten new and four modified items relevant to trials impacted by the pandemic. As their focus is different, the majority of the new and modified reporting items are unique in our recommendations. Specifically, new or modified reporting

items 1c, 4c, 7c, 12b, 13c, 14c, 18, 19b, and 19c have not been covered or mentioned. Therefore, our easy to use checklist is complementary to what is currently available to the best of our knowledge.

Despite the clear strengths of our study, there are some limitations. One limitation is that our study was conducted on articles published in the three top oncology journals. Hence, the observed proportions of inadequate reporting are likely underestimated. However, our recommendations may be more impactful as reporting quality tends to be lower if we consider all journals (10). Another limitation is that we did not assess a large number of trials conducted during the pandemic that are likely to be published in the coming years. However, as mentioned earlier, the reporting practice of recently published studies is expected to be similar to those impacted by COVID-19. Our recommendations aims to act as a preventative measure by reducing reporting inadequacy.

Conclusions

In conclusion, our key findings highlight the need to re-emphasize and refine the set of reporting items of CONSORT for clinical trials conducted during a pandemic or other force majeure events. Therefore, we propose a set of new and modified reporting items for authors to safeguard transparency and enhance the quality of reporting and value of trials impacted by trials impacted by various types of force majeure events.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2160/coif). THL reports this study partially supported by University Postgraduate Fellowships of HKU Foundation. EEV reports consulting fees and payment/honoraria from AbbVie, AstraZeneca, Beigene, BioNTech, Eli Lilly, EMD Serono, Genentech/Roche, GlaxoSmithKline, Merck and Novatis, outside the submitted work. HP reports personal fees from Genentech, outside the submitted work. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 Summary table for whether the reporting items were reported or not

Reporting items	Reported	Not reported
MM-YY when the enrollment begins and ends	The months and years of interest were specified in the main text (Methods section or Results section)	The months and years of interest cannot be found in the main text
MM-YY when the treatment begins and ends	The months and years of interest were specified in the main text (Methods section or Results section)	The months and years of interest cannot be found in the main text
MM-YY of data cutoff	The months and years of interest were specified in the main text, such as the Results section	The months and years of interest cannot be found in the main text
Length of Treatment	Surgery: Not applicable Chemotherapy and radiotherapy: Relevant information was provided either in the form of (I) whole treatment duration or (II) cycle counts along with the length of each cycle	Surgery: Not applicable Chemotherapy and radiotherapy: Either the cycle number or the length of each cycle were not provided
Locations where patients were treated	Reported in supplementary material: The authors stated that readers should refer to the supplementary materials for further information Reported in the main text: If relevant information can be found in the main text, the articles will be subclassified into Region-level", "Country-Level", or "Site-level" based on the reported information	No information about where patients were treated can be found in the main text and/or in the supplementary material
Treatment discontinuation	Descriptions such as "treatment discontinuation" and "patients were removed from the treatment arm" were found in the Results section, with numbers (or percentages) being provided. Articles will be further classified as "with reasons" or "without reasons" based on whether the reasons were mentioned or not	No information about treatment discontinuation can be found in the main text and/or in the supplementary material
Treatment delay	Descriptions such as "dose delay", "dose interruption", "treatment delay", and "treatment interruption" were found in the Results section, with numbers (or percentages) being provided. Articles will be further classified as "with reasons" or "without reasons" based on whether the reasons were mentioned or not	No information about treatment delay can be found in the main text and/or in the supplementary material

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Table S2 Key takeaways from recent literatures on impact of COVID-19 on clinical trials

Key takeaways from recent literatures on impact of COVID-19 on clinical trials	Reference + page/paragraph
Study sites/locations were affected by the pandemic	(Boughey *et al.*, 2021) (12): Page 2, paragraph 3
Remote data capture and collection	(Boughey *et al.*, 2021) (12): Page 5, paragraph 2 (Ali and Riches, 2021) (13): Page 4, paragraph 2
Changes to protocol interventions due to COVID-19	(Ali and Riches, 2021) (13): Page 4, paragraph 2 (Boughey *et al.*, 2021) (12): Page 2, paragraph 3 (Onesti *et al.*, 2021) (14): Page 7, paragraph 1
Changes to trial outcomes happen before or after a pre-planned interim analysis	(Meyer *et al.*, 2020) (7): Page 5, paragraph 9
The need for sensitivity analyses	(Meyer *et al.*, 2020) (7): Page 6, table 3
The need to address missing data	(Meyer *et al.*, 2020) (7): Page 8, paragraph 1
Participants experienced treatment delay	(Boughey *et al.*, 2021) (12): Page 2, paragraph 5
Treatment period can be impacted by lockdowns	(Sathian *et al.*, 2020) (22): Page 7, paragraph 3
COVID-19 impacted the study accrual rate	(Boughey *et al.*, 2021) (12): Page 1, paragraph 1
Relevant adverse events can be associated with COVID-19	(Ali and Riches, 2021) (13): Page 4, paragraph 3
Laboratory test delays can impact adverse events assessments	(Boughey *et al.*, 2021) (12): Page 3, paragraph 6

References

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Table S3 Full checklist integrated with the CONSORT[1,^]

Section/Topic	Item No.	Checklist item
Title and abstract		
	1a	Identification as a randomised trial in the title
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)
	1c	Indicate whether this trial was conducted during the force majeure event in the abstract
Introduction		
Background and objectives	2a	Scientific background and explanation of rationale
	2b	Specific objectives or hypotheses
Methods		
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons
Participants	4a	Eligibility criteria for participants
	4b	Settings and locations where the data were collected
	4c	Specify the study locations (such as community clinics and academic hospitals) in the supplement, including whether the study sites were affected by the force majeure event after trial commencement
	4d	If 4b includes remote data capture, describe the data collection process
Interventions	5a	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered
	5b	Any changes to protocol interventions due to COVID-19, with reasons
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed
	6b	Any changes to trial outcomes after the trial commenced, with reasons
Sample size	7a	How sample size was determined
	7b	When applicable, explanation of any interim analyses and stopping guidelines
	7c	If yes to 6b and if 7b is applicable, did the changes to trial outcomes happen before or after a pre-planned interim analysis
Randomisation:		
Sequence generation	8a	Method used to generate the random allocation sequence
	8b	Type of randomisation; details of any restriction (such as blocking and block size)
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how
	11b	If relevant, description of the similarity of interventions
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes
	12b	Methods for additional analyses, such as subgroup analyses, adjusted analyses, and sensitivity analyses
	12c	Methods for addressing missing data
Results		
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome
	13b	For each group, losses and exclusions after randomisation, together with reasons
	13c	For each group, the numbers of participants experiencing treatment delay, with reasons
Recruitment	14a	Dates defining the periods of recruitment, treatment, and follow-up
	14b	Why the trial ended or was stopped
	14c	Indicate whether the force majeure event impacted the study accrual rate
Baseline data	15a	A table showing baseline demographic and clinical characteristics for each group
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses, adjusted analyses, sensitivity analyses, distinguishing pre-specified from exploratory
Harms	19a	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)
	19b	If applicable, are the adverse events associated with the force majeure event
	19c	If applicable, for each group, the numbers of participants experiencing laboratory test delays for assessing adverse events, with reasons
Discussion		
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses
Generalisability	21	Generalizability (external validity, applicability) of the trial findings
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence and the impact of the force majeure event
Other information		
Registration	23	Registration number and name of trial registry
Protocol	24	Where the full trial protocol can be accessed, if available
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders

[1] Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. Journal of Pharmacology and Pharmacotherapeutics 2010;1:100-107. ^ New and modified items are listed in *Table 3*.

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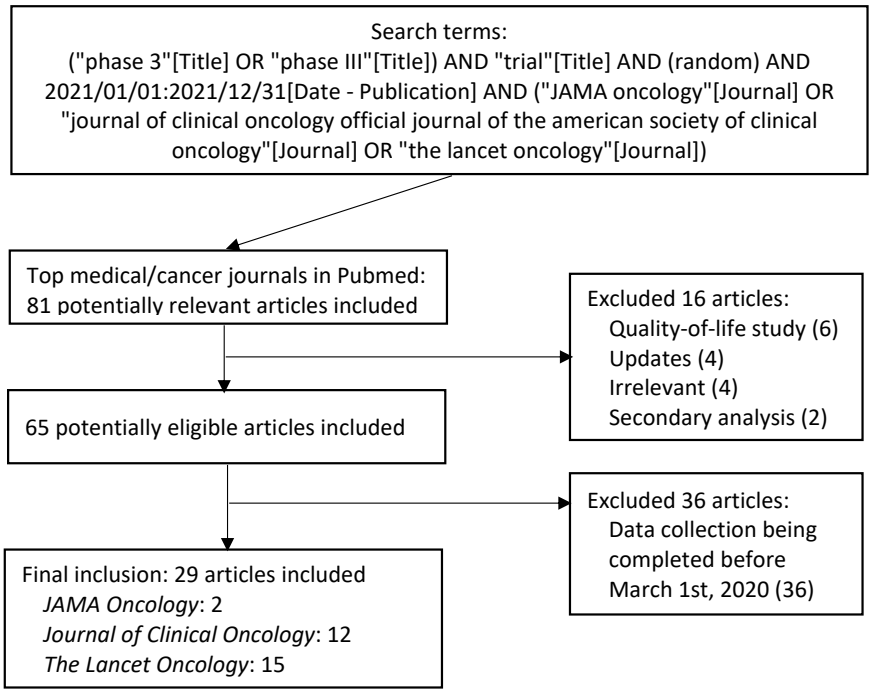

Figure S1 Process for literature search on trials impacted by COVID-19.

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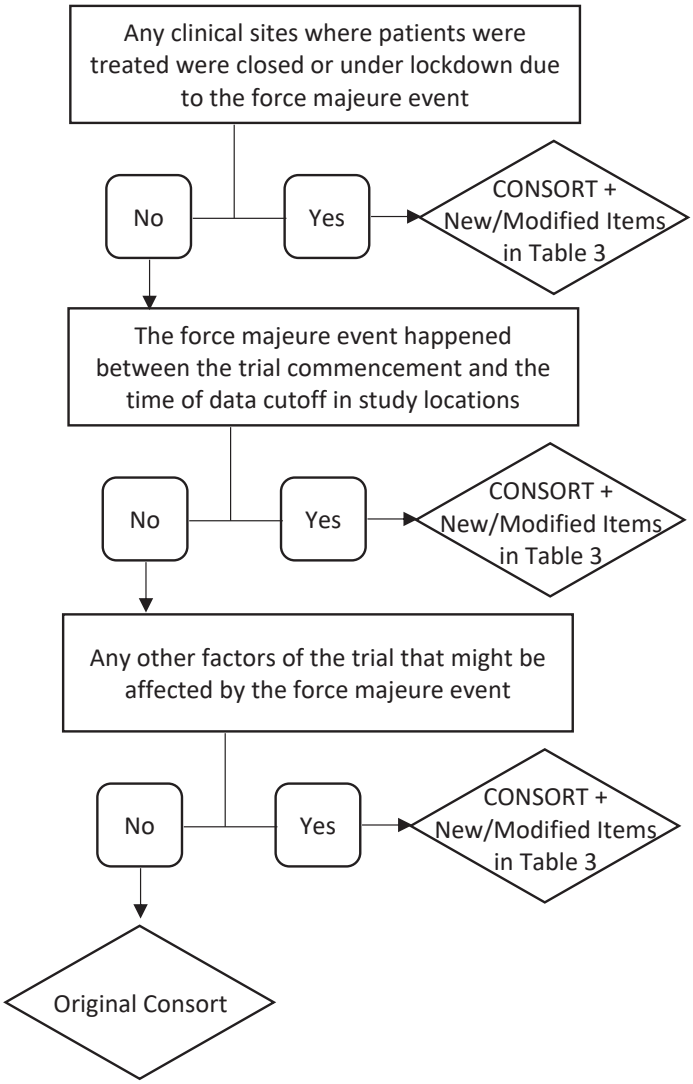

Figure S2 Flow diagram to assist in the decision-making process on whether to follow the new recommendations.

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