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Guidelines for Reporting Trial Protocols and Completed Trials Modified Due to the COVID-19 Pandemic and Other Extenuating Circumstances
The CONSERVE 2021 Statement

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IMPORTANCE Extenuating circumstances can trigger unplanned changes to randomized trials and introduce methodological, ethical, feasibility, and analytical challenges that can potentially compromise the validity of findings. Numerous randomized trials have required changes in response to the COVID-19 pandemic, but guidance for reporting such modifications is incomplete.

OBJECTIVE As a joint extension for the CONSORT and SPIRIT reporting guidelines, CONSERVE (CONSORT and SPIRIT Extension for RCTs Revised in Extenuating Circumstances) aims to improve reporting of trial protocols and completed trials that undergo important modifications in response to extenuating circumstances.

EVIDENCE A panel of 37 international trial investigators, patient representatives, methodologists and statisticians, ethicists, funders, regulators, and journal editors convened to develop the guideline. The panel developed CONSERVE following an accelerated, iterative process between June 2020 and February 2021 involving (1) a rapid literature review of multiple databases (OVID Medline, OVID EMBASE, and EBSCO CINAHL) and gray literature sources from 2003 to March 2021; (2) consensus-based panelist meetings using a modified Delphi process and surveys; and (3) a global survey of trial stakeholders.

FINDINGS The rapid review yielded 41 673 citations, of which 38 titles were relevant, including emerging guidance from regulatory and funding agencies for managing the effects of the COVID-19 pandemic on trials. However, no generalizable guidance for all circumstances in which trials and trial protocols might face unanticipated modifications were identified. The CONSERVE panel used these findings to develop a consensus reporting guidelines following 4 rounds of meetings and surveys. Responses were received from 198 professionals from 34 countries, of whom 90% (n = 178) indicated that they understood the concept definitions and 85.4% (n = 169) indicated that they understood and could use the implementation tool. Feedback from survey respondents was used to finalize the guideline and confirm that the guideline's core concepts were applicable and had utility for the trial community. CONSERVE incorporates an implementation tool and checklists tailored to trial reports and trial protocols for which extenuating circumstances have resulted in important modifications to the intended study procedures. The checklists include 4 sections capturing extenuating circumstances, important modifications, responsible parties, and interim data analyses.

CONCLUSIONS AND RELEVANCE CONSERVE offers an extension to CONSORT and SPIRIT that could improve the transparency, quality, and completeness of reporting important modifications to trials in extenuating circumstances such as COVID-19.

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Supplemental content

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Randomized trials are an essential tool to inform health care, policy, and regulatory decisions concerning the effects of medical interventions. Forethought and diligence in trial design, statistical approaches, implementation, and analysis are necessary to minimize trial modifications after participant enrollment, which can introduce methodological, ethical, feasibility, and analytical challenges. Amendments to trial procedures are common, and circumstances such as new safety or efficacy information, regulatory requirements, or changes in the standard of care can make those changes unavoidable.[1] Modifications can also introduce biases, raising doubts about the validity of the conclusion of a clinical trial.[2,3]

COVID-19 has fundamentally changed everyday life, patient care, and health research. Numerous trials that were underway prior to the COVID-19 pandemic faced unavoidable modifications in response to the pandemic, such as changes to methods of recruitment, intervention delivery, outcome assessment (eg, substituting virtual visits for in-person ones), statistical analysis, and sometimes study design. As of January 29, 2021, 2043 trials registered with ClinicalTrials.gov had been terminated, withdrawn, or suspended because of COVID-19, affecting more than 129 000 participants and interrupting plans to recruit more than 4 million future participants.[4] Although some health regulatory agencies released guidance on trial modifications due to the COVID-19 pandemic, no consensus exists on how such changes and their implications should be reported.[5-8]

Reporting guidelines can improve the completeness and transparency of research reports by defining a minimum set of items to address. While CONSORT (Consolidated Standards of Reporting Trials) 2010 and SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 guide reporting for completed trials and trial protocols, respectively, there is limited guidance for reporting trial modifications.[9,10] Thorough and consistent reporting of trials that undergo modifications could enhance trial interpretation and transparency, reduce research waste, and facilitate understanding of how trialists respond and adjust to unforeseen circumstances related to major disruptions, such as the COVID-19 pandemic. As a joint extension for CONSORT and SPIRIT, CONSERVE (CONSORT and SPIRIT Extension for RCTs Revised in Extenuating Circumstances) aims to provide guidance to improve the reporting of trials and trial protocols that undergo important modifications in response to extenuating circumstances.

Key Points

Question What information should be included in a trial protocol or completed trial article when the study had to undergo important modifications in response to extenuating circumstances such as COVID-19?

Findings Developed using a consensus process, a rapid review, and a survey of the international trials community, CONSERVE (CONSORT and SPIRIT Extension for RCTs Revised in Extenuating Circumstances) offers guidance for reporting trials and trial protocols that undergo important modifications in response to extenuating circumstances such as the COVID-19 pandemic.

Meaning CONSERVE offers guidance that could help improve the transparency, quality, and completeness of reporting important modifications to trials in extenuating circumstances.

Methods

CONSERVE Guideline Development Procedure and Panel

The CONSERVE Panel that convened to develop the guideline was composed of 37 trial investigators, trial methodologists, patient representatives, ethicists, funders, regulators, and journal editors, including CONSORT and SPIRIT executive committee members. Panelists were recruited through professional networks to ensure global and interprofessional representation. CONSERVE was developed between June 2020 and February 2021 following a process adapted from the reporting guideline development procedure of Moher et al,[11] modified to replace face-to-face meetings with virtual meetings and emphasizing rapid completion given the unprecedented disruption of trials in the context of the COVID-19 pandemic. The panel wrote and registered a protocol (available through the Open Science Framework at https://osf.io/ms8bz)[12] for the guideline development process involving 3 main elements: (1) rapid review, (2) consensus-based meetings and surveys, and (3) a global survey of the trials community. Although the guideline development timeline was extended, the guideline development process proceeded per protocol. The guideline development process did not involve human subjects research as defined by the Tri-Council Policy Statement (Canada) and therefore was outside the scope of research ethics committee review.[13]

Rapid Review

Panelists conducted a rapid review of guidance on modifications to trials.[14] A review protocol and search strategy was registered through the Open Science Framework.[15]

In brief, a search was conducted for guidance and processes for reporting on modifications to trials and trial protocols, including any type of document from 2003 through August 2020 indexed in the OVID Medline, OVID EMBASE, or EBSCO CINAHL databases and gray literature sources including the US Food and Drug Administration (FDA), the UK National Health Service's Health Research Authority, the US National Institutes of Health, and the UK National Institute for Health Research in any language. Reference lists of included articles were manually screened to identify additional documents. Searches were conducted by a health research librarian and peer reviewed using the Peer Review of Electronic Search Strategies (PRESS) guideline.[16]

Reports on circumstances in which modifications had been prespecified in the protocol, such as adaptive trial designs, were excluded. Reports that involved analysis techniques for missing data were also excluded. Database searches were updated on February 26, 2021; gray literature searches were updated to March 10, 2021 (Supplement 1). The search yielded 41 673 citations, of which 3735 were duplicates, and panelists conducted independent and duplicate screening of titles and abstracts using Covidence software, yielding 38 relevant titles (Supplement 1). The rapid review identified no comprehensive guidance overlapping with the purpose and intent of CONSERVE. All searches are available in Supplement 1.

Consensus-Based Meetings and Surveys

Since CONSERVE was envisioned as a joint extension of the CONSORT 2010 and SPIRIT 2013, the first meeting was a virtual gathering of panelists drawn from the SPIRIT-CONSORT executive

committee to develop a prototype for CONSERVE. This prototype offered definitions of key concepts, items from the CONSORT and SPIRIT checklists that would require refinement when trials undergo important modifications, and an implementation tool to be used to report on these modifications.

The entire CONSERVE panel convened through a series of 4 virtual meetings to revise this prototype and build consensus. These meetings were intended to integrate and accelerate the Delphi processes and replace in-person meetings conventionally used to develop reporting guidelines.[11] Consensus was defined as being achieved when no panelist called for further revisions.

Online surveys conducted using Google Forms presented the evolving CONSERVE prototypes in between meetings and sought dissenting views, gaps, and revisions. Survey results structured discussions at the subsequent virtual meetings, where panelists proposed and discussed solutions to problems prior to developing a new prototype. The panel achieved consensus following 3 meetings. Through a fourth, final meeting, the panel refined the resulting guideline and checklists by incorporating the results of the rapid literature review and survey of the global trials community.

Global Survey of Trials Community

The panel developed an online survey targeting an international group of trial stakeholders including trial investigators, trial methodologists, trial staff, funders, regulators, ethicists, patient and patient organization representatives, journal publishers, and editors. The survey was conducted to gather feedback to refine the emerging draft guideline; to determine whether it was appropriate and operable for people who are engaged with trials and trial reporting, including public-facing patient representatives; and to identify case studies. The survey was sent by email to a sample of 113 investigators listed as primary contacts for trials registered as ongoing in April 2020, as identified from the search portal of the World Health Organization's International Clinical Trials Registry Platform. CONSERVE panelists also distributed the survey widely by email within their professional networks. The panel planned to continue distributing the survey until responses were received from all geographic regions and all target stakeholder groups, including investigators, methodologists and statisticians, trial staff, ethicists, editors and publishers, sponsors, regulators, and funders.

Responses were received from 198 professionals from 34 countries, including 61 respondents from low- and middle-income countries. The top 5 represented countries were the United Kingdom (n = 59), Canada (n = 24), India (n = 15), United States (n = 11), and Australia (n = 9). Briefly, 90% (178/198) of respondents indicated that they understood the CONSERVE concept definitions and 85.4% (169/198) indicated that they understood and could use the CONSERVE implementation tool. Survey questions and response summaries are included in Supplement 1. Feedback from survey respondents was used to finalize the guideline and confirm that the core concepts were suited for widespread implementation.

Results

Scope of CONSERVE

CONSERVE is an extension to the core CONSORT 2010 and SPIRIT 2013 statements and should be used in conjunction with these statements and their explanatory materials.[9,10,17,18] CONSERVE is designed to guide reporting for trials that have undergone important modifications in extenuating circumstances (**Figure**). The concept of extenuating circumstances is intended to limit the scope of CONSERVE to circumstances in which changes to a trial were prompted by unavoidable situations beyond the control of study investigators, sponsors, or funders. The concept of important modifications is intended to limit the scope of CONSERVE to cases for which those modifications have substantive implications for the study at a scientific, ethical, feasibility, inferential, or analytical level. Although the COVID-19 pandemic is the exemplar that prompted the development of CONSERVE, the approach is applicable to other extenuating circumstances that result in important modifications to a trial, such as natural disaster, strikes and other personnel disruptions, regulatory changes, or changes to the clinical standard of care.

CONSERVE is not a mechanism to redress poor trial design, and it does not encourage unwarranted trial modifications, especially post hoc changes to favor positive results based on accumulating trial data. CONSERVE is based on the observations that protocol amendments are common and that in some circumstances important modifications can be necessary, unavoidable, or beneficial.[1] Rather than abandoning trial data and the investments that contributed to data collection, it is better to report the unanticipated circumstances and trial modifications rigorously and transparently.[19] CONSERVE provides guidance to support that rigor and transparency.

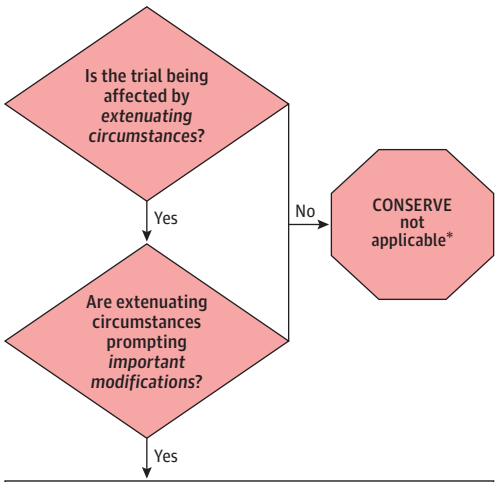
The CONSERVE implementation tool (Figure) provides a pathway to determine when CONSERVE should be used to report on trials and trial protocols and provides guidance for its application.

CONSERVE Checklists

The CONSERVE checklists are summarized in the implementation tool and provided in Supplement 2. The CONSERVE checklists consist of 4 sections: (1) extenuating circumstances, (2) important modifications including impacts and mitigating strategies, (3) responsible parties, and (4) interim data. The **Table** provides narrative case studies of trials[20-23] that included important modifications in extenuating circumstances and samples of CONSERVE checklist items that might be addressed in a trial report concerning these types of studies.

CONSERVE provides 2 checklists to support authors in reporting how their trial addressed important modifications in extenuating circumstances. CONSERVE-CONSORT is designed for reporting completed trial results, while CONSERVE-SPIRIT is for reporting trial protocols. Both checklists (Supplement 2) share a common format. The first section of each checklist refers to the extenuating circumstances, responsible parties, interim data, and important modifications. The second section provides an itemized list with rows for each item from the core CONSORT or SPIRIT checklists. The columns offer checkboxes to indicate if that item was unaffected, was directly affected by the extenuating circumstances, or was modified by the study team as a mitigating strategy in response to the extenuating circumstances. A completed checklist should be made available whenever CONSERVE is used for reporting a trial or trial protocol. Because extenuating circumstances can potentially lead to modifications in any aspect of a trial, the CONSERVE checklists incorporate a list of all items from the SPIRIT and CONSORT statements.[9,10]

Figure. CONSERVE Implementation Tool



CONSERVE Checklists:
Use CONSERVE-CONSORT for trial reports.
Use CONSERVE-SPIRIT for trial protocols.

I. **Extenuating circumstances:** Describe the circumstances and how they constitute *extenuating circumstances*.

II. **Important modifications:**
   A. Describe how modifications are *important modifications*.
   B. Describe the *impacts* and *mitigating strategies*, including their rationale and implications for the trial.
   C. Provide a modification timeline.

III. **Responsible parties:** State who planned, reviewed, and approved the modifications.

IV. **Interim data:** If modifications were informed by trial data, describe how the interim data were used, including whether they were examined by study group, and whether the individuals reviewing the data were blinded to the treatment allocation.

*CONSERVE was developed specifically for important modifications in extenuating circumstances, but may enhance reporting in a wider range of situations.

Definitions

Extenuating circumstances:
Unavoidable situations that prompt modifications to a trial. These are not usually under the control of study investigators, sponsors, or funders. The impact of the COVID-19 pandemic on studies already underway is an exemplar. Other cases could include natural disasters, civil unrest, or other externalities that inhibit a trial unavoidably.

Important modifications:
"Modifications" refer to any changes to a trial or the environment in which it occurs. "Important" modifications refer to those changes that could have a potentially meaningful effect on the study's:
- objectives or research question;
- ethical acceptability, including benefits and harms to participants;
- internal validity and generalizability;
- feasibility; or
- analytical methods and statistical power.

Important trial modifications may include impacts and mitigating strategies implemented by the study team, as defined below.

Impacts:
Aspects of the trial that are directly affected or changed by the extenuating circumstance and are not under the control of investigators, sponsors, or funders.

Mitigation strategies:
Aspects of the trial that are modified by the study investigators, sponsor, or funder to respond to the extenuating circumstances and manage the impacts on the trial.

CONSERVE-CONSORT or CONSERVE-SPIRIT should be used instead of CONSORT or SPIRIT when reporting on trials or trial protocols that have undergone important modifications. Authors may add items from other SPIRIT or CONSORT extensions as applicable. Investigators should ensure that the trial registry record is updated to reflect any changes to registered information. Authors should report the items listed in the CONSERVE checklists as applicable throughout the completed trial or protocol. In some circumstances, more limited modifications may be reported with a concise statement or paragraph in the study article's methods section, whereas in more complex cases modifications may appear throughout the various sections of the article. In cases in which reporting the requisite details requires more space than journal word counts allow, a supplement can be provided to outline the effects of the extenuating circumstances on the trial.

Extenuating Circumstances

Authors should describe the circumstances that led to the trial modifications, including how the circumstances are extenuating. Extenuating circumstances refer to unavoidable situations that prompt modifications to a trial and that are not usually under the control of study investigators, sponsors, or funders (Figure). Extenuating circumstances share elements with the contract law concept of force majeure, referring to external events such as wars, strikes, riots, or epidemics that prevent parties from fulfilling their contractual obligations.[8] Similarly, extenuating circumstances are unavoidable external events that would prevent trial investigators or participants from adhering to a trial protocol or would necessitate protocol modifications. This is not to suggest that extenuating circumstances must be universally external, unpredictable, and unavoidable but rather that the circumstances would not have been reasonably foreseen or incorporated as part of the study protocol.[24] Generally, extenuating circumstances would not include resources shortages, insufficient enrollment to complete the trial as planned, or other factors that might be addressed in a pilot or feasibility study.[25]

Circumstances that are extenuating for one trial may not be extenuating for another. For example, while many trials would approach war or an act of terrorism as an extenuating circumstance, trials concerning combat injuries would likely not.[26] Therefore, it is important that authors consider and explain how modifications to the study were prompted by unavoidable situations beyond the control of investigators, sponsors, or funders and why those modifications were important from a scientific, ethical, pragmatic, or analytical perspective.

Table. Examples of Trials Undergoing Important Modifications in Extenuating Circumstances

Narrative	Sample of CONSERVE items
Example 1: out-of-hospital care trial modified by a change in regional care policies (Canada)[20]	
In a multicenter stepped-wedge cluster randomized pragmatic trial, regional government enacted a policy change partway through the rollout that mandated widespread use of a modified version of the experimental intervention as the new standard of care. The trialists identified this policy change as an extenuating circumstance leading to a premature and unanticipated modification to the implementation schedule at 9 months, before the planned completion at 12 months. The authors determined that a sufficient number of clusters had completed implementation of the planned intervention to allow analysis of the primary outcome but were unable to use the final 3 months of the stepped-wedge design (after the policy change) for the planned analysis. The investigators' mitigating strategies included omission of the final study period from the randomized clinical trial analysis, an extended observational data collection period for 3 months beyond the anticipated stop date, and a revised design and analysis plan to include 3 conditions: usual care, planned intervention, and an uncontrolled modified intervention condition.	• Extenuating circumstance: a change to the regional standard of care incorporating aspects of the experimental intervention before trial completion • Impacts: usual care treatment protocols unexpectedly altered mid-trial • Mitigating strategies: final period of the stepped-wedge design eliminated from the analysis of the trial; data collection extended to include an uncontrolled observational period • These are important modifications because the change in standards of care could have effects on the study's ability to address its objectives, analytical methods, and statistical power.
Example 2: critical care trial modified by COVID-19 (Canada)[21]	
Investigators evaluated the effect of small-volume blood collection tubes vs standard tubes to reduce red blood cell transfusion in critical care patients in a pragmatic multicenter, stepped-wedge cluster trial at 25 sites in Canada. The COVID-19 pandemic delayed implementation of the intervention at some sites due to clinical workload, pandemic preparedness activities, and infection control precautions, but the trial was ultimately completed. The types of patients admitted to the critical care units (and their corresponding prognoses) may have changed substantially after the start of the COVID-19 pandemic, with variable proportions of COVID-19 and elective surgery patients across sites. The prevalence of other underlying conditions leading to critical care unit admissions also changed in unanticipated ways. The authors interpreted these as extenuating circumstances and implemented mitigating strategies including changes to the statistical analysis plan to mitigate the effects of these changes in the patient population.	• Extenuating circumstance: COVID-19 and its effects on critical care units • Impacts: change in study population • Mitigating strategies: modified analysis plan to mitigate the effects of changes in the patient population • These are important modifications that had implications for study feasibility and analytical methods in this trial.
Example 3: oral rotavirus vaccine trial modified by security threats (Niger)[22]	
A 2-group multisite trial was conducted in rural Niger to assess the effect of a low-cost, heat-stable rotavirus vaccine compared with placebo to prevent laboratory-confirmed severe rotavirus gastroenteritis. Terrorism in the region inhibited access to some areas, affecting outcome assessments and access to the laboratory. This introduced ethical challenges as study staff and participants worked to continue study operations despite the security threat. Participants were listed as lost to follow-up because they could not access outcome assessment facilities per protocol. The authors interpreted this extenuating circumstance as a threat to the study's ethical foundations and analysis plan. Had the situation continued, mitigating strategies might have included revised sample size calculations, modified outcome assessment procedures when security threats precluded access to laboratories, and a revised analysis plan incorporating sensitivity analyses for participants lost to follow-up in extenuating circumstances. The trial was reported without these details.	• Extenuating circumstance: local terrorism/security threats • Impacts: participants lost to follow-up, ethical and safety challenges for study staff and participants • Mitigating strategies: revised sample size calculations, outcome assessment procedures, and analysis plan • These are important modifications because they had meaningful effects for the study's ethical acceptability, analytical methods, and statistical power.
Example 4: systemic therapy for prostate cancer (United Kingdom and Switzerland)[23]	
The STAMPEDE trial was a multicenter, multigroup, multistage platform trial evaluating the efficacy and safety of multiple novel systemic therapies compared with standard care for hormone-sensitive prostate cancer. A planned comparison was celecoxib plus hormone therapy vs hormone therapy alone. Prior to beginning recruitment in 2004, rofecoxib was withdrawn from the market by the manufacturer for safety concerns about cardiovascular toxicity, and regulatory agencies stopped all trials involving cyclooxygenase 2 inhibitors. The STAMPEDE investigators could not recruit to the celecoxib group and had to reassess the risk-benefit balance of the intervention. They modified the eligibility criteria to exclude any potential participants who had substantial cardiovascular disease, and the start of recruitment to the celecoxib group was delayed by 1 year. The intervention duration was also reduced, and cardiovascular risks were added to the consent materials. The overall implications for the trial were that recruitment was likely slowed by the highly publicized safety concerns and the shortened intervention duration may not have been sufficiently long to show benefit.	• Extenuating circumstance: regulators stopped cyclooxygenase 2 inhibitor trials due to new evidence of cardiovascular harms • Impacts: unable to start recruiting participants to celecoxib group; altered risk-benefit balance • Mitigating strategies: added eligibility to exclude patients with cardiac contraindications; reduced maximum duration of cyclooxygenase 2 intervention; revised informed consent materials to address cardiovascular risks • These are important modifications because they affected the study's ethical acceptability and feasibility.

Important Modifications

Important modifications incorporate 2 concepts. First, *modification* refers to any change to a trial. The term *modification* is used rather than *amendment* because a modification can be any kind of revision to the anticipated or ongoing trial, regardless of whether it triggers a formal protocol amendment and regardless of whether it represents a change to the trial itself or the context in which the trial occurs. For example, the study by Siegal et al[21] conducted in critical care units encountered changes in the populations and underlying conditions of patients admitted to these settings due to the COVID-19 pandemic. The investigators modified their analysis plan to mitigate the effect of these changes (Table). This could represent an important modification to trials conducted in critical care settings regardless of whether such a change triggered an amendment to the study protocol. Second, "important" refers to the subset of modifications that could have a potentially meaningful effect on the study objectives or research question, ethical acceptability (including benefits and harms to participants), internal validity, generalizability, feasibility, or analytical methods and statistical power. Many trials undergo amendments for a range of pragmatic and administrative reasons that do not necessarily constitute important modifications, for example, adding a recruitment site to an existing multicenter trial without modifying the study in any other way. Authors should report the rationale for important modifications and the associated implications for the trial.

Important modifications can manifest as impacts on the trial or as mitigating strategies. *Impacts* refer to aspects of the trial that are directly affected or changed by the extenuating circumstance and that are not under the control of investigators, sponsors, or funders. For example, a rotavirus vaccine trial conducted in Niger by

Isanaka et al[22] was affected by extenuating circumstances when the threat of local terrorism prevented participants from being transported to regional health centers for outcome assessments, precluding some follow-up visits from occurring per protocol (Table). In this case, the extenuating circumstance was terrorism, which affected the outcomes, data collection methods, and participant flow (SPIRIT items 12 and 18; CONSORT items 13 and 17). The trial by Vaillancourt et al[20] on out-of-hospital cervical spine immobilization was stopped early when regional authorities enacted a new policy mandating a modified immobilization rule and adopting many aspects of the trial's experimental intervention as standard of care (Table). In this example, the extenuating circumstance was regional policy change, and the impacts affected both the interventions (SPIRIT item 11; CONSORT item 5) and the numbers analyzed (SPIRIT item 20; CONSORT item 16).

Mitigating strategies refer to the aspects of the trial that are modified by the study investigators, sponsor, or funder in response to the extenuating circumstances or to manage the impacts on the trial. For example, in the rotavirus vaccine trial,[22] investigators were unable to implement mitigating strategies that would enable data collection and therefore reported the cases in which participants could not access outcome assessments or laboratories as protocol deviations (Table). Had security concerns worsened, alternative mitigating strategies might have included revised sample size calculations (SPIRIT item 14; CONSORT item 7), revised outcome assessment procedures for participants facing security concerns (SPIRIT item 18A; CONSORT item 6), or changes to the analysis plan including new ancillary analyses (SPIRIT item 20; CONSORT items 16 and 18). In a trial by James et al[23] involving celecoxib for hormone-sensitive prostate cancer, investigators were unable to implement the intended intervention because of unanticipated regulatory changes concerning the use of celecoxib in trials (Table). The investigators' mitigating strategies included new exclusion criteria for patients with contraindications to celecoxib use (SPIRIT item 10; CONSORT item 4), changes in the intervention duration (SPIRIT item 11; CONSORT item 5), and revisions to the consent materials (SPIRIT item 26).

Authors should provide a modification timeline, including the dates when extenuating circumstances were identified, the dates when those circumstances took effect on the trial, and the numbers of participants or clusters who had enrolled and completed the trial before and after extenuating circumstances prompted modifications to the trial.[8]

Responsible Parties

Authors should report the parties responsible for planning, reviewing, and approving modifications as well as the responsibilities of each of these parties. Depending on the specifics of the trial, investigators, study staff, participants, regulators, research ethics committees, data monitoring committees, sponsors, and funders may all be involved in planning, reviewing, and approving trial modifications.

Interim Data

Authors should report whether accumulating trial data were used to inform modifications, especially if interim examination of those data had the potential to introduce bias. For example, using data concerning recruitment rate or adherence would not generally introduce bias, whereas using outcome data by study group would have a greater potential to bias the choice of mitigating strategies used to respond to extenuating circumstances. Authors should report who accessed and reviewed the data and should describe how the study data were used. It is also important to report whether data were examined by study group and whether decision-makers were blinded to the intervention allocation. In addition, authors should report whether accumulating data were used in an ad hoc manner or according to an analysis plan.

Examining interim outcome data can bias trial results and interpretation and introduce analytical and ethical challenges when interim analyses are not prespecified or lead to early study termination.[27-32] Similar concerns arise if interim data are used to inform unplanned revisions to study procedures. When trials are affected by extenuating circumstances, however, it may be reasonable in some instances to use outcome data to plan and implement mitigating strategies.

Rather than conducting ad hoc interim analyses in a fully ad hoc manner, trialists can reduce the chance of introducing bias by creating a plan for these interim analyses a priori and detailing how the findings will inform further decisions. These previously unanticipated analyses can be conducted in a planned manner by documenting the intended analysis in the protocol and determining how those analyses will inform modifications a priori.

Discussion

CONSERVE aims to provide guidance to help improve the quality, completeness, and transparency of reporting of important modifications due to extenuating circumstances for completed trials and trial protocols. The guidance is designed to be a practical resource for investigators and methodologists, ethicists, editors and publishers, sponsors, regulators and funders, study participants, and the public as they navigate trial reporting in extenuating circumstances, such as the COVID-19 pandemic. The evolving pandemic with its varied global disease burden and government responses has continued to affect clinical trials in diverse ways. CONSERVE discourages unnecessary modifications to trials but acknowledges that managing unanticipated events is an inherent part of the scientific enterprise.

Although CONSERVE was developed in the context of the COVID-19 pandemic, it applies to reporting on other important modifications to trials. This could help address a gap in existing trial reporting guidance that predates the COVID-19 pandemic and will persist beyond the pandemic. For example, CONSERVE might have enhanced reporting on trials modified by public health emergencies such as the 2014-2016 Ebola virus epidemic, natural disasters, or other unavoidable logistical and ethical concerns.[33-37] By promoting complete and transparent reporting of trial modifications, CONSERVE also allows the research community to learn from how extenuating circumstances have been managed, examine the overall impact of those circumstances, and take modifications into account when interpreting trial results. While the COVID-19 pandemic continues to cause disruption to trials worldwide, it provides an opportunity to assess the manner in which important clinical trial modifications are made in response to a variety of extenuating circumstances. The international survey yielded examples of trials that encountered extenuating circumstances including regulatory changes, new standards of care, and security threats (Table).[20-23]

CONSERVE may help to reduce the publication biases and wasted research investments that can occur when trials deviate from their protocols.[3] By supporting transparency, CONSERVE may also promote public trust in science when studies encounter unanticipated circumstances.[38] Consistent reporting of trials that encounter extenuating circumstances could also prompt trialists to develop plans for a wider range of potential disruptions in trial protocols.

CONSERVE complements regulatory guidance on modifying trials in the context of the COVID-19 pandemic. For example, the UK Medicines and Healthcare Products Regulatory Agency set guidance for trial investigators to assess the risks and benefits of ongoing trials during COVID-19 and to consider options including halting recruitment, adapting delivery processes, stopping or suspending the trial, or mitigating risks as the trial proceeds.[39] Guidance from the FDA on trials during the COVID-19 pandemic recommended that trialists describe the contingency measures implemented, list how and which participants were affected including how participation was altered, and provide analyses and discussions that address the effect on safety and efficacy.[5] Similar recommendations were made by the Norwegian Medicines Agency and the South African Health Products Regulatory Authority, while the European Medicines Agency (EMA) provided guidance on the methodological aspects of ongoing clinical trials.[6-8] The EMA guidance outlined the importance of describing specific dates and durations of issues external to the trial (eg, lockdowns and travel restrictions) and discussed when data review may be warranted to inform study decisions. Guidance from the FDA also addressed statistical methodology as it relates to meeting trial objectives during the pandemic.[40] However, existing guidelines did not describe the connections among modifications to the conduct of trials, statistical analysis, and reporting. Other reports have provided analyses on the management of missing data in trials due to COVID-19,[41] ethical dimensions of conducting trials during public health emergencies,[33,42,43] and the challenges of trial sponsorship during a pandemic.[44-46]

Clinical and research specialty societies have also provided guidance on conducting trials during the pandemic, including in oncology, cardiovascular disease and heart failure, and hepatology.[46-50] These resources provide methodological guidance, while CONSERVE delivers a framework for reporting what decisions were made, why they were made, and the corresponding impact. Some journals have provided reporting recommendations to authors regarding trials directly affected by the COVID-19 pandemic. Editorials have called on trial authors to describe pandemic-related issues in the methods sections of articles, including changes in study protocol, trial delays or interruptions, issues with missing data, and effects on statistical power.[51-53]

The CONSERVE statement has limitations. First, CONSERVE was developed rapidly using a modified process to engage rapidly with a global community of trial investigators, methodologists, ethicists, funders, regulators, journal editors, and patient representatives. Unlike prior reporting guidelines, this process adapted the conventional Delphi process and incorporated several steps to solicit detailed feedback and achieve consensus with a large group of trial professionals and public representatives who refined the process, but substituted in-person discussions with virtual meetings to ensure that dissenting views could be addressed. Second, given that many ongoing trials affected by the pandemic have not yet been published, only a few reports have described how investigators have responded to the extenuating circumstances, limiting the examples available about COVID-19. Third, the global survey sought to capture a large, international body of interdisciplinary persons working on and with trials, and those respondents provided examples and feedback about how CONSERVE could be used. Despite its international representation, including respondents from low- and middle-income countries, CONSERVE may not have captured all relevant perspectives.

Implementation will be supported by making CONSERVE widely available, including through the SPIRIT and CONSORT websites and other reporting guideline resources such as the Enhancing the Quality and Transparency of Health Research (EQUATOR) Network (https://www.equator-network.org/). The CONSERVE panel will also work with all trial stakeholders including investigators, journals, regulators, and funders to disseminate and endorse the statement. To reach a larger audience, the panel also encourages translation of the CONSERVE checklists to other languages.

Conclusions

CONSERVE offers an extension to CONSORT and SPIRIT that could improve the transparency, quality, and completeness of reporting important modifications to trials in extenuating circumstances such as COVID-19.

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