Editorial: Reporting Clinical Trials with Important Modifications Due to Extenuating Circumstances, Including the COVID-19 Pandemic: CONSERVE 2021

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Conflict of interest: None declared

Abstract

During 2020 and 2021, the COVID-19 pandemic has resulted in interruptions and cancellations of clinical trials and has delayed drug development in all areas except SARS-CoV-2 vaccine development. A further concern is the need to rapidly share anonymized datasets and improve opportunities to conduct randomized clinical trials (RCTs) in low-resource developing countries, particularly for oncology trials and for other infectious diseases. The Consolidated Standards of Reporting Trials (CONSORT) 2010 and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 currently guide the reporting of trial protocols and completed RCTs, respectively. Extenuating circumstances or unavoidable situations may occur that are beyond the control of study sponsors and investigators. On June 21, 2021, the CONSORT and SPIRIT Extension for RCTs Revised in Extenuating Circumstance (CONSERVE) was published. The scope of CONSERVE 2021 includes modifications that have substantive implications for the feasibility, ethical conduct, scientific content, and study analysis. This Editorial aims to provide the background to CONSERVE 2021 and show how these guidelines may reduce the number of clinical trials currently being paused or discontinued due to the COVID-19 pandemic, particularly in poorly resourced and developing countries.

Keywords: Editorial • Clinical Trial • Guidelines as Topic • COVID-19

During 2020 and 2021, the COVID-19 pandemic has resulted in delays and cancellations of clinical trials and drug development [1]. This time of uncertainty has resulted in increased pressure on regulatory authorities, clinical researchers, and policymakers, who are required to conduct clinical trials and studies quickly but safely [1]. The COVID-19 pandemic has also been associated with increasing numbers of clinical trials that have been terminated prematurely [2]. At this time, these pressures have highlighted some fundamental issues, particularly in the conduct and reporting of randomized clinical trials (RCTs), that have previously been of concern and have highlighted the importance of well-designed large-scale coordinated and collaborative RCTs [1]. A further concern is the need to rapidly share anonymized datasets and improve opportunities to conduct RCTs in low-resource developing countries, particularly for oncology trials in other infectious diseases [1,3,4]. The effects of the COVID-19 pandemic on trial launches in oncology have raised concerns regarding reduced drug development when patients with cancer are also undergoing delays in treatment [3,5]. These delays result from the prioritization of vaccine development for SARS-CoV-2 and clinical management of patients with COVID-19, mainly due to the emergence of new SARS-CoV-2 variants [3,5].

Guidelines for the conduct and reporting of RCTs have been established to ensure that trials are ethical, thorough, and standardized and that the trial results can be compared [6]. The Consolidated Standards of Reporting Trials (CONSORT) 2010 and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 currently guide the reporting of trial protocols and completed RCTs, respectively [7,8]. Extenuating circumstances or unavoidable situations may occur that are beyond the control of study sponsors and investigators. The extenuating circumstances that may modify a clinical trial include pandemic infectious disease, natural disasters, regulatory changes, or changes to clinical standards of care or patient management. However, there has been a lack of guidance for modifying the conduct and reporting of clinical trials in extenuating circumstances until recently.

On June 21, 2021, the CONSORT and SPIRIT Extension for RCTs Revised in Extenuating Circumstance (CONSERVE) was published [9]. The scope of CONSERVE 2021 includes modifications that have substantive implications for the feasibility, ethical conduct, scientific content, and study analysis, as a joint extension for the current CONSORT and SPIRIT reporting guidelines [7-9]. CONSERVE 2021 aims to help trial investigators...
identify the information required in the trial protocol or the completed trial report following significant modifications in response to extenuating circumstances, including the current COVID-19 pandemic [9]. The evidence to support the development of the CONSERVE 2021 guidelines was evaluated and analyzed by a panel of 37 international trial investigators, statisticians, patient representatives, funding representatives, ethicists, study regulators, and journal editors between June 2020 and February 2021 [9]. The panel analyzed a rapid literature review of several international databases, including OVID Medline, OVID EMBASE, EBSCO CINAHL, and the ‘grey’ literature from January 2003 to March 2021 [9]. The CONSERVE 2021 development process also included consensus-based panelist meetings, a modified Delphi process, and a global survey of clinical trial stakeholders [9]. The rapid literature review identified 41,673 citations, of which 38 were relevant, including emerging guidance from funding and regulatory agencies to manage the effects of the COVID-19 pandemic on clinical trials [9]. The CONSERVE 2021 guidelines were developed to incorporate an implementation tool and study checklists tailored to clinical trial reports and protocols when extenuating circumstances result in important modifications to the planned study procedures [9].

CONSERVE 2021 provides two reporting checklists [9]. The CONSERVE-CONSORT checklist guides the reporting of completed clinical trial results; the CONSERVE-SPIRIT checklist guides the reporting of clinical trial protocols [9]. The checklists include four sections: extenuating circumstances, important modifications, responsible parties, and interim data analyses [9].

The COVID-19 pandemic accelerated the CONSERVE 2021 guidelines, which also include modifications that can adapt to any other extenuating circumstances [9]. For example, in 2020, the COVID-19 Dexamethasone (CoDEX) Randomized Clinical Trial studied intravenous dexamethasone combined with standard care, compared with standard care alone [10]. The results showed a significant increase in the number of survival days and days free of mechanical ventilation during 28 days for intravenous dexamethasone combined with standard care compared with standard care alone [10]. This RCT was conducted in 41 intensive care units (ICUs) throughout Brazil (NCT04327401) but was discontinued early due to the publication of a related study before reaching the planned study sample size of 350 patients [10].

‘Pandemic’ CONSERVE 2021 may improve the quality and transparency of reporting of key modifications for completed trials and trial protocols for other pandemics [9]. For example, had the CONSERVE guidelines been developed earlier, they may have assisted in reporting studies associated with the 2014-2016 Ebola virus epidemic [11]. The CONSERVE 2021 guidelines complement current regulatory guidance on modifying trials due to the COVID-19 pandemic [9]. The US Food and Drug Administration has provided guidance on clinical trials during the COVID-19 pandemic [12]. The FDA recommends that contingency measures be implemented during the trial conduct and requires identifying trial participants affected by COVID-19 [12]. The FDA also requires details of how COVID-19 alters participation in the trial and the effects on the safety and efficacy of the therapy or medical device undergoing clinical trial [12]. Also, in the UK, the Medicines and Healthcare Products Regulatory Agency (MHRA) has recently provided guidance for clinical trial investigators to evaluate the benefits and risks of ongoing trials conducted during the COVID-19 pandemic, with options that include halting trial recruitment, suspending the trial, or mitigating emerging patient risks during the conduct of the trial [13].

During 2020 and 2021, specialty research and clinical societies have also guided clinical trials during the COVID-19 pandemic, including hepatology, oncology, and cardiovascular disease [14,15]. These recent study resources have provided methodological guidance [14,15]. CONSERVE 2021 delivers a framework to identify and report decisions made for the extenuating circumstances, when and why they were made, and their impact on the trial [9]. In the future, authors of reported clinical trials may be asked to include a description of COVID-19 pandemic-related issues in the methods section of future manuscripts submitted for publication [9]. These include trial interruptions or delays, any changes in the study protocol, effects on the statistical power due to recruitment problems, and any reasons for missing data [9].

Conclusions

The 2021 CONSERVE protocol and guidelines provide an extension to the CONSORT and SPIRIT guidelines to improve the transparency, quality, and content of reporting for important modifications to RCTs in extenuating circumstances, such as the COVID-19 pandemic [9]. These guidelines may reduce the number of clinical trials currently being paused or discontinued due to the COVID-19 pandemic, particularly in poorly resourced and developing countries. It is also reassuring to have increasingly robust guidelines in place to prepare for whatever the future holds for COVID-19 and future extenuating circumstances, including new pandemic infectious diseases.
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