UNIVERSITY OF SPLIT
SCHOOL OF MEDICINE

MIA STRIKIĆ, MD

REPORTING CHARACTERISTICS OF COVID-19 PHARMACOLOGICAL INTERVENTION TRIALS REGISTERED IN CLINICALTRIALS.GOV AND IN PUBLICATIONS

Doctoral Dissertation

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Mentor: Associate Professor Shelly Melissa Pranić, University of Split School of Medicine, Cochrane, Croatia

The dissertation is based on two scientific papers:

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2. Strikić M, Pranić SM. Evaluation of consistency in adverse event reporting between trial registry and publications in COVID-19 pharmacological intervention trials. Int J Clin Pharm. 2026 Apr 13;21. doi: https://doi.org/10.1007/s11096-026-02130-2.

DEDICATION

Thank you to my family: my parents, my sister, my brother, and my grandparents, for supporting me through this process. Thank you, Josip, for helping with the technical part.

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LIST OF ABBREVIATIONS

ACT- Applicable Clinical Trial

AE- Adverse event

AI- Artificial Intelligence

CI- confidence interval

CONSORT- Consolidated Standards of Reporting Trials

COVID-19 - Coronavirus disease 2019

CT. gov- Public registry of clinical trials data and results sponsored by the National Institutes of Health in the United States of America

EMA- European Medicines Agency

EUA- Emergency Use Authorization

EudraCT- European Union Drug Regulatory Authorities Clinical Trials

FDA- U.S. Food and Drug Administration

FDAAA- Food and Drug Administration Amendments Act

ICMJE- International Committee of Medical Journal Editors

IPD- Individual participant data

LFA- Lateral Flow Assay

N/A or NA- not applicable

NCT- National Clinical Trial

NIH- National Institutes of Health

OAE- Other adverse event

PHS- the Public Health Service

PRESS- Peer Review of Electronic Search Strategies

RCT- Randomized controlled trial

RNA- ribonucleic acid

RT-PCR- Reverse Transcription Polymerase Chain Reaction

SAE- Serious adverse event

SARS-CoV-2- Severe Acute Respiratory Syndrome Coronavirus 2

SPSS- Statistical Package for Software Solutions

STROBE- Strengthening the reporting of observational studies in epidemiology

TEAE- Treatment-Emergent Adverse Event

TRDS- Trial Registration Data Set

UTN- Universal Trial Number

WAME- the World Association of Medical Editors

WHO- World Health Organization

WMA- the World Medical Association

1. INTRODUCTION

1.1. Coronavirus disease 2019 (COVID-19)

COVID-19 is a disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (1). This disease was recognized as a major health problem after the first outbreak in Wuhan, China (2–5). The initial outbreak, primarily linked to bats (6,7), started at a small local seafood market in Wuhan (8–10). The disease spread worldwide, mainly affecting Thailand, Japan, South Korea, Iran, and Singapore (11–13), resulting in over 2 million deaths globally (14–16). On January 8, 2020, genetic sequencing confirmed that the virus which causes SARS-CoV-2 might be the reason of the outbreak and global pandemic (9,17). The pandemic was declared on March 11, 2020, by the World Health Organization (WHO) (5,18).

A coronavirus that caused a pneumonia outbreak in Wuhan (17,19) was shortly called the novel coronavirus (2019-nCoV) (20,21). By February 11, 2020, the virus got a name, „Severe Acute Respiratory Syndrome Coronavirus 2“ (SARS-CoV-2) (22,23). This virus is RNA-positive and single-stranded (24). It is a highly transmissible (25) virus that can cause severe pneumonia with fatal outcomes (26). Some investigators believe that SARS-CoV-2 may be from bats (14,27). Human coronavirus is a β-coronavirus (22,24,28,29) and a zoonotic pathogen (25). It spreads from an intermediate host to humans (25,30–33). It includes SARS-CoV and Middle Eastern Respiratory Syndrome CoV (MERS-CoV) (34). SARS-CoV-2 has spread more widely but has a lower mortality rate than MERS-CoV and SARS-CoV (35).

As of November 9, 2025, the WHO reported a total of 778,922,858 cases, with the United States accounting for 103 million cases (36), as shown in Figure 1. Additionally, there were 7,103,341 deaths reported, with the U.S. leading in fatalities (36).

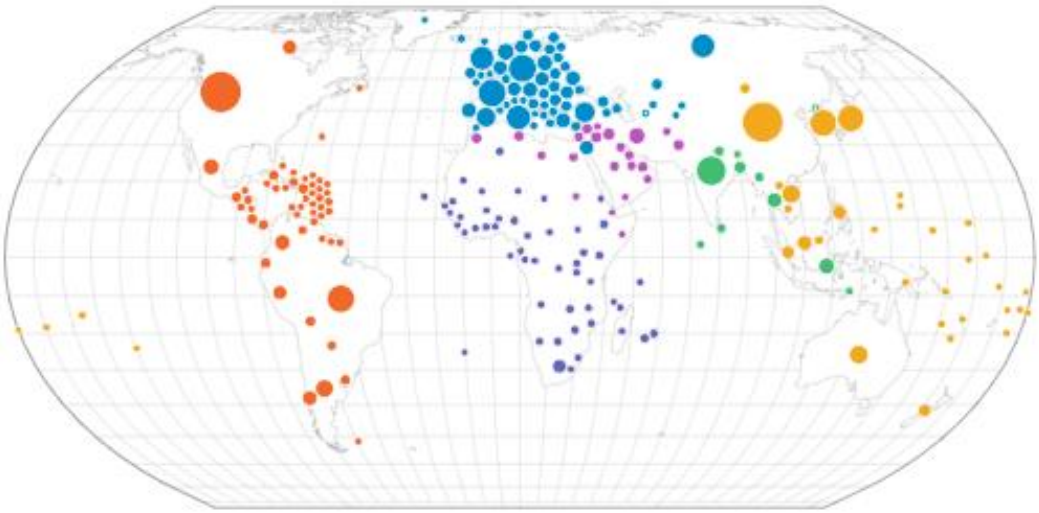


Figure 1. Total number of COVID-19 cases reported in the world
Source: (36) COVID-19 cases | WHO COVID-19 dashboard. Available from: https://data.who.int/dashboards/covid19/cases (CC BY 4.0)

Respiratory illnesses that result from this infection may vary in severity (14,34,37). Its clinical signs range from no symptoms at all (38) to severe, life-threatening conditions (39,40). The typical incubation period is about six days (34), with symptoms such as fever, shortness of breath, cough, or diarrhea (41–43). Older adults, especially those 65 and older, can be in a higher risk of complications due to underlying health problems (42,44). Many patients also experience changes in taste and a reduced sense of smell (45–47). Headaches, dizziness, and even acute cerebrovascular events have been reported (48,49). Some of these symptoms lasted beyond the COVID-19 infection (50).

Table 1. COVID-19 disease severity and symptoms

Mild	fever, cough, fatigue, diarrhea
Moderate	dyspnea, mild pneumonia
Severe	severe pneumonia, organ failure, death

Source: (51) COVID-19 symptoms and severity. Available from: https://www.who.int/westernpacific/emergencies/covid-19/information/asymptomatic-covid-19.

Long COVID is a term that was not universally defined at the start of the pandemic. The United Kingdom's National Institute for Health and Care Excellence guidelines later defined it

as symptoms lasting longer than four weeks (52). This definition means that the symptomatic phase of the illness can last between four and twelve weeks. It includes post-COVID-19 syndrome, which may extend beyond twelve weeks depending on symptom duration (53). The WHO defines post-COVID-19 syndrome as the presence of symptoms persisting for three months after infection (54). It has been reported that symptoms can persist for up to 6 months (55) during or after acute COVID-19 (56). We can use other terms to describe this condition, such as long-haul COVID (57), post-acute COVID-19 syndrome (58), and post-acute sequelae of COVID-19 (59).

The syndrome can affect multiple organ systems and impact patients across all levels of disease severity (55). The most commonly reported symptoms are dyspnea and fatigue (55,60). Dyspnea, which means shortness of breath (61), is a common issue. Other symptoms related to this syndrome include headaches, joint pain, loss of smell and taste, hair loss, insomnia (62,63), and gastrointestinal problems (43,64). Less frequently reported symptoms are chills, ear pain, and pernio (55,62). The primary gastrointestinal symptoms are anorexia, diarrhea, followed by vomiting and nausea (64,65), while abdominal pain is rare (64). These symptoms have been observed in patients with Middle East Respiratory Syndrome (MERS) and severe acute respiratory syndrome (SARS) (55).

It has been observed that gastrointestinal symptoms are reported among patients with respiratory symptoms (65). Most of these gastrointestinal symptoms are mild (65), although some can be severe. One complication of COVID-19 is liver (65,66) and pancreatic injury (67,68). The mechanisms and causes of these complications are not fully understood. Additionally, some rare complications include acute pancreatitis, acute appendicitis, bowel perforation, and obstruction (69,70). Endoscopy is often used to detect gastrointestinal bleeding, which is considered urgent (71), and to identify important findings at the start of COVID-19 (71). These findings include ulcers in the duodenum, stomach, and esophagus, as well as edema and erosions in the upper gastrointestinal system (71–73).

Cardiac involvement during the COVID-19 pandemic was vital for understanding multisystem organ failure. Microvascular dysfunction, tachycardia (53,74), increased risk of thromboembolic events (53,75), and endotheliopathy (53,76) all contribute to multiorgan failure (53). These phenomena are directly connected with higher mortality during hospital treatment and an increased risk of septicemic shock (53,77,78). The most commonly reported symptoms in adults included palpitations, arrhythmias, tachycardia, and bradycardia (53). Fatigue was the most frequently reported symptom in both pediatric and adult populations (53).

It is reported that some patients develop postural orthostatic tachycardia syndrome (79). This syndrome involves various cardiovascular autonomic disorders (80) and can be triggered by viral infections (79). It is characterized by an increased heart rate (80) and symptoms of orthostatic intolerance (79). Additional symptoms include fatigue, cephalalgia, and other nonspecific signs of post- COVID-19 syndrome (79). The elevated heart rate can also result from factors such as fever, myocarditis, hypoxia, and anxiety (79).

Accurately and swiftly diagnosing COVID-19 with the right tool is crucial to prevent further spread of infection (81). The most used method for diagnosis is real-time reverse transcription-PCR (RT-PCR) on nasopharyngeal samples (82–84). It detects genomic RNA (81). This technique is fast, highly sensitive, and reliable (85). RT-PCR is considered the gold standard for detecting SARS-CoV-2 (81,86) and is used worldwide for other diseases (87,88). EUA-approved test kits are authorized for use only in specific laboratories, with the full list available on the FDA site (89). The test's sensitivity depends on the amount of RNA in the sample, and results may be negative or positive for COVID-19 (81). However, only serology tests can identify current or past COVID-19 infections by detecting antibodies (81). The main advantage of LFA serology tests is their suitability for at-home use. The ELISA serology test, on the other hand, is more commonly performed in laboratories (81).

Treatment options for COVID-19 quickly evolved to prevent further complications. Therapeutic strategies focus on reducing disease severity. The primary options include antiviral treatments, adjunct therapies, and immunotherapies (90). The use of direct antivirals has been crucial in decreasing disease progression (90,91).

Few antivirals were tested during the pandemic. Remdesivir was the first approved emergency-use treatment during the pandemic. It was approved by the FDA (92). It was approved on October 22, 2020 (92). It is an RNA polymerase inhibitor, best known for reducing recovery time in hospitalized patients (90,93); its impact on mortality is limited (90). Nirmatrelvir and ritonavir, known as Paxlovid, are the first approved oral treatments for mild-to-moderate disease (94). They are protease inhibitors approved under Emergency Use Authorization (94). Molnupiravir was granted for an emergency use authorization by the FDA (95). It induces RNA mutations and errors, inhibiting viral replication (90). The FDA approved other treatment options as replacement therapies for COVID-19 to treat and support patients (95). Tocilizumab is an antiviral that inhibits the interleukin-6 receptor and reduces inflammation (96); baricitinib is an immune-modulating antiviral (95) that reduces Janus kinase signaling (96). Anakinra and vilobelimab are immunomodulators approved under emergency

use authorization for adults. Regiocit replacement solution is authorized under emergency use and is used as a replacement solution (95).

To prevent COVID-19 from worsening, the FDA approved vaccines for use. There are only two mRNA vaccines approved for use (97). One Novavax COVID-19 vaccine, Nuvaxovid, is approved for patients aged 12 and older (97).

1.2. Trial registration

Providing transparent data in clinical trials is essential for supporting evidence-based decision-making in medical practice (61,62). This critical information influences the decisions of doctors, patients, and researchers. The WHO described a clinical trial as a prospective study that explores novel treatment options and their effects on human health (63). In June 2007, the International Committee of Medical Journal Editors (ICMJE) adopted this definition of a clinical trial (98).

1.2.1. ICMJE

In order to upgrade transparency in clinical trial registration, the ICMJE requires registration before publication in a journal (99). This rule applies to all clinical trials enrolled after July 1, 2025 (98). In 1978, ICMJE created a document called Uniform Requirements for Manuscripts Submitted to Biomedical Journals (URMs) (100). The document was renamed to „Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals“ in August 2013 (98). The most important updates in the document include the four criteria for authorship (101). This change was driven by issues involving authors denying responsibility. It is crucial to know that by accepting authorship of a paper, each author assumes responsibility and accountability for the work (101).

ICMJE is made up of editors from 17 journals, representatives from the U.S. National Library of Medicine, and the World Association of Medical Editors (WAME) (102). By April 2025, the ICMJE will stop providing a list of journals that follow its recommendations because some listed journals do not comply with them (102). The ICMJE updated „Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals“ in January 2026. The ICMJE also revised sections on sponsor agreements, academic freedom, scientific misconduct, trial registration, and reporting of funders and supporters (103). The change regarding clinical trial registration relates to authors' access to data, stating that all authors should have access to the data supporting the study results. Editors may request details

about which specific authors had access to the data during analysis, especially when there is collaboration between authors from academic or nonacademic institutions (103).

1.2.2. WHO TRDS items

The next step in standardizing clinical trial registration occurred in 2006, when the WHO created the Trial Registration Data Set (TRDS) items (104). WHO TRDS items specify the essential information about the clinical trial required by WHO and the ICMJE. This set aims to ensure accurate registration and publication in a journal (105–107).

The TRDS has been expanded to include four new elements: Ethics Review, Summary Results, and Completion Date (108). In June 2017, the ICMJE mandated an IPD sharing statement for full registration of trials that begin enrollment on or after January 2019 (109). The WHO TRDS set is now available in version 1.3.1, comprising 24 items (Table 2) (110).

Table 2**.** World Health Organization Trial Registration Data Set items (v.1.3.1)

Ordinal number	**NAME OF THE ITEM**	**EXPLANATION**
1.	Primary Registry and Trial Identifying Number	*Name of Primary Registry, and the unique number assigned to the trial.*
2.	Date of Registration in Primary Registry	*Date when the trial was officially registered in the Primary Registry.*
3.	Secondary Identifying Numbers	*Other identifiers besides the Trial Identifying Number allocated by the Primary Registry, if any. These included: The Universal Trial Number (UTN), identifiers assigned by the sponsor (record Sponsor name and Sponsor-issued trial number e.g.protocol number)), etc.*
4.	Source(s) of Monetary or Material Support	*Major source(s) of monetary or material support for the trial.*
5.	Primary Sponsor	*The individual, organization, group or other legal entity which takes*

		responsibility for initiating, managing and/ or financing the study.
6.	Secondary Sponsor(s)	*Additional individuals, organizations or other legal persons, that have agreed with the primary sponsor to take on responsibilities of sponsorship.*
7.	Contact for Public Queries	*A contact who will respond to general queries.*
8.	Contact for Scientific Queries	*The Principal Investigator may delegate responsibility for dealing with scientific enquiries to a scientific contact for the trial.*
9.	Public Title	*Title to be in easily understood language.*
10.	Scientific Title	*Scientific title appears in the protocol submitted for funding and ethical review.*
11.	Countries of Recruitment	*The countries from which participants are recruited aat the time of registration.*
12.	Helath Condition(s) or Problem(s) Studied	*Primary health condition(s) or problem(s) studied*
13.	Intervention(s)	*The name of intervention used in the trial plus intervention description.*
14.	Key Inclusion and Exclusion Criteria	*Inclusion and exclusion criteria in order to select participants, including age and sex.*
15.	Study Type	*Study type includes type of study, method of allocation, masking, assignment, purpose, and phase (if applicable).*

16.	Date of First Enrollment	*Date of the enrollment of the first participant.*
17.	Sample Size	*Sample size includes number of participants that the trial plans to enrol in total, and number of participants that the trial has enrolled.*
18.	Recruitment Status	*Recruitment status of the trial: pending, recruiting, suspended, complete, other.*
19.	Primary Outcome(s)	*Outcomes are events, variables, or experiences that are measured because it is believed that they are induced by the intervention.*
20.	Key Secondary Outcome(s)	*Outcomes which are secondary interest or that are measured at timepoints of secondary interest.*
21.	Ethics Review	*This item process iformation of the trial record in the primary register database. It includes: status, date of approval, name and contact details of Ethics committee(s).*
22.	Completion date	*Date when the study was completed.The date when the final data for a study were collected.*
23.	Summary Results	*This item includes: date of posting of result summaries, date of the first journal publication of results, URL hyperlink(s), baseline characteristics, participant flow, adverse events, outcome measures, URL link to protocol file(s) with a version and a date, brief summary.*

24.	IPD sharing statement	*Statement about intending sharing individual clinical trial participant data (IPD). It may be plan to share IPD (Yes, No) or plan description.*

Abbreviations: IPD- Individual Participant Data

Source: (110) WHO data set https://www.who.int/tools/clinical-trials-registry-platform/network/who-data-set.

1.2.3. Declaration of Helsinki

A set of ethical guidelines for research involving human participants was established in 1964. These guidelines define ethical responsibilities during research and were designed by the World Medical Association. The document was last updated in 2013 to address new ethical challenges. According to Article 35 of the Declaration of Helsinki, all investigations that include human participants must be registered. This registration must be done in a public database before recruiting the first participant in the research. Additionally, Article 36 states that responsible parties (researchers, authors, sponsors, publishers, and editors) are required to publish research results and follow guidelines for ethical reporting (111). The 2013 revision emphasizes the importance of sharing research findings and providing compensation for research-related injuries (112). The latest revision in 2024 highlights the importance of scientific integrity to prevent research misconduct (113).

1.3. ClinicalTrials.gov

1.3.1. ClinicalTrials.gov registry

Complete and transparent reporting in clinical trials is crucial (114–117). The first law requiring registration on ClinicalTrials.gov was the Food and Drug Administration Modernization Act of 1997 (FDAMA), section 113(104), which established the initial database for trials funded by private or public sources. This law tasked the National Institutes of Health with creating a registry containing information on trials investigating drugs, devices, or biologicals for serious or life-threatening conditions (104). Later, the ICMJE mandated that investigators and sponsors of clinical trials make information publicly available as a prerequisite for journal publication (118). The Food and Drug Administration (FDA) Amendments Act (FDAAA) of September 27, 2007, expanded the requirement that clinical

trials be registered and that basic results be reported within one year of trial completion. This applies to non-experimental FDA-approved drugs, devices, and biologicals beyond phase 1 that have at least one US-based site (119). In January 2017, a revised Federal Policy for the Protection of Human Subjects was issued. It took effect on July 19, 2018 (120). This updated Common Rule requires that the consent form used for participant enrollment be publicly accessible (121).

The Final Rule, known as FDAAA 801, has been in effect since January 18, 2017, and expanded the requirements for registration and results in the registry (122). ClinicalTrials.gov is the largest online registry of clinical trials, and has been available since February 29, 2000. The registry includes studies from all 50 U.S. states and 193 countries. It lists human participants in clinical trials. Once a clinical trial is registered, the history of changes and modifications made during the research can be found in a trial's archive of saved changes, monitored from the initial to the most recent registration (123).

1.3.2. Applicable Clinical Trial (ACT)

Trial registration is required for studies classified as applicable clinical trials. ACTs are defined in section 402(j) of the Public Health Service (PHS) Act and include the following:

- Controlled clinical investigation of any FDA-regulated drug or biological product for any disease or condition;
- Certain studies of FDA-regulated medical devices, including pediatric postmarket surveillance required by the FDA, are included. This excludes small clinical trials testing prototype devices.

ACTs include interventional trials of FDA-regulated drugs, device products, or biological products that meet one of the following criteria:

- The trial is conducted under an FDA investigational new drug or device application;
- Involves a drug, biological product, or device manufactured in the United States and exported for research;
- The trial involves one or multiple sites in the United States.

The responsible party may authorize the National Institutes of Health (NIH) to publicly post registration information for a drug, biological product, or device that has not been previously approved by the FDA (122). The „Checklist and Elaboration for Evaluating Whether a Clinical Trial or Study is an Applicable Clinical Trial (ACT)" is a comprehensive document

designed to help determine the requirements for clinical trials initiated after January 18, 2017 (122). However, this document can also be useful for trials initiated before January 18, 2017, even though those trials are not subject to the expanded registration requirements in the Final Rule.

The types of studies that are not subject to registration and those whose results are not covered by section 402 (j) of the PHS Act.

- Phase 1 trials on drugs or biological products, including those used as research tools to explore disease processes or biological phenomena;
- Trials that are not interventional, including cohort studies;
- Trials that do not investigate drug, biologicals, or device;
- Trials that test prototype devices, or the primary outcome of the trial is not related to the health outcome.

1.3.3. Publication of results of clinical trials

The primary objective of a clinical trial should be to publish the research findings in the appropriate scientific journal. This is essential for clinical decision-making and can be vital to establishing new clinical guidelines (124).

It is essential that published results are reported transparently, clearly, and accurately, with corresponding data in a registry.

The Consolidated Standards of Reporting Trials (CONSORT) extension was created by the EQUATOR Network (125) to improve the quality of reporting randomized controlled trials. It was included in the CONSORT 2010 statement. The CONSORT statement was first issued in 1996 to enhance reporting quality (126) and was endorsed by more than 400 journals (127). The CONSORT 2010 was made as a 25-item checklist. The most recent CONSORT 2025 now features a 30-item checklist for reporting the flow of participants and results of randomized trials (128). Seven items were added, three items revised, and one item removed (129).

2. OBJECTIVES AND HYPOTHESIS

2.1. Research objectives

1. Our research objectives concerning discrepancies in data reporting from the registry are:
2. to assess the completeness of reporting for WHO TRDS items on ClinicalTrials.gov trials registered on or after January 1, 2020, and last updated on or before May 31, 2021, from initial registration to final registration;
3. to assess the completeness of WHO TRDS items reporting ClinicalTrials.gov trials registered on or after January 1, 2020, and updated on or before May 31, 2021, from final registration to subsequent publication;
4. to assess changes in WHO TRDS item reporting of ClinicalTrials.gov trials of pharmacological interventions for COVID-19-infected patients registered on or after January 1, 2020, through the last update on or before May 31, 2021, from initial to final registration;
5. to assess changes in WHO TRDS items reporting on ClinicalTrials.gov trials of pharmacological interventions for COVID-19-infected patients registered on or after January 1, 2020, through updates on or before May 31, 2021, from the last registration to subsequent publications;
6. to assess the completeness of registered results data from the initial to the final registration;
7. to assess the completeness of registered results data from the last registration to the subsequent publication.

The research objectives related to discrepancies in reporting adverse events and all-cause mortality are:

1. to assess the completeness of adverse event data reporting from RCTs on pharmacological interventions, including biologics, used to treat COVID-19 registered on ClinicalTrials.gov and in relevant publications;
2. to assess the completeness of reporting all-cause mortality data from RCTs on pharmacological interventions, including biologics, used to treat COVID-19 registered on ClinicalTrials.gov and in related publications.

2.2. Hypotheses

2.2.1. Discrepancies in reporting of data from ClinicalTrials.gov:

1. There is no difference in the completeness of WHO TRDS items in the ClinicalTrials.gov registry for COVID-19 RCTs registered on or after January 1, 2020, and updated on or before May 31, 2021;
2. There are no major changes in the information provided by the WHO TRDS items from the initial to the final registration;
3. There are no major changes in the information provided by the WHO TRDS items from the last registration to publication;
4. There is no difference in the overall completeness of results reporting from the last registration to publication.

2.2.2. Discrepancies in safety reporting between ClinicalTrials.gov and corresponding publications:

1. There are no major changes in the description of the SAEs from the last registration to publications for RCTs that examined pharmacological interventions to treat COVID-19;
2. There are no major changes in the description of the OAEs from the last registration to publications for RCTs that examined pharmacological interventions to treat COVID-19;
3. There are no major changes in the description of all-cause mortality from the last registration to publication for RCTs that examined pharmacological interventions to treat COVID-19.

4. METHODOLOGY

3.1. Discrepancies in reporting of data from ClinicalTrials.gov registry

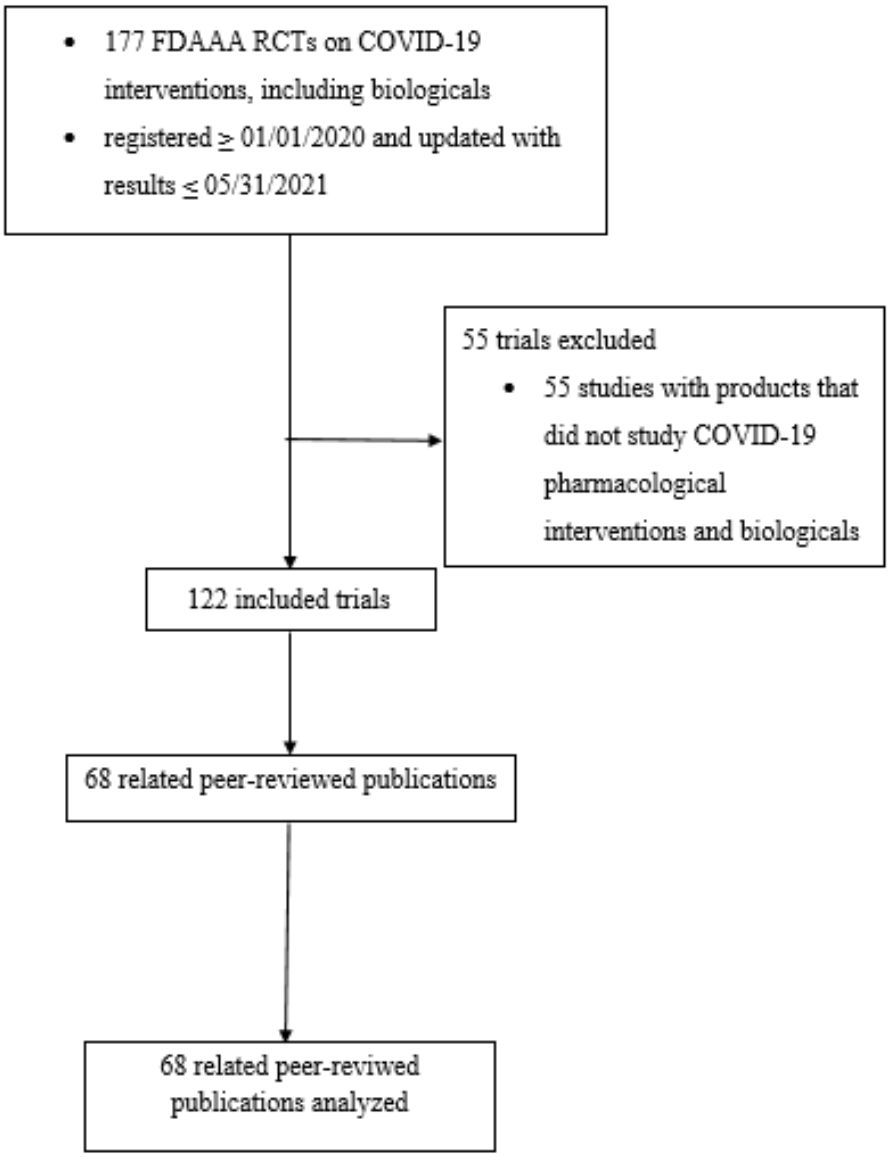
3.1.1. Sample and inclusion criteria

Our inclusion criteria for the cohort were:

- FDAAA-covered trials that studied pharmacological interventions to treat COVID-19 registered in the ClinicalTrials.gov database on or after January 1, 2020, and updated on or before May 31, 2021, along with any corresponding publications in peer-reviewed journals;
- with results;
- interventional type; and
- all study phases.

We excluded trials that did not study COVID-19 pharmacological interventions and biologicals, and non-RCT studies. We excluded from our cohort protocols and non-results trials, editorials and reviews, and preprints (Figure 2).

Figure 2. Study flowchart for the selection of trials for assessing completeness and changes between two sources



3.1.2. Trial search strategy

We examined trials that studied pharmacological interventions to treat COVID-19. We included only registered trials in the ClinicalTrials.gov registry on or after January 1, 2020, to trials updated on or before May 31, 2021,, along with any corresponding publications in peer-reviewed journals. The following filters were used to search ClinicalTrials.gov registry: terms: COVID-19, SARS-CoV-2, coronavirus, pharmacological interventions, biologicals; study phase: all study phases; study type: interventional type; study results: with results. We extracted data from these trials that met our inclusion criteria.

3.1.3. Publication search strategy

We extracted only the corresponding full publications published in peer-reviewed journals. We searched databases: PubMed, Web of Science, Google Scholar, and Scopus using the study title and National Clinical Trial (NCT) identifier to find corresponding full-text publications in peer-reviewed journals, regardless of whether they were in ICMJE member journals. Search strategies were as follows: for PubMed: ("Study title") OR (NCT number); for Scopus: ("Study title") AND (NCT number); for Google Scholar: ("Study title") AND (NCT number); for Web of Science: ("Study title") AND (NCT number).

3.1.4. ClinicalTrials.gov data extraction and comparisons

We extracted data for 24 of the WHO TRDS items, but some were excluded from the analysis. When assessing completeness in trials, Item 1 was excluded from the completeness analysis at the initial and finalregistration. Items 7 and 8 were excluded from the analysis of completeness in the last registration and publication. Item 9 was excluded from the analysis of completeness in publication. We excluded Item 21 from the completeness analysis at the first and last registration. We excluded Item 23 from the initial registration analysis.

Data were collected from the ClinicalTrials.gov website and imported into an Excel spreadsheet, with specific inclusion and exclusion criteria used as filter parameters. The ClinicalTrials.gov platform allows simultaneous extraction of basic protocol information from multiple RCTs using a single search query. This process led to the selection of an eligible cohort of RCTs for analysis, along with basic data used as secondary outcome variables in this study.

Completeness in trials at initial registration was evaluated using 19 WHO TRDS items: Item 2, Item 3, Item 4, Item 5, Item 6, Item 9, Item 10, Item 11, Item 12, Item 13, Item 14, Item 15, Item 16, Item 17, Item 18, Item 19, Item 20, Item 22, and Item 24

Completeness in trials at last registration was evaluated using 20 WHO TRDS items: Item 2, Item 3, Item 4, Item 5, Item 6, Item 9, Item 10, Item 11, Item 12, Item 13, Item 14, Item 15, Item 16, Item 17, Item 18, Item 19, Item 20, Item 22, Item 23, and Item 24.

Completeness in trial reports at publication was evaluated using 21 WHO TRDS items: Item 1, Item 2, Item 3, Item 4, Item 5, Item 6, Item 10, Item 11, Item 12, Item 13, Item 14, Item 15, Item 16, Item 17, Item 18, Item 19, Item 20, Item 21, Item 22, Item 23, and Item 24.

When comparing changes in trials from the initial to the final registration, we excluded Item 1, Items 7, Item 8, and 21. When comparing the changes between the final registration and publication, we excluded Items 7, Item 8, and 9.

Changes in trials from the initial to the last registration were assessed using 20 WHO TRDS items: Item 2, Item 3, Item 4, Item 5, Item 6, Item 9, Item 10, Item 11, Item 12, Item 13, Item 14, Item 15, Item 16, Item 17, Item 18, Item 19, Item 20, Item 22, Item 23, Item 24.

Changes from the last registration to publication were assessed with the 19 WHO TRDS items: Item 2, Item 3, Item 4, Item 5, Item 6, Item 10, Item 11, Item 12, Item 13, Item 14, Item 15, Item 16, Item 17, Item 18, Item 19, Item 20, Item 22, Item 23, and Item 24.

Item 1 was used solely to identify the randomized controlled trials in our study. Items 7 and 8 were not visible in the registry because ClinicalTrials.gov does not routinely list contact information for completed trials. Item 9 does not appear in the publication because only a scientific title was used in the published articles. We did not extract data for Item 21 because ClinicalTrials.gov does not publicly post this item, and we did not extract data for Item 23 because there was no information about results in the initial registration.

The data extraction was made independently by two investigators. We aimed to reduce biases. After the initial data extraction, the two authors resolved any disagreements that occured during their extractions and evaluations. We resolved these disagreements through a consensus discussion. We expected to have a moderate agreement on differences in trial descriptions regarding the condition, funding source, and study design characteristics, which we expect to have moderate agreement on (130,131). We considered an item as missing if information was missing in certain fields or if the terminology was uninformative (132).

3.1.5. Extraction and comparison of data from publications

In our research, we used specific criteria to evaluate discrepancies in the reporting of clinical trial data (133). Described changes included qualitative alterations. Under qualitative alterations, we considered differences in the meaning of information which was provided in a

registry field. We described quantitative differences, such as variations in numerical entries (134). We entered data in Microsoft Excel spreadsheet and used coding key.

We analyzed differences in the frequency of uninformative items and changes in RCTs that had at least one uninformative or altered item at different time points. We based our analysis tracking information (registration and start dates), outcome measures, trial descriptive information (study design data), recruitment information (eligibility criteria, sample size, and study site details), and administrative information (identifying information, availability of individual patient data, and funders).

3.1.6. Statistical analysis

Data were independently extracted, collected, and evaluated by two authors. We entered the extracted data from the registry into a Microsoft Excel spreadsheet. We used a coding key.

We performed analyses using IBM SPSS Statistics 21 (SPSS, Inc., an IBM company, Chicago, IL, USA). We compared frequencies of discrepancy items using the Chi-square test. We conducted a post-hoc analysis with Bonferroni correction. This was performed in order to control for multiple comparisons. We used 95% confidence intervals 8CI) to present percentages, frequencies, or medians with 95% confidence intervals (CI). We considered a $P<0.05$ as a statistically significant.

3.2. Discrepancies between safety reports on ClinicalTrials.gov and related publications

3.2.1. Sample and inclusion criteria

We included:

- FDAAA-covered trials;
- interventional trials that studied COVID-19 pharmacological interventions, including biologicals registered or published on or after January 1, 2020, and updated on or before May 31, 2021, which include adverse events;

  with results, and
- at all recruitment statuses.

We searched for corresponding publications in peer-reviewed journals to compare registered data with published results.

Information about expected and unexpected events that might happen during the clinical trial is submitted to ClinicalTrials.gov in three categories: Serious Adverse Event (SAE), Other Adverse Event (OAE), and All-Cause Mortality. In our study, we looked at trials of all recruitment statuses with results. We included trials registered or published on or after January 1, 2020, and updated on or before May 31, 2021. These included trias had at least one OAE or SAE. By using the timeframe, we provided at least one year for the publication of results. Using the endpoint classification information for each trial, we selected trials that studied pharmacological interventions to improve a condition or that reported adverse events associated with the intervention. We excluded trials that did not studied COVID-19 pharmacological interventions or biologicals, non-RCT studies. We excluded protocols, non-results trials, editorials, reviews, and preprints fom our analysis.

3.2.2. Trial search strategy

We examined trials of COVID-19 pharmacological interventions registered in ClinicalTrials.gov registry on or after January 1, 2020, and updated on or before May 31, 2021, along with any corresponding publications in peer-reviewed journals. We used the following filters to search ClinicalTrials.gov registry in the Advanced Search feature: terms: COVID-19, SARS-CoV-2, coronavirus, pharmacological interventions, biologicals; study phase: all study phases; study type: interventional type; study results: with results. We extracted trials that met our inclusion criteria.

3.2.3. Publication search strategy

We examined trials of COVID-19 pharmacological interventions registered in ClinicalTrials.gov registry on or after January 1, 2020, and updated on or before May 31, 2021, along with any corresponding publications in peer-reviewed journals. We used the following filters to search ClinicalTrials.gov registry in the Advanced Search feature: terms: COVID-19, SARS-CoV-2, coronavirus, pharmacological interventions, biologicals; study phase: all study phases; study type: interventional type; study results: with results. We extracted trials that met our inclusion criteria.

3.2.4. ClinicalTrials.gov data extraction and comparisons

We identified and included RCTs that reported at least one OAE or SAE, and extracted the number of participants affected by any OAE or SAE, as well as all-cause mortality, reported

by the trial investigators to ClinicalTrials.gov and related publications. We considered comparisons of OAE counts, SAE counts, and all-cause mortality to be mismatched if they did not align between the ClinicalTrials.gov results data and the corresponding publications.

One author (MS) collected extracted data from the registry between the last registration and publication. The verification was performed by another investigator (SMP) (130). We entered and extracted data into a standardized Excel spreadsheet. We used a coding key.

We considered reporting complete in the registry if it included tables reporting the number of affected participants out of those at risk for each adverse event, as required (135).

In related peer-reviewed publications, we considered reporting as complete if the occurrence of SAEs, OAEs, or deaths was explicitly stated (136). We followed the Consolidated Standards of Reporting Trials (CONSORT) extension. We made an agreement to use the term "Adverse Event" as it appears in registry (136). We considered reporting as inconsistent when AEs descriptions were different between two sources. Regarding the number of affected participants by AEs and the total number of AEs, we agreed to consider it as inconsistent if numbers were different between the registry and publications.

We used the term „adverse event" consistently with the registry and aligned with harms concept as defined in the CONSORT extension.

We used adverse events classification as either serious or other types based on registry definitions. Adverse events include both serious and non-serious cases. The word harm was used only in reporting contexts, and treatment-emergent adverse events (TEAEs) were mentioned only when explicitly documented in the registry or publication.

We evaluated differences in adverse event descriptions based on the presence and number of adverse event categories. We considered similar medical terms describing the same clinical event concordant and did not mark them as discrepancies. When adverse events were reported at different levels of aggregation between the registry and the publication, we classified this as a discrepancy due to differences in the numbers and categories reported. A discrepancy was identified when adverse events were described using different clinical terminology, grouped in one source but separated in the other, or reported in one source but omitted in the other. Adverse events and all-cause mortality were considered not to occur only if explicitly reported as zero. The absence of reported adverse events or all-cause mortality was classified as missing data and recorded as omitted.

Discrepancies in numerical entries were identified using an objective rule, under which any difference between the registry and the publication was deemed inconsistent reporting. No

threshold for clinical significance was applied, as the main purpose of this study was to evaluate the completeness and consistency of safety reporting.

Data extraction was performed independently by two investigators (MS and SP) to minimize potential biases. Potential disagreements in data extraction were resolved through consensus discussions. This discussion was held if there were disagreements about the condition, funding source, and study design characteristics (130,131).

3.2.5. Statistical analysis

Data were independently extracted, collected, and evaluated by two authors. We used an Excel spreadsheet and coding key. We used frequencies (n) and percentages (%) by category to represent descriptive analysis. We used the chi-square test to compare frequencies. We used Cohen's effect size (ϕ) for Chi-square analysis and (κ) with corresponding 95% confidence intervals (CI).

For this analysis, we used IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA).

3.2.6. Ethical Principles

We did not seek an approval from institutional ethics committee. We performed a cross-sectional study based on database data. We did not conduct experimental procedures or gathered patient data. We declare that there were no conflicts of interest.

4. RESULTS

4.1. Characteristics of COVID-19 pharmacologic trial data registered in ClinicalTrials.gov and corresponding publications

4.1.1. Baseline characteristics

We identified 177 RCTs that met our inclusion criteria (Figure 4). After applying exclusion criteria, we selected 122 eligible trials. 55 trials examined non COVID-19 interventions and were excluded from the analysis. Of the 122 eligible trials, we found 68 had peer-reviewed related publications (Figure 3).

The majority of registered trials at final registration were phase 2 (n=54, 44%), double-blinded (n=44, 36%), and placebo-controlled (n=62, 51%). Most trials with published results that recorded phase were phase 3 (n=19, 28%), double-blind (n=44, 64%), and placebo-controlled (n=41, 61%) (Tables 3 and 4).

Registered trials on COVID-19 pharmacologicals, including biologicals, reported the recruitment region at initial registration (n=78, 64%). In the latest registration, all trials reported the recruitment region, with 24 being multicenter trials (35%). We identified that 61 % (n=75) trials did not start before registration.

Majority of trials at initial registration (n=69, 57%) and their corresponding publications (n=37, 54%) were not industry-funded.

The most common intervention was hydroxychloroquine (n=8, 12%), used with azithromycin in 2% of the related publications. Remdesivir was used in 6 (9%) published trials with tocilizumab (n=1, 2%). It was used with interferon beta-1a in one case(2%). A total of 41 (60%) publications did not start prior to registration. Biological interventions were investigated in 23 (34%) publications.

Most publications, specifically 61 (90%), were from multicenter trials, while 7 (10%) came from single-center studies. Of the 115 multicenter trials (94%), 53 (43%) were industry-funded. In contrast, the 7 single-center trials (6%) were not industry-funded. One was funded by a community-based organization, three by universities, and three by hospitals and medical centers.

Figure 3. Study flowchart for the selection of trials for assessing adverse event and death reporting

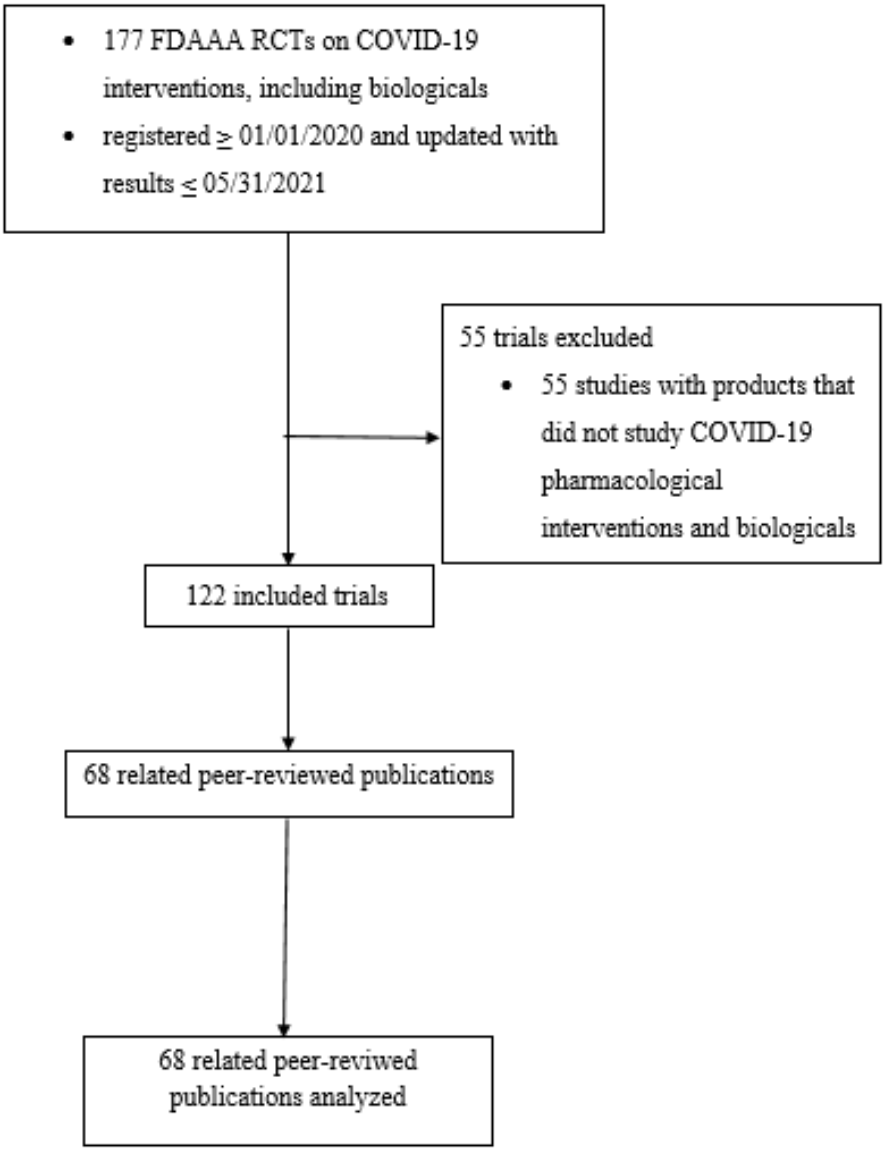


Table 3. Baseline characteristics of COVID-19 pharmacological intervention trials registered in ClinicalTrials.gov from the first to the last registration

		Initial registration *(ClinicalTrials.gov)*, n, (%)	**Last registration *(ClinicalTrials.gov)*, n, (%)**
Phase*	N/A	3 (2)	3 (2)
	1	14 (12)	12 (10)
	1/2	6 (5)	7 (6)
	2	55 (45)	54 (44)
	2/3	9 (7)	7 (6)
	3	31 (26)	36 (30)
	4	4 (3)	3 (2)
Masking†	Open label	39 (32)	39 (32)
	Single blind	9 (7)	6 (5)
	Double blind	43 (35)	44 (36)
	Triple blind	8 (7)	11 (9)
	Quadruple blind	23 (19)	22 (18)
Control	Placebo	62 (51)	62 (51)
	Active	33 (27)	31 (25)
	Both	13 (11)	15 (13)
	No control group	9 (7)	9 (7)
	Not receiving anything	5 (4)	5 (4)
Assignment	Single group	11 (9)	9 (7)
	Parallel	97 (80)	101 (84)
	Cross-over	3 (2)	2 (1)
	Factorial	5 (4)	3 (2)
	Sequined	6 (5)	7 (6)
		Total 122 (100)	Total 122 (100)

Abbreviations: COVID-19 - Coronavirus Disease 2019, RCT – Randomized Controlled Trial

*, †Data as entered by investigators in ClinicalTrials.gov.

n refers to the number of trials; the % was calculated using the total number of trials in the table as the denominator.

Table 4. Baseline characteristics of COVID-19 pharmacological intervention trials with results published

		Last registration *(ClinicalTrials.gov)*, n, (%)	**Publication, n, (%)**
Phase*	N/A	3 (2)	0 (0)
	1	12 (10)	3 (4)
	1/2	7 (6)	1 (2)
	2	54 (44)	15 (22)
	2/3	7 (6)	3 (4)
	3	36 (30)	19 (28)
	4	3 (2)	0 (0)
	Unspecified	0 (0)	27 (40)
Masking†	Open label	39 (32)	10 (15)
	Single label	6 (5)	3 (4)
	Double blind	44 (36)	44 (64)
	Triple blind	11 (9)	0 (0)
	Quadruple blind	22 (18)	1 (2)
	Unspecified	0 (0)	10 (15)
Control	Placebo	62 (51)	41 (60)
	Active	31 (25)	15 (22)
	Both	15 (13)	8 (12)
	No control group	9 (7)	3 (4)
	Not receiving anything	5 (4)	1 (2)
Assignment	Single group	9 (7)	2 (3)
	Parallel	101 (84)	59 (87)
	Cross-over	2 (1)	1 (2)
	Sequenced	7 (6)	1 (2)
	Factorial	3 (2)	0 (0)
	Unspecified	0 (0)	5 (6)
		Total 122 (100)	Total 68 (100)

Abbreviations: COVID-19 - Coronavirus Disease 2019, RCT – Randomized Controlled Trial

*, †Data as entered by investigators in ClinicalTrials.gov.

n refers to the number of trials; the % was calculated using the total number of trials in the table as the denominator.

4.1.2. Completeness of WHO TRDS trial registration data set items

Table 5 displays which TRDS items were absent from the firts to the final entry in the registry and related publications. We recorded that none of the WHO items appeared in any other registry field in the first registration. Mainly, the Secondary Identifying Number was missing in 95 (78%) trials at the initial entry, while the IPD sharing statement was absent in 52 (76%) of the related publications (Table 5).

Table 5. Missing WHO TRDS items in ClinicalTrials.gov from the initial to the last registration and corresponding publication

WHO TRDS ITEM	**Initial registration (*ClinicalTrials.gov*), n, (%)**	**Last registration (*ClinicalTrials.gov*) n, (%)**	**Publications, n, (%)**
Date of Registration in Primary Registry	0 (0)	0 (0)	1 (2)
Secondary Identifying Number	95 (78)[a]	1 (0.8)	39 (57)[b]
Source(s) of Monetary or Material Support	0 (0)	0 (0)	20 (30)
Primary Sponsor	0 (0)	0 (0)	14 (21)[f]
Secondary Sponsor	0 (0)	0 (0)	6 (9)[e]
Public Title	0 (0)	0 (0)	N/A
Scientific Title	0 (0)	0 (0)	0 (0)
Countries of Recruitment	44 (36)	0 (0)	3 (4)
Health Condition(s) or Problem(s) Studied	0 (0)	0 (0)	4 (6)
Intervention(s)	0 (0)	0 (0)	0 (0)
Key Inclusion and Exclusion criteria	0 (0)	0 (0)	2 (3)
Study Type	0 (0)	0 (0)	1 (1)
Date of First Enrollment	0 (0)	0 (0)	5 (7)
Sample Size	0 (0)	0 (0)	0 (0)
Recruitment Status	0 (0)	0 (0)	4 (6)
Primary Outcome(s)	0 (0)	0 (0)	5 (7)
Key Secondary Outcome(s)	12 (10)	13 (11)	8 (12)
Ethics Review	N/A	N/A	34 (50)

Completion Date	0 (0)	0 (0)	6 (9)
Summary Results	N/A	0 (0)	5 (7)
IPD Sharing Statement	23 (19)[c]	17 (14)[d]	52 (76)

Abbreviations: WHO- World Health Organization; TRDS- Trial Registration Data Set; IPD- Individual Participant Data; N/A- not applicable

n refers to the number of trials; the % was calculated using the total number of trials in the table as the denominator.

[a,b]$P < 0.001$ vs. last registration, Bonferroni post-hoc test. [c,d]$P < 0.001$ vs. publication data, Bonferroni post-hoc test. [e]$P = 0.002$ vs. initial and last registration, Bonferroni post-hoc test. [f]$P < 0.001$ vs. initial and last registration, Bonferroni post-hoc test.

4.1.3. Changes to the WHO TRDS trial registration data set items

Changes were documented in all RCTs between the first and last registrations and in all corresponding publications (Tables 6 and 7). Modifications to WHO TRDS items were observed across all included trials. We recorded that the majority of changes from initial to last registration occured in completion date (97%). Additionally, the secondary identifying number was changed in 90% of RCTs. We recorded 40 (33%) changes to the brief title after initial registration, and in all cases, the changes were made to make it more descriptive. The changes for the official title were recorded in 25 (20%) cases for the same reason. The IPD data sharing statement was altered after initial registration in 13 (11%) cases, and in 2 (2%) trials, it was added post-registration. Most changes in the health conditions studied (n=17, 14%) occurred after initial registration, with only one (1%) case of an addition after registration. Three (3%) trials had a new condition added. Notably, interventions were mostly updated descriptively (n=78, 64%), with only two (2%) interventions added after registration. Changes to inclusion criteria involved additions after initial registration in 23 (19%) trials and deletions of two or more criteria in 22 (18%) trials. In 7 (6%) cases, multiple criteria were both deleted and added after registration. In 6 (5%) trials, criteria were changed such that two or more were deleted, while only five (4%) trials had a single criterion deleted. Regarding exclusion criteria, most changes (n=30, 25%) involved additions after registration. Thirteen (11%) changes were made to the description of the intervention, with 5 (4%) involving the deletion or addition of multiple criteria, and 7 (6%) involving the deletion of a single criterion or the addition of new ones.

Changes to „Study Type“ mainly involved modifications to study design (n=23, 19%), with phase changes (n=7, 6%) and descriptive updates after registration (n=5, 4%) also noted. The study start date was changed after registration to a later date in 88 (72%) cases, to an earlier date in 16 (13%) cases, and, in 17 (14%) cases, the specific day was left unspecified. Only one (1%) case involved an addition after registration. Number participants was reported as larger at the last registration than at the initial registration in 38 (31%) trials, whereas the majority (n=49, 40%) had a smaller sample size at the last registration. In 20 (16%) trials, new primary outcomes were added after initial registration. Only one (1%) trial added a primary outcome after registration while deleting an existing one. A total of 9 (7%) cases involved deleting outcomes. Changes in descriptions after registration were recorded in 57 (47%). The secondary outcomes were mostly changed by adding outcomes after registration (n=64, 52%), with 41 (34%) involving the deletion of existing outcomes. Changes in outcome descriptions after registration were recorded in 40 (33%) trials. Only eight (7%) changes involved adding new outcomes after registration and deleting existing ones.

Table 6. Changes in WHO TRDS items regarding study descriptions in the ClinicalTrials.gov registry between the first and the last registration

Changes in WHO TRDS items	**Initial to last registration (n=122), n(%)**
Date of Registration in Primary Registry	122 (99)
Secondary Identifying Number	110 (90)
Source(s) of Monetary or Material Support	4 (3)
Primary Sponsor	4 (3)
Secondary Sponsor	4 (3)
Public Title	40 (33)
Scientific Title	25 (20)
Countries of Recruitment	47 (39)
Health Condition(s) or Problem(s) Studied	21 (17)
Intervention(s)	80 (66)
Key Inclusion and Exclusion Criteria	96 (79)
Study Type	35 (29)
Date of First Enrollment	122 (100)
Sample Size	87 (71)
Recruitment Status	122 (100)
Primary Outcome(s)	87 (71)
Key Secondary Outcome(s)	153 (125)
Completion Date	118 (97)
IPD sharing statement	15 (12)

Abbreviations: WHO- World Health Organization; TRDS- Trial Registration Data Set; IPD- Individual Participant Data.

n refers to the number of trials; the % was calculated using the total number of trials in the table as the denominator.

Table 7. Changes in WHO TRDS items regarding study descriptions in the ClinicalTrials.gov registry between the last registration and corresponding publications

Changes in WHO TRDS items	**The last registration and corresponding publications (n=122), n (%)**
Date of Registration in Primary Registry	32 (26)
Secondary Identifying Number	62 (51)
Source(s) of Monetary or Material Support	43 (35)
Primary Sponsor	43 (35)
Secondary Sponsor(s)	43 (35)
Scientific Title	68 (56)
Countries of Recruitment	12 (10)
Health Condition(s) or Problem(s) Studied	20 (16)
Intervention(s)	2 (2)
Key Inclusion and Exclusion Criteria	94 (77)
Study Type	49 (40)
Date of First Enrollment	32 (26)
Sample Size	17 (14)
Primary Outcome(s)	9 (7)
Key Secondary Outcome(s)	1 (1)
Ethics Review	68 (56)
Completion Date	58 (48)
IPD sharing statement	14 (11)

Abbreviations: WHO- World Health Organization; TRDS- Trial Registration Data Set; IPD- Individual Participant Data.

n refers to the number of trials; the % was calculated using the total number of trials in the table as the denominator.

The secondary identifying number was changed in most publications (n=62, 51%). In 39 trials (32%), it was missing in the corresponding publications; in 6 trials (5%), it was the same as in the last registration; and in 16 trials (13%), it was changed in the publications. Only 1 trial (1%) had it added during the last update before publication. The primary sponsor was recorded in 31 (25%) published trials, modified in 6 (5%), and omitted in 6 (5%). Changes in the scientific title appeared as variations in the title description, providing more details about the study design than were present in the registry for all 68 relevant publications.

The enrolled countries were changed in 7 (6%) trials, in the article, from what is listed in the registry, and for 5 (4%) published articles, it was not listed. Regarding the health conditions studied, 16% of the articles, or 20 in total, reported changes, all of which involved providing a more detailed description of the condition than the registry. Similarly, the interventions were modified in only 2 (2%) articles, with changes described as adding more details about the study's intervention. Inclusion criteria were modified in 51 cases. Most of these changes (n=39, 32%) involved the omission of inclusion criteria in the published articles, while in 4 (3%) trials, new criteria were added. Similarly, 4 (3%) trials reported updates to the inclusion criteria in the articles compared to the registry. Only 1 (1%) article omitted a criterion and added a new one, and another (1%) article omitted criteria while including more informative ones. In 2 (2%) trials, the inclusion criteria were missing from the last registration.

Most changes in exclusion criteria involved omitting criteria in the article for 28 (23%) trials, and only 2 (2%) trial involved both omitting a criterion and adding new criteria in the article. In 6 (5%) trials, a new criterion was added in the article, similar to 6 (5%) trials, where the change was recorded as more informative exclusion criteria in the article compared to the registry. Only 1 (1%) trial lacked exclusion criteria in its last registration.

In 30 (25%) trials, the study type was more clearly described in the registry than in the article. In 14 (11%) trials, the study design (type of masking) was reported to have changed in the article. Only 2 (2%) trials recorded a change in phase in the article. One (1%) trial contained more information about study design in the registry than in the article. Another (1%) trial was recorded to have other changes in study design, and one (1%) trial had a more informative study design in the registry along with a change in study design in the article. The study start date was changed in 18 (15%) trials, was updated to a later date (by comparing the date in the article versus the registry), and 10 (8%) trials lacked a date in the related publication. Only 2 (2%) trials had the date added during the final update before publication. In 2 (2%) trials, the date was recorded as earlier (according to the date in the article versus the registry). Enrollment was reported as higher in articles than in the registry in 7 (6%) trials, but lower in 10 (8%). Changes

in primary outcomes were recorded in 2 (2%) cases where registered outcomes were introduced in the article. The majority of changes (n=7, 6%) occurred when registered outcomes were omitted from the article. Regarding the study completion date, 19 (16%) trials had changes to a later date (according to the date in the article vs. the registry). 32 trials (26%) were changed as a shift to an earlier date (according to the date in the article vs. the registry). However, only 6 (5%) trials reported this item as missing in the article.

4.1.4. Informativeness of WHO TRDS items from first to last registration and their corresponding publications

We identified an uninformative representation of the data in the registry and related peer-reviewed publications (Table 8). Most trials had uninformative items in their initial registration. The majority contained uninformative items due to unexplained methodology (Table 8).

Table 8. Uninformativeness of WHO TRDS items in the ClinicalTrials.gov registry and corresponding publications

		Uninformativeness (n)				
Uninformative WHO TRDS item	**Trials with uninformative WHO TRDS item, n (%)**	**Missing dosage**	**Code instead of name**	**Unexplained terminology**	**Unexplained or short entry**	**Unexplained methodology**
Initial registration (*ClinicalTrials.gov)*	122 (100)					
Intervention (s)	101 (83)	34 (28)	1 (1)	2 (2)	64 (52)	0 (0)
Key Inclusion and Exclusion Criteria	110 (90)	0 (0)	0 (0)	43 (35)	67 (55)	0 (0)
Study Type	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Date of First Enrollment	26 (21)	0 (0)	0 (0)	0 (0)	26 (21)	0 (0)
Primary Outcome(s)	116 (95)	0 (0)	0 (0)	1 (1)	1 (1)	114 (93)
Key Secondary Outcomes	111 (91)	0 (0)	0 (0)	1 (1)	0 (0)	110 (90)
Completion Date	35 (29)	0 (0)	0 (0)	0 (0)	35 (29)	0 (0)
The last registration (*ClinicalTrials.gov)*	121 (99)					
Scientific Title	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0(0)
Intervention(s)	92 (75)	17 (14)	1 (1)	2 (2)	72 (59)	0 (0)
Key Inclusion and Exclusion Criteria	105 (86)	0 (0)	0 (0)	47 (39)	58 (48)	0 (0)
Date of First Enrollment	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)

Primary Outcome(s)	82 (67)	0 (0)	0 (0)	6 (5)	7 (6)	69 (57)
Key Secondary Outcomes	77 (63)	0 (0)	0 (0)	10 (8)	3 (2)	64 (52)
Completion Date	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Publications	68 (56)					
Countries of Recruitment	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Intervention(s)	3 (2)	1 (1)	1 (1)	0 (0)	1 (1)	0 (0)
Key Inclusion and Exclusion Criteria	54 (44)	0 (0)	0 (0)	2 (2)	52 (43)	0 (0)
Study Type	62 (51)	0 (0)	0 (0)	0 (0)	62 (51)	0 (0)
Date of First Enrollment	6 (5)	0 (0)	0 (0)	0 (0)	6 (5)	0 (0)
Primary Outcome(s)	22 (18)	0 (0)	0 (0)	0 (0)	3 (2)	18 (15)
Key Secondary Outcomes	22 (18)	0 (0)	0 (0)	1 (1)	3 (2)	18 (15)
Ethics Review	4 (3)	0 (0)	0 (0)	0 (0)	4 (3)	0 (0)
Completion Date	6 (5)	0 (0)	0 (0)	0 (0)	6 (5)	0 (0)
IPD sharing statement	2 (2)	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)

Abbreviations: WHO- World Health Organization; TRDS- Trial Registration Data Set; IPD- Individual Participant Data.

n refers to the number of trials; percentages were calculated using the total number of trials in the table as the denominator.

4.1.5. Completeness of the presentation of the results

All published trials reported participant flow data. Baseline descriptions were present in 66 (54%) published trials. Sixty- seven (55%) trials reported SAEs in the ClinicalTrials.gov registry, while 54 (44%) published trials reported SAEs. OAEs were reported in 66 (97%) trials in ClinicalTrials.gov registry and in 48 (71%) published trials. Item related to mortality, named as „All-cause Mortality," was analyzed in 68 (56%) trials in the registry and in 56 (68%) publications.

4.2. Safety reporting from clinical trials on COVID-19 pharmacological interventions registered in the ClinicalTrials.gov and in corresponding publications

4.2.1. Baseline characteristics

We analyzed 68 trials with published results for discrepancies in adverse event and all-cause mortality data (Figure 5). Most trials with results published (n=41/122, 34%) did not start before registration. Most trials were double-blind (n=44/122, 65%), randomized (n=64/68, 52%), industry-funded (n=31/122, 25%), and placebo-controlled (n=41/122, 34%). Drugs were the most common intervention in the publications (n=44/122, 36%), primarily in the parallel assignment (n=59/122, 48%). Biological interventions were used in 19% publications (n=23/122).

We recorded that the most common intervention was hydroxychloroquine (n=8/122, 7%). It was used with azithromycin in 1 trial (1%). Remdesivir was present in six trials (5%). It was used with tocilizumab in 1 trial and with interferon beta-1a in 1 case (1%).

4.2.2. Adverse event reporting from clinical trials on COVID-19 pharmacological interventions registered in the ClinicalTrials.gov and in corresponding publications

We recorded that the majority of trials inconsistently reported AEs. This includes SAEs and OAEs reporting (Table 9).

We recorded that all trials in ClinicalTrials.gov reported OAEs. One trial did not report SAEs (n=1/68, 2%). We found that the frequency threshold for OAEs was reported in every trial in the registry (n=68/68, 100%), while only 24% (n=16/68) of the trials in the publication reported it. The differences in reporting and omitting SAEs between ClinicalTrials.gov and the publications were statistically significant with a small to moderate effect sizes. The discrepancy in reporting rates and omission of OAEs and deaths was moderate.

Table 9. Reporting adverse events for COVID-19 pharmacological interventions RCTs (n=68) with published results for trials registered on or after January 1, 2020, and updated on or before 31 May 2021 in ClinicalTrials.gov

	ClinicalTrials.gov, n=122	**Publications, n=68**	**Effect size[a] (95% CI)**	***P*-value[b]**
Reporting rate, n (%)				
SAEs	67 (99)	57 (84)	0.26 (0.10-0.42)	0.003
OAEs	68 100)	57 (84)	0.30 (0.14-0.46)	0.001
AEs reported as zero (n, %)				
SAEs	9 (13)	9 (13)	N/A	1.000
OAEs	9 (13)	3 (4)	N/A	0.070
AEs omitted (n, %)				
SAEs	1 (2)	11 (16)	0.26 (0.10-0.42)	0.003
OAEs	0 (0)	11 (16)	0.30 (0.14-0.46)	0.001

Abbreviations: AE- Adverse Event, COVID-19 - Coronavirus Disease 2019, *CI – Confidence Interval*, RCT – Randomized Controlled Trial, SAE– Serious Adverse Event, OAE – Other Adverse Event.

n refers to the number of trials; percentages were calculated using the total number of trials in the table as the denominator.

[a]Cohen's effect size (ϕ); r*anges from 0.10 to 0.50, where 0.30 represents a moderate magnitude.*

[b]Chi-square test with the significance level considered at < 0.05.

Table 10. Reporting serious adverse events (SAEs) and other adverse events (OAEs) for COVID-19 pharmacological interventions RCTs (n=68) with published results for trials registered on or after January 1, 2020, and updated on or before 31 May 2021 in ClinicalTrials.gov

	Reporting rate SAE, n (%)	**Reporting rate OAE, n (%)**
Different number of descriptions		
Yes	49 (72)	55 (81)
No	19 (28)	13 (19)
If a different number of descriptions	SAE (n=49)	OAE (n=55)
Less in the register	6 (12)	23 (42)
More in the register	33 (67)	21 (38)
Omitted in the publication (n=68)	11 (16)	11 (16)
Not applicable (N/A) (n=68)	19 (28)	13 (19)
Different sum of affected participants by AE		
Yes	35 (51)	55 (81)
No	33 (49)	13 (19)
If a different sum of affected participants (n=35)		n=55
Less participants in the register	8 (23)	30 (55)
More patients in the register	17 (49)	14 (25)
Omitted sum of participants in the publication (n=68)	11 (16)	11 (16)
Not applicable (N/A) (n=68)	33 (49)	0 (0)

Abbreviations: AE- Adverse Event, COVID-19 - Coronavirus Disease 2019, RCT- Randomized Controlled Trial, SAE- Serious Adverse Event, OAE- Other Adverse Event

n refers to the number of trials; percentages were calculated using the total number of trials in the table as the denominator.

We observed discrepancies in the number of SAE in 49 (72%) publications. Most of these publications, 33 (67%) trials, had more SAE descriptions listed in the registry than in the corresponding publications. Only 6 (12%) trials reported fewer descriptions in the registry compared to the publications. SAE descriptions were omitted in 11 (16%) publications, while in 19 (28%) publications, we marked "Not Applicable“ because no values were reported in either source. Regarding the number of affected patients for each SAE, we found that 17 (49%) trials reported more patients affected by SAE in the registry (Table 10).

Discrepancies regarding the OAEs descriptions between two sources were identified in the most trials (n=55/68, 81%). The most common discrepancy was that the registry contained fewer descriptions than the publications, noted in 23 (42%) trials. The majority of most discrepancies in the number of patients affected by OAEs (n=55/68, 81%) involved fewer patients documented in the registry than in the publications, occurring in 30 (55%) trials.

4.2.3. Deaths reporting from clinical trials on COVID-19 pharmacological interventions registered in the ClinicalTrials.gov and in corresponding publications

All trials reported all-cause mortality in the registry. Most trials inconsistently reported all-cause mortality data (Table 11). Data on all-cause mortality were omitted in 14 (21%) publications. We recorded that 31% trials reported all-cause mortality as in the registry. Among them, 18% trials reported all-cause mortality as zero in the peer-reviewed publications. This shows a discrepancy between the two sources.

Table 11. Reporting deaths for COVID-19 pharmacological interventions RCTs (n=68) with published results for trials registered on or after January 1, 2020, and updated on or before 31 May 2021 in ClinicalTrials.gov

	ClinicalTrials.gov	**Publication**	**Effect size[a] (95% CI)**	***P*-value[b]**
Reporting rate, n (%)				
Deaths	68 (100)	54 (79)	0.34 (0.18-0.50)	0.001
Reported as zero (n, %)				
Deaths	21 (31)	12 (18)	N/A	0.072
Omitted (n, %)				
Deaths	0 (0)	14 (21)	0.34 (0.18-0.50)	R40.001

Abbreviations: COVID-19 - Coronavirus Disease 2019, *CI – Confidence Interval*, RCT – Randomized Controlled Trial.

n refers to the number of trials; percentages were calculated using the total number of trials in the table as the denominator.

[a]Cohen's effect size (ϕ); r*anges from 0.10 to 0.50, where 0.30 represents a moderate magnitude.*

[b]Chi-square test with the significance level considered at < 0.05.

5. DISCUSSION

5.1. Reporting characteristics of clinical trial data on COVID-19 pharmacologicals registered in ClinicalTrials.gov and related publications

Our study found that discrepancies in WHO TRDS items were common across multiple sources. We observed reporting inconsistencies across 122 COVID-19 RCTs. There are several reasons for these reporting discrepancies during the COVID-19 pandemic. Since COVID-19 was declared a global health emergency (137), publication rates in journals (138–140) increased rapidly (138). Ranaud et al. (138) noted that changes in publication standards and trends were driven by faster peer-review processes, a focus on pandemic-related topics, and increased pressure to share findings quickly. As a result, Grüßer et al. (140) concluded that the urgent need to publish during the epidemic likely compromised methodological rigor and reporting transparency, potentially affecting the validity and completeness of trial data interpretation. To improve the credibility and long-term value of public health research, authors are exploring ways to enhance research procedures, including study design, data sharing, and transparency (139). Our findings support similar observations. Furthermore, our study shows that incomplete reporting continues even in high-impact journals (141,142).

Our findings indicated that some authors had previously identified incomplete reporting in high-impact-factor journals (132,142–144). We recorded that the majority of the registered trials had incomplete initial registration. Additionally, the registration improved from incomplete to ready for publication. It is possible that investigators modified trial details to better match published reports, although this practice may raise concerns about selective reporting (145).

More than half of the trials at initial registration were recorded to have missing items. These items differed from those at final registration and from the corresponding publications. The most common missing items were the IPD sharing statement at the last registration (14%) and the associated publications (76%). These findings indicate that this item is present in only a small number of RCTs despite the ethical obligation (109) and the requirement (146) for publication in ICMJE journals. Our results align with the findings reported by Blanco et al. (146), presenting that non-prospective registrations in an ICMJE-accepted registry were published in high-impact journals claiming adherence to ICMJE standards. The trend of rapid publication during COVID-19, driven by the need for quick ethics approvals, was reflected in the fact that 50% of publications reported ethics committee approvals.

Changes were documented in all RCTs registered on ClinicalTrials.gov and in all corresponding publications. These changes mainly resulted from collective updates, such as

deleting, adding, or modifying the methodology. It is notable that alterations were recorded in interventions, sample sizes, and outcomes from the initial to the final registration. More than half of the trials also had unjustified changes to their primary and secondary outcomes. This pattern continued when examining changes from the last registration to the related publications.

Uninformative WHO TRDS items appeared in all trials initially and in 99% of trials at the last registration. The frequency of these uninformative items decreased in published reports. It is concerning that most of these uninformative items involved interventions, key inclusion and exclusion criteria, and outcomes. Additionally, more details about the study design were found in the registry than in the corresponding publications.

Our findings show that most trials in the registry (n=69, 57%) and their corresponding publications (n=37, 54%) were not industry-funded. Conversely, in the literature, industry-funded trials are associated with incomplete and inconsistent reporting (141,142).

5.1.1. Limitations of the first study

We analyzed RCTs listed in the ClinicalTrials.gov registry, the largest online registry (147,148). However, findings showed that most COVID-19 trials were registered in the Chinese Clinical Trials Registry (149). This presents a limitation because, due to the selection and use of data from ClinicalTrials.gov, some trials registered in the Chinese Clinical Trials Registry might be excluded. Since our study is retrospective, interpreting the qualitative data may be subjective, which could result in significant modifications in the items and outcomes.

We explored the ClinicalTrials.gov registry and relevant journal publications in the database before pre-registering the study. However, the methodology remained unchanged after data collection began. We recorded that the reliability of the extracted data regarding major changes remained high. The kappa range was between 0.80 and 1.00. We recorded the lowest kappa 0.80 (CI 0.59-1.00) for major changes. These changes were recorded between the last registration and the corresponding peer-reviewed publications. Regarding the related publications, some registry numbers were not provided, so we could not locate those publications. We performed the extraction and analysis by two authors. We did not include a third author. Any potential disagreements were resolved through consensus.

We excluded protocols, preprints, editorials, reviews, and non-results trials, which can be considered limitations. Instead of using the PRESS guideline, we relied on study-specific information to identify publications. Finally, since our sample of studies and related publications is small, any differences or changes in data presentation should be interpreted with caution.

5.2. Safety reporting from clinical trials on COVID-19 pharmacological interventions registered in ClinicalTrials.gov and in corresponding publications

Our second study on safety reporting for COVID-19 trials revealed inconsistencies in the data between the two sources. Only 2% trial did not report OAEs, while most trials (n=55, 81%) reported OAEs inconsistently between the last registry and the publications. The representation of OAEs and patients affected by other adverse events in related peer-reviewed publications was more extensive than in the registry. This may be because the reporting threshold was lower in more than half of the publications. Similar findings were reported by Jurić et al. (150) and Paladin and Pranić (151).

We found that the majority of the analyzed publications reported SAEs, but many underreported them compared to the registry. Omission of SAEs was found in only 11 (16%) publications, but 9 (13%) explicitly stated zero SAEs. Several authors (152–158) also noted similar discrepancies in SAE reporting.

We found that 18% of relevant papers reported deaths as zero, despite nearly half of them having inconsistent death reporting. Our analysis revealed a discrepancy in how death reports were recorded between the two sources. Both sources reported deaths differently, and some authors reported similar findings (157,159,160).

Accurate reporting of all-cause mortality is vital from both ethical and methodological perspectives. The ability of physicians to thoroughly assess the safety of pharmacological interventions can be hindered by inconsistent and incomplete reporting of mortality data. This also complicates trial oversight activities such as data review and safety monitoring. Some authors have emphasized the urgent need to improve regulatory standards by trialists (150,151). One recommendation to enhance transparent event reporting is to fully document key data in the registries (151). Additionally, a checklist suggested by an author aims to help editors identify data inconsistencies in manuscripts submitted to journals (161).

The safety profile of important COVID-19 treatments, including biologics, is unclear due to inconsistencies in adverse event reporting across COVID-19 trials. To better inform treatment decisions, it is essential to improve the reporting of adverse events and mortality data between the ClinicalTrials.gov registry and related publications through policy changes. Addressing discrepancies and incomplete reports can be done by requiring cross-checks of safety data from both sources. Additionally, investigators could benefit from using and studying about CONSORT principles, consistent adverse event reporting in registries, and regulatory requirements.

5.2.1. Limitations of the second study

We analyzed only trials in the ClinicalTrials.gov registry. We chose this registry because it is the largest web-based registry (147,148). The analysis of discrepancies was based on standards applied to both sources. We found that the data's reliability regarding discrepancies between the two sources was high. We searched the registry and related peer-reviewed publications in a database before pre-registering the study. The methodology remained consistent throughout the data extraction process.

We excluded protocols, preprints, editorials, reviews, and non-results trials, which may be a limitation. Additionally, we did not rate recorded discrepancies between two data sources by grades, and we did not investigate links between trial features and discrepancies. Finally, our sample of studies and related publications is small, so any findings or differences in data presentation must be approached with caution.

6. CONCLUSION

The completeness and integrity of WHO TRDS items for COVID-19 pharmacological intervention trials are insufficient, despite recommendations and regulations. More complete WHO TRDS items are found in the latest registration and related publications compared to the initial registration.

We tracked modifications to WHO TRDS items throughout all trials from initial registration to final publication.

The data in WHO TRDS items provide the best insights into COVID-19 pharmacological intervention trials found in relevant publications, while the least informative data are in the initial registration on ClinicalTrials.gov.

Other adverse events and all-cause mortality were recorded in all trials in the registry. One trial in the registry did not include the serious adverse events. Serious adverse events were recorded more often in the registry than in the corresponding publications.

The investigator should verify the accuracy of data for each WHO TRDS item relevant to a specific clinical trial. Additional data checks are also necessary by journal editors before publishing results from COVID-19 pharmacological interventions. By providing precise individual-trial data from various sources can reduce publication discrepancies and transparency in data presentation will be improved. Furthermore, the inconsistent and incomplete reporting of AEs and all-cause mortality data in publications jeopardizes patient safety. A more thorough comparison of registered and reported AE and death data in submitted manuscripts is also essential during the trial publication process.

7. SUMMARY

Title: Reporting characteristics of COVID-19 pharmacological intervention trials registered in ClinicalTrials.gov and in publications

Background: Accurate and complete reporting of COVID-19 RCTs and adverse events is essential for clinical practice. The COVID-19 pandemic led to overreporting and an explosion of articles. We conducted this research to evaluate the integrity and consistency of reporting COVID-19 pharmacological intervention trials.

Methods: We performed a cross-sectional analysis of trials that met our criteria. We included trilas from January 1, 2020, to May 31, 2021. The study included 177 RCTs along with 68 peer-reviewed publications. We followed the STROBE checklist. The study was pre-registered.

Results: During the trial, 19 WHO TRDS items were modified. We extracted data from 122 RCTs and 68 peer-reviewed publications. There were fewer missing data-sharing statements in the registry than in publications. We independently assessed RCTs to achieve $\kappa \geq 0.80$, ensuring a high reliability of data extraction (kappa range: 0.80–1.00). 72 % publications had inconsistent numbers of SAE descriptions. More than half (35/68 [51%]) of the trials had discrepancies in the reported number of patients affected by each SAE. We found that 11/68 [16%] publications omitted death data in the registry.

Conclusion: Our results confirmed that discrepancies in the reporting of WHO TRDS item data in the registry persist despite existing recommendations and guidelines. We stress a to improve essential reporting to support updated treatment decisions for COVID-19.

Keywords: COVID-10; ClinicalTrials.gov; SARS-CoV-2; randomized controlled trials; undesired events; reporting; all-cause mortality; patient safety; checklist.

8. SAŽETAK

Naslov: Karakteristike izvještavanja kliničkih ispitivanja o COVID-19 farmakološkim intervencijama u ClinicalTrials.gov i publikacijama

Cilj: Cilj našeg istraživanja bio je procijeniti potpunost i promjene podataka za registracijski skup podataka o kliničkom ispitivanju Svjetske zdravstvene organizacije za klinička ispitivanja lijekova COVID-19, uključujući i biološke lijekove. Također, cilj je bio i procijeniti integritet izvještavanja neželjenih događaja, uključujući smrtnost u COVID-19 randomiziranim kliničkim ispitivanjima. Proučavali smo klinička ispitivanja registrirana u ClinicalTrials.gov registru i pripadajuće članke u recenziranim časopisima.

Metode: Proveli smo presječnu studiju randomiziranih kliničkih ispitivanja registriranih u registru ClinicalTrials.gov na dan 1. siječnja 2022. godine ili kasnije, ažuriranu na dan 31. svibnja 2022. godine ili kasnije. Studija je obuhvatila 177 randomiziranih kliničkih ispitivanja i 68 pripadajućih članaka u recenziranim časopisima. Slijedili smo smjernice za pisanje opažajnih studija (STROBE kontrolna lista), a studija je prethodno registrirana na OSF platformi.

Rezultati: Tijekom provođenja ispitivanja zabilježene su promjene u 19 od 24 registra podataka o kliničkom ispitivanju za 122 randomizirana klinička ispitivanja i 68 pripadajućih članaka u recenziranim časopisima. U člancima je više nedostajalo izjava o dijeljenju podataka (52/68 [76%]) u usporedbi s početnom registracijom (23/122 [19%]) i posljednjom registracijom (17/122 [14%]). Svaki autor je evaluirao randomizirana klinička ispitivanja neovisno o drugom, kako bi se postigla vrijednost $\kappa \geq 0,80$, s visokim stupnjem pouzdanosti (raspon kappa: 0,80–1,00). Što se tiče integriteta izvještavanja neželjenih događaja, većina članaka u recenziranim časopisima (49/68 [72%]) imala je neskladan broj opisa ozbiljnih neželjenih događaja, a u 35/68 [51%] članaka zabilježen je odstupanje u broju pacijenata pogođenih neželjenim događajem. Otkrili smo da 11/68 [16%] članaka nije izvijestilo o smrtnosti pacijenata u usporedbi s podacima u registru ClinicalTrials.gov.

Zaključak: Rezultati našeg istraživanja su utvrdili da je nedosljedno izvještavanje registracijskih skupova podataka o kliničkim ispitivanjima u registru ClinicalTrials.gov i dalje problem unatoč preporukama i smjernicama. Nedosljedno izvještavanje neželjenih događaja ostalo je visoko u randomiziranim kliničkim ispitivanjima o COVID-19 farmakološkim intervencijama, uključujući biološke lijekove. Postoji hitna potreba za poboljšanjem izvještavanja kako bi se unaprijedilo donošenje odluka u liječenju bolesti COVID-19.

Ključne riječi: COVID-19; ClinicalTrials.gov; SARS-CoV-2; randomizirana klinička ispitivanja; neželjeni događaji; izvještavanje: smrtnost; sigurnost pacijenata; kontrolna lista.

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9. LAY SUMMARY

The aim of our study was to investigate the completeness and discrepancies of exported data for RCTs on COVID-19 interventions, and the accuracy of reported adverse events and all-cause mortality in those trials. We included RCTs exported from ClinicalTrials.gov and related publications in peer-reviewed journals.

Included RCTs investigated pharmacological interventions for COVID-19, including biologicals, and were registered on or after January 1, 2020, with updates on or after May 31, 2021. A total of 177 RCTs with 68 related publications were analyzed. We followed the STROBE checklist, and the study was pre-registered on the OSF platform.

In the first part of the research, we evaluated the integrity of WHO TRDS items reporting in included trials. We found that the inconsistent reporting was high. In the second part of the research, we investigated the accuracy of reporting adverse events and deaths. We found that discrepancies between the registry and the corresponding publications were high.

In summary, our findings confirmed the need for improved COVID-19 reporting.

10. LAIČKI SAŽETAK

Cilj našeg istraživanja bio je procijeniti potpunost i promjene podataka za Registracijski skupa podataka o kliničkim ispitivanjima Svjetske zdravstvene organizacije za klinička ispitivanja lijekova za COVID-19, uključujući i biološke lijekove. Cilj druge studije u sklopu ovog istraživanja je bio procijeniti integritet izvještavanja neželjenih u randomiziranim kliničkim ispitivanjima za COVID-19 farmakološke intervencije, uključujući biološke lijekove.

Proučavali smo randomizirana klinička ispitivanja registrirana u registru ClinicalTrials.gov s pripadajućim člancima u recenziranim časopisima. Uključili smo smo randomizirana klinička ispitivanja registrirana u registru ClinicalTrials.gov na dan 1. siječnja 2022. godine ili kasnije, ažurirana na dan 31. svibnja 2022. godine ili kasnije. Istraživanje je obuhvatilo 177 randomiziranih kliničkih ispitivanja i 68 pripadajućih članaka u recenziranim časopisima. Slijedili smo smjernice za pisanje opažajnih studija (STROBE lista), a istraživanje je registrirano na OSF platformi.

U prvom dijelu istraživanja, ispitivali smo promjene i potpunost izvještavanja Registracijskog skupa podataka o kliničkim ispitivanjima za uključena klinička ispitivanja. Pronašli smo da je razina nepotpunosti i velikih promjena između dva izvora visoka.

U drugom dijelu istraživanja, proučavali smo integritet izvještavanja neželjenih pojava i smrtnosti između dva izvora. Pronašli smo da je stopa nepotpunosti i različitog izvještavanja visoka.

Zaključno, naše istraživanje pokazalo je da postoji prostor za poboljšanje izvještavanja u randomiziranim kliničkim ispitivanjima koja istražuju farmakološke intervencije kod COVID-19, uključujući i biološke lijekove.

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12. BIOGRAPHY

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Education:

University of Split, School of Medicine- PhD program TRIBE (2021-2024)

University of Split, School of Medicine (2014-2020)

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Cambridge FCE First exam ESOL Level 1 Certificate 2011

Work experience:

Residency in Psychiatry, Teaching Institute for Public Health Split, Mental Health Department (2022–present)

Medical doctor in occupational medicine, MD (2021-2022)

Medical doctor in family practice, Community health center Split (2020-2021)

Publications:

1. Strikić M, Pranić SM. Completeness and changes in data reporting pharmacological interventions to treat COVID-19. Sci Rep. 2025 Jul 2;15(1):22989. doi: 10.1038/s41598-025-06308-y. PMID: 40593026; PMCID: PMC12215962.
2. Strikić M, Pranić SM. Evaluation of consistency in adverse event reporting between trial registry and publications in COVID-19 pharmacological intervention trials. Int J Clin Pharm. 2026 Apr 13;21. doi: https://doi.org/10.1007/s11096-026-02130-2.

Professional training:

March 2026 European Psychiatry Congress, EPA Prague, Czech Republic

November 2025 „Mobilni rehabilitacijski timovi“ Split, Psychiatry Clinic Vrapče and HZJZ

November 2025, part of the committee „9. međuškolskog natjecanja u javnozdravstvenom projektu“ NZJZ „Pretežno vedro“

November 2025 regional conference „Ovisnosti 360“ Split, Psychiatry Clinic Vrapče, and community Papa Ivan XXIII.

November 2025 Conference „Od prevencije do inkluzije - 30 godina zajedno“ Split, Liga za prevenciju ovisnosti

April 2025 European Psychiatry Congress, EPA Madrid, Spain

April 2025 Young Psychiatrists Forum, Crikvenica

March 2025 EU PROMENS Mental Health Exchange Programme, Wessenufer, Linz, Vienna

February 2025 – December 2025: First-degree Group Analysis Program 'Uvodnik' at the Institute for Group Analysis in Zagreb, as part of psychiatry residency.

October 2024 16th Croatian Cochrane Symposium, Split, Croatia

October 2024 Congress 19th Croatian Psychiatry Days, Vodice

June 2024 8th World Conference on Research Integrity (WCRI), Athens, Greece

Maj 2024. XV međunarodna škola specijalizacije EPCD: Addiction diseases and violence: The role of family and society, Pula

April 2024 Young Psychiatrist Forum at Trakošćan

April 2024 Postgraduate Course, 1st Category: „Praktična primjena chat-botova u svakodnevnom psihijatrijskom radu, Psychiatry Clinic Vrapče"

October 2023 Congress 18th Croatian Psychiatry Days, Poreč