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Investigation of ethics as part of a research integrity assessment of randomized controlled trials in COVID-19 evidence syntheses

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Strengths and limitations of this study

- The study uses a meta-epidemiological approach to systematically assess ethical compliance in COVID-19 RCTs, using both primary study reports and trial registration records for a comprehensive evaluation.
- Active engagement with study authors to obtain missing information or clarify inconsistencies improves the accuracy and completeness of the ethical assessments.
- The reliance on reported data in study publications and trial registrations, which may be incomplete or inaccurate, limits the reliability of the ethical compliance assessment.
- The absence of standardized, internationally recognized procedures for reporting ethics approval and other ethical items complicates consistent and accurate classification across diverse studies.
- The lack of a global registry for ethics committees (ECs) hinders the verification of ethics committees, making it difficult to fully assess the ethical compliance of studies, particularly when national recognition of ECs is unclear or unavailable.

Protocol registration

The protocol for the meta-epidemiological study was registered on OSF (https://osf.io/3bzeg).

Keywords

Randomized controlled trial, ethics, ethics approval, evidence synthesis, systematic review, research integrity

Background

The basis for reliable results in evidence syntheses is the knowledge of the trustworthiness of the underlying research evidence base. Research that follows the principles of research integrity ensures trustworthiness. To date, producers of evidence syntheses have not routinely assessed the research integrity of studies included in their evidence syntheses. Critical appraisal tools, such as Cochrane Risk of Bias tool 2 (RoB 2) and Grading of Recommendations, Assessment, Development and Evaluation (GRADE), used to assess the internal and external validity of study results do not necessarily address aspects of research integrity.[1 2] Thus far, there is an ongoing debate on how to appraise research integrity, and several projects are ongoing to develop trustworthiness screening and research integrity assessment tools for producers of evidence syntheses.[3-5]

Most researchers associate research integrity to the use of honest and verifiable methods in proposing, performing, and evaluating research, but research integrity also comprises adhering to (inter)national and commonly accepted guidelines, regulations, norms or standards.[6] Clinical studies should follow good clinical practice (GCP) - a code of international ethical and scientific standards for designing, recording and reporting studies that involve the participation of human subjects.[7] GCP provides assurance that a study's results are credible and accurate and that the rights and confidentiality of the study subjects are protected.[8] The World Medical Association (WMA) has developed the Declaration of Helsinki which states that "physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards" […] and that a "research protocol must be submitted for consideration, comment, guidance and approval to the concerned [independent] research ethics committee before the study begins".[9]

Compliance of clinical studies with ethical standards can only be reliably assessed if details on ethics are fully reported in study reports. Unfortunately, the reporting of ethics in randomized controlled trials (RCTs) is currently not included as an item in the Consolidated Standards of Reporting Trials (CONSORT 2010) statement.[10] Given the lack of standardization in reporting, it is unclear how ethics of RCTs should be assessed within an evidence synthesis and what impact an assessment may have on the results and conclusions of evidence syntheses.

This paper is part of a meta-epidemiological study which applies a novel and non-validated tool, designed for a research integrity assessment (RIA) of RCTs in evidence synthesis,[11] to a pool of RCTs included in COVID-19 systematic reviews. In this part, we focus on the assessment of the third domain of the RIA tool, i.e. ethics approval of RCTs. Two other papers, one on prospective trial registration and the other on the impact of RIA on results of evidence syntheses are in preparation (### or published elsewhere when available ###).

In this part, we present reporting of ethical details in the study reports of recent RCTs, provide guidance for producers of evidence synthesis on how to assess ethics in RCTs, and discuss the feasibility of the tool for its use in evidence synthesis regarding assessment of ethics in RCTs.

Methods

The protocol for the meta-epidemiological study has been published, including the search for RCTs and the assessment of ethics (https://osf.io/3bzeg). We extracted and analyzed additional study data, which was not prospectively planned, but designed post hoc to describe the study pool in detail. Additional analyses are indicated as such.

Selection of RCTs for assessment with the RIA tool

We searched for Cochrane reviews (CRs) and non-Cochrane systematic reviews (SRs) with or without meta-analysis evaluating 13 interventions for the prevention or treatment of SARS-CoV-2 infection and COVID-19 in humans, irrespective of SARS-CoV-2 diagnosis, disease severity or treatment setting. Pairwise and network meta-analyses were eligible. We included full text, peer-reviewed journal publications of systematic reviews. Preprints of systematic reviews, scoping reviews and narrative reviews were not eligible. We restricted the inclusion to publications in English. Further details on inclusion criteria of CRs and SRs in terms of population, interventions, and comparators are described in the protocol (https://osf.io/3bzeg).

Two reviewers independently searched for all eligible CRs and SRs with regard to study design, population and relevant interventions in PubMed to 09 June 2022. The search strategy is provided in the protocol (https://osf.io/3bzeg). One reviewer selected the CR (or its update) and the SR (or its update) to each of the relevant interventions with the largest RCT pool based on the most recent search date or the broadest inclusion criteria. The study pool of RCTs for further testing of RIA consisted of the primary studies included in the eligible systematic reviews. RCTs published as journal publications, preprints, or unpublished with results posted in trial registries were eligible. Depending on the type of published results, either journal publications, preprints, or trial registration records were considered as 'primary study reports'. Multiple primary study reports of a study (e.g. journal publication and preprint) were not pooled for our assessment but were separately assessed as included in the original systematic review.

In the present study, we excluded retracted RCTs (i.e. first domain of the RIA) and studies which were incorrectly included in the selected evidence syntheses as RCTs, although the studies clearly stated that a non-randomized study design was used. All RCTs, which were not previously excluded, were assessed in this study, irrespective of the registration status (i.e. second domain of the RIA). We documented the screening and selection process of systematic reviews and RCTs in a PRISMA flow diagram including reasons for exclusion at the full-text screening stage.

Data extraction of study characteristics

One reviewer (i.e. the third reviewer in the meta-epidemiological RIA study, FW) extracted details on ethics for all RCTs included in this study from the primary study reports, supplemental materials, study protocols, and trial registration records to September 2023. Where available, original data extractions made by two independent reviewers on ethics approval in the RIA study were used and checked by the third reviewer (FW). If double extracted data were not available (i.e. for RCTs which previously did not pass domain 1 and 2 of the RIA), or if discrepant extractions between pairs of reviewers occurred, a third reviewer (FW) extracted missing data or solved conflicts for this study.

Originally, the third domain of the RIA on ethics approval included five items for the assessment of RCTs [11], i.e. reporting of an ethics approval statement in the primary study report, name and location of the ethics committee (EC), national recognition status of the EC according to country, ethics approval number (EN), and written informed consent (WIC). In this study, one reviewer (FW) additionally extracted the date of the ethics approval and the date of study start as reported in the primary study report and in the trial registration records. We also extracted the following information of all RCTs, i.e. sample size, setting (single-centre vs national multi-centre vs international multi-centre), location (i.e. country) where the study was conducted, and the trial registry with registration number where the study was registered.

Assessment of ethics in RCTs

1. *Statement on ethics approval*

We investigated whether the RCTs included an informative statement on ethics approval in the primary study report. Every statement on ethics approval was counted, if it at least mentioned that an EC (e.g. approved by an institutional ethics committee) granted the approval or the EN was reported. The EC did not have to be named. Generic declarations, such as “this study was conducted in accordance with the declaration of Helsinki and/or with the local regulations” were considered as insufficient. If no (sufficient) statement on ethics approval was reported in the primary study document, we contacted the study authors via E-mail for further information.

2. *Name and location of ethics committee*

We assessed whether RCTs reported the name and location of at least one EC in the primary study report. We accepted reporting of at least one EC as sufficient for single-centre as well as for multi-centre RCTs. A generic statement, e.g. “ethics approval obtained from several IRBs, according to site”, without further specifications were considered as insufficient. If the

name and location of the EC were not reported in the primary study report, we searched for the corresponding trial registration record of registered RCTs, and if not successful, we contacted the study authors via E-mail for further information.

3. Recognition status of ethics committees

An ethics committee should have a national recognition status and there should be a national government department responsible for recording the national recognition status. To determine the recognition status of a reported EC, a new strategy was developed and applied by the third reviewer (FW), which was not included in the original RIA. We conducted a primary search in Google (https://www.google.de) following a standardized procedure, where the search was initiated by introducing the name and address of the EC as reported, supplemented by keywords, such as 'ethics committee' (or. i.e. EC), 'institutional review board' (or i.e. IRB), or 'research ethics committee' (or i.e. REC). With this primary search (latest search on 27.07.2023), we could identify national registries/directories of ECs for a total of 22 countries described in our RCT pool, which were provided by official organizations (i.e. ministry of health, bioethics/research entities). These directories were considered as reliable sources. Additionally, four international directories listing local and independent ECs/IRBs and ethics regulations of various countries were also retrieved: two country-specific online databases (for low- and middle-income countries: https://healthresearchwebafrica.org.za/en, and for Europe: http://www.eurecnet.org/index.html), which provide clinical research regulatory information (i.e. up-to-date ethical regulations, list of accredited EC/IRB); one online database of the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP, https://www.aahrpp.org/), which provides current information about their independently accredited entities worldwide; as well as the website of the WHO Research Ethics Review Committee (https://www.who.int/groups/research-ethics-review-committee). All national and international sources are listed in Additional File 1.

In cases where an EC/IRB could not be located in any of the sources on the list, indirect searches through the website of the institution where the study took place were performed. An independent EC/IRB was considered as 'recognized' if the institution provided a statement and/or documents proving national accreditation. These ECs/IRBs were also added to the list of sources (Additional File 1). If the search still remained futile, the recognition status of the EC/IRB was deemed as 'unclear'.

4. Ethics approval number

We assessed whether RCTs reported at least one EN in the primary study report. We accepted reporting of at least one EN as sufficient for single-center as well as for multi-center RCTs. If

no EN was reported in the primary study report, we searched the trial registration record of registered RCTs, and if not successful, we contacted the study authors via E-mail for further information.

5. Written informed consent

We assessed if the primary study report included a statement on whether the RCT has obtained written informed consent from all participants or their relatives prior to enrollment. In case of an insufficient (i.e. unclear if written) statement or the lack of it, we contacted the study authors via E-mail for further information.

RIA judgement of RCTs considering ethics

Studies that sufficiently reported and fulfilled all of the original five RIA items were assessed as 'no concern' (i.e. considered eligible for evidence synthesis).[11] Studies with at least one item assessed as insufficient (i.e. unclear/not found/not reported) were classified as 'awaiting classification' (i.e. considered ineligible for evidence synthesis until clarification).[11] Since there is no standardized recommendation for the reporting of ethical considerations in an RCT such as the CONSORT 2010 statement,[10] we decided not to exclude any RCT due to missing information. However, studies with confirmed lack of an ethics approval in general or lack of WIC were assessed as 'exclude' (i.e. considered ineligible for evidence synthesis).

Authors of the RCTs classified as 'awaiting classification' were contacted in order to obtain missing information and/or clarify inconsistencies/concerns. Authors of unpublished RCTs (i.e. only trial registration records available) were not contacted, since those studies cannot be adequately assessed with current RIA items comparing journal publications or preprints with trial registration records. Authors had 14 days to respond. If a study author provided complete information, the RCT was upgraded to 'no concern'. Study authors, who did not provide any feedback, were reminded via E-mail and were given additional seven days to reply. The categorization of the RCTs remained 'awaiting classification', if incomplete or no response was received.

For presentation in this study, we differentiated two subcategories of reasons for 'awaiting classification' regarding ethics, i.e. research integrity-(RI)-related and reporting-related reasons. As true RI-related reason, we counted if the EC was not recognized (i.e. EC reported, but not found in our sources or sources not available). Reporting-related reasons included lack of or insufficient statement on ethics approval or EC, non-reporting of EN, and unclear or not reported WIC. However, it should be noted that non-reporting itself is problematic in terms of RI.

Date of ethics approval

In this study, we also extracted and assessed additional items on ethics approval, which were not included in the original RIA, i.e. the date of ethics approval and study start, and the timing of ethics approval. Additionally extracted and assessed items did not change the RI assessment for the ethics domain in this study. We assessed whether RCTs reported the date of ethics approval in the primary study report. We accepted reporting of at least one ethics approval date as sufficient for single-centre as well as for multi-centre RCTs. A generic statement, e.g. “ethics approval has been obtained prior to enrollment of the first subject”, has been considered as insufficient, if no further details pertaining the date of the ethics approval had been disclosed. If the ethics approval date was not reported in the primary study report, we searched for the corresponding trial registration record of registered RCTs. For all RCTs, where we identified an ethics approval date, we assessed whether the ethics approval was obtained before start of the study (i.e. prospectively). We used the dates referred to ‘study start’ as defined by different trial registry platforms and the study start date reported in the publication or preprint. Several RCTs reported different dates of study start and ethics approval, as they took place in several locations (i.e. conducted as multi-centre RCTs). A RCT was considered as having obtained a prospective ethics approval, if true for at least one site. An ethics approval date after study start was considered either as retrospective ethics approval in case of single-centre settings or as ‘potentially retrospective’ in case of multi-centre settings.

Statistical analysis and presentation of data

This study has been designed to facilitate a descriptive data analysis. We did not perform any statistical hypothesis testing, as this part of the study was not prospectively planned, but designed post hoc to disseminate relevant findings. We compared the categories of RCTs assessed as ‘no concern’, ‘awaiting classification’ and ‘exclude’, regarding reporting of ethics approval date, setting, location, sample size, and trial registry. Descriptive statistics and frequency tables were used to present and compare categorical variables (e.g., sample size, setting, location, and trial registry).

Due to the large number of studies, we only referenced individual studies in the following results section if less than ten studies are referred to. We restricted referencing of studies to our investigations on the original ethics items for RIA. Data and digital object identifiers (doi) for all individual studies are available online (https://doi.org/10.17605/OSF.IO/9VZME).

Results

A total of 206 RCTs included in 23 evidence syntheses (i.e. 13 CRs and ten SRs, Additional File 2) investigating interventions of interest for treatment or prevention of SARS-CoV-2 infection were identified by our search (Additional File 3). We included 188 RCTs in this study and excluded eight retracted RCTs and ten studies which turned out to be non-randomized studies. Of 188 RCTs, 149 were published in journals, 33 were published on a preprint server, and the remaining six RCTs were unpublished with results only posted on a trial registration database. References and all baseline details of included RCTs reported in the following (i.e. ethic details, sample size, setting, country, and trial registration) are available online (https://doi.org/10.17605/OSF.IO/9VZME).

Of 188 RCTs, 174 published and one unpublished RCT included an informative statement on ethics approval in the primary study report (Table 1). Three published RCTs have not reported any statement on ethics approval (Kishoria-2020, Li-2021, Mareev-2021). Five published RCTs included a general statement, e.g. following international principles, applicable laws and regulations (Chen-2020a, Dougan-2021a, Dougan-2021b, Gupta-2021a, Podder-2020). The study authors of theses eight published RCTs were contacted to confirm ethics approval. Upon request, one study author (Mareev-2021) confirmed ethics approval without providing further details (i.e. EN).

Of 188 RCTs, 130 published and one unpublished RCT provided the name and location of at least one EC in the primary study report (Table 1). Eleven published RCTs included only a generic statement without further reference to the name and location of the EC, including eight international multi-centre RCTs. Forty-one published RCTs and five unpublished RCTs did not indicate the name and/or the location of at least one EC in the primary study report. Eight published RCTs provided this information exclusively in the trial registration record (Chen-2020b, Galan-2021, Huang-2020, Soin-2021, Spinner-2020, Thakar-2021). Upon request, 12 study authors supplied the name and location of ECs. In 37 RCTs, the EC remained unreported or unclear. Of 151 RCTs with reported or identified name and location of at least one EC, 134 were classified as recognized (Table 1). The national recognition status of the ECs in the remaining 17 RCTs was unclear. For 14 RCTs, the EC could not be identified in any of our sources (Additional File 1) and for the remaining three RCTs there was no source available (i.e., two RCTs from Iraq: Hashim-2020, Rasheed-2020; one from Russia: Mareev-2021).

Eighty-one published RCTs and one unpublished RCT included the EN in the primary study report (Table 1). One hundred one published RCTs and five unpublished RCTs did not report any EN in the primary study report. For 25 RCTs, the EN was identified in the trial registration records. For another 19 published RCTs, the study authors provided the EN upon request. The EN was not found for 57 published RCTs.

Of 188 RCTs, 165 published RCTs and all six unpublished RCTs included a statement that WIC was obtained (Table 1). In 14 RCTs, a statement on informed consent has been reported, however, it remained unclear if written. Three study authors confirmed having obtained written informed consent from all participants upon request (Gonzalez-2021, Okumus-2021, van den Berg-2022). In three RCTs, the publication contained no statement on WIC (Galan-2021, Li-2021, Mareev-2021).

Table 1: Reporting and identification of ethics details in RCTs

Ethics details	RCTs, n (%)	
	Journal/preprint articles (n = 182)	Registration records (n = 6)
Statement on ethics approval		
Reported in primary study report*	174 (96%)	1 (17%)
Insufficiently reported/not reported	8 (5/3) (4%)	5 (0/5) (83%)
Identified by author request	1	N/A
Not found/unclear	7	N/A
Name and Location of Ethics Committee (EC)		
Reported in primary study report*	130 (71%)	1 (17%)
Insufficiently reported (generic statement)/not reported	52 (11/41) (29%)	5 (0/5) (83%)
Identified in the trial registration record	8	N/A
Identified by author request	12	N/A
Not found/unclear	32	N/A
EC recognized (n = 151)		
Yes	133	1
Unclear	17	0
Due to EC not found in source	14	0
Due to EC not found, no source available	3	0
Ethics approval number		
Reported in primary study report*	81 (45%)	1 (17%)
Not reported	101 (55%)	5 (83%)
Identified in the trial registration record	25	N/A
Identified by author request	19	N/A
Not found	57	N/A
Written informed consent		
Reported in primary study report	165 (91%)	6 (100%)
Insufficiently reported/not reported	17 (14/3) (9%)	0
Clarified by author request	3	N/A
Not found/unclear	14	N/A

Abbreviations: Ethics committee (EC), randomized controlled trials (RCTs)

Footnotes:

* Primary study report = publication/preprint or registration record, if RCT unpublished

Of the 188 RCTs, 41% sufficiently reported and fulfilled all items required for the assessment of the ethics approval in the primary study report and/or the trial registration record, i.e. 77 published RCTs and one unpublished RCT (Table 2). We classified these RCTs as 'no concern'. After the first assessment round, 105 published RCTs and five unpublished RCTs incompletely reported at least one item required to assess the ethics domain and were categorized as 'awaiting classification'. None of the RCTs were excluded, since there was no RCT with a confirmed lack of an ethics approval or WIC. Of the 110 RCTs categorized as 'awaiting classification', 95 study authors were contacted due to missing information regarding statement of ethics approval, EC, EN, and/or WIC (Table 2). Study authors of 25 RCTs responded and 21 RCTs were finally upgraded to 'no concern'. One study author provided sufficient information, however, the EC was not found in our source and the RCT remained 'awaiting classification' (Sadeghipour-2021). Three RCTs remained 'awaiting classification' due to incomplete or insufficient responses (Abd-Elsalam-2021a, Ali-2022, Mareev-2021) and study authors of 70 RCTs did not respond at all. Fifteen study authors were not contacted, which included five unpublished RCTs and ten RCTs providing complete information in the primary study reports, however, the EC could either not be found in the source, or there was no source available to verify the recognition status of the ECs (Table 2). Following author request, a total of 99 RCTs were considered as 'no concern' and 89 RCTs remained as 'awaiting classification'.

Table 2: Summary of RI assessment based on provided ethics information

Information on ethics	No concern	Awaiting classification	Exclude
Reporting of information (n = 188)			
Information completely reported in publication and/or in registration record(s)	78	0	N/A
Journal/preprint publication	77	0	N/A
Registration records	1	0	N/A
Information incompletely reported in publication and/or in registration record(s	0	110	N/A
Journal/preprint publication	0	105	N/A
Registration records	0	5	N/A
Retrieval of information of RCTs 'awaiting classification' (n = 110) (i.e. author request)			
Study author contacted for missing information or inconsistencies	21	74	N/A
Completely provided by study author	21	1[a]	N/A
Response insufficient or not complete	0	3	N/A
No response received	0	70	N/A
Study author not contacted for following reason	0	15	N/A
Only registration record available	0	5	N/A
Information complete, but EC not found in source	0	8	N/A
Information complete, but no source for national ECs available	0	2	N/A
Final assessment	99	89	0

Abbreviations: Ethics committee (EC)

Footnotes:

[a] Sadeghipour-2021 (INSPIRATION) provided complete information, but EC was not found in source (national recognition unclear)

We have differentiated the reasons for 'awaiting classification' in reporting-related and RI-related reasons (Table 3). Several RCTs comprised more than one reason for 'awaiting classification' of both types, i.e. RI-related and reporting-related. Most RCTs were 'awaiting classification' due to reporting-related reasons. Predominantly, an EN was not reported in 62 RCTs, followed by insufficient or not reported EC in 37 RCTs. Seventeen cases of RI-related reasons were counted which are not due to non-reporting, but to a lack of EC recognition.

Table 3: Reasons for awaiting classification

Reasons for awaiting classification (n = 89), after author request with or without response	
Reporting-related reasons[a]	
Statement on ethics approval insufficient or not reported	12[b]
EC insufficient or not reported	37[b]
EN not reported	62[b]
WIC unclear or not reported	14
RI-related reasons	
EC reported, but national recognition unclear	17
EC not found in source	14
No source available	3

Abbreviations: Ethics committee (EC), ethics approval number (EN), research integrity (RI), written informed consent (WIC)

Footnotes:

[a] Some RCTs have more than one reason for 'awaiting classification', therefore, the sum of all reasons exceeds the total number of RCTs in 'awaiting classification'

[b] including five RCTs available as registration records only

In this study, we extracted and assessed the date of ethics approval in addition to the original five RIA domains. Five published RCTs (Chowdhury-2021, Gonzalez-2021, Thakar-2021, Vallejos-2021, van den Berg-2022) and one unpublished RCT (NCT04392141) reported the date of ethics approval in the primary study report, and in all cases the ethics approval had been obtained prior to study start (Table 4). Six published RCTs (Bennett-Guerrero-2021, Chen-2021, Faisal-2021, Hamdy Salman-2020, Okomus-2021, Rasheed-2020) included a general statement (e.g. ethics approval obtained prior to enrolment), without specifying the date of ethics approval. One hundred seventy one published and five unpublished RCTs did not provide the ethics approval date in the primary study report. For 74 of the 177 published RCTs the ethics approval date could be identified in one or more trial registration record, i.e. 50 registrations in EUCTR, 15 in ISRCTN, 12 in IRCT, seven in ChiCTR, and two in CTRI (Additional File 4). In total, the ethics approval date for 103 published RCTs could not be retrieved despite active search. Of 80 RCTs with identified ethics approval date, 63 RCTs had obtained the ethics approval prior to study start/enrollment of the first subject for at least one site, including 15 single-centre RCTs, 34 national multi-centre and 14 international multi-centre RCTs. Fourteen RCTs presented inconsistencies in the study start dates reported in the primary study reports and the trial registration records resulting in different assessments of ethics approval timing. Of these 14 RCTs with inconsistencies, six were single-centre (Babalola-2022, Chen-2020b, Farahani-2020, Huang-2020, Kharazmi-2022, Pouladzadeh-2021), two were national multi-centre RCTs (Corral-Gudino-2021, Wang-2020a), and the remaining six RCTs were international multi-centre RCTs (Eom-2021, Gupta-2021a, Gupta-2021b, Rosas-2021a, Spinner-2020, Tardif-2021), in which the primary study location remained unclear (i.e. possibly different date of EA). Two published national multi-centre RCTs from China (Li-2020, Li-2021) and one international multi-centre RCT (Pan-2020) received an ethics approval after study start and were considered as 'potentially retrospective'. The study authors did not provide any feedback upon request.

Table 4: Ethics approval date of RCTs

Ethics approval date	RCTs, n (%)	
	Journal/preprint articles (n = 182)	Registration records (n = 6)
Reporting of ethics approval date		
Reported in primary study report*	5 (3%)	1 (17%)
Insufficiently reported/not reported	177 (6/171) (97%)	5 (83%)
Identified in the trial registration record	74	N/A
Not found/unclear	103	N/A
Ethics approval obtained prior to study start (n = 80)		
Yes[a]	62	1
Unclear	14	0
No	3	0

Abbreviations: Randomized controlled trials (RCTs)

Footnotes:

* Primary study report = publication/preprint or registration record, if RCT unpublished

[a] for at least one site

The frequency of reporting of the ethics approval date was similar in RCTs assessed as 'no concern' and 'awaiting classification' for the original RIA domain 3, with 45% (45 of 99) and 39% (35 of 89), respectively. However, two of three RCTs with 'potentially retrospective' ethics approval (Li-2020, Li-2021) were assessed as 'awaiting classification'.

The comparison of RCTs with sufficiently reported ethics approval regarding all items (i.e., 'no concern', n = 99) compared to those with insufficient, inconsistent, or missing ethics approval details (i.e., 'awaiting classification', n = 89) revealed a similar distribution regarding the study setting, i.e. international multi-centre (18% vs 16%), national multi-centre (47% vs 49%), and single-centre (35% vs 35%) (Table 5). According to the countries of study conduct, 66% of the European RCTs were assessed as 'no concern', whereas 71% of the North American RCTs were 'awaiting classification' (Table 5). Half of all single-centre RCTs were from Asia with 58% assessed as 'awaiting classification'.

Twelve RCTs were not registered and eight of them were assessed as 'awaiting classification' for the RIA domain on ethics approval (Table 5). ClinicalTrials.gov was the most used platform for trial registration among the registered RCTs, with no difference in the number of registrations between RCTs assessed as 'no concern' compared to 'awaiting classification' (76 vs 66). We identified nine registrations on ChiCTR and all nine belonged to RCTs which were assessed as 'awaiting classification'. In contrast, all 15 registrations in the WHO ISRCTN registry belonged to RCTs assessed as 'no concern'.

There was a slight difference between RCTs categorized as 'no concern' compared to 'awaiting classification' in terms of the sample sizes, i.e. 54% vs 39% randomized 200 or more participants, and the median sample size was 240 vs 131 participants.

Table 5: Characteristics of RCTs classified as 'no concern' and 'awaiting classification' (n = 188)

Study characteristics	No concern (n = 99)	Awaiting classification (n = 89)
Setting and Location		
Multi-center, international (n = 32)	18	14
Multi-center, national (n = 90)	46	44
Africa	1	0
Asia	10	12
Australia	0	0
Europe	22	14
North America	5	13
South America	8	5
Single-center (n = 66)	35	31
Africa	6	3
Asia	14	19
Australia	0	0
Europe	5	0
North America	2	4
South America	8	5
Trial Registry[a]		
ClinicalTrials.gov (n = 142)	76	66
EUCTR (n = 56)	35	21
ISRCTN (n = 15)	15	0
IRCT (n = 12)	7	5
ChiCTR (n = 9)	0	9
CTRI (n = 6)	4	2
ReBec (n = 5)	4	1
Other[b] (n = 4)	3	1
RCTs without trial registration (n = 12)	4	8
Sample size; randomized patients		
Median (IQR)	240 (91 to 777)	131 (65 to 420)
Less than 100 participants (n = 60)	26	34
100 to less than 200 participants (n = 40)	20	20
200 or more participants (n = 88)	53	35

Abbreviations: Randomized controlled trials (RCTs), interquartile range (IQR), EU Clinical Trials Register (EUCTR), International Standard Randomised Controlled Trial Number (ISRCTN), Iranian Registry of Clinical Trials (IRCT), Chinese Clinical Study Register (ChiCTR), Clinical Trials Registry India (CTRI), Brazilian Registry of Clinical Trials (ReBec), Spanish Clinical Study Registry [Registro Español de Estudios Clínicos] (REec), Indonesia Clinical Research Registry (INA), Saudi Clinical Study Registry (SCTR)

Footnotes:

[a] Some RCTs were registered in different trial registries and/or with different numbers in the same registry, therefore, the sum of all registrations exceeds the total number of RCTs in the categories 'no concern' and 'awaiting classification'

[b] Includes two registrations in REec, one in INA, and one in SCTR

Discussion

Reporting of ethics in COVID-19 RCTs is insufficient. Only 41% of RCTs sufficiently reported and fulfilled all items required for the assessment of ethics in the primary study report and/or the trial registration record, whereas 59% of RCTs incompletely reported on ethics items and were categorized as 'awaiting classification'. In our study, registration records have proven to be important sources for ethical details as we were able to identify details for 33 ethical items. Furthermore, we made a major effort and sent requests to the authors of 50% of included RCTs for missing information or clarifying inconsistencies. This enabled an upgrade of another 11% of the RCTs from 'awaiting classification' to 'no concern'. Finally, almost half of all RCTs were considered as 'no concern' and the other half remained 'awaiting classification', i.e. not eligible for evidence synthesis due to uncertainties.

Originally, we planned to assess RCTs with confirmed lack of an ethics approval or lack of WIC as 'exclude', i.e. not eligible for evidence synthesis as problematic in terms of research integrity. According to the recommendations of the International Committee of Medical Journal Editors (ICMJE), a study article must indicate whether WIC had been obtained.[12] About 10% of RCTs in our study did not sufficiently report on WIC. However, in no case, we were clearly able to demonstrate that ethics approval or WIC was not present. A main obstacle to a reliable assessment is that we cannot determine with certainty whether there was actually a violation of research integrity from an ethical perspective that goes beyond the problem of non-reporting.

The reporting of ethics in clinical studies has improved little over the years. Zoccatelli et al determined that 97% of the studies published in 2011 in the European Journal of Anaesthesiology declared an ethics approval, of which 85% reported the name and location of EC and 69% provided EN.[13] Yank et al estimated a lack of ethics approval statement in 18% of the studies carried out after 1997 and a tenth of the RCTs did not report having obtained WIC.[14] A hurdle might be that reporting of ethics in RCTs is currently not included as an item in the CONSORT 2010 checklist, the most important reporting guideline for RCTs.[10] We assume that reporting could be improved if CONSORT would include ethical items, due to its major impact on reporting quality of RCTs in the past.[15] An update of the CONSORT 2010 checklist is currently in progress and we expect consideration of ethics as ethics committees and regulatory agencies will be important stakeholders.[15] The current situation requires that we first increase awareness of the importance of reporting ethics in study reports before producers of evidence syntheses can reliably assess ethics in the context of research integrity. The good news, reporting for specific items of RCTs can be improved over time as shown for another CONSORT item, i.e. the registration of studies, even if it is a slow process.[16] In another part of our meta-epidemiological study, we showed that nine of ten RCTs reported a trial registration number in the primary study report (### insert reference when available ###).

Our post hoc comparison of RCTs assessed as 'no concern' with those assessed as 'awaiting classification' revealed a similar distribution regarding study setting and country, and only a slight difference regarding the median sample size. The fact that the large international multi-center studies behaved similarly in the reporting of ethics as the small single-centre studies could be another indication of the lack of awareness of the importance of full reporting.

Our study outlines the essential role trial registries play in the assessment of ethics approval, on the one hand, acting as a checkpoint, in which all studies providing a trial registration must comply with the available regulations on ethics approval (i.e. prospective ethics approval, WIC prior to study start and registration), and on the other hand, acting as facilitators of information to assessors, displaying all items concerning ethics approval publicly. Even though most trial registries, especially those listed as 'primary registries in the WHO network', explicitly require proof of ethics approval prior to trial registration, our study reveals that several registries do not always enforce these requirements. This is especially true for ChiCTR as none of the seven RCTs registered with nine registrations on this platform were considered as 'no concern', due to either inconsistencies or non-reporting of ethics details. In contrast, all 15 RCTs registered on ISRCTN were deemed as 'no concern'. Among the registries used by our RCTs, ISRCTN, ChiCTR, EUCTR, CTRI, and IRCT provided detailed information pertaining ethics approval as a standard feature, which was very useful for our assessment. Other platforms, such as ClinicalTrials.gov, where most of the RCTs were registered, do not supply information related to ethics approval as a standard.

Conversely, ECs can play an essential role in increasing trial registration if they follow a system recently launched in the UK, where the Health Research Authority, the UK ethics regulator that oversees all ethics committees in the country, directly register trials to achieve 100% clinical trial registration (https://www.hra.nhs.uk/about-us/news-updates/new-partnership-guarantees-full-picture-uk-clinical-trials/).

While author response request has been established as another practical way to obtain missing information and/or clarify inconsistencies, this method is time consuming and not effective in about three-quarters of all requests. Whether this effort can be carried out as part of an evidence synthesis mainly depends on the available resources and considerations on time and timeliness in individual cases. However, improved reporting would significantly reduce this time expenditure.

We have underpinned our assurance of adequate ethics through the national recognition of the ethics committees. The unavailability of updated national and/or international directories for accredited ECs/IRBs in a universal language hinders the assessment of ethics. The search for national sources was time-consuming. About 10% of the RCTs were approved by an EC, which after an extensive search, could not be found in any source, and therefore their

recognition status remains unclear. The language barrier might play an important role in the search for sources. This finding differs amply with those of Zoccatelli et al., who were unable to identify 41% of the ECs of their study pool.[13] On the other hand, however, our sources used for the assessment of the recognition status might be out-of-date, and vice versa, the EC might have been deactivated or lost national recognition status by the time of the approval provided to the study authors, and was during our assessment reactivated or regained national recognition status. A regularly updated international register of the recognized EC and IRBs would support the assessment of ethics in evidence synthesis.

Our study has several limitations. Our assessment is dependent on details reported in study reports. As stated by Tramèr[17] and Yank et al[14], even when details pertaining to ethics approval are reported or provided by the author, there are no guarantees as to whether the approved protocol matches the study performed. Furthermore, we did not contact the EC to verify whether either the authors obtained ethics approval, nor the information provided was consistent with the approval documents, nor the EC was recognized by the time of approval. We did not take into account the role of the journals in the assessment of this domain, although they may act as a checkpoint to screen ethical unsound studies and there may be great differences between different journals, as stated by Myles et al.[18] Our search was conducted exclusively in English, which may hamper the retrieval of sources of EC in non-English countries.

Finally, we need an extensive discussion in the research community on which ethical items should be used for a reliable assessment. The ongoing INSPECT-SR project is developing a tool to identify problematic RCTs in systematic reviews of healthcare-related interventions by critical discussion with different experts in the field on which checks are useful to determine a study's authenticity, and ethics is one the checks.[19] Although currently not an item of the RIA ethics domain, we suggest the assessment of the ethics approval date as a new item. Even if the problems of poor reporting also apply for this item, we were able to identify two published national multi-centre RCTs from China (Li-2020, Li-2021), which received an ethics approval after study start, which is clearly an unethical practice. As it is unethical, we already excluded another study from China[20] in a Cochrane review on nirmatrelvir/ritonavir for COVID-19[21] as recruitment of participants started about 20 days before ethics approval was obtained.

In our view, it is essential to include ethics in the research integrity assessment of RCTs as part of evidence synthesis in the future. However, poor reporting - even if a research integrity issue on its own - complicates a reliable assessment. Nevertheless, including ethics in the checklist of evidence syntheses and in reporting guidelines of clinical studies is especially important to increase awareness in the scientific community about the need for high ethical standards in human research.[22] Therefore, at present, we suggest to assess ethics in RCTs

during a research integrity assessment included in the evidence synthesis process, however, not to exclude studies assessed as 'awaiting classification' from the study pool and meta-analysis, but instead perform sensitivity analysis to investigate robustness of the results. In RIA, we have chosen a hierarchical approach excluding retracted RCTs, RCTs without prospective registration, and RCTs without ethics approval, etc. to work more efficiently. This approach was based on the assumption that prospective trial registration and ethics are international standards and restrictions would not result in the loss of large, well-conducted RCTs. The question now is whether RIA domains should not be isolated exclusion criteria, but should be considered as part of a more holistic approach that includes prospective registration, ethics and governance, to overcome the risk of losing relevant RCTs.

Conclusion

This study highlights two main issues concerning ethics approval in RCTs. First, reporting of ethical aspects in RCTs is poor. Second, as under-reporting cannot be excluded, the assessment of ethics as part of the RIA tool is currently not reliable. The lack of standardized procedures and guidelines for reporting information regarding ethics approval in the primary study record impedes the assessment of ethics, and therefore, leaves producers of evidence synthesis with a high number of RCTs, which are not eligible for evidence synthesis (i.e. RCTs categorized as 'awaiting classification'). Furthermore, we determined that trial registries play an essential role as providers of information pertaining to ethics approval and as sentinels, ensuring that RCTs are carried out according to available ethics regulations.

List of abbreviations

AAHRPP	Association for the Accreditation of Human Research Protection Programs, Inc.
ChiCTR	Chinese Clinical Trial Register
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019
CR	Cochrane review
CTRI	Clinical Trials Registry India
doi	Data and digital object identifier
EA	Ethics approval
EC	Ethics committee
EN	Ethics approval number
EUCTR	EU Clinical Trials Register
GCP	Good clinical practice
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional review board
IRCT	Iranian Registry of Clinical Trials
ISRCTN	International Standard Randomized Controlled Trial Number
OSF	Open Science Framework
RCT	Randomized controlled trial
REC	Research ethics committee
RI	Research integrity
RIA	Research integrity assessment
RoB	Risk of Bias
SARS-CoV-2	Severe acute respiratory syndrome coronavirus type 2
SR	Systematic review
WHO	World Health Organization
WIC	Written informed consent
WMA	World Medical Association

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Competing interests

The authors declare that they have no financial competing interests. SW and PM are authors of Cochrane reviews which include studies assessed in the meta-epidemiological RIA study.

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Contributors

FW: study design, acquisition of data, analysis, interpretation, drafting the article,
TP: interpretation, acquisition of data, reviewing the article,
ES: expertise in clinical trial regulation, interpretation, reviewing the article,
PM: expertise in conduct of RCTs, interpretation, reviewing the article,
SW: study design, acquisition of data, analysis, interpretation, drafting the article.
The manuscript has been read and approved by all co-authors.

This study is part of a medical doctoral thesis (FW).

Patient and Public Involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

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Additional File 1: Directory of consulted sources for ethics committees, last edited on 27.07.2023

Country	Source provided by a national organization	Source provided by an international organization	Institutional source	Notes
Argentina	https://www.argentina.gob.ar/salud/investigaciones/comites https://buenosaires.gob.ar/sites/default/files/2023-09/Lista_nueva_cei_efectores_no_gcba_4-sep-2023.pdf https://www.argentina.gob.ar/sites/default/files/2022/06/listado_comites_acreditados_8-7-2022.pdf	Not found	https://med.unne.edu.ar/institucional/gestion-academica-y-administrativa/secretaria-de-ciencia-y-tecnologia/comite-de-bioetica-en-investigacion-de-ciencias-de-la-salud/	
Bahrain	Not found	Not found	https://www.dcri.com/bahrain/research/research-ethics-committee	
Bangladesh	Not found	https://healthresearchwebafrica.org.za/en/bangladesh/institution	Not found	
Belgium	https://www.famhp.be/sites/default/files/Lijst%20EC's%20-%20Liste%20CE_1.pdf	Not found	Not found	
Brazil	https://plataformabrasil.saude.gov.br/login.jsf	Not found	Not found	CONEP= Brazilian committee of ethics in Human Research
Chile	Not found	Not found	https://eticayseguridad.uc.cl/images/DR._143-2020._Regulation_of_the_scientific_ethics_committees_of_health_UC_-_English.pdf	
China	Not found	https://www.aahrpp.org/find-an-accredited-organization	Not found	
Colombia	https://aciccolombia.org/lista-de-comites-de-etica-en-colombia/	https://healthresearchwebafrica.org.za/en/colombia/institution	Not found	National source not used
Ecuador	Not found	Not found	https://www.usfq.edu.ec/en/human-research-ethics-committee-ceish	
Egypt	http://www.enrec.org/directory	Not found	Not found	

36/bmjopen-2024-092244 on 24 March 2025. Downloaded from

France	http://urcest.com/les-cpp-en-ile-de-france http://cppouest1.fr/mediawiki/index.php?title=Accueil	Not found	Not found	
Germany	https://www.bfarm.de/DE/Medizinprodukte/Ueberblick/Institutionen/Ethikkommissionen/_node.html	Not found	Not found	
Greece	Not found	http://www.eurecnet.org/information/greece.html	Not found	
India	https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdf-documents/list-ofecommittee2022.pdf https://cdsco.gov.in/opencms/opencms/en/Clinical-Trial/Ethics-Committee/Ethics-Committee-Re-Registration/ https://www.ncdirindia.org/All_Committee.html	Not found	Not found	
Indonesia	Not found	https://www.ncdirindia.org/All_Committee.html	Not found	official website of National Institute of Health Research and Development on 07.02.24 not available, https://health-policy-systems.biomedcentral.com/articles/10.1186/s12961-015-0024-9
Iran	Not found	https://healthresearchwebafrica.org.za/en/iran/institution	Not found	
Iraq	Not found	Not found	Not found	Source not found
Israel	Not found	Not found	https://rnd.sheba.co.il/Research_Authority	Link no longer available (last visited 07.2023)
Italy	https://www.aifa.gov.it/documents/20142/1123276/Comunicazione_gestione_studi_clinici_in_emergenza_COVID-19-EN_17.09.2020.pdf	Not found	Not found	
Mexico	https://www.gob.mx/cms/uploads/attachment/file/801449/Registros_CEI.01022023.pdf	Not found	Not found	

Nigeria	https://nhrec.net/registered-health-research-ethics-committees-in-nigeria-hrec/	Not found	Not found	
Norway	https://rekportalen.no/#omrek/REK	Not found	Not found	
Oman	Not found	Not found	https://royalhospital.med.om/pdf/RH-Research-Policy.pdf	
Pakistan	nbcpakistan.org.pk/assets/list_of_ercin_publicprivatemedicalcolleges.docx	Not found	Not found	
Qatar	Not found	Not found	https://www.sidra.org/EN/About-Us/Our-Accreditations/Pages/default.aspx#	
Russia	Not found	Not found	Not found	Source not found
Saudi Arabia	https://www.moh.gov.sa/en/Ministry/MediaCenter/Publications/Pages/Annual-Research-Report-2016.pdf	Not found	Not found	
Singapore	Not found	https://www.aahrpp.org/find-an-accredited-organization	Not found	
South Africa	https://www.health.gov.za/wp-content/uploads/2022/05/NHREC-Registration-List-of-Human-RECs-Animal-RECs-registered-with-NHREC.pdf	Not found	Not found	
South Korea	Not found	https://www.aahrpp.org/find-an-accredited-organization	Not found	
Spain	https://www.aemps.gob.es/medicamentos-de-uso-humano/investigacion_medicamentos/investigacionclinica_ceim/	Not found	Not found	
Sweden	https://etikprovningsmyndigheten.se/en/	Not found	Not found	
Taiwan	https://www.taiwanclinicaltrials.tw/spotlight/clinical_trial_overview/c_IRB/introduce	Not found	Not found	
The Netherlands	https://english.ccmo.nl/mrecs/accredited-mrecs	Not found	Not found	
Turkey	https://www.titck.gov.tr/dinamikmodul/84	Not found	Not found	

Uganda	Not found	https://healthresearchwebafrica.org.za/en/uganda/institution	Not found		
UK	https://www.hra.nhs.uk/about-us/committees-and-services/res-and-recs/search-research-ethics-committees/	Not found	Not found		
USA	https://ohrp.cit.nih.gov/search/irbsearch.aspx	Not found	Not found		
Multisite	N/A	https://www.who.int/groups/research-ethics-review-committee	N/A		WHO ethics review committee

Additional File 2: References to included Cochrane reviews and systematic reviews

We selected 23 evidence syntheses with the largest RCT pool in our search on 13 different interventions for prevention or treatment of COVID-19[1-23]; 13 were Cochrane reviews[2 3 5-7 11 13 15-17 19-21] and ten were non-Cochrane systematic reviews[1 4 8-10 12 14 18 22 23]. Three systematic reviews investigated two different interventions with the largest RCT pool in our search, i.e. Deng-2022 (convalescent plasma and SARS-CoV-2-neutralising monoclonal antibodies)[4], Siemieniuk-2020 (hydroxychloroquine or chloroquine and systemic corticosteroids)[18], and Zhang-2021(antibiotics and inhaled corticosteroids)[23].

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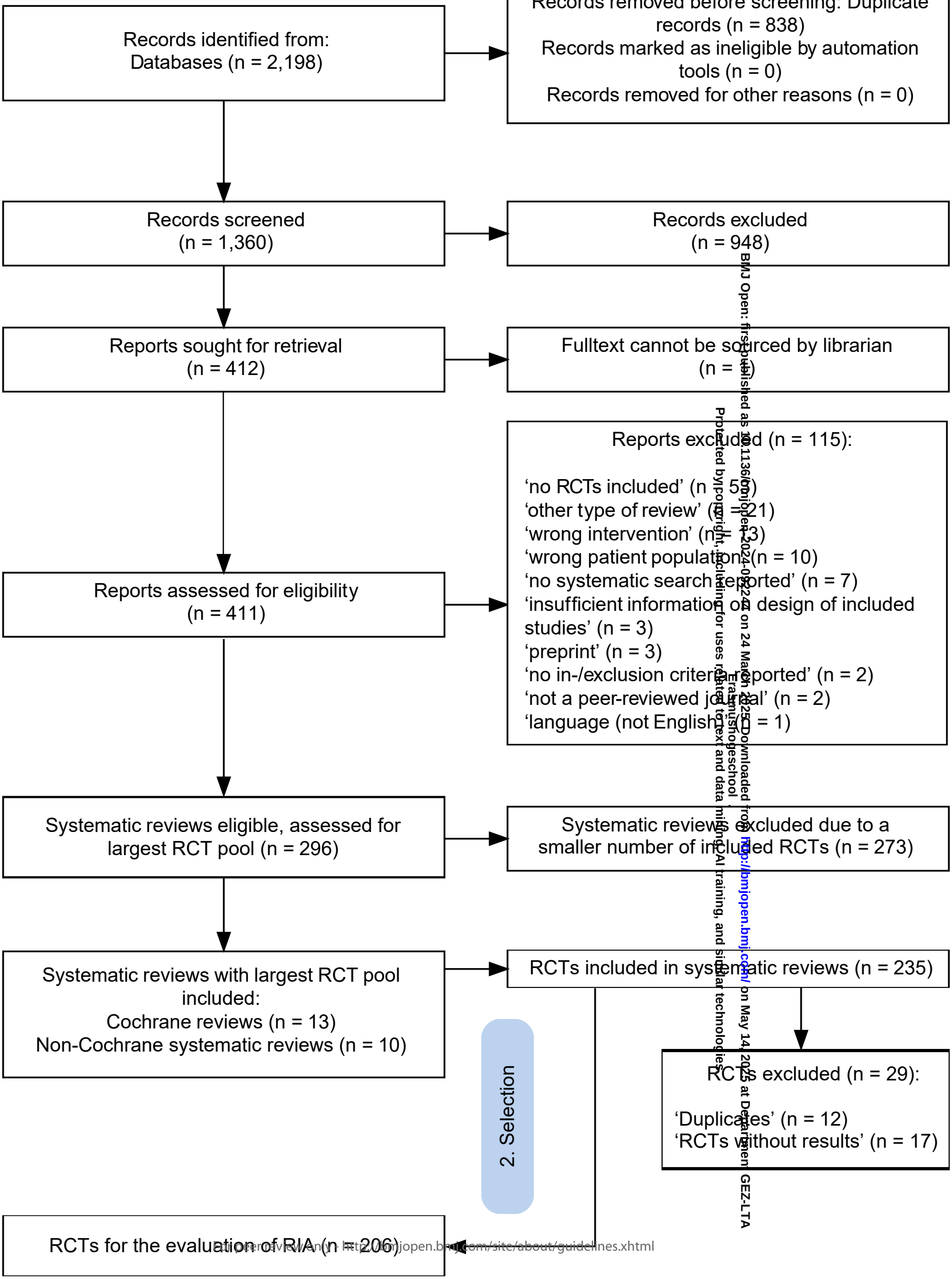
Selection of RCTs for assessment with the RIA tool



Additional File 4: Ethics approval date reported in trial registry records. (n = 74)[a]

Published RCTs	Registered on	EA Date identified on
ACTIV-3/TICO-2021b	NCT, EUCTR	EUCTR
Ader-2021	NCT, EUCTR	EUCTR
Ader-2022	NCT, EUCTR	EUCTR
Agarwal-2020	CTRI	CTRI
Babalola-2022	ISRCTN	ISRCTN
Baldeón-2022	ISRCTN	ISRCTN
Butler-2021 (PRINCIPLE)	ISRCTN, EUCTR	ISRCTN, EUCTR
Caricchio-2021	NCT, EUCTR	EUCTR
Chaccour-2021	NCT, EUCTR	EUCTR
Chen-2020b	ChiCTR	ChiCTR
Chen-2020c	ChiCTR	ChiCTR
CORIMUNO-2021	NCT, EUCTR	EUCTR
CORIMUNO-2022	NCT, EUCTR	EUCTR
Corral-Gudino-2021	EUCTR, REec	EUCTR
Davoodi-2020	IRCT	IRCT
Declercq-2021	NCT, EUCTR	EUCTR
Deftereos-2020	NCT, EUCTR	EUCTR
Dequin-2020	NCT, EUCTR	EUCTR
Dorward-2022 (PRINCIPLE)	ISRCTN, EUCTR	ISRCTN, EUCTR
Dubée-2020	NCT, EUCTR	EUCTR
Edalatifard-2020	IRCT	IRCT
Entrenas Castillo-2020	NCT, EUCTR	EUCTR
Eom-2021	NCT, EUCTR	EUCTR
Farahani-2020	IRCT	IRCT
Ghaderkhani-2020	IRCT	IRCT
Gupta-2021a, COMET-ICE	NCT, EUCTR	EUCTR
Gupta-2021b, COMET-ICE	NCT, EUCTR	EUCTR
Hermine-2021	NCT, EUCTR	EUCTR
Hinks-2021	NCT, EUCTR	EUCTR
Huang-2020	ChiCTR	ChiCTR
Jamaati-2021	IRCT	IRCT

Karakike-2021	NCT, EUCTR	EUCTR
Kharazmi-2022	IRCT	IRCT
Kirti-2021	CTRI	CTRI
Körper-2021	NCT, EUCTR	EUCTR
Kyriazopoulou-2021	NCT, EUCTR	EUCTR
Lescure-2021	NCT, EUCTR	EUCTR
Li-2020	ChiCTR	ChiCTR
Li-2021	ChiCTR (3x)	ChiCTR
Merchante-2022	NCT, EUCTR, REec	EUCTR
Mitjà-2020a	NCT, EUCTR	EUCTR
Mitjà-2020b	NCT, EUCTR	EUCTR
Mitjà-2020c	NCT, EUCTR	EUCTR
Niaee-2021	IRCT	IRCT
O'Brien-2022	NCT, EUCTR	EUCTR
Pan-2020 (SOLIDARITY)	NCT, ISRCT	ISRCTN
Pouladzadeh-2021	IRCT	IRCT
PRINCIPLE-2021	ISRCTN, EUCTR	ISRCTN, EUCTR
Ranjbar-2021	IRCT	IRCT
RECOVERY-2020a	ISRCTN, EUCTR, NCT	ISRCTN, EUCTR
RECOVERY-2020b	ISRCTN, EUCTR, NCT	ISRCTN, EUCTR
RECOVERY-2021a	ISRCTN, EUCTR, NCT	ISRCTN, EUCTR
RECOVERY-2021b	ISRCTN, EUCTR, NCT	ISRCTN, EUCTR
RECOVERY-2021c	ISRCTN, EUCTR, NCT	ISRCTN, EUCTR
RECOVERY-2021d	ISRCTN, EUCTR, NCT	ISRCTN, EUCTR
RECOVERY-2022	ISRCTN, EUCTR, NCT	ISRCTN, EUCTR
Rosas-2021a	NCT, EUCTR	EUCTR
Rosas-2021b	NCT, EUCTR	EUCTR
Salama-2021	NCT, EUCTR	EUCTR
Salehzadeh-2020	IRCT	IRCT

Salvarani-2021	NCT, EUCTR	EUCTR
Sancho-López-2021	EUCTR	EUCTR
Sekhavati-2020	IRCT	IRCT
Shahbaznejad-2021	IRCT	IRCT
Sivapalan-2021	NCT, EUCTR	EUCTR
Somersan-Karakaya-2022	NCT, EUCTR	EUCTR
Spinner-2020	ISRCTN, EUCTR, NCT	ISRCTN, EUCTR
Tang-2020	ChiCTR	ChiCTR
Tardif-2021	NCT, EUCTR	EUCTR
Wang-2020a	ChiCTR	ChiCTR
Weinreich-2021a, (phase 1-2)	NCT, EUCTR	EUCTR
Weinreich-2021b, (phase 1-2)	NCT, EUCTR	EUCTR
Weinreich-2021c, (phase 3)	NCT, EUCTR	EUCTR
Yu-2021b (PRINCIPLE)	ISRCTN, EUCTR	ISRCTN, EUCTR

Footnotes:

* Unpublished study, EA date reported on the trial registry record.

[a] n = 74 published RCTs, several RCTs were registered more than once and/or in different registries.

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Investigation of ethics approval as part of a research integrity assessment of randomized controlled trials in COVID-19 evidence syntheses: a meta-epidemiological study

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Abstract

Objectives

Ethical compliance of randomized controlled trials (RCTs) documented as ethics committee approval is vital for participant protection but is often overlooked by evidence synthesis producers despite regulatory mandates. We aimed to systematically assess reporting of ethics approval and informed consent (IC) in RCTs included in evidence syntheses and examined its potential impact on the study pool as part of a research integrity assessment.

Design Meta-epidemiological study.

Setting Assessment of ethics approval; domain 3 of the Research Integrity Assessment (RIA) tool developed for evidence syntheses.

Participants/subjects COVID-19 RCTs included in evidence syntheses.

Primary outcomes We extracted ethical items from study reports, i.e. ethics approval statements, ethics committee (EC) details, ethics approval numbers (EN), IC, and verified national recognition of ECs. RCTs were assessed regarding ethics approval and categorized as 'no concern', 'awaiting classification', or 'exclude' from the study pool. We also examined the impact of study settings on ethics approval reporting and discussed assessment reliability.

Results We included 188 RCTs. 93% of primary study reports contained an ethics statement, 70% provided EC details, 44% reported EN, and 91% mentioned IC. Trial registration records identified the EC in eight RCTs and EN in 25 RCTs. Overall, 41% of RCTs reported all ethical items. Authors of 95 RCTs were contacted for missing information, yielding 22 satisfactory responses. Of the 151 RCTs with identified ECs, 88% were nationally recognized. Overall, 53% of RCTs were classified as 'no concern', 47% as 'awaiting classification', and none were excluded. Most were 'awaiting classification' due to reporting-related reasons. No significant differences in ethics approval reporting were observed across study settings, countries, or sample sizes.

Conclusions Reporting of ethical items in RCTs remains inadequate. Including ethics approval details in reporting guidelines such as CONSORT could improve this. Current under-reporting issues limit the reliability of the RIA tool's ethics approval assessment.

Protocol registration

The protocol is available on OSF (https://osf.io/3bzeg).

Strengths and limitations of this study

- The study uses a meta-epidemiological approach to systematically assess ethics approval in COVID-19 RCTs, using both primary study reports and trial registration records for a comprehensive evaluation.
- Active engagement with study authors to obtain missing information or clarify inconsistencies improves the accuracy and completeness of the ethics approval assessments.
- The reliance on reported data in study publications and trial registrations, which may be incomplete or inaccurate, limits the reliability of the ethics approval assessment.
- The absence of standardized, internationally recognized procedures for reporting ethics approval and other ethical items complicates consistent and accurate assessment across diverse studies.
- The lack of a global registry for ethics committees hinders the verification of their national recognition status, and therefore the assessment of ethics approval of studies.

Keywords

Randomized controlled trial, ethics, ethics approval, evidence synthesis, systematic review, research integrity

Background

The basis for reliable results in evidence syntheses is the knowledge of the trustworthiness of the underlying research evidence base. Research that follows the principles of research integrity ensures trustworthiness. To date, producers of evidence syntheses have not routinely assessed the research integrity of studies included in their evidence syntheses. Critical appraisal tools, such as Cochrane Risk of Bias tool 2 (RoB 2) and Grading of Recommendations, Assessment, Development and Evaluation (GRADE), used to assess the internal and external validity of study results, do not necessarily address aspects of research integrity.[1 2] There is an ongoing debate on how to appraise research integrity, and several projects are ongoing to develop trustworthiness screening and research integrity assessment tools for producers of evidence syntheses.[3-6]

Most researchers associate research integrity with the use of honest and verifiable methods in proposing, performing, and evaluating research, but research integrity also comprises adhering to (inter)national and commonly accepted guidelines, regulations, norms and standards.[7] Clinical studies should follow good clinical practice (GCP) - a code of international ethical and scientific standards for designing, recording and reporting studies that involve the participation of human subjects.[8] The World Medical Association (WMA) has developed the Declaration of Helsinki which states that “physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards” […] and that a “research protocol must be submitted for consideration, comment, guidance and approval to the concerned [independent] research ethics committee before the study begins”.[9] We distinguish between the 'ethical compliance' of a clinical trial, which refers to adherence to research ethics as determined by ethics committees, and the process of 'obtaining ethical approval' by study investigators or funders.[10]

Compliance of clinical studies with ethics approval standards can only be reliably assessed if details are fully reported in study reports. Unfortunately, the reporting of ethics approval in randomized controlled trials (RCTs) is currently not included as an item in the Consolidated Standards of Reporting Trials (CONSORT 2010) statement.[11] Given the lack of standardization in reporting, it is unclear how ethics approval of RCTs should be assessed within an evidence synthesis and what impact an assessment may have on the results and conclusions of evidence syntheses.

This paper is part of a meta-epidemiological study which applies a novel and non-validated tool, designed for a research integrity assessment (RIA) of interventional RCTs of an investigational medicinal product (IMP) in the context of an evidence synthesis,[12] to a pool of RCTs included in COVID-19 systematic reviews. In this part, we focus on the assessment of

the third domain of the RIA tool, i.e. ethics approval of RCTs. We present reporting of ethics approval and informed consent in the study reports of recent RCTs, provide guidance for producers of evidence synthesis on how to assess ethics approval, and discuss the feasibility of the tool for its use in evidence synthesis.

Methods

The protocol for the meta-epidemiological study has been published, including the search for RCTs and the assessment of ethics approval (https://osf.io/3bzeg). We extracted and analyzed additional study data, which was not prospectively planned, but designed post hoc to describe the study pool in detail. Additional analyses are indicated as such.

Selection of RCTs for assessment with the RIA tool

We searched for Cochrane reviews (CRs) and non-Cochrane systematic reviews (SRs) with or without meta-analysis evaluating 13 interventions for the prevention or treatment of SARS-CoV-2 infection and COVID-19 in humans, irrespective of SARS-CoV-2 diagnosis, disease severity or treatment setting. Pairwise and network meta-analyses were eligible. We included full text, peer-reviewed journal publications of systematic reviews. Preprints of systematic reviews, scoping reviews and narrative reviews were not eligible. We restricted the inclusion to publications in English. Further details on inclusion criteria of CRs and SRs in terms of population, interventions, and comparators are described in the protocol (https://osf.io/3bzeg).

Two reviewers independently searched for all eligible CRs and SRs with regard to study design, population and relevant interventions in PubMed to 09 June 2022. The search strategy is provided in the protocol (https://osf.io/3bzeg). One reviewer selected the CR (or its update) and the SR (or its update) to each of the relevant interventions with the largest RCT pool based on the most recent search date or the broadest inclusion criteria. The study pool of RCTs for further testing of RIA consisted of the primary studies included in the eligible systematic reviews. RCTs published as journal publications, preprints, or unpublished with results posted in trial registries were eligible. Depending on the type of published results, either journal publications, preprints, or trial registration records were considered as 'primary study reports'. Multiple primary study reports of a study (e.g. journal publication and preprint) were not pooled for our assessment but were separately assessed as included in the original systematic review.

In the present study, we excluded retracted RCTs (i.e. first domain of the RIA) and studies which were incorrectly included in the selected evidence syntheses as RCTs, although the studies clearly stated that a non-randomized study design was used. All RCTs, which were not previously excluded, were assessed in this study, irrespective of the registration status (i.e. second domain of the RIA). We documented the screening and selection process of systematic reviews and RCTs in a PRISMA flow diagram including reasons for exclusion at the full-text screening stage.

Data extraction of study characteristics

One reviewer (i.e. the third reviewer in the meta-epidemiological RIA study, FW) extracted details on ethics approval for all RCTs included in this study from the primary study reports, supplemental materials, study protocols, and trial registration records to September 2023. Where available, original data extractions made by two independent reviewers on ethics approval in the RIA study were used and checked by the third reviewer (FW). If double extracted data were not available (i.e. for RCTs which previously did not pass domain 1 and 2 of the RIA), or if discrepant extractions between pairs of reviewers occurred, a third reviewer (FW) extracted missing data or solved conflicts for this study.

Originally, the third domain of the RIA on ethics approval included five items for the assessment of RCTs,[12] i.e. reporting of an ethics approval statement in the primary study report, name and location of the ethics committee (EC) (or alternatively named, 'institutional review board' (IRB), 'research ethics committee' (REC)), national recognition status of the EC according to country, ethics approval number (EN), and informed consent (IC). In this study, one reviewer (FW) additionally extracted the date of the ethics approval (i.e. date of ethics opinion) and the date of study start as reported in the primary study report and in the trial registration records. We also extracted the following information from all RCTs, i.e. sample size, setting (single-centre vs national multi-centre vs international multi-centre), location (i.e. country) where the study was conducted, and the trial registry with registration number where the study was registered.

Assessment of ethics in RCTs

1. *Statement on ethics approval*

We investigated whether the RCTs included an informative statement on ethics approval in the primary study report. Every statement on ethics approval was counted, if it at least mentioned that an EC granted the approval (e.g. approved by an institutional ethics committee) or the EN was reported. The EC did not have to be named. Generic declarations, such as "this study was conducted in accordance with the Declaration of Helsinki and/or with the local regulations" were considered as insufficient. If no (sufficient) statement on ethics approval was reported in the primary study document, we contacted the study authors via E-mail for further information.

2. *Name and location of ethics committee*

We assessed whether RCTs reported the name and location of at least one EC in the primary study report. We accepted reporting of at least one EC as sufficient for single-centre as well as for multi-centre RCTs. Generic statements, e.g. "ethics approval obtained from several

IRBs, according to site", without further specifications were considered as insufficient. If the name and location of the EC was not reported in the primary study report, we searched for the corresponding trial registration record of registered RCTs, and if not successful, we contacted the study authors via E-mail for further information.

3. Recognition status of ethics committees

Interventional RCTs of an IMP in humans need ethics approval (i.e. ethics opinion) by an authorized institution such as an EC.[9 13] The EC should have a national recognition status and there should be a national government department responsible for recording the committee's national recognition status. To determine the recognition status of a reported EC, a new strategy was developed and applied by the third reviewer (FW), which was not included in the original RIA. We conducted a primary search in Google (https://www.google.de) following a standardized procedure, where the search was initiated by introducing the name and address of the EC as reported, supplemented by keywords, such as 'ethics committee' or 'EC', 'institutional review board' or 'IRB', or 'research ethics committee' or 'REC'. With this primary search (latest search on 27.07.2023), we could identify national registries or directories of ECs for a total of 22 countries described in our RCT pool, which were provided by official organizations (i.e. the Ministry of Health, or bioethics or research entities). These directories were considered reliable sources. Additionally, four international directories listing local and independent ECs/IRBs and ethics regulations of various countries were also retrieved: two country-specific online databases (for low- and middle-income countries: https://healthresearchwebafrica.org.za/en, and for Europe: http://www.eurecnet.org/index.html), which provide clinical research regulatory information (i.e. up-to-date ethical regulations, list of accredited EC/IRB); one online database of the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP, https://www.aahrpp.org/), which provides current information about their independently accredited entities worldwide; as well as the website of the WHO Research Ethics Review Committee (https://www.who.int/groups/research-ethics-review-committee). All national and international sources are listed in Additional File 1.

In cases where an EC/IRB could not be located in any of the sources on the list, indirect searches through the website of the institution where the study took place were performed. An independent EC/IRB was considered as 'recognized' if the institution provided a statement and/or documents proving national accreditation. These ECs/IRBs were also added to the list of sources (Additional File 1). If the search still remained futile, the recognition status of the EC/IRB was deemed to be 'unclear'.

4. Ethics approval number

We assessed whether RCTs reported at least one EN in the primary study report. We accepted reporting of at least one EN as sufficient for single-center as well as for multi-center RCTs. If no EN was reported in the primary study report, we searched the trial registration record of registered RCTs, and if not successful, we contacted the study authors via E-mail for further information.

5. Informed consent

We assessed if the primary study report included a statement on whether the RCT has obtained written informed consent (including electronically signed informed consent forms) from all participants or their relatives prior to enrollment. We also accepted verbal informed consent, if explicitly approved by an EC. In case of an insufficient statement or the lack of it, we contacted the study authors via E-mail for further information.

RIA judgement of RCTs considering ethics

Studies that sufficiently reported and fulfilled all of the original five RIA items were assessed as 'no concern' (i.e. considered eligible for evidence synthesis).[12] Studies with at least one item assessed as insufficient (i.e. unclear/not found/not reported) were classified as 'awaiting classification' (i.e. considered ineligible for evidence synthesis until clarification).[12] Since there is no standardized recommendation for the reporting of ethical considerations in an RCT such as the CONSORT 2010 statement,[11] we decided not to exclude any RCT due to missing information. However, studies with confirmed lack of an ethics approval in general or lack of IC were assessed as 'exclude' (i.e. considered ineligible for evidence synthesis).

Authors of the RCTs classified as 'awaiting classification' were contacted in order to obtain missing information and clarify inconsistencies or concerns. Authors of unpublished RCTs (i.e. only trial registration records available) were not contacted, since those studies cannot be adequately assessed with current RIA items comparing journal publications or preprints with trial registration records. Authors had 14 days to respond. If a study author provided complete information, the RCT was upgraded to 'no concern'. Study authors who did not provide any feedback were reminded via E-mail and were given an additional seven days to reply. The categorization of the RCTs remained 'awaiting classification', if incomplete or no response was received.

For presentation in this study, we differentiated two subcategories of reasons for 'awaiting classification' regarding ethics, i.e. research integrity-(RI)-related and reporting-related reasons. We considered a RI-related reason to be the non-existence of an EC (i.e. EC reported, but not found in our sources or an inability to establish the existence of the EC from

any source). Reporting-related reasons included lack of or insufficient statement on ethics approval or EC, non-reporting of EN, and unclear or not reported IC. However, it should be noted that non-reporting itself is problematic in terms of RI.

Date of ethics approval

In this study, we also extracted and assessed additional items related to ethics approval, which were not included in the original RIA, i.e. the date of ethics approval (also defined as the date of ethics opinion) and study start, and the timing of ethics approval. Additionally extracted and assessed items did not change the RI assessment for the ethics approval domain in this study. We assessed whether RCTs reported the date of ethics approval in the primary study report. We accepted reporting of at least one ethics approval date as sufficient for single-centre as well as for multi-centre RCTs. A generic statement, e.g. “ethics approval has been obtained prior to enrollment of the first subject”, was considered insufficient, if no further details pertaining the date of the ethics approval were disclosed. If the ethics approval date was not reported in the primary study report, we searched for the corresponding trial registration record of registered RCTs. For all RCTs, where we identified an ethics approval date, we assessed whether the ethics approval was obtained before the start of the study (i.e. prospectively). We used the dates referred to ‘study start’ as defined by different trial registry platforms and the study start date reported in the publication or preprint. Several RCTs reported different dates of study start and ethics approval, as they took place in several locations (i.e. conducted as multi-centre RCTs). A RCT was considered as having obtained a prospective ethics approval, if true for at least one site. An ethics approval date after study start was considered either as retrospective ethics approval in case of single-centre settings or as ‘potentially retrospective’ in case of multi-centre settings.

Statistical analysis and presentation of data

This study has been designed to facilitate a descriptive data analysis. We did not perform any statistical hypothesis testing, as this part of the study was not prospectively planned, but designed post hoc to disseminate relevant findings. We compared the categories of RCTs assessed as ‘no concern’, ‘awaiting classification’ and ‘exclude’, regarding reporting of ethics approval date, setting, location, sample size, and trial registry. Descriptive statistics and frequency tables were used to present and compare variables (e.g., sample size, setting, location, and trial registry).

Due to the large number of studies, we only referenced individual studies in the following results section if less than ten studies are referred to. We restricted referencing of studies to

our investigations on the original ethics items for RIA. Data and digital object identifiers (doi) for all individual studies are available online [dataset].[14]

Results

A total of 206 RCTs included in 23 evidence syntheses (i.e. 13 CRs and ten SRs, Additional File 2) investigating interventions of interest for treatment or prevention of SARS-CoV-2 infection were identified by our search (Additional File 3). We included 188 RCTs in this study and excluded eight retracted RCTs and ten studies which turned out to be non-randomized studies. Of 188 RCTs, 149 were published in journals, 33 were published on a preprint server, and the remaining six RCTs were unpublished with results only posted on a trial registration database. References and all baseline details of included RCTs reported in the following (i.e. ethical items, sample size, setting, country, and trial registration) are available online [dataset].[14]

Of 188 RCTs, 174 published and one unpublished RCT included an informative statement on ethics approval in the primary study report (Table 1). Three published RCTs have not reported any statement on ethics approval (Kishoria-2020, Li-2021, Mareev-2021). Five published RCTs included a general statement, e.g. following international principles, applicable laws and regulations (Chen-2020a, Dougan-2021a, Dougan-2021b, Gupta-2021a, Podder-2020). The study authors of theses eight published RCTs were contacted to confirm ethics approval. Upon request, one study author (Mareev-2021) confirmed ethics approval without providing further details (i.e. EN).

Of 188 RCTs, 130 published and one unpublished RCT provided the name and location of at least one EC in the primary study report (Table 1). Eleven published RCTs included only a generic statement without further reference to the name and location of the EC, including eight international multi-centre RCTs. Forty-one published RCTs and five unpublished RCTs did not indicate the name and/or the location of at least one EC in the primary study report. Eight published RCTs provided this information exclusively in the trial registration record (Chen-2020b, Galan-2021, Huang-2020, Soin-2021, Spinner-2020, Thakar-2021). Upon request, 12 study authors supplied the name and location of ECs. In 37 RCTs, the EC remained unreported or unclear. Of 151 RCTs with reported or identified name and location of at least one EC, 134 were classified as recognized (Table 1). The national recognition status of the ECs in the remaining 17 RCTs was unclear. For 14 RCTs, the EC could not be identified in any of our sources (Additional File 1) and for the remaining three RCTs there was no source available (i.e., two RCTs from Iraq: Hashim-2020, Rasheed-2020; one from Russia: Mareev-2021).

Eighty-one published RCTs and one unpublished RCT included the EN in the primary study report (Table 1). One hundred one published RCTs and five unpublished RCTs did not report any EN in the primary study report. For 25 RCTs, the EN was identified in the trial registration records. For another 19 published RCTs, the study authors provided the EN upon request. The EN was not found for 57 published RCTs.

Of 188 RCTs, 165 published RCTs and all six unpublished RCTs included a statement that IC was obtained (Table 1); 163 obtained IC in written form and two RCTs obtained verbal or written IC which was approved by an EC (Dequin-2020, Derde-2021). In 14 RCTs, a statement on IC was reported, however, it was unclear if it was written consent or verbal, but approved by an EC. Three study authors confirmed having obtained written IC from all participants upon request (Gonzalez-2021, Okumus-2021, van den Berg-2022). In three RCTs, the publication contained no statement on IC (Galan-2021, Li-2021, Mareev-2021).

Table 1: Reporting and identification of ethics details in RCTs

Ethics details	RCTs, n (%)	
	Journal/preprint articles (n = 182)	Registration records (n = 6)
Statement on ethics approval		
Reported in primary study report*	174 (96%)	1 (17%)
Insufficiently reported/not reported	8 (5/3) (4%)	5 (0/5) (83%)
Identified by author request	1	N/A
Not found/unclear	7	N/A
Name and location of Ethics Committee (EC)		
Reported in primary study report*	130 (71%)	1 (17%)
Insufficiently reported (generic statement)/not reported	52 (11/41) (29%)	5 (0/5) (83%)
Identified in the trial registration record	8	N/A
Identified by author request	12	N/A
Not found/unclear	32	N/A
EC recognized (n = 151)		
Yes	133	1
Unclear	17	0
Due to EC not found in source	14	0
Due to EC not found, no source available	3	0
Ethics approval number		
Reported in primary study report*	81 (45%)	1 (17%)
Not reported	101 (55%)	5 (83%)
Identified in the trial registration record	25	N/A
Identified by author request	19	N/A
Not found	57	N/A
Informed consent		
Reported in primary study report	165 (91%)	6 (100%)
Insufficiently reported/not reported	17 (14/3) (9%)	0
Clarified by author request	3	N/A
Not found/unclear	14	N/A

Abbreviations: Ethics committee (EC), randomized controlled trials (RCTs)

Footnotes:

* Primary study report = publication/preprint or registration record, if RCT unpublished

Of the 188 RCTs, 41% sufficiently reported and fulfilled all items required for the assessment of the ethics approval in the primary study report and/or the trial registration record, i.e. 77 published RCTs and one unpublished RCT (Table 2). We classified these RCTs as 'no concern'. After the first assessment round, 105 published RCTs and five unpublished RCTs incompletely reported at least one item required to assess the ethics approval domain and were categorized as 'awaiting classification'. None of the RCTs were excluded, since there was no RCT with a confirmed lack of an ethics approval or IC. Of the 110 RCTs categorized as 'awaiting classification', 95 study authors were contacted due to missing information regarding statement of ethics approval, EC, EN, and/or IC (Table 2). Study authors of 25 RCTs responded and 21 RCTs were finally upgraded to 'no concern'. One study author provided sufficient information, however, the EC was not found in our sources (i.e. unclear national recognition status) and the RCT remained 'awaiting classification' (Sadeghipour-2021). Three RCTs remained 'awaiting classification' due to incomplete or insufficient responses (Abd-Elsalam-2021a, Ali-2022, Mareev-2021) and study authors of 70 RCTs did not respond at all. Fifteen study authors were not contacted, which included five unpublished RCTs and ten RCTs providing complete information in the primary study reports, however, the EC could either not be found in our sources, or there was no source available to verify the recognition status of the ECs (Table 2). Following author request, a total of 99 RCTs were considered as 'no concern' and 89 RCTs remained as 'awaiting classification'.

Table 2: Summary of RI assessment based on provided ethics information

Information on ethics	No concern	Awaiting classification	Exclude
Reporting of information (n = 188)			
Information completely reported in publication and/or in registration record(s)	78	0	N/A
Journal/preprint publication	77	0	N/A
Registration records	1	0	N/A
Information incompletely reported in publication and/or in registration record(s)	0	110	N/A
Journal/preprint publication	0	105	N/A
Registration records	0	5	N/A
Retrieval of information of RCTs 'awaiting classification' (n = 110) (i.e. author request)			
Study author contacted for missing information or inconsistencies	21	74	N/A
Information completed by study author	21	1[a]	N/A
Response insufficient or not complete	0	3	N/A
No response received	0	70	N/A
Study author not contacted for following reason	0	15	N/A
Only registration record available	0	5	N/A
Information complete, but EC not found in source	0	8	N/A
Information complete, but no source for national ECs available	0	2	N/A
Final assessment	99	89	0

Abbreviations: Ethics committee (EC)

Footnotes:

[a] Sadeghipour-2021 (INSPIRATION) provided complete information, but EC was not found in source (national recognition unclear)

We have differentiated the reasons for 'awaiting classification' in reporting-related and RI-related reasons (Table 3). Several RCTs comprised more than one reason for 'awaiting classification' of both types, i.e. RI-related and reporting-related. Most RCTs were 'awaiting classification' due to reporting-related reasons. Predominantly, an EN was not reported in 62 RCTs, followed by insufficient or not reported EC in 37 RCTs. Seventeen cases of RI-related reasons were counted which are not due to non-reporting, but to a lack of EC recognition.

Table 3: Reasons for awaiting classification

Reasons for awaiting classification (n = 89), after author request with or without response	
Reporting-related reasons[a]	
Statement on ethics approval insufficient or not reported	12[b]
EC insufficient or not reported	37[b]
EN not reported	62[b]
IC unclear or not reported	14
RI-related reasons	
EC reported, but national recognition unclear	17
EC not found in source	14
No source available	3

Abbreviations: Ethics committee (EC), ethics approval number (EN), research integrity (RI), informed consent (IC)

Footnotes:

[a] Some RCTs have more than one reason for 'awaiting classification', therefore, the sum of all reasons exceeds the total number of RCTs in 'awaiting classification'

[b] Including five RCTs available as registration records only

In this study, we extracted and assessed the date of ethics approval (i.e. date of ethics opinion) in addition to the original five RIA domains. Five published RCTs (Chowdhury-2021, Gonzalez-2021, Thakar-2021, Vallejos-2021, van den Berg-2022) and one unpublished RCT (NCT04392141) reported the date of ethics approval in the primary study report, and in all cases the ethics approval had been obtained prior to study start (Table 4). Six published RCTs (Bennett-Guerrero-2021, Chen-2021, Faisal-2021, Hamdy Salman-2020, Okumus-2021, Rasheed-2020) included a general statement (e.g. ethics approval obtained prior to enrolment), without specifying the date of ethics approval. One hundred seventy one published and five unpublished RCTs did not provide the ethics approval date in the primary study report. For 74 of the 177 published RCTs the ethics approval date could be identified in one or more trial registration record, i.e. 50 registrations in EUCTR, 15 in ISRCTN, 12 in IRCT, seven in ChiCTR, and two in CTRI (Additional File 4). In total, the ethics approval date for 103 published RCTs could not be retrieved despite active search. Of 80 RCTs with an identified ethics approval date, 63 RCTs had obtained the ethics approval prior to study start/enrollment of the first subject for at least one site, including 15 single-centre RCTs, 34 national multi-centre and 14 international multi-centre RCTs. Fourteen RCTs presented inconsistencies in the study start dates reported in the primary study reports and the trial registration records resulting in different assessments of ethics approval timing. Of these 14 RCTs with inconsistencies, six were single-centre (Babalola-2022, Chen-2020b, Farahani-2020, Huang-2020, Kharazmi-2022, Pouladzadeh-2021), two were national multi-centre RCTs (Corral-Gudino-2021, Wang-2020a), and the remaining six RCTs were international multi-centre RCTs (Eom-2021, Gupta-2021a, Gupta-2021b, Rosas-2021a, Spinner-2020, Tardif-2021), in which the primary study location remained unclear (i.e. possibly different date of EA). Two published national multi-centre RCTs from China (Li-2020, Li-2021) and one international multi-centre RCT (Pan-2020) received an ethics approval after study start and were considered 'potentially retrospective' according to the publicly available information from the trial registries. The study authors did not provide any feedback upon request leaving us unable to clarify the dates.

Table 4: Ethics approval date of RCTs

Ethics approval date (i.e. date of ethics opinion)	RCTs, n (%)	
	Journal/preprint articles (n = 182)	Registration records (n = 6)
Reporting of ethics approval date		
Reported in primary study report*	5 (3%)	1 (17%)
Insufficiently reported/not reported	177 (6/171) (97%)	5 (83%)
Identified in the trial registration record	74	N/A
Not found/unclear	103	N/A
Ethics approval obtained prior to study start (n = 80)		
Yes[a]	62	1
Unclear	14	0
No	3	0

Abbreviations: Randomized controlled trials (RCTs)

Footnotes:

* Primary study report = publication/preprint or registration record, if RCT unpublished

[a] For at least one site

The frequency of reporting of the ethics approval date was similar in RCTs assessed as 'no concern' with 45% (45 of 99) and 'awaiting classification' with 39% (35 of 89). However, two of three RCTs with 'potentially retrospective' ethics approval (Li-2020, Li-2021) were assessed as 'awaiting classification' while the other was assessed as 'no concern' (Pan-2020).

The comparison of RCTs with sufficiently reported ethics approval regarding all items (i.e., 'no concern', n = 99) compared to those with insufficient, inconsistent, or missing ethics approval details (i.e., 'awaiting classification', n = 89) revealed a similar distribution regarding the study setting, i.e. international multi-centre (18% vs 16%), national multi-centre (47% vs 49%), and single-centre (35% vs 35%) (Table 5). According to the countries of study conduct, 66% of the European RCTs were assessed as 'no concern', whereas 71% of the North American RCTs were 'awaiting classification' (Table 5). Half of all single-centre RCTs were from Asia with 58% assessed as 'awaiting classification'.

Twelve RCTs were not registered and eight of them were assessed as 'awaiting classification' for the RIA domain on ethics approval (Table 5). ClinicalTrials.gov was the most used platform for trial registration among the registered RCTs, with no difference in the number of registrations between RCTs assessed as 'no concern' compared to 'awaiting classification' (76 vs 66). We identified nine registrations on ChiCTR and all nine belonged to RCTs which were assessed as 'awaiting classification'. In contrast, all 15 registrations in the WHO ISRCTN registry belonged to RCTs assessed as 'no concern'.

There was a slight difference between RCTs categorized as 'no concern' compared to 'awaiting classification' in terms of the sample sizes, i.e. 54% vs 39% randomized 200 or more participants, and the median sample size was 240 vs 131 participants.

Table 5: Characteristics of RCTs classified as 'no concern' and 'awaiting classification' (n = 188)

Study characteristics	No concern (n = 99)	Awaiting classification (n = 89)
Setting and location		
Multi-center, international (n = 32)	18	14
Multi-center, national (n = 90)	46	44
Africa	1	0
Asia	10	12
Australia	0	0
Europe	22	14
North America	5	13
South America	8	5
Single-center (n = 66)	35	31
Africa	6	3
Asia	14	19
Australia	0	0
Europe	5	0
North America	2	4
South America	8	5
Trial Registry[a]		
ClinicalTrials.gov (n = 142)	76	66
EUCTR (n = 56)	35	21
ISRCTN (n = 15)	15	0
IRCT (n = 12)	7	5
ChiCTR (n = 9)	0	9
CTRI (n = 6)	4	2
ReBec (n = 5)	4	1
Other[b] (n = 4)	3	1
RCTs without trial registration (n = 12)	4	8
Sample size; randomized patients		
Median (IQR)	240 (91 to 777)	131 (65 to 420)
Less than 100 participants (n = 60)	26	34
100 to less than 200 participants (n = 40)	20	20
200 or more participants (n = 88)	53	35

Abbreviations: Randomized controlled trials (RCTs), interquartile range (IQR), EU Clinical Trials Register (EUCTR), International Standard Randomised Controlled Trial Number (ISRCTN), Iranian Registry of Clinical Trials (IRCT), Chinese Clinical Study Register (ChiCTR), Clinical Trials Registry India (CTRI), Brazilian Registry of Clinical Trials (ReBec), Spanish Clinical Study Registry [Registro Español de Estudios Clínicos] (REec), Indonesia Clinical Research Registry (INA), Saudi Clinical Study Registry (SCTR)

Footnotes:

[a] Some RCTs were registered in different trial registries and/or with different numbers in the same registry, therefore, the sum of all registrations exceeds the total number of RCTs in the categories 'no concern' and 'awaiting classification'

[b] Includes two registrations in REec, one in INA, and one in SCTR

Discussion

Reporting of ethics approval in COVID-19 RCTs is insufficient. Only 41% of RCTs sufficiently reported and fulfilled all items required for the assessment of ethics approval in the primary study report and/or the trial registration record, whereas 59% of RCTs incompletely reported ethics items and were categorized as 'awaiting classification'. In our study, registration records have proven to be important sources for ethics approval details as we were able to identify details for 33 items. Furthermore, authors of 50% of included RCTs were contacted due to missing information or to clarify inconsistencies. This enabled an upgrade of another 11% of the RCTs from 'awaiting classification' to 'no concern'. Finally, almost half of all RCTs were considered of 'no concern' and the other half remained 'awaiting classification', i.e. not eligible for evidence synthesis due to uncertainties regarding ethics approval according to the RIA tool.

Originally, we planned to assess RCTs with confirmed lack of an ethics approval or lack of IC as 'exclude', i.e. not eligible for evidence synthesis as problematic in terms of research integrity. About 10% of RCTs in our study pool did not sufficiently report on IC. However, in no case, we were clearly able to demonstrate that ethics approval or IC was not present. A main obstacle to a reliable assessment is that we cannot determine with certainty whether there was actually a violation of research integrity in terms of obtaining ethics approval and IC for a clinical study that goes beyond the problem of non-reporting.

The reporting of ethics approval in clinical studies has improved little over the years. Zoccatelli et al determined that 97% of the studies published in 2011 in the European Journal of Anaesthesiology declared an ethics approval, of which 85% reported the name and location of EC and 69% provided EN.[15] Yank et al estimated a lack of ethics approval statement in 18% of the studies carried out after 1997 and a tenth of the RCTs did not report having obtained written IC.[16] A hurdle might be that reporting of ethics approval in RCTs is currently not included as an item in the CONSORT 2010 checklist, the most important reporting guideline for RCTs.[11] We assume that reporting could be improved if CONSORT would include items on ethics approval, due to its major impact on reporting quality of RCTs in the past, as shown for the registration of studies.[17] An update of the CONSORT 2010 checklist is currently in progress and we expect consideration of ethics approval as ethics committees and regulatory agencies will be important stakeholders.[18] The current situation requires that we first increase awareness of the importance of reporting ethics approval in study reports before producers of evidence syntheses can reliably assess this aspect in the context of research integrity.

Our post hoc comparison of RCTs assessed as 'no concern' with those assessed as 'awaiting classification' revealed a similar distribution regarding study setting and country, and only a slight difference regarding the median sample size. The fact that the large international multi-

center studies behaved similarly in the reporting of ethics approval as the small single-centre studies could be another indication of the lack of awareness of the importance of full reporting.

Our study outlines the essential role trial registries play in the assessment of ethics approval. Even though most trial registries, especially those listed as 'primary registries in the WHO network', explicitly require proof of ethics approval prior to trial registration, our study reveals that several registries do not always enforce these requirements. This is especially true for ChiCTR as none of the seven RCTs registered with nine registrations on this platform were considered as 'no concern', due to inconsistencies or non-reporting of ethics details. Among the registries used by our RCTs, ISRCTN, ChiCTR, EUCTR, CTRI, and IRCT provided detailed information pertaining ethics approval as a standard feature. Other platforms, such as ClinicalTrials.gov, where most of the RCTs were registered, do not supply information related to ethics approval as standard.

While author response request has been established as another practical way to obtain missing information or clarify inconsistencies, this method is time consuming and not effective in about three-quarters of all requests. Whether this effort can be carried out as part of an evidence synthesis mainly depends on the available resources and considerations on time and timeliness in individual cases. However, improved reporting would significantly reduce this time expenditure.

We have underpinned our assurance of adequate ethics approval through the national recognition of the ethics committees. The unavailability of updated national or international directories for accredited ECs/IRBs hinders our assessment. The search for national sources was time-consuming. About 10% of the RCTs were approved by an EC, which after an extensive search, could not be found in any source, and therefore their recognition status remains unclear. The language barrier might play an important role in the search for sources. This finding differs with those of Zoccatelli et al, who were unable to identify 41% of the ECs of their study pool.[15] On the other hand, our sources used for the assessment of the recognition status might be out-of-date: the EC might have been deactivated or lost national recognition status by the time of the approval provided to the study authors, or the committee may have lost but then regained national recognition status by the time of our search. A regularly updated international register of the recognized EC and IRBs would support the assessment of ethics in evidence synthesis.

One of the included studies, a large multi-centre RCT (Pan-2020), used an online GCP-compliant system for data collection across many collaborating sites and countries. The designers of such systems could lock data entry until the ethics committee grants favourable opinion and authorizes unlocking for the initiation of study recruitment. Simple technological

solutions such as this could help to harmonize new technologies with older international standards.[9]

Our study has several limitations. Our assessment is dependent on details reported in study reports. As stated by Tramèr[19] and Yank et al[16], even when details pertaining to ethics approval are reported or provided by the author, there are no guarantees as to whether the approved protocol matches the study performed. Furthermore, we did not contact the EC to verify whether the authors obtained ethics approval, the information provided was consistent with the approval documents, or the EC was nationally recognized at the time of approval. We did not take into account the role of the journals in the assessment of this domain, although they may act as a checkpoint to screen ethically unsound studies and there may be great differences between different journals, as stated by Myles et al.[20] Our search was conducted exclusively in English, which may hamper the retrieval of sources of EC in non-native English-speaking countries.

Finally, we need an extensive discussion in the research community on which ethical items should be used for a reliable assessment. The ongoing INSPECT-SR project is developing a tool to identify problematic RCTs in systematic reviews of healthcare-related interventions by critical discussion with different experts in the field on which checks are useful to determine a study's authenticity, and ethics is one the checks.[21] Although currently not an item of the RIA ethics approval domain, we suggest the assessment of the ethics approval date as a new item.

In our view, it is essential to include ethics approval in the research integrity assessment of RCTs as part of evidence synthesis in the future. However, poor reporting - even if a research integrity issue on its own - complicates a reliable assessment. Nevertheless, including ethics approval in the checklist of evidence syntheses and in reporting guidelines of clinical studies is especially important to increase awareness in the scientific community about the need for high ethical standards in human research.[22] Therefore, at present, we suggest to assess ethics approval in RCTs during a research integrity assessment included in the evidence synthesis process, however, not to exclude studies assessed as 'awaiting classification' from the study pool and meta-analysis, but instead perform sensitivity analysis to investigate robustness of the results.

Conclusion

This study highlights two main issues concerning ethics approval in RCTs. First, reporting of ethical approval in RCTs is poor. Second, as under-reporting cannot be excluded, the assessment of ethics as part of the RIA tool is currently not reliable. The lack of standardized procedures and guidelines for reporting information regarding ethics approval in the primary

study record impedes the assessment, and therefore, leaves producers of evidence synthesis with a high number of RCTs which are not (completely) eligible for evidence synthesis (i.e. RCTs categorized as 'awaiting classification'). Updated reporting guidelines may improve this issue. Furthermore, we determined that trial registries play an essential role as providers of information pertaining to ethics approval and as sentinels, ensuring that RCTs are carried out according to available ethics regulations.

List of abbreviations

AAHRPP	Association for the Accreditation of Human Research Protection Programs, Inc.
ChiCTR	Chinese Clinical Trial Register
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019
CR	Cochrane review
CTRI	Clinical Trials Registry India
doi	Data and digital object identifier
EA	Ethics approval
EC	Ethics committee
EN	Ethics approval number
EUCTR	EU Clinical Trials Register
GCP	Good clinical practice
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
IC	Informed Consent
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional review board
IRCT	Iranian Registry of Clinical Trials
ISRCTN	International Standard Randomized Controlled Trial Number
OSF	Open Science Framework
RCT	Randomized controlled trial
REC	Research ethics committee
RI	Research integrity
RIA	Research integrity assessment
RoB	Risk of Bias
SARS-CoV-2	Severe acute respiratory syndrome coronavirus type 2
SR	Systematic review
WHO	World Health Organization
WMA	World Medical Association

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Datasets are included in this published article, supplementary information files, or available from the OSF repository, DOI: 10.17605/OSF.IO/9VZME.

Competing interests

The authors declare that they have no financial competing interests. SW and PM are authors of Cochrane reviews which include studies assessed in the meta-epidemiological RIA study.

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Contributors

FW: study design, acquisition of data, analysis, interpretation, drafting the article,
TP: interpretation, acquisition of data, reviewing the article,
ES: expertise in clinical trial regulation, interpretation, reviewing the article,
PM: expertise in conduct of RCTs, interpretation, reviewing the article,
SW: study design, acquisition of data, analysis, interpretation, drafting the article.
The manuscript has been read and approved by all co-authors.
SW is the guarantor.

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Patient and Public Involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

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Additional File 1: Directory of consulted sources for ethics committees, last edited on 27.07.2023

Country	Source provided by a national organization	Source provided by an international organization	Institutional source	Notes
Argentina	https://www.argentina.gob.ar/salud/investigaciones/comites https://buenosaires.gob.ar/sites/default/files/2023-09/Lista_nueva_cei_efectores_no_gcba_4-sep-2023.pdf https://www.argentina.gob.ar/sites/default/files/2022/06/listado_comites_acreditados_8-7-2022.pdf	Not found	https://med.unne.edu.ar/institucional/gestion-academica-y-administrativa/secretaria-de-ciencia-y-tecnologia/comite-de-bioetica-en-investigacion-de-ciencias-de-la-salud/	
Bahrain	Not found	Not found	https://www.dcc.com/bahrain/research/research-ethics-committee	
Bangladesh	Not found	https://healthresearchwebafrica.org.za/en/bangladesh/institution	Not found	
Belgium	https://www.famhp.be/sites/default/files/Lijst%20EC's%20-%20Liste%20CE_1.pdf	Not found	Not found	
Brazil	https://plataformabrasil.saude.gov.br/login.jsf	Not found	Not found	CONEP= Brazilian committee of ethics in Human Research
Chile	Not found	Not found	https://eticaysegguridad.uc.cl/images/DR._143-2020._Regulation_of_the_scientific_ethics_committees_of_health_UC_-_English.pdf	
China	Not found	https://www.aahrpp.org/find-an-accredited-organization	Not found	
Colombia	https://aciccolombia.org/lista-de-comites-de-etica-en-colombia/	https://healthresearchwebafrica.org.za/en/colombia/institution	Not found	National source not used
Ecuador	Not found	Not found	https://www.usfq.edu.ec/en/human-research-ethics-committee-ceish	
Egypt	http://www.enrec.org/directory	Not found	Not found	

10.1136/bmjopen-2024-092244 on 24 March 2025. Downloaded from

France	http://urcest.com/les-cpp-en-ile-de-france http://cppouest1.fr/mediawiki/index.php?title=Accueil	Not found	Not found	
Germany	https://www.bfarm.de/DE/Medizinprodukte/Ueberblick/Institutionen/Ethikkommissionen/_node.html	Not found	Not found	
Greece	Not found	http://www.eurecnet.org/information/greece.html	Not found	
India	https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdf-documents/list-ofecommittee2022.pdf https://cdsco.gov.in/opencms/opencms/en/Clinical-Trial/Ethics-Committee/Ethics-Committee-Re-Registration/ https://www.ncdirindia.org/All_Committee.html	Not found	Not found	
Indonesia	Not found	https://www.ncdirindia.org/All_Committee.html	Not found	official website of National Institute of Health Research and Development on 07.02.24 not available, https://health-policy-systems.biomedcentral.com/articles/10.1186/s12961-015-0024-9
Iran	Not found	https://healthresearchwebafrica.org.za/en/iran/institution	Not found	
Iraq	Not found	Not found	Not found	Source not found
Israel	Not found	Not found	https://rnd.sheba.co.il/Research_Authority	Link no longer available (last visited 07.2023)
Italy	https://www.aifa.gov.it/documents/20142/1123276/Comunicazione_gestione_studi_clinici_in_emergenza_COVID-19-EN_17.09.2020.pdf	Not found	Not found	
Mexico	https://www.gob.mx/cms/uploads/attachment/file/801449/Registros_CEI.01022023.pdf	Not found	Not found	

Nigeria	https://nhrec.net/registered-health-research-ethics-committees-in-nigeria-hrec/	Not found	Not found	
Norway	https://rekportalen.no/#omrek/REK	Not found	Not found	
Oman	Not found	Not found	https://royalhospital.med.om/pdf/RH-Research-Policy.pdf	
Pakistan	nbcpakistan.org.pk/assets/list_of_ercin_publicprivatemedicalcolleges.docx	Not found	Not found	
Qatar	Not found	Not found	https://www.sidra.org/EN/About-Us/Our-Accreditations/Pages/default.aspx#	
Russia	Not found	Not found	Not found	Source not found
Saudi Arabia	https://www.moh.gov.sa/en/Ministry/MediaCenter/Publications/Pages/Annual-Research-Report-2016.pdf	Not found	Not found	
Singapore	Not found	https://www.aahrpp.org/find-an-accredited-organization	Not found	
South Africa	https://www.health.gov.za/wp-content/uploads/2022/05/NHREC-Registration-List-of-Human-RECs-Animal-RECs-registered-with-NHREC.pdf	Not found	Not found	
South Korea	Not found	https://www.aahrpp.org/find-an-accredited-organization	Not found	
Spain	https://www.aemps.gob.es/medicamentos-de-uso-humano/investigacion_medicamentos/investigacionclinica_ceim/	Not found	Not found	
Sweden	https://etikprovningsmyndigheten.se/en/	Not found	Not found	
Taiwan	https://www.taiwanclinicaltrials.tw/spotlight/clinical_trial_overview/c_IRB/introduce	Not found	Not found	
The Netherlands	https://english.ccmo.nl/mrecs/accredited-mrecs	Not found	Not found	
Turkey	https://www.titck.gov.tr/dinamikmodul/84	Not found	Not found	

Uganda	Not found	https://healthresearchwebafrica.org.za/en/uganda/institution	Not found		
UK	https://www.hra.nhs.uk/about-us/committees-and-services/res-and-recs/search-research-ethics-committees/	Not found	Not found		
USA	https://ohrp.cit.nih.gov/search/irbsearch.aspx	Not found	Not found		
Multisite	N/A	https://www.who.int/groups/research-ethics-review-committee	N/A		WHO ethics review committee

Additional File 2: References to included Cochrane reviews and systematic reviews

We selected 23 evidence syntheses with the largest RCT pool in our search on 13 different interventions for prevention or treatment of COVID-19[1-23]; 13 were Cochrane reviews[2 3 5-7 11 13 15-17 19-21] and ten were non-Cochrane systematic reviews[1 4 8-10 12 14 18 22 23]. Three systematic reviews investigated two different interventions with the largest RCT pool in our search, i.e. Deng-2022 (convalescent plasma and SARS-CoV-2-neutralising monoclonal antibodies)[4], Siemieniuk-2020 (hydroxychloroquine or chloroquine and systemic corticosteroids)[18], and Zhang-2021(antibiotics and inhaled corticosteroids)[23].

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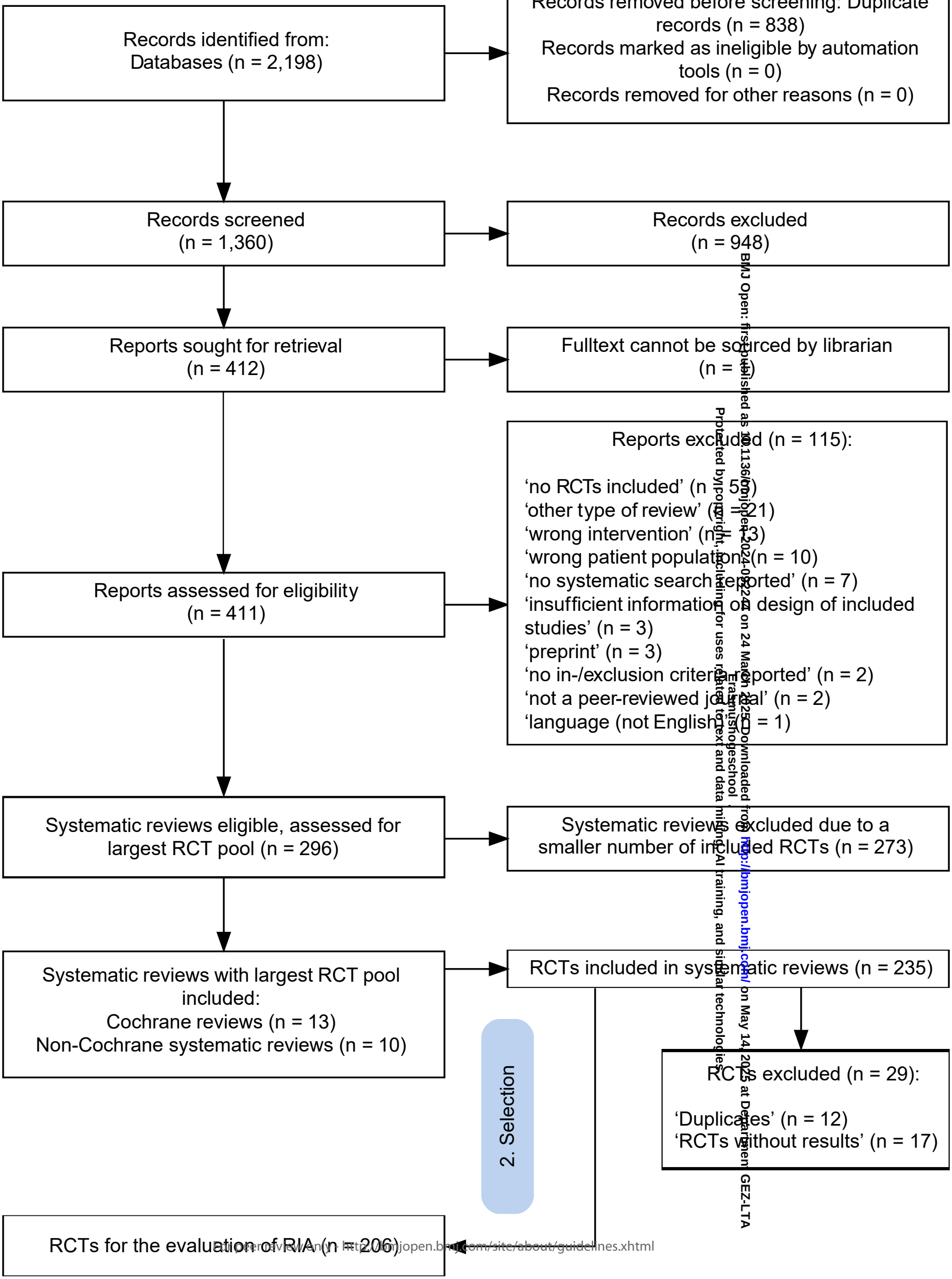
Selection of RCTs for assessment with the RIA tool



Additional File 4: Ethics approval date reported in trial registry records. (n = 74)[a]

Published RCTs	Registered on	EA Date identified on
ACTIV-3/TICO-2021b	NCT, EUCTR	EUCTR
Ader-2021	NCT, EUCTR	EUCTR
Ader-2022	NCT, EUCTR	EUCTR
Agarwal-2020	CTRI	CTRI
Babalola-2022	ISRCTN	ISRCTN
Baldeón-2022	ISRCTN	ISRCTN
Butler-2021 (PRINCIPLE)	ISRCTN, EUCTR	ISRCTN, EUCTR
Caricchio-2021	NCT, EUCTR	EUCTR
Chaccour-2021	NCT, EUCTR	EUCTR
Chen-2020b	ChiCTR	ChiCTR
Chen-2020c	ChiCTR	ChiCTR
CORIMUNO-2021	NCT, EUCTR	EUCTR
CORIMUNO-2022	NCT, EUCTR	EUCTR
Corral-Gudino-2021	EUCTR, REec	EUCTR
Davoodi-2020	IRCT	IRCT
Declercq-2021	NCT, EUCTR	EUCTR
Deftereos-2020	NCT, EUCTR	EUCTR
Dequin-2020	NCT, EUCTR	EUCTR
Dorward-2022 (PRINCIPLE)	ISRCTN, EUCTR	ISRCTN, EUCTR
Dubée-2020	NCT, EUCTR	EUCTR
Edalatifard-2020	IRCT	IRCT
Entrenas Castillo-2020	NCT, EUCTR	EUCTR
Eom-2021	NCT, EUCTR	EUCTR
Farahani-2020	IRCT	IRCT
Ghaderkhani-2020	IRCT	IRCT
Gupta-2021a, COMET-ICE	NCT, EUCTR	EUCTR
Gupta-2021b, COMET-ICE	NCT, EUCTR	EUCTR
Hermine-2021	NCT, EUCTR	EUCTR
Hinks-2021	NCT, EUCTR	EUCTR
Huang-2020	ChiCTR	ChiCTR
Jamaati-2021	IRCT	IRCT

Karakike-2021	NCT, EUCTR	EUCTR
Kharazmi-2022	IRCT	IRCT
Kirti-2021	CTRI	CTRI
Körper-2021	NCT, EUCTR	EUCTR
Kyriazopoulou-2021	NCT, EUCTR	EUCTR
Lescure-2021	NCT, EUCTR	EUCTR
Li-2020	ChiCTR	ChiCTR
Li-2021	ChiCTR (3x)	ChiCTR
Merchante-2022	NCT, EUCTR, REec	EUCTR
Mitjà-2020a	NCT, EUCTR	EUCTR
Mitjà-2020b	NCT, EUCTR	EUCTR
Mitjà-2020c	NCT, EUCTR	EUCTR
Niaee-2021	IRCT	IRCT
O'Brien-2022	NCT, EUCTR	EUCTR
Pan-2020 (SOLIDARITY)	NCT, ISRCT	ISRCTN
Pouladzadeh-2021	IRCT	IRCT
PRINCIPLE-2021	ISRCTN, EUCTR	ISRCTN, EUCTR
Ranjbar-2021	IRCT	IRCT
RECOVERY-2020a	ISRCTN, EUCTR, NCT	ISRCTN, EUCTR
RECOVERY-2020b	ISRCTN, EUCTR, NCT	ISRCTN, EUCTR
RECOVERY-2021a	ISRCTN, EUCTR, NCT	ISRCTN, EUCTR
RECOVERY-2021b	ISRCTN, EUCTR, NCT	ISRCTN, EUCTR
RECOVERY-2021c	ISRCTN, EUCTR, NCT	ISRCTN, EUCTR
RECOVERY-2021d	ISRCTN, EUCTR, NCT	ISRCTN, EUCTR
RECOVERY-2022	ISRCTN, EUCTR, NCT	ISRCTN, EUCTR
Rosas-2021a	NCT, EUCTR	EUCTR
Rosas-2021b	NCT, EUCTR	EUCTR
Salama-2021	NCT, EUCTR	EUCTR
Salehzadeh-2020	IRCT	IRCT

Salvarani-2021	NCT, EUCTR	EUCTR
Sancho-López-2021	EUCTR	EUCTR
Sekhavati-2020	IRCT	IRCT
Shahbaznejad-2021	IRCT	IRCT
Sivapalan-2021	NCT, EUCTR	EUCTR
Somersan-Karakaya-2022	NCT, EUCTR	EUCTR
Spinner-2020	ISRCTN, EUCTR, NCT	ISRCTN, EUCTR
Tang-2020	ChiCTR	ChiCTR
Tardif-2021	NCT, EUCTR	EUCTR
Wang-2020a	ChiCTR	ChiCTR
Weinreich-2021a, (phase 1-2)	NCT, EUCTR	EUCTR
Weinreich-2021b, (phase 1-2)	NCT, EUCTR	EUCTR
Weinreich-2021c, (phase 3)	NCT, EUCTR	EUCTR
Yu-2021b (PRINCIPLE)	ISRCTN, EUCTR	ISRCTN, EUCTR

Footnotes:

* Unpublished study, EA date reported on the trial registry record.

[a] n = 74 published RCTs, several RCTs were registered more than once and/or in different registries.