Journal of Clinical Epidemiology 141 (2022) 175–186

Journal of Clinical Epidemiology

SERIES

Reporting transparency and completeness in Trials: Paper 2 - reporting of randomised trials using registries was often inadequate and hindered the interpretation of results

Kimberly A. Mc Cord[a], Mahrukh Imran[b], Danielle B. Rice[b,c], Stephen J. McCall[d,e], Linda Kwakkenbos[f], Margaret Sampson[g], Ole Fröbert[h], Chris Gale[i], Sinéad M. Langan[j], David Moher[k], Clare Relton[l], Merrick Zwarenstein[m,n], Edmund Juszczak[d,v], Brett D. Thombs[b,c,o,p,q,r,s], Lars G. Hemkens[a,t,u,*], on behalf of the CONSORT Extension *for* Trials Conducted Using Cohorts *and* Routinely Collected Data Group[$]

[a] *Basel Institute for Clinical Epidemiology and Biostatistics, Department of Clinical Research, University Hospital Basel, University of Basel, Basel, Switzerland*
[b] *Lady Davis Institute for Medical Research, Jewish General Hospital, Montréal, Quebec, Canada*
[c] *Department of Psychology, McGill University, Montreal, Quebec, Canada*
[d] *National Perinatal Epidemiology Unit Clinical Trials Unit, Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom*
[e] *Center for Research on Population and Health, Faculty of Health Sciences, American University of Beirut, Ras Beirut, Lebanon*
[f] *Behavioural Science Institute, Clinical Psychology, Radboud University, Nijmegen, the Netherlands*
[g] *Library Services, Children's Hospital of Eastern Ontario, Ottawa, Canada*
[h] *Department of Cardiology, Faculty of Health, Örebro University, Örebro, UK*
[i] *Neonatal Medicine, School of Public Health, Faculty of Medicine, Imperial College London, London, UK*
[j] *Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK*
[k] *Centre for Journalology, Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada*
[l] *Centre for Clinical Trials and Methodology, Barts Institute of Population Health Science, Queen Mary University, London, UK*
[m] *Centre for Studies in Family Medicine, Department of Family Medicine, Schulich School of Medicine & Dentistry, Western University, London, Ontario, Canada*
[n] *Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada*
[o] *Department of Psychiatry, McGill University, Montreal, Quebec, Canada*
[p] *Departments of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada*
[q] *Department of Medicine, McGill University, Montreal, Quebec, Canada*
[r] *Department of Educational and Counselling Psychology, McGill University, Montreal, Quebec, Canada*
[s] *Biomedical Ethics Unit, McGill University, Montreal, Quebec, Canada*
[t] *Meta-Research Innovation Center Berlin (METRIC-B), Berlin Institute of Health, Berlin, Germany*
[u] *Meta-Research Innovation Center at Stanford (METRICS), Stanford University, Stanford, California, USA*
[v] *Nottingham Clinical Trials Unit, University of Nottingham, University Park, Nottingham, United Kingdom*

Accepted 7 September 2021; Available online 12 September 2021

Abstract

Objective: Registries are important data sources for randomized controlled trials (RCTs), but reporting of how they are used may be inadequate. The objective was to describe the current adequacy of reporting of RCTs using registries.

Funding: The development of CONSORT-ROUTINE and the present review were funded by grants from the Canadian Institutes of Health Research (PI Thombs, #PJT-156172; PIs Thombs and Kwakkenbos, #PCS-161863) and from the United Kingdom National Institute of Health Research (NIHR) Clinical Trials Unit Support Funding. (PI Juszczak, Co-PI Gale, supported salary of SM). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. Dr. Langan was supported by a Wellcome Senior Clinical Fellowship in Science (205039/Z/16/Z). Dr. Moher is supported by a University Research Chair (uOttawa). Dr. Gale was supported by the United Kingdom Medical Research Council through a Clinician Scientist Fellowship. Dr. Thombs was supported by a Tier 1 Canada Research Chair.

Declaration of Competing Interest: All authors have completed the ICJME uniform disclosure form and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years

[$] CONSORT Extension for Trials Conducted Using Cohorts and Routinely Collected Data Group: Eric I. Benchimol; Isabelle Boutron; Marion K. Campbell; David Erlinge; John Fletcher; Jon Nicholl; Philippe Ravaud; Maureen Sauvé; Lehana Thabane; David Torgerson; Rudolf Uher; Helena M. Verkooijen.

* Corresponding author. Tel.: +41612653100

https://doi.org/10.1016/j.jclinepi.2021.09.012

Study Design and Setting: We used a database of trials using registries from a scoping review supporting the development of the 2021 CONSORT extension for Trials Conducted Using Cohorts and Routinely Collected Data (CONSORT-ROUTINE). Reporting completeness of 13 CONSORT-ROUTINE items was assessed.

Results: We assessed reports of 47 RCTs that used a registry, published between 2011 and 2018. Of the 13 CONSORT-ROUTINE items, 6 were adequately reported in at least half of reports (2 in at least 80%). The 7 other items were related to routinely collected data source eligibility (32% adequate), data linkage (8% adequate), validation and completeness of data used for outcome assessment (8% adequate), validation and completeness of data used for participant recruitment (0% adequate), participant flow (9% adequate), registry funding (6% adequate) and interpretation of results in consideration of registry use (25% adequate).

Conclusion: Reporting of trials using registries was often poor, particularly details on data linkage and quality. Better reporting is needed for appropriate interpretation of the results of these trials.

Keywords: Registries; CONSORT; CONSORT-ROUTINE; Randomised controlled trials; Reporting guideline; Routinely collected data

What is new?

- Adequate reporting of essential features of randomized trials is critical but often inadequate in biomedical journals.
- The reporting of randomized trials using registries was inadequate for several critical details that are required for replication, bias assessment, interpretation and application of trial results.
- This study highlights an even lower reporting quality for registry-specific reporting items compared to the CONSORT 2010 statement items

1. Introduction

Registries are repositories of health information with those registered sharing a common characteristic, such as a disease, a drug treatment or health exposure [1]. They can be used to monitor the progression of a health condition and are often utilized to explore etiology, progression and potential treatments or cures of diseases and adherence to treatment guidelines. Registries are a type of routinely collected data that are increasingly utilized as a framework to support randomized controlled trials (RCTs) [2–4]. Compared to traditional RCTs, which are dependent on primary data collection within the trial, RCTs conducted using routinely collected data, including registries, may allow the exploration of pragmatic questions in so called "real world settings," potentially increasing the applicability of the results [5]. Traditional RCTs are often expensive, particularly due to the costs of setting up a specific research and data collection infrastructure; leveraging the environment of a registry may greatly reduce expenditures associated with assessing a novel treatment or choosing the best among alternative treatment choices [6]. Nonetheless, designing and maintaining registries is itself expensive, and access to the registry data can have costs [7–9].

The use of routinely collected data to conduct trials is a novel approach and requires reporting of elements that are not part of traditional RCTs. This extra reporting facilitates replication and assessment of biases and applicability. For example, consent processes may be different from and more diverse than in traditional trials, and the completeness and accuracy of data that were not collected for the purpose of a specific trial may require special consideration. The advantage of potentially better applicability of findings from such trials may be lost if there is a mismatch between key aspects of participants in the data source in relation to a target population [10], but for an assessment of this, there must be adequate and complete reporting needs.

Traditional RCTs are often reported inadequately,[11] and with the added complexity in new trial designs using routinely collected data, reporting challenges may increase. To address the novel reporting needs of trials conducted using routinely collected data, an extension of the Consolidated Standards of Reporting Trials (CONSORT) 2010 guideline [12] for the reporting of RCTs conducted using cohorts and routinely collected data has been developed and published in 2021 (CONSORT-ROUTINE)[13]. The present study used reports of trials using registry data that were identified in a scoping review informing our guideline development process.

We aimed to: (1) describe characteristics of RCTs conducted using registry data and published after the CONSORT 2010 statement; and (2) assess and describe the quality of reporting of the trials' reports in peer-reviewed journals. Similar analyses for trials using electronic health records (EHRs) [14] and administrative databases [15] are reported elsewhere.

2. Methods

A protocol for this study was made publicly available in the Open Science Framework: https://osf.io/x75gf/.

2.1. Inclusion and exclusion criteria for RCTs using registries

Reports of trials that utilized registries to select patients or ascertain outcomes in any way were included in the present study. Thus, we included RCTs that utilized registries as a supporting data source, as well as RCTs fully embedded within a registry framework (registry-based RCTs). Although RCTs using registries as an intervention were also eligible for inclusion, we identified no such trials in our literature search as this is typically a feature of trials using EHRs. Our definition of registry was based on that of the European Medicines Agency and the Clinical Trials Transformation Initiative as "an organized system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition, or exposure, and that is followed over time."[16]; and "Entry in a registry is generally defined either by diagnosis of a disease (disease registry) or prescription of a drug, device, or other treatment (exposure registry)" [17] (Appendix 1). The main scoping review (see below) searched for publications from 2007 – 2018, but here we limited our sample to RCTs published after 2010, when the CONSORT 2010 statement was published. Methodological reviews, commentaries, trial protocols, cost-effectiveness studies or RCTs assessing non-health outcomes were excluded. The detailed inclusion/exclusion criteria are shown in Appendix 1.

2.2. Search strategy and study selection

A literature search was performed for the scoping review in the framework of the CONSORT-ROUTINE [18]. Briefly, the scoping review aimed to identify items important for reporting by trials conducted using cohorts and routinely collected data, including registries, EHRs, and administrative data as well as to identify examples of good reporting. The database search was designed and conducted by an experienced research librarian (MS) familiar with knowledge synthesis related to research methods and reporting with input from the project team and was peer reviewed using the Peer Review of the Electronic Search Strategy (PRESS) [19]. Databases were searched from January 2007 – March 2018 and included Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE and EBM Reviews - Cochrane Methodology Registry (Final issue, third Quarter 2012) (search strategy in Appendix 2). References were imported into RefWorks, and duplicates were removed. References were then imported into the systematic review software DistillerSR (Evidence Partners, Ottawa, Canada) [20]. This literature search served the purpose of identifying a representative sample of RCTs using routinely collected data to inform the development of the reporting guideline; it was not a complete assessment of all the available published trials using routinely collected data.

Two reviewers independently screened the titles and abstracts of publications in random order using a liberal accelerated method, where titles and abstracts are screened by one reviewer and only excluded publications are screened by a second reviewer [21]. The random order ensured that the reviewers were unaware about the other reviewer's decision on any given title and abstract. Two reviewers then screened the full texts independently and resolved any disagreements with discussion and consensus (involving a third reviewer where necessary).

2.3. Data extraction

For all RCTs, two independent reviewers extracted data from the full text reports on whether the registry was utilized (1) to identify and recruit patients only, (2) to ascertain outcomes only, (3) for both patient recruitment and outcome assessment. Furthermore, we extracted the RCTs' characteristics (publication year, sample size, country of data collection, randomization type, registry use) and PICO information (Population, Intervention, Comparator and Outcome) (Table 1). We also classified publications into primary and secondary reports to evaluate any differences in the quality of reporting. Primary publications were reports on the trial's primary patient outcome(s) and may also report other trial outcomes Although secondary publications were reports on only secondary patient outcomes or other post-hoc outcomes (if a report referred to a previous publication or did not specify outcome status but referred to a previous publication of results, then the report was categorized as secondary). Any disagreements were resolved in consultation with a third reviewer.

2.4. Evaluation of completeness and transparency of reporting

Two independent reviewers assessed the reporting transparency and completeness for all new and modified items from the CONSORT-ROUTINE checklist. For the modified items, we additionally performed the reporting assessment for the CONSORT 2010 version in an attempt to distinguish potential poor reporting of the trials in general (and according to the reporting standard at the time of publication of the included trial) from the modified portion. For such pairs of original and modified items, we evaluated separately the original item (as written) and, the modified part. Reporting of items that remained unmodified from the CONSORT 2010 statement were not assessed. Of note, a reporting assessment was not performed separately for the item on allocation concealment, as the modification was a clarification of the original item related to the use of routinely collected data.

We defined the completeness of reporting as "Adequately reported" when the reviewers could clearly identify

Table 1. Characteristics of trials conducted using registries

	RCTs using registries for:			
	PI only N (%)	***OA only N (%)***	***PI and OA N (%)***	***Total N (%)***
	10 (28%)	23 (51%)	14 (21%)	47 (100%)
Registry used for primary outcome ascertainment (versus no or unclear[a])	0 (0%)	21 (91%)	12 (86%)	33 (70%)
Publication type				
Primary	7 (70%)	14 (61%)	13 (93%)	34 (72%)
Secondary	3 (30%)	9 (39%)	1 (7%)	13 (28%)
Sample size (median [IQR])	737 [300-6846]	2029 [268-2774]	2722 [680-7736]	1826 [347-3618]
Year (median [IQR])	2015 [2013-2016]	2015 [2013-2016]	2015 [2013-2017]	2015 [2013-2016]
Setting				
Primary care	0 (0%)	3 (13%)	1 (7%)	4 (8%)
Inpatient	1 (10%)	14 (61%)	4 (29%)	19 (40%)
Outpatient	0 (0%)	1 (4%)	1 (7%)	2 (4%)
Community medicine	9 (90%)	5 (22%)	8 (57%)	22 (47%)
Country				
Scandinavia	1 (10%)	15 (65%)	5 (36%)	21 (45%)
USA	4 (40%)	4 (17%)	4 (29%)	12 (25%)
Continental Europe	3 (30%)	3 (13%)	1 (7%)	7 (15%)
Australia	1 (10%)	0 (0%)	2 (14%)	3 (6%)
UK	0 (0%)	0 (0%)	1 (7%)	1 (2%)
Other[b]	1 (10%)	1 (4%)	1 (7%)	3 (6%)
Medical specialty				
Cardiology	-	12 (52%)	5 (36%)	17 (36%)
Oncology	7 (70%)	2 (9%)	3 (21%)	12 (25%)
Internal medicine	0 (0%)	3 (13%)	5 (36%)	8 (17%)
Neurology/Psychiatry	1 (10%)	3 (13%)	1 (7%)	5 (11%)
Pediatrics	1 (10%)	2 (9%)	0 (0%)	3 (6%)
Other[c]	1 (10%)	1 (4%)	0 (0%)	2 (4%)
Intervention				
Surgery	0 (0%)	10 (43%)	4 (29%)	14 (30%)
Guideline/reminder	0 (0%)	2 (9%)	4 (29%)	6 (13%)
Drug	1 (10%)	5 (22%)	-	6 (13%)
Screening	3 (30%)	1 (4%)	1 (7%)	5 (11%)
Education/coaching	2 (20%)	3 (13%)	1 (7%)	6 (13%)
Lifestyle	2 (20%)	1 (4%)	1 (7%)	4 (8%)
Multiple	0 (0%)	1 (4%)	1 (7%)	2 (4%)
Other[d]	2 (20%)	0 (0%)	2 (14%)	4 (8%)
Comparator				
Usual care	8 (80%)	9 (39%)	12 (86%)	29 (62%)
Active comparator	1 (10%)	11 (48%)	2 (14%)	14 (30%)
Placebo	1 (10%)	3 (13%)	0 (0%)	4 (8%)
Outcome				
Composite	0 (0%)	12 (52%)	1 (7%)	13 (28%)
Disease occurrence/AE	1 (10%)	4 (17%)	1 (7%)	6 (13%)
Mortality	-	3 (13%)	4 (29%)	7 (15%)
Self-reported	4 (40%)	0 (0%)	0 (0%)	4 (8%)

(*continued on next page*)

Table 1 (*continued*)

	RCTs using registries for:			
	PI only N (%)	OA only N (%)	PI and OA N (%)	Total N (%)
Uptake of treatment	2 (20%)	2 (9%)	3 (21%)	7 (15%)
Quality improvement	1 (10%)	0 (0%)	1 (7%)	2 (4%)
Other[e]	2 (20%)	2 (8%)	4 (28%)	8 (17%)

PI: Patient identification; OA: Outcome assessment; AE: adverse events; RCT: randomised controlled trial.
[a] Unclear for one trial in 'PI and OA' category; Other includes:
[b] Iran and Israel;
[c] Intensive care and Nephrology;
[d] Networking intervention, oxygen therapy, enhanced invitation letter and quality improvement;
[e] Surrogate, Fatigue Impact Scale (FIS) score, letter response rate, minimum differences of interest (MDI) of weight loss, time to hospitalization and management of key modifiable risk factors.

the required details for each item in the RCT publication, "Partially reported" when some of the details were clearly identifiable by the reviewers in the publication (but not all, if applicable) or if the information was implied but not clearly stated by the authors, "Inadequately reported" or "Not reported" when the reviewers could not identify the required details for the item in the publication, and "Not applicable" in cases where the reporting item was not relevant to the trial (for example, if the RCT only used the registry to ascertain outcomes, patient identification or participant flow items would not be relevant). We used a coding manual to ensure consistent assessment of reporting (see Appendix 3) which was also used in related studies on the completeness and transparency of reporting in administrative databases and EHRs [14–15].

The CONSORT 2010 and extension items are widely accepted as the minimum required information for each RCT publication, therefore we did not search for additional publications to complement missing information even if the authors mentioned that such information was published elsewhere.

Any disagreements were resolved by consensus. Data extraction was performed using Distiller SR by one investigator and validated by a second investigator using the DistillerSR Quality Control function.

2.5. Data analysis

All data were reported as simple frequency statistics such as absolute frequencies, medians and interquartile ranges (IQRs). No formal test statistics were performed.

3. Results

3.1. Characteristics of included RCTs

Of the 47 included publications (Fig 1), 23 (51%) described trials that used registries to assess outcomes only, another 14 (21%) used them for both patient identification and outcome assessment and the remaining 10 (28%) of them used it for patient identification only (Table 2). Thirty-four (72%) were primary publications, and 13 (28%) were secondary publications.

The largest number of RCTs using registries were performed in Scandinavian countries (21 of 47; 45%), followed by the United States of America ($n = 12$; 25%) and Continental Europe ($n = 7$; 15%) (Table 2). The median sample size was 1826 participants [IQR 347-3618]. Five trials had a cluster design, and the median number of participants per cluster was 136 [IQR 17-312]. The most frequently researched medical specialties were cardiology ($n = 17$; 36%), oncology ($n = 12$; 25%) and internal medicine ($n = 8$; 17%). The interventions most frequently tested were surgical or invasive procedures ($n = 14$; 30%), delivery of guidelines and reminders to clinicians ($n = 6$; 13%) and drugs ($n = 6$; 13%); although the comparators were mostly usual care ($n = 29$; 62%), active comparators ($n = 14$; 30%) or placebo ($n = 4$; 8%) (Table 2).

3.2. Baseline assessment of completeness and transparency of reporting

CONSORT 2010 Items with Modifications in CONSORT-ROUTINE

Eight CONSORT 2010 items were modified in *CONSORT-ROUTINE*. The CONSORT 2010 version of these 6 of these items ("Structured summary," "Trial design," "Eligibility criteria," "Outcome definition," "Participant flow" and "Interpretation") were adequately reported in over 90% of the trials. Details on "Allocation concealment mechanism" and "Funding" were reported adequately in only 55% (26 of 47) and 68% (32 of 47) of the trials, respectively (Table 2).

The modified portions of these items were adequately reported in less than half of the trial reports, with the exception of mentioning the use of a cohort or routinely collected data in the trial, which was typically adequately stated in the abstract (40 of 47; 85%. The name and use of a registry were almost always reported in the main text

Table 2. Completeness and transparency of reporting for CONSORT 2010 items that were modified, modified items, and new items in CONSORT-ROUTINE[a].

	Item[b]	*CONSORT 2010 Items, CONSORT-ROUTINE modifications, and new CONSORT-ROUTINE items*	*n = 47*			
			Adequately reported n (%)	*Partially reported n (%)*	*Inadequately or not reported n (%)*	*Not applicable N (%)*
Title and abstract						
	1b	CONSORT 2010: Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts).	43 (91%)	4 (9%)	0 (0%)	-
		Modified CONSORT-ROUTINE: Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts). *Specify that a cohort or routinely collected data were used to conduct the trial and, if applicable, provide the name of the cohort or routinely collected database(s)*	40 (85%)	1 (2%)	6 (13%)	-
Methods						
Trial design	3a	CONSORT 2010: Description of trial design (such as parallel, factorial) including allocation ratio	46 (98%)	0 (0%)	1 (2%)	-
		Modified CONSORT-ROUTINE: Description of trial design (such as parallel, factorial) including allocation ratio, *that a cohort or routinely collected database(s) was used to conduct the trial (such as electronic health record, registry) and how the data were used within the trial (such as identification of eligible trial participants, trial outcomes)*	46 (98%)	1 (2%)	0 (0%)	-
Cohort or routinely collected database	ROUTINE-1	New CONSORT-ROUTINE: Name, if applicable, and description of the cohort or routinely collected database(s) used to conduct the trial, including information on the setting (such as primary care), locations, and dates, (such as periods of recruitment, follow-up, and data collection)	24 (51%)	21 (45%)	2 (4%)	-
	ROUTINE-2	New CONSORT-ROUTINE: Eligibility criteria for participants in the cohort or routinely collected database(s)	15 (32%)	15 (32%)	17 (36%)	-
	ROUTINE-3	New CONSORT-ROUTINE: State whether the study included person-level, institutional-level, or other data linkage across two or more databases and, if so, linkage techniques and methods used to evaluate completeness and accuracy of linkage	4 (8%)	15 (32%)	28 (60%)	-
Trial participants	4a	CONSORT 2010: Eligibility criteria for participants	46 (98%)	1 (2%)	0 (0%)	-

(*continued on next page*)

Table 2 (*continued*)

	Item[b]	CONSORT 2010 Items, CONSORT-ROUTINE modifications, and new CONSORT-ROUTINE items	n = 47			
			Adequately reported n (%)	Partially reported n (%)	Inadequately or not reported n (%)	Not applicable N (%)
		Modified CONSORT-ROUTINE: Eligibility criteria for trial participants, *including information on how to access the list of codes and algorithms used to identify eligible participants, information on accuracy and completeness of data used to ascertain eligibility, and methods used to validate accuracy and completeness (e.g., monitoring, adjudication), if applicable*	0 (0%)	4 (9%)	19 (40%)	24 (51%)
	ROUTINE-4	New CONSORT-ROUTINE: Describe whether and how consent was obtained	33 (70%)	5 (11%)	9 (19%)	-
Outcomes	6a	CONSORT 2010: Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	45 (96%)	2 (4%)	0 (0%)	-
		Modified CONSORT-ROUTINE: Completely defined pre-specified primary and secondary outcome measures, including how and when they were ascertained and *the cohort or routinely collected database(s) used to ascertain each outcome*	35 (75%)	2 (4%)	0 (0%)	10 (21%)
	ROUTINE-5	New CONSORT-ROUTINE: Information on how to access the list of codes and algorithms used to define or derive the outcomes from the cohort or routinely collected database(s) used to conduct the trial, information on accuracy and completeness of outcome variables, and methods used to validate accuracy and completeness (e.g., monitoring, adjudication), if applicable	3 (6%)	15 (32%)	21 (45%)	8 (17%)
Allocation concealment mechanism	9	CONSORT 2010: Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned[c] Modified CONSORT-ROUTINE: Mechanism used to implement the random allocation sequence *(such as embedding an automated randomiser within the cohort or routinely collected database(s)),* describing any steps taken to conceal the sequence until interventions were assigned[c]	26 (55%)	3 (6%)	18 (38%)	-
Results						
Participant flow (a diagram is strongly recommended)	13a	CONSORT 2010: For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	46 (98%)	1 (2%)	0 (0%)	-

(*continued on next page*)

Table 2 (*continued*)

	Item[b]	***CONSORT 2010 Items, CONSORT-ROUTINE modifications, and new CONSORT-ROUTINE items***	***n = 47***			
			Adequately reported n (%)	***Partially reported n (%)***	***Inadequately or not reported n (%)***	***Not applicable N (%)***
		Modified CONSORT-ROUTINE: For each group, the number of participants **in** *the cohort or routinely collected database(s) used to conduct the trial and the numbers screened for eligibility,* randomly assigned*, offered and accepted interventions (e.g., cohort multiple RCTs),* received intended treatment, and analysed for the primary outcome	2 (4%)	5 (11%)	16 (34%)	24 (51%)
Discussion						
Interpretation	22	CONSORT 2010: Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	46 (98%)	1 (2%)	0 (0%)	-
		Modified CONSORT-ROUTINE: Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence, *including the implications of using data that were not collected to answer the trial research questions*	12 (25%)	8 (17%)	27 (57%)	-
Other information						
Funding	25	CONSORT 2010: Sources of funding and other support (such as supply of drugs), role of funders	32 (68%)	5 (11%)	10 (21%)	-
		Modified CONSORT-ROUTINE: Sources of funding and other support *for both the trial and the cohort or routinely collected database(s), role of funders*	3 (6%)	25 (53%)	19 (40%)	-

[a] For modified items, modifications are shown in italics. For those items, only portion modified was evaluated. Not all items will be applicable to all trials.
[b] Item numbers reflect numbers in original 2010 CONSORT checklist that were modified or new items. New items are designated by "ROUTINE"
[c] Original and modified items not rated separately because modification was minor.

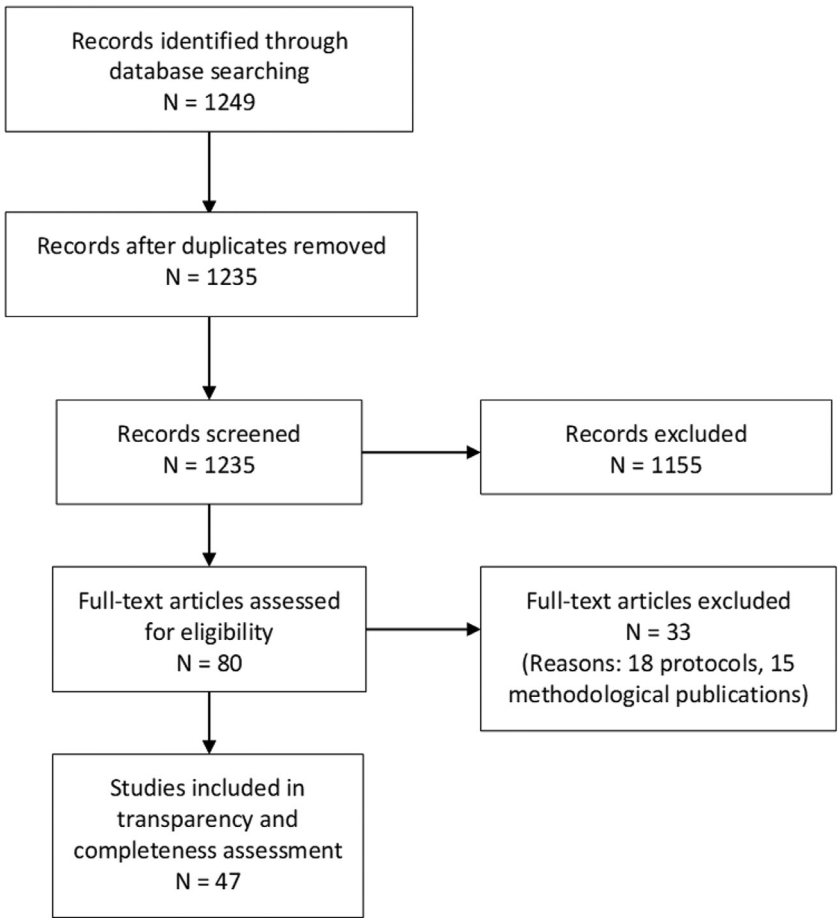

Fig. 1. Flow diagram of publication selection process – randomised controlled trials conducted using registries.

(46 of 47; 98%). Most studies also adequately reported the details on how and when registries were used for each of the outcomes (35 of 47; 75%).

When the registry was used to identify eligible patients to facilitate trial recruitment, the codes and algorithms used were never adequately reported (0 of 23 where applicable [0%]). Information on the embedding of a random allocation sequence within the registry would have been assessable in only about one half of the publications (adequately reported in 26 out of 47 trials; 55%). Although the participant flow was almost perfectly reported for the CONSORT 2010 item, additional details from the CONSORT-ROUTINE extension were almost never adequately reported (2 of 23 where applicable [9%]); meaning that it was difficult to determine which participants from the registry were randomized, excluded, lost to follow up or included in the analysis. The implications of using a cohort or routinely collected data in the RCT and discussing its strengths and limitations, was adequately reported in a quarter of our sample, making it difficult to ascertain whether the authors considered and addressed such implications when designing and interpreting their trial (12 of 47, 25%). Details of funding for the registry were adequately reported in 6% (3 of 47) of the publications, leaving it often unclear if the funders of the registry had any involvement in the trial design and interpretation.

Reporting of the CONSORT 2010 items was overall similar in primary and secondary publications (see Appendix 4).

New Items in CONSORT-ROUTINE

Of the five new CONSORT-ROUTINE items, two were adequately reported in more than half of the 47 trial reports, although the reporting was insufficient for the other three items (Table 2).

The criteria defining eligibility for participation in the registry were adequately reported in only 32% of the publications (15 of 47). Users of these publications would not have had sufficient information on data linkage (adequately reported in 4 of 47 trials, 8%) and information on the codes and algorithms used for outcome measurement and their accuracy and completeness was adequately provided for only 3 reports (out of 39 where applicable; 8%).

4. Discussion

Our assessment of the reporting of 47 systematically identified articles on RCTs that used registries showed that

key information addressed by established CONSORT 2010 items was often adequately reported, Although crucial details that are increasingly recognized as being essential for trials using registry data were lacking for most of them. Critical information on data linkage and data quality were typically missing.

Issues of data validation and endpoint adjudication, Although often being considered the Achilles heel of using routinely collected data [5–22], were not adequately reported in the trials that we assessed. Additionally, issues of applicability and generalizability were difficult to interpret because the eligibility for inclusion in the registry was rarely reported. Details on linkage methodology between registries or other routinely collected data, which can add errors and biases due to incomplete or incorrect matching of the participant, were pervasively difficult to ascertain.

Because the interpretation of the strengths and limitations of RCTs is evaluated through all of these items, this level of improper reporting introduces clearly avoidable waste of such research, some of them may render this trial research useless and the related investments and resources might be research waste [23]. These findings highlight the importance of developing a reporting guideline for RCTs using routinely collected data to guide authors in reporting the critical items required for appropriate assessment and potential replication of these novel trials, which until now had not existed. No standards were available to the authors, reviewers and editors of the trial publications that we assessed.

Our results for the CONSORT 2010 items are consistent with previously published data on the insufficient quality of reporting in biomedicine, although the reporting quality of the CONSORT 2010 items in our sample was markedly higher than previously published [11-24,25]. For example, in a review of pre-post CONSORT extension for Abstracts [25], seven items had an adherence below 50% for 164 RCTs published in the after years of the extension being published (post-CONSORT-A) [25]. Nevertheless, a trend of improvement was seen between 2005 and 2016 which may indicate a continued improvement in the reporting of CONSORT items [25]. Across the CONSORT 2010 items, “allocation concealment mechanism” was the one that was most frequently not well reported (adequate in 55% of trials), which is still an improvement compared to a proportion of 25% found in an analysis of trial reports published before CONSORT 2011 [26].

This is the first evaluation of registry-specific reporting in RCTs, but the findings are comparable to those observed in non-randomized studies [24]: the use of routinely collected data was often described in titles or abstracts (85%), and the characteristics of the data source and settings were adequately reported in half of the studies (51%). However, details on the coding pertinent to the selection of participants and ascertainment of outcomes (0% and 8% adequate) as well as aspects pertaining to data source linkage (8% adequate) were not sufficiently reported in most studies.

Furthermore, our findings were consistent with those of studies on trials conducted using other routinely collected data (EHR [14] or administrative data) [15]. For all three data sources, the reporting of elements related to the use of routinely collected data (the CONSORT-ROUTINE items) were overall inadequately reported, although trials using registry data were overall better reported than the other sources.

There are a several limitations with our study.

Firstly, we performed an assessment of the reporting quality, which is to some degree subjective. We aimed to address this by using prespecified criteria and we performed all extractions systematically and in duplicate.

Secondly, the search strategy was developed for a different scope than that of this specific study, which may have rendered a sample less representative. By identifying RCTs using search terms related to registries in the English literature to inform a reporting guideline, our sample was not an exhaustive review of the entire literature, and we did not aim to provide a comprehensive overview of all published trials using registries. Thus, the distribution of the characteristics of RCTs using registries (such as geographical location and medical specialty) may not be fully representative of the research landscape in this field. However, we have no reason to believe that we have substantially underestimated the quality of reporting and that our conclusions would be different with a different sampling strategy. The identification of the trials used for this sample depended on information in the abstract or in keywords which probably has led to an overestimation of the reporting quality for this item (item 1b; this item would almost always be reported in our sample or we would have identified the trial only via keywords). To determine overall eligibility, we had to know that a registry was used – this implies an overestimation of the reporting quality overall for any item that relates to the general use of a registry.

Thirdly, a third of our sample included publications that were not the main publications, and we did not consider alternative/primary publications even when authors reported that additional information could be found elsewhere. We believe that the minimum reporting standards as developed in CONSORT-ROUTINE should be accessible in all primary and secondary RCT publications for adequate reporting.

Fourthly, we did not pose a distinction in the types of RCTs using registries included. For example, there may well be a difference in the quality of reporting of a RCT that used a registry to assess a secondary outcome (a trial supported by registry data) and a registry-based RCT, where the trial is fully planned and embedded within the infrastructure of a registry. It is possible that these two types of registry utilizations would be subject to different levels of reporting quality.

5. Conclusion

In conclusion, our assessment of the reporting transparency and completeness indicates that RCTs conducted using registries are currently inadequately reported for several critical details. The implications are that the user of such a trial report would not have sufficient information to replicate the trial, assess potential biases or to apply the trial findings. The new CONSORT-ROUTINE provides guidance to improve reporting of these types of trials and highlights the need for its uptake by all involved stakeholders, including authors, peer-reviewers and journals editors.

Availability of data and materials

Additional data beyond that reported in the main and supplementary materials can be requested from the corresponding author.

CRediT authorship contribution statement

Kimberly A. Mc Cord: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Writing original draft. **Mahrukh Imran:** Conceptualization, Data curation, Investigation, Methodology, Validation, Writing review & editing. **Danielle B. Rice:** Conceptualization, Data curation, Investigation, Methodology, Validation, Writing review & editing. **Stephen J. McCall:** Conceptualization, Data curation, Investigation, Methodology, Validation, Writing review & editing. **Linda Kwakkenbos:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Writing review & editing. **Margaret Sampson:** Conceptualization, Methodology, Search, Writing review & editing. **Ole FrÖbert:** Conceptualization, Funding acquisition, Methodology, Writing review & editing. Chris Gale: Conceptualization, Funding acquisition, Methodology, Writing review & editing. **Sinéad M. Langan:** Conceptualization, Methodology, Writing review & editing. **David Moher:** Conceptualization, Methodology, Writing review & editing. **Clare Relton:** Conceptualization, Funding acquisition, Methodology, Writing review & editing. **Merrick Zwarenstein:** Conceptualization, Methodology, Writing review & editing. **Edmund Juszczak:** Conceptualization, Funding acquisition, Methodology, Writing review & editing. **Brett D. Thombs:** Conceptualization, Formal analysis, Methodology, Supervision, Writing review & editing, Funding acquisition. **Lars G. Hemkens:** Conceptualization, Formal analysis, Methodology, Supervision, Writing review & editing.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jclinepi.2021.09.012.

References

[1] Gliklich RE DN. Registries for evaluating patient outcomes: a user's Guide. AHRQ, (US) 2014:2. (3rd edition).

[2] Mc Cord KA, Al-Shahi Salman R, Treweek S, et al. Routinely collected data for randomized trials: promises, barriers, and implications. Trials 2018;19(1):29. https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-017-2394-. doi:10.1186/s13063-017-2394-5.

[3] Lauer MS, D, Agostino RBS. The randomized registry trial — the next disruptive technology in clinical research? N Engl J Med 2013;369(17):1579–81. doi:10.1056/NEJMp1310102.

[4] James S, Rao SV, Granger CB. Registry-based randomized clinical trials–a new clinical trial paradigm. Nat Rev Cardiol 2015;12(5):312–16. doi:10.1038/nrcardio.2015.33.

[5] Hemkens LG. How routinely collected data for randomized trials provide long-term randomized real-world evidence. JAMA Network Open 2018;1(8) e186014-e186014. doi:10.1001/jamanetworkopen.2018.6014.

[6] Mc Cord KA, Ewald H, Ladanie A, et al. Current use and costs of electronic health records for clinical trial research: a descriptive study. CMAJ Open 2019;7(1):E23–32. doi:10.9778/cmajo.20180096.

[7] Cole Beebe M, Subramanian S, Tangka FKL, Weir HK, Babcock F, Trebino D. An analysis of cancer registry cost data: methodology and results. J Registry Manag 2018;45(2):58–64.

[8] McKenna VB, Sager A, Gunn JE, Tormey P, Barry MA. Immunization registries: costs and savings. Public Health Rep 2002;117(4):386–92.

[9] Tangka FKL, Subramanian S, Beebe MC, et al. Cost of operating central cancer registries and factors that affect cost: findings from an economic evaluation of centers for disease control and prevention national program of cancer registries. J Public Health Manag Pract 2016;22(5):452–60. doi:10.1097/PHH.0000000000000349.

[10] Lasch F, Weber K, Koch A. Commentary: On the levels of patient selection in registry-based randomized controlled trials. Trials 2019;20(1):100. doi:10.1186/s13063-019-3214-x.

[11] Dechartres A, Trinquart L, Atal I, et al. Evolution of poor reporting and inadequate methods over time in 20 920 randomised controlled trials included in Cochrane reviews: research on research study. BMJ 2017;357. https://www.bmj.com/content/357/bmj.j2490.long. doi:10.1136/bmj.j2490.

[12] Schulz KF, Altman DG, Moher D. Statement: updated guidelines for reporting parallel group randomised trials. Trials 2010;11 32-32. doi:10.1186/1745-6215-11-32.

[13] Kwakkenbos L, Imran M, McCall SJ, McCord KA, Fröbert O, Hemkens LG, Zwarenstein M, Relton C, Rice DB, Langan SM, Benchimol EI, Thabane L, Campbell MK, Sampson M, Erlinge D, Verkooijen HM, Moher D, Boutron I, Ravaud P, Nicholl J, Uher R, Sauvé M, Fletcher J, Torgerson D, Gale C, Juszczak E, Thombs BD. CONSORT extension for the reporting of randomised controlled trials conducted using cohorts and routinely collected data (CONSORT-ROUTINE): checklist with explanation and elaboration. BMJ. 2021 Apr 29;373:n857. doi: 10.1136/bmj.n857. PMID: 33926904; PMCID: PMC8082311.

[14] Mc Cord K, Kwakkenbos L, Sampson M, Jawad S, Zwarenstein M, Relton C, Langan SM, Moher D, Fröbert O, Thombs BD, Gale C, Juszczak E; CONSORT Extension for Trials Conducted Using Cohorts and RoutinelyCollected Data Group. J Clin Epidemiol. 2021 Sep 12:S0895-4356(21)00291-2. doi: 10.1016/j.jclinepi.2021.09.011. Online ahead of print. PMID: 34525409

[15] Imran M, Mc Cord K, McCall SJ, Kwakkenbos L, Sampson M, Fröbert O, Gale C, Hemkens LG, Langan SM, Moher D, Relton C, Zwarenstein M, Juszczak E, Thombs BD; CONSORT Extension for Trials Conducted Using Cohorts and Routinely Collected Data Group. J Clin Epidemiol. 2021 Sep 11:S0895-4356(21)00290-0. doi: 10.1016/j.jclinepi.2021.09.010. Online ahead of print.

[16] European Medicines Agency. Patient registries. European Medicines Agency. Published September 17, 2018. Accessed March 24, 2021. Available at: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/patient-registries

[17] Clinical Trials Transformation Initiative. CTTI recommendations: registry trials. Available at: https://www.ctti-clinicaltrials.org/files/recommendations/registrytrials-recs.pdf 2020

[18] Kwakkenbos L, Imran M, McCord KA, Sampson M, Fröbert O, Gale C, Hemkens LG, Langan SM, Moher D, Relton C, Zwarenstein M, Benchimol EI, Boutron I, Campbell MK, Erlinge D, Jawad S, Ravaud P, Rice DB, Sauve M, van Staa TP, Thabane L, Uher R, Verkooijen HM, Juszczak E, Thombs BD. Protocol for a scoping review to support development of a CONSORT extension for randomised controlled trials using cohorts and routinely collected health data. BMJ Open 2018;8(8):e025266 PMID: 30082372; PMCID: PMC6078273. doi:10.1136/bmjopen-2018-025266.

[19] McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS peer review of electronic search strategies: 2015 guideline statement. J Clin Epidemiol 2016;75:40–6. doi:10.1016/j.jclinepi.2016.01.021.

[20] Evidence Partners. Distiller SR. *Data management software.*; 2015.

[21] Khangura S, Konnyu K, Cushman R, Grimshaw J, Moher D. Evidence summaries: the evolution of a rapid review approach. Systematic Reviews 2012;1(1):10. doi:10.1186/2046-4053-1-10.

[22] Seltzer JH, Heise T, Carson P, et al. Use of endpoint adjudication to improve the quality and validity of endpoint assessment for medical device development and post marketing evaluation: Rationale and best practices. A report from the cardiac safety research consortium. American Heart Journal 2017;190(0):10.

[23] Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. The Lancet 2009;374(9683):86–9. doi:10.1016/S0140-6736(09)60329-9.

[24] Hemkens LG, Benchimol EI, Langan SM, et al. The reporting of studies using routinely collected health data was often insufficient. J Clin Epidemiol 2016;79:104–11. doi:10.1016/j.jclinepi.2016.06.005.

[25] Speich B, Mc Cord KA, Agarwal A, et al. Reporting quality of journal abstracts for surgical randomized controlled trials before and after the implementation of the consort extension for abstracts. World J Surg 2019;43(10):2371–8. doi:10.1007/s00268-019-05064-1.

[26] Hopewell S, Dutton S, Yu LM, Chan AW, Altman DG. The quality of reports of randomised trials in 2000 and 2006: comparative study of articles indexed in PubMed. BMJ 2010;340:c723. doi:10.1136/bmj.c723.