USING ELECTRONIC HEALTH RECORD OR DISEASE REGISTRY DATA FOR CLINICAL TRIALS – A FRAMEWORK OF PRACTICE

(PROJECT No. 129740)

Professor Edmund Juszczak,
Dr Chris Gale, Dr Stephen McCall

Ed.juszczak@nottingham.ac.uk

Foreword

Our original application for funding in 2017, as the title illustrates, was to investigate the use of electronic health record (EHR) or disease registry data for clinical trials.

We proposed to develop guidance for stakeholders – trialists, Clinical Trial Units, reviewers, funders, healthcare professionals, participants – outlining the additional components to be considered when designing, analysing and reporting a clinical trial using an EHR database or existing registry.

Our plan was outlined following the guidance for developers of health research reporting guidelines laid out by Moher et al., PLoS Medicine 2010 http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1000217; including:

- A systematic review of the literature and existing guidance regarding electronic health record (EHR) and registry trials (including seeking evidence on the quality or reporting and potential sources of bias in such studies) – work stream 1
- An online Delphi consensus process (to identify minimum reporting components for trials using EHR databases or disease registries) followed by a face-to-face consensus meeting with relevant stakeholders (to identify design, analysis and reporting components relevant to trials using EHR databases or disease registries) – work stream 2
- Development of a CONSORT extension for trials using EHR databases or disease registries – work stream 3

At the time we submitted our proposal, we became aware of a CONSORT Extension for Cohort-and Registry-embedded Trials that was registered on the EQUATOR network.

Our proposed extension was fundamentally different from this registered extension but complementary in that it was primarily concerned with the use of EHR data for clinical trials, rather than data collected through an established cohort, administrative dataset or disease registry.

Having identified this other project, we contacted the authors and rapidly became part of an international collaboration addressing the use of cohorts and routinely-collected data in clinical trials (including cohorts, administrative databases, disease registries and electronic health records), EJ being designated the lead on the electronic health records theme.

The registration on the EQUATOR network was subsequently updated https://www.equator-network.org/library/reporting-guidelines-under-development/reporting-guidelines-under-development-for-clinical-trials/#STRUCT.

We have endeavoured to report on the one element of this collaboration (the largest), namely clinical trials using electronic health records, and apologise for any subsequent confusion, since it has been hard to divorce our theme from the overall project.

The ultimate output is a CONSORT statement extension for randomised controlled trials (RCTs) using cohorts and routinely-collected health data, CONSORT-ROUTINE, which, of course, includes RCTs using electronic health records.

Contents

List of Tables

List of Figures

Abstract

Background: Randomised controlled trials (RCTs) are increasingly being conducted using existing sources of data such as cohorts, electronic health records, administrative databases and disease registries. Transparent and complete reporting of RCTs conducted using existing data sources requires inclusion of additional information. This reporting guideline is an extension of the 2010 version of the Consolidated Standards of Reporting Trials (CONSORT) Statement for RCTs using cohorts and routinely-collected health data (CONSORT-ROUTINE).

Methods: A 'long list' of potential reporting items was identified through two methods: firstly, the additional items were identified from existing relevant reporting guidelines, including the Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) and REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statements. Secondly, a scoping review of RCTs published from 2011–2018 using cohorts and routinely-collected health data was undertaken and potential reporting items extracted. The 'long list' was entered into a three-stage Delphi consensus exercise of trialists and methodologists to assess the importance of each item for inclusion in the final CONSORT extension checklist, which was finalised at a face-to-face meeting of experts.

Results: A long list of 27 items was created and 125 experts registered for the three-round Delphi exercise (92, 77 and 62 experts participated in each round respectively). Consensus was reached on 21 out of 27 items in the Delphi exercise, and during the consensus meeting 8 additional items and 7 modified items were included in the final checklist. The checklist was disseminated and discussed through an invited session in May 2019 at the Society for Clinical Trials conference in New Orleans. Corresponding explanations and examples for each modified and additional item were developed for publication and further dissemination.

Conclusion: We have produced a reporting guideline to facilitate transparent reporting of RCTs using cohorts and routinely-collected health data. Use of this guideline will assist evaluations of rigour and reproducibility, enhance understanding of the methodology, and make the results more useful for trialists, clinicians, journal editors, reviewers, guideline authors and funders.

Introduction

Large definitive randomised controlled trials (RCTs) are challenging to undertake. Key challenges include recruitment (1) and extensive monitoring and regulatory requirements (2), both of which increase the resources required to complete RCTs. In response, new approaches to conducting RCTs have been developed including using existing data structures, such as cohorts and routinely-collected data. Routinely-collected data consists of three overlapping data systems: electronic health records (EHR), administrative databases and disease registries. These data structures offer the opportunity to conduct RCTs efficiently through automatic systems to identify potential participants, assess their eligibility, record consent, randomise, and collect all trial data (3).

The Consolidated Standards of Reporting Trials (CONSORT) 2010 Statement checklist is a 25-item instrument that was established to facilitate transparent and complete reporting of RCTs (4). A systematic review showed that RCTs published within journals that endorsed the CONSORT guideline had more complete reporting than journals that did not (5). The original statement was designed for parallel-group trials, and CONSORT extensions have been adapted to meet the reporting requirements of other RCT designs (6-8). RCTs conducted using cohorts and routinely-collected data have specific reporting requirements, including issues regarding data quality and the enrolment and consent process. As a result, a tailored reporting guideline is required to facilitate clear and transparent reporting of RCTs conducted using these data sources. The ultimate aim of this project was to develop and publish a CONSORT reporting extension for RCTs conducted using cohorts and routinely-collected data (CONSORT-ROUTINE) (9).

Methods

The overall process, timeline and the strategy for the development of a CONSORT extension for cohorts and routinely-collected data is illustrated in Figure 1 (9).

Project steering committee

This included experts in conducting RCTs using cohorts and routinely-collected data and RCT methodology. The core team, which undertook the work, included members from the University of Oxford (EJ, SM), Imperial College London (CG), London School of Hygiene & Tropical Medicine (SL), McGill University (BT, MI and LK), Queen Mary's University London (CR), University of Basel (LH and KM), University of Western Ontario (MZ) and Örebro University (OF).

'Long list' creation

A long list of items was created using two methods. First, the original CONSORT checklist was used as a template for adapting existing items and identifying areas for additional items, which were extracted from guidelines such as the STROBE (10) and RECORD statements (11). Secondly, a scoping review was undertaken to identify additional reporting items from RCTs that use cohorts or existing data sources.

Scoping review

This was prospectively registered (12), and the objective was to identify reporting needs for trials conducted using cohorts and routinely-collected data (including EHRs, administrative databases and disease registries) and to find examples of good reporting. Reviews focusing on the four separate components were conducted by different teams; this report focuses on the EHR review which was led and undertaken by the team at the National Perinatal Epidemiology Unit (NPEU) (EJ, SM), University of Oxford and Imperial College London (CG). The four reviews included protocols or reports of RCTs that had used routinely-collected data for **both** identification/screening for participants and ascertainment of trial outcomes. Trial methodology papers that were relevant to these types of trials were also included in the review.

Figure 1. The process and timeline of the CONSORT-ROUTINE extension development strategy.

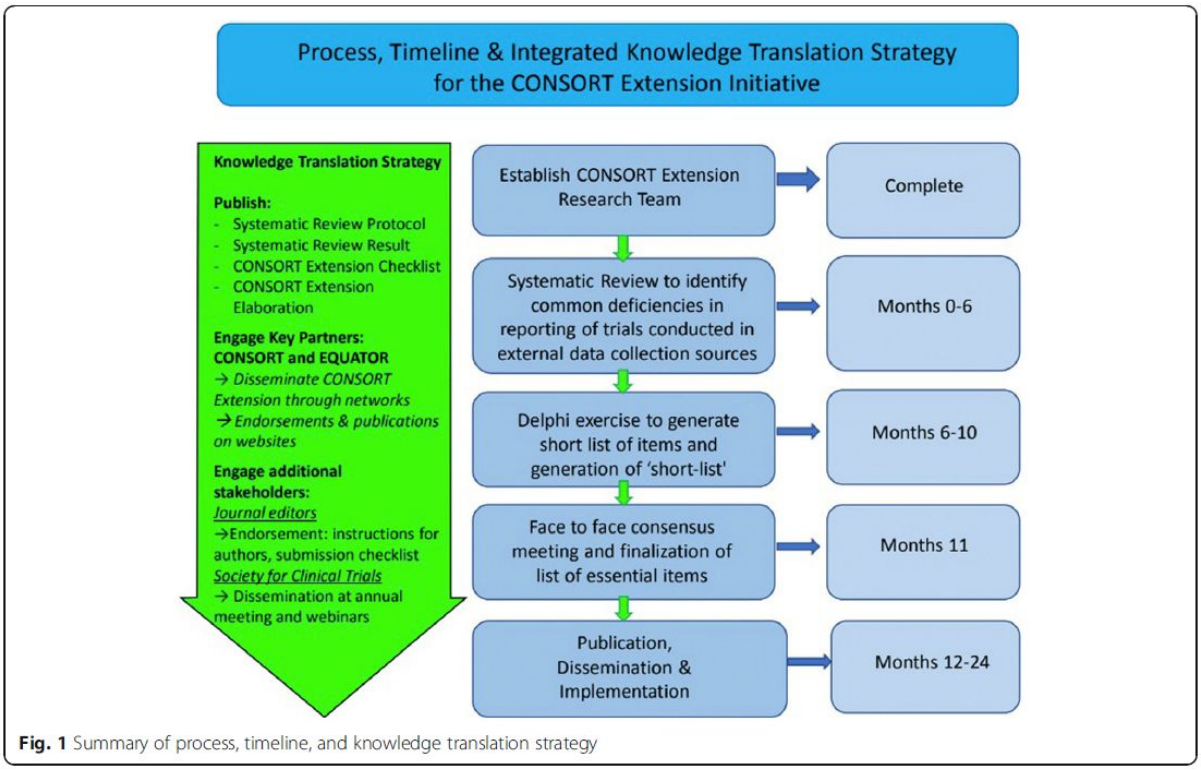


Fig. 1 Summary of process, timeline, and knowledge translation strategy

Search strategy

Separate searches were performed to identify publications describing methodology, trial protocols and results from RCTs that were conducted using (1) EHRs, (2) registries, (3) administrative databases, or (4) cohorts. Searches were undertaken in 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). Searches were conducted covering 2007–18 which allowed the identification of recent publications. The references were imported from the database into RefWorks, and duplicates were removed. The references were then imported into the systematic review software DistillerSR (Evidence Partners, Ottawa, Canada, (13)). A coding manual, tailored to each data source to identify and code publications for inclusion, was developed and followed by independent coders.

Two reviewers (MI, SJ) independently screened the titles and abstracts. A 'liberal accelerated method', where titles and abstracts are screened by one reviewer and excluded articles are screened by a second reviewer, was used to identify articles for inclusion for full text review.

Reviewers were blinded to whether the other reviewer had already decided on any given title and abstract. Full texts were screened independently by two reviewers (SM and MI), and discordant cases were resolved by a third reviewer (BT or LK). At the full text screening, each reviewer indicated how the data source (e.g., EHR data) was used: not at all, data source used for identification of participants/recruitment, ascertainment of outcomes, both identification of participants/recruitment and outcomes, or for delivering the intervention. Publications reporting trials where an existing data source was used as part of delivering the intervention were identified in this review but were not included in the wider CONSORT scoping review, unless they also used an existing data source for both identification/screening for participants and ascertainment of trial outcomes.

Data extraction

Data were extracted only from RCTs that used the data source for both the recruitment of participants and ascertainment of outcomes. Using articles from the four separate reviews, potential gaps in reporting or relevant areas to the reporting of these RCTs provided the evidence for the creation of additional checklist items. In addition, these reviews identified modifications to existing 'long list' checklist items. Finally, publications were screened for potential examples of good reporting for each item on the 'long list'. Two investigators (SM and EJ) double-checked the 'long list' for redundancy (i.e., to check whether the suggested items were specific to cohorts and routinely-collected data – it was not our role or intention to modify or rewrite original CONSORT items pertinent to all trial designs) and duplication.

Additional scoping review

The scoping review was expanded to explore how EHRs were used within RCTs and to describe the characteristics of these RCTs. Using the results of the full text screening, trials that had either used the data source for identification of participants/recruitment, ascertainment of outcomes or for delivering the intervention were included. In a separate data extraction form, further information about the trials such as type of RCT, setting, location, sample size, intervention, comparator and outcome was collected. These results are reported separately from the CONSORT scoping review.

Delphi exercise

Stakeholders

Key stakeholders were identified to participate in the three-round Delphi exercise (see Appendix A for details). A global invitation to trials and methodology experts was sent out using networks including the UKCRC CTU network and MRC trials methodology framework.

Three-round Delphi exercise

The 'long list' formed the basis for a three-round online Delphi consensus exercise to identify reporting items deemed essential for inclusion in the CONSORT extension. The Delphi participants were asked to score each proposed 'long list' item. Scoring comprised a 5-point Likert scale with a score of 1 or 2 deemed non-essential, 3 for further discussion and 4 or 5 deemed highly essential. Consensus was reached for an item when at least two-thirds of the Delphi participants rated it either essential or non-essential. If an item reached consensus, it was not entered into the next round of the Delphi exercise. Comments were invited from respondents to address whether they thought any other important reporting items had been omitted.

Face-to-face consensus meeting

A consensus meeting was held at Imperial College, London on 13–14 May 2019 (see Appendix A for list of stakeholders). All items were taken forward to the consensus meeting. Items that reached consensus were then ratified, modified or excluded at the meeting, and those items that had not reached consensus were reviewed for inclusion. In addition, items that were not included in the Delphi exercise were discussed and were either included, modified or excluded through consensus. At the consensus meeting, items that did not meet consensus went forward to a vote. For an item to be included in the final checklist, at least 80% of attendees had to be in favour of including the item.

Roles of collaborators

This project formed part of an international collaboration with each of four teams focused on one particular routine data source. The team at the NPEU, University of Oxford and Imperial College London completed the systematic review on RCTs using EHRs and this review yielded the largest number of articles (~200 full texts) and planned to publish the results of the systematic review separately, alongside a baseline assessment of the quality of reporting

assessed against the CONSORT-ROUTINE extension. The McGill team undertook the review on RCTs using administrative databases and conducted the whole administrative process for undertaking the Delphi exercise process and face-to-face meeting (the latter with help from the UK team). Collaborators from the University of Basel, University of Western Ontario and Örebro University focused on registries. Steering committee members attended bi-weekly teleconferences to discuss progress of the scoping review, 'long list' items, Delphi results, administrative processes and planning for the face-to-face consensus meeting. They also assisted in the identification of stakeholders and participated in the face-to-face consensus meeting. The NPEU, University of Oxford team and Imperial College London jointly led the development of the presentation at the Society for Clinical Trials, New Orleans in May 2019 with the Canadian team (BT, MI) and led the submission of an abstract to the International Clinical Trials Methodology Conference in Brighton in October 2019, which was also accepted for oral presentation.

Results

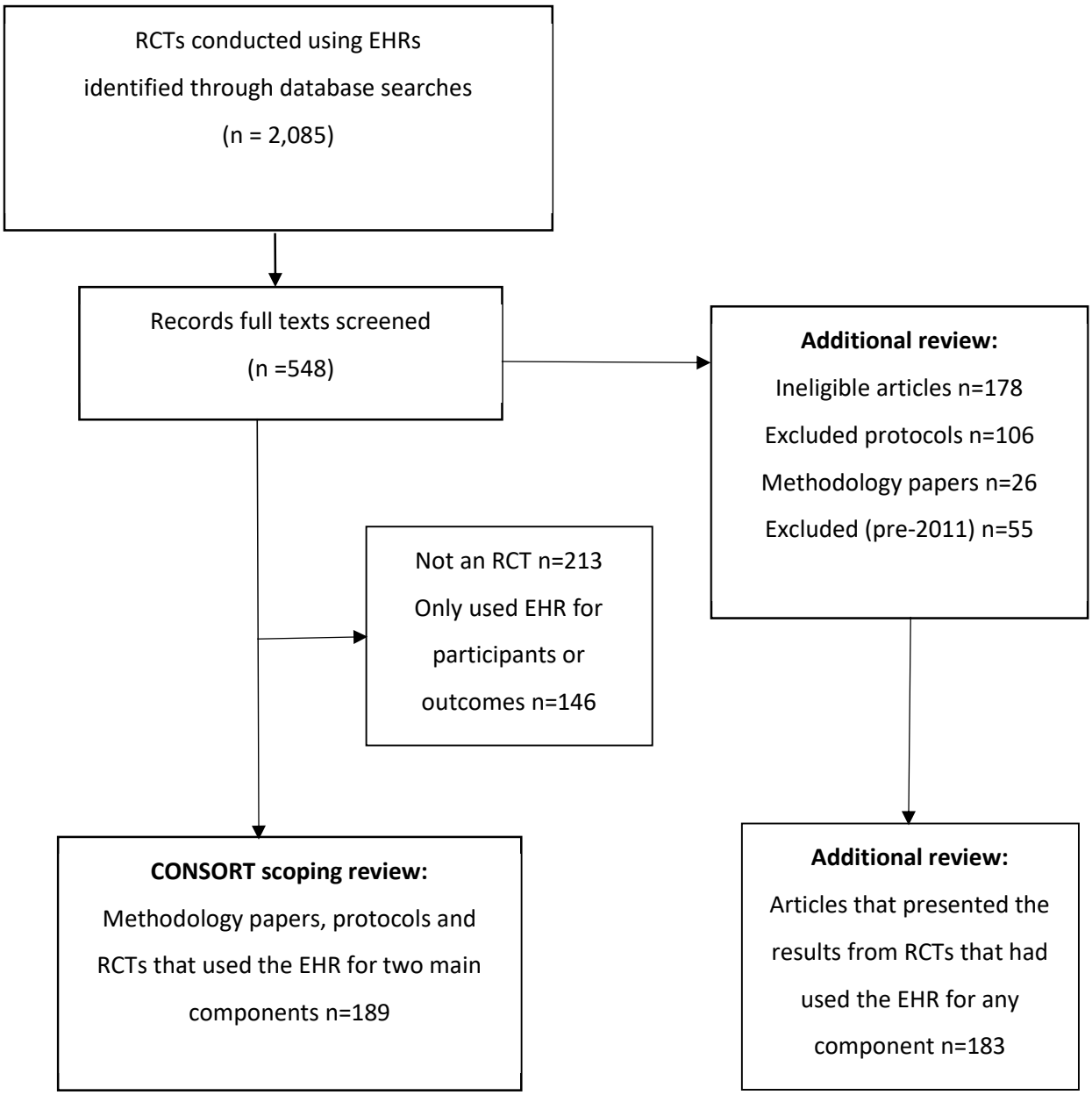
Scoping review for CONSORT extension

The results of the scoping review are presented in Table 1. The largest number of identified articles related to RCTs conducted using electronic health records. The derivation and screening of articles included in the review conducted by the NPEU, University of Oxford and Imperial College London team are presented in Figure 2. The 'long list' consisting of 7 modified and 20 additional items, were derived from the existing CONSORT 2010, RECORD and STROBE guidelines or scoping review.

Table 1. Results of the scoping review for each data source

	Number of protocols or RCT results publications	Number of methodology papers
Review of RCTs conducted using the following data sources		
1. Electronic health records (Oxford-led)	169	20
2. Registries	12	11
3. Administrative databases	24	0
4. Cohorts	65	17

Figure 2. PRISMA flow chart of studies included in the review examining RCTs conducted using electronic health records.



Additional review

The breakdown of studies included in the wider additional review by 'use of the EHR' is presented in Figure 3. The Figure illustrates that almost half of published EHR RCTs used the EHR for all three components of the trial (identification of participants, delivery of intervention and collection of outcomes). Further characteristics about these trials are presented in Table 2.

Figure 3. Description of how the electronic health records were used within the total sample of published RCTs meeting eligibility criteria (n = 183)

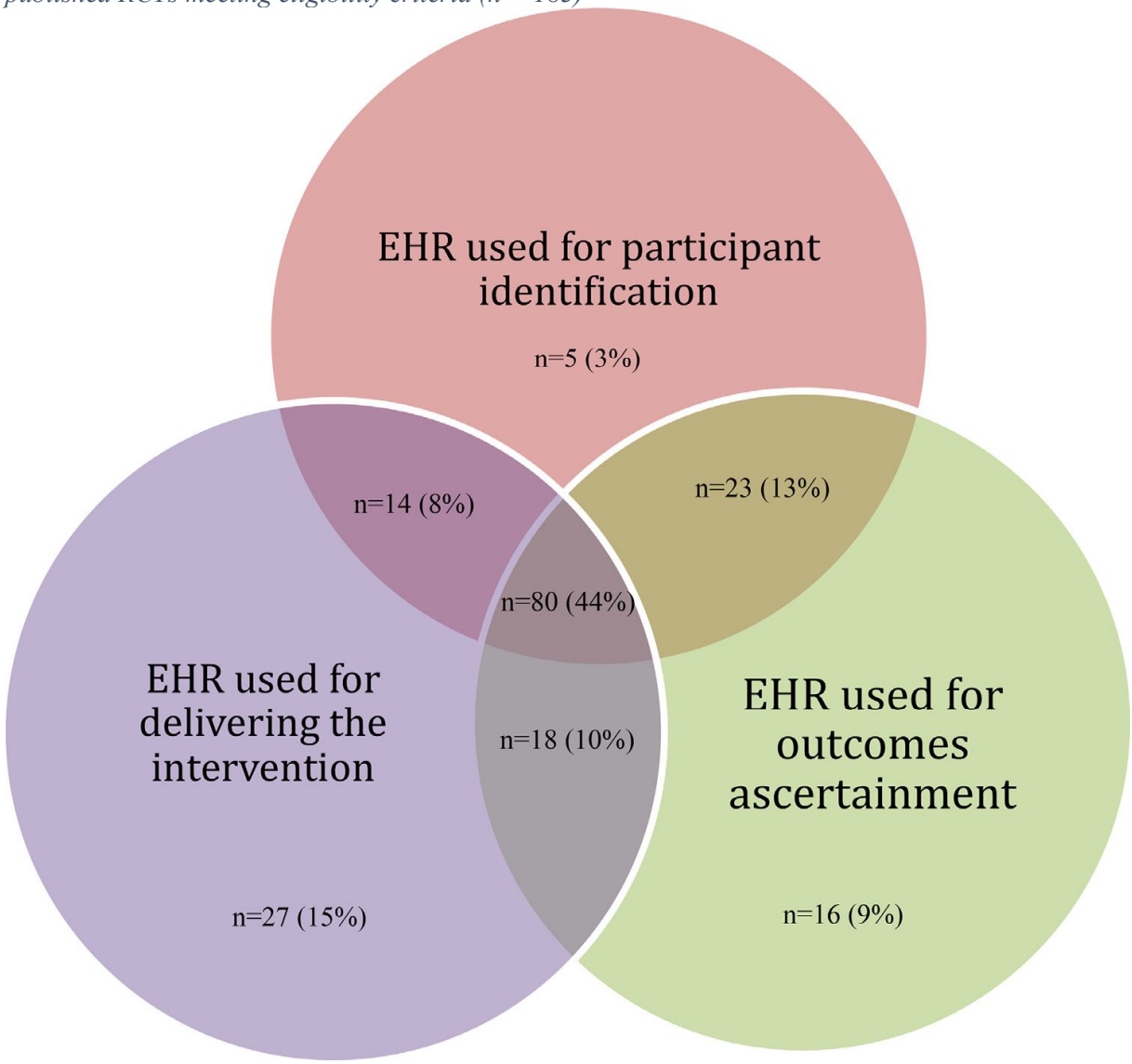


Table 2. Characteristics of trials conducted using electronic health records

	Number (%) of cluster randomised trials (n = 84)		Number (%) of individually randomised trials (n = 99)		Total (n = 183)	
Setting						
Primary Care, Accident & Emergency or Outpatient	71	(84.5)	73	(73.7)	144	(78.7)
Inpatient	9	(10.7)	16	(16.2)	25	(13.7)
Other	4	(4.8)	10	(10.1)	14	(7.7)
Country						
North America	65	(77.4)	78	(78.8)	143	(78.1)
Europe	18	(21.4)	12	(12.1)	30	(16.4)
Rest of the World	1	(1.2)	9	(9.1)	10	(5.5)
Speciality or Thematic of Interest						
Internal Medicine or General Medicine	53	(63.1)	59	(59.6)	112	(61.2)
Mental Health or Neurology	3	(3.6)	7	(7.1)	10	(5.5)
Vaccinations	8	(9.5)	7	(7.1)	15	(8.2)
Paediatrics	4	(4.8)	8	(8.1)	12	(6.6)
Behavioural Risk Factors[a]	8	(9.5)	9	(9.1)	17	(9.3)
Other	8	(9.5)	9	(9.1)	17	(9.3)
Intervention						
Guideline or Reminder-based	43	(51.2)	44	(44.4)	87	(47.5)
Other	29	(34.5)	46	(46.5)	75	(41.0)
Screening	12	(14.3)	9	(9.1)	21	(11.5)
Comparator						
Active Comparison Group	12	(14.3)	20	(20.2)	32	(17.5)
Usual care	71	(84.5)	74	(74.7)	145	(79.2)
Placebo	0	(0.0)	1	(1)	1	(0.5)
Unclear	1	(1.2)	4	(4)	5	(2.7)
Outcome						
Mortality, Disease Occurrence or Composite	4	(4.8)	5	(5.1)	9	(4.9)
No Primary Outcome	4	(4.8)	12	(12.1)	16	(8.7)
Other	19	(22.6)	14	(14.1)	33	(18.0)
Self-reported	7	(8.3)	22	(22.2)	29	(15.8)
Surrogate	14	(16.7)	17	(17.2)	31	(17.0)
Up Take of Treatment or Service	36	(42.9)	29	(29.3)	65	(35.6)
EHR used for Intervention[b]						
Clinical Decision Support	59	(70.2)	32	(32.3)	91	(49.7)
EHR not used for Intervention	19	(22.6)	25	(25.3)	44	(24.0)
Other	1	(1.2)	5	(5.1)	6	(3.3)
Personal Health Record	3	(3.6)	20	(20.2)	23	(12.6)
Telehealth	2	(2.4)	17	(17.2)	19	(10.4)
EHR for used for Primary Outcome(s)[b]						
No/Not Clear	20	(23.8)	45	(45.5)	65	(35.5)
Yes	64	(76.2)	54	(54.5)	118	(64.5)
Sample size						
Number of Clusters (median and IQR)	27	(15-56)				
Number of Participants (median and IQR)	4,447	(613-20,904)	415	(123-2,239)		
Total Number of Participants	2,311,604		302,055			

[a] Includes: Smoking, obesity, alcohol or opioid use.
[b] Definitions were adapted from Hemkens and Mc Cord, 2019, CMAJ (7)

IQR denotes interquartile range (25th percentile to 75th percentile)

Venn diagram and table published in: McCall *et al*. Reporting Transparency and Completeness in Trials: Paper 4 - Reporting of randomised controlled trials conducted using routinely-collected electronic records – room for improvement. J Clin Epidemiol. 2022 Jan;141:198-209. doi: 10.1016/j.jclinepi.2021.09.011. (p.202 & 203). Reproduced under the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/)

There were 84 (45%) cluster trials and 99 individually randomised trials (54%). The vast majority were conducted in North America (78%), set in primary care, Accident & Emergency or outpatient clinics (79%) and the most common speciality was Internal Medicine or General Medicine (61%). Around half of the interventions were guideline or reminder-based systems and 4 out of 5 trials used 'usual care' as the comparator. If the EHR was used for delivering the intervention, a clinical decision support tool was the most popular method (in almost half of cases). However, this differed substantially depending on the whether it was a cluster (70%) or individually randomised trial (32%). The most common outcome was the uptake of a treatment or service (~1 in 3), and nearly 2 in 3 trials used the EHR to identify the primary outcome. In terms of sample size, for cluster trials the average number of participants was 4,447 (interquartile range [IQR] 613 to 20,904) with, on average, 27 clusters (IQR 15 to 56); for individually randomised trials the average number of participants was much smaller, at 415 (IQR 123 to 2,239).

Delphi exercise

The 'long list' of 27 items was assessed by 125 experts in the three-round Delphi exercise, where 92, 77 and 62 experts participated in each round, respectively. In stage 1, with a response rate of 72% from the invited experts, 14 out of 27 items (52%) reached consensus. In stage 2, the remaining 13 items were rated by respondents and 2 (15%) items reached consensus. In the final stage, consensus for inclusion was reached for a further 5 items. This gave a total of 21 out of 27 items reaching consensus in the Delphi process and no item reached consensus for exclusion. The consensus status for each item in the 'long list' is reported in full in Imran M, *et al*. *BMJ Open* 2021;**11**:e049093. doi:10.1136/bmjopen-2021-049093 in Table 1 (p.8-15).

Face-to-face consensus meeting

A face-to-face consensus meeting was held at Imperial College London from 13–14 May 2019. The attendees comprised the Steering Committee and CONSORT extension group (see Acknowledgement section). During the face-to-face consensus meeting, out of the original 27 'long list' items, 5 new items and 8 modified items were agreed to be included in the final checklist for the CONSORT-ROUTINE extension on RCTs conducted using cohorts and routinely-collected data (see Table 3).

Table 3. Checklist for reporting of trials conducted using cohorts or routinely collected data: comparison of the extension with the CONSORT 2010 statement

Section/topic	Item No	CONSORT 2010 checklist item	Extension for trials conducted using cohorts or routinely collected data
Title and abstract			
	1a	Identification as a randomised trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	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) (modified)
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	—
	2b	Specific objectives or hypotheses	—
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	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) (modified)
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	—
Cohort or routinely collected database (new section heading)	ROUTINE-1	—	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) (new)
	ROUTINE-2	—	Eligibility criteria for participants in the cohort or routinely collected database(s) (new)
	ROUTINE-3		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 (new)
Trial participants (modified from "Participants")	4a	Eligibility criteria for participants	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 (eg, monitoring, adjudication), if applicable (modified)
	4b	Settings and locations where the data were collected	—
	ROUTINE-4	—	Describe whether and how consent was obtained (new)
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	—
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	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 (modified)
	ROUTINE-5	—	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 (eg, monitoring, adjudication), if applicable (new)
	6b	Any changes to trial outcomes after the trial commenced, with reasons	—
Sample size	7a	How sample size was determined	—
	7b	When applicable, explanation of any interim analyses and stopping guidelines	—
Sequence generation	8a	Method used to generate the random allocation sequence	—
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	—
Allocation concealment mechanism	9	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	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 (modified)
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	—
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	—
	11b	If relevant, description of the similarity of interventions	—
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	—
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	—

Section/topic	Item No	CONSORT 2010 checklist item	Extension for trials conducted using cohorts or routinely collected data
Results			
Participant flow (diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	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 (eg, cohort multiple RCTs), received intended treatment, and analysed for the primary outcome (modified)
	13b	For each group, losses and exclusions after randomisation, together with reasons	—
Recruitment	14a	Dates defining the periods of recruitment and follow-up	—
	14b	Why the trial ended or was stopped	—
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	—
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	—
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	—
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	—
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	—
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	—
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	—
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	—
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	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 (modified)
Other information			
Registration	23	Registration number and name of trial registry	—
Protocol	24	Where the full trial protocol can be accessed, if available	—
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Sources of funding and other support for both the trial and the cohort or routinely collected database(s), role of funders (modified)

RCT=randomised controlled trial.

Published in: Kwakkenbos *et al.* 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;373:n857 https://doi.org/10.1136/bmj.n857 (p4-5).Reproduced under the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/)

Future value of this work

RCTs using routinely-collected data are increasing in popularity and this CONSORT extension is timely as it provides a benchmark of reporting for these type of RCTs, which will become normal practice. Thus, this work funded by the NIHR will have a great impact on both the methodological rigour of the conduct and the quality of reporting of such RCTs globally. In addition, transparency of reporting has the secondary impact of improving the quality of RCTs. This NIHR-funded project will therefore provide an indirect benefit of reducing research waste.

Dissemination

During this project, outputs were published and disseminated at three international conferences, and eight publications have resulted (full details are listed below). Two protocols describing the CONSORT extension and scoping review have been published (9, 12). Subsequently, a methods paper and three related systematic reviews examining RCTs that use routinely-collected data EHRs have been published together alongside an editorial. The ultimate intended output of this project, the CONSORT extension checklist and corresponding explanation and elaboration document, has been published in an Open Access journal and is freely available through the EQUATOR network and CONSORT statement extension websites.

It is anticipated that an extension of the CONSORT statement would encourage improved conduct and reporting of these types of trials. As a by-product, it is likely that this body of work will encourage transparent reporting, which has the potential to reduce research waste.

Outputs from this project

Publications - Protocols

1. Kwakkenbos L, **Juszczak E**, Hemkens LG, Sampson M, Fröbert O, Relton C, **Gale C**, Zwarenstein M, Langan SM, Moher D, Boutron I, Ravaud P, Campbell MK, Mc Cord KA, van Staa TP, Thabane L, Uher R, Verkooijen HM, Benchimol EI, Erlinge D, Sauvé M, Torgerson D, Thombs BD. Protocol for the development of a CONSORT extension for RCTs using cohorts and routinely collected health data. Res Integr Peer Rev. 2018 Oct 29;3:9. doi: 10.1186/s41073-018-0053-3.
2. 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 Aug 5;8(8):e025266. doi: 10.1136/bmjopen-2018-025266.

Peer-reviewed publications

1. 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.
2. Imran M, Kwakkenbos L, **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. Methods and results used in the development of a consensus-driven extension to the Consolidated Standards of Reporting Trials (CONSORT) statement for trials

conducted using cohorts and routinely collected data (CONSORT-ROUTINE). BMJ Open. 2021 Apr 29;11(4):e049093. doi: 10.1136/bmjopen-2021-049093.

3. Hemkens LG, **Juszczak E**, Thombs BD. Reporting transparency and completeness in trials: Paper 1: Introduction - Better reporting for disruptive clinical trials using routinely collected data. J Clin Epidemiol. 2022 Jan;141:172-174. doi: 10.1016/j.jclinepi.2021.09.017. Epub 2021 Sep 12.
4. Mc Cord KA, Imran M, Rice DB, **McCall SJ**, Kwakkenbos L, Sampson M, Fröbert O, **Gale C**, Langan SM, Moher D, Relton C, Zwarenstein M, **Juszczak E**, Thombs BD, Hemkens LG; CONSORT Extension for Trials Conducted Using Cohorts and Routinely Collected Data Group. Reporting transparency and completeness in Trials: Paper 2 - reporting of randomised trials using registries was often inadequate and hindered the interpretation of results. J Clin Epidemiol. 2022 Jan;141:175-186. doi: 10.1016/j.jclinepi.2021.09.012. Epub 2021 Sep 12.
5. 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. Reporting transparency and completeness in trials: Paper 3 - trials conducted using administrative databases do not adequately report elements related to use of databases. J Clin Epidemiol. 2022 Jan;141:187-197. doi: 10.1016/j.jclinepi.2021.09.010. Epub 2021 Sep 11.
6. **McCall SJ**, Imran M, Hemkens LG, 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 Routinely Collected Data Group. Reporting transparency and completeness in trials: Paper 4 - reporting of randomised controlled trials conducted using routinely collected electronic records - room for improvement. J Clin Epidemiol. 2022 Jan;141:198-209. doi: 10.1016/j.jclinepi.2021.09.011. Epub 2021 Sep 12.

Conference presentations

1. Relton C., on behalf of CONSORT-ROUTINE steering committee. Rethinking the architecture of pragmatic trials: A review of trials within both researcher generated

and routine healthcare data structures. Society for Clinical Trials, Oregon, USA, May 2018.

2. **McCall S.**, on behalf of CONSORT-ROUTINE steering committee. CONSORT extension for trials conducted using routinely-collected data. Nuffield Department of Population Health Annual Symposium, University of Oxford, Oxford, UK. March 2019.
3. Campbell, M., **McCall, S., Gale, C., Juszczak, E.**, Thombs, B., Thabane, L., on behalf of CONSORT-ROUTINE steering committee. CONSORT Extension for trials conducted using cohorts and routinely-collected health data. Society for Clinical Trials, New Orleans, USA, May 2019.
4. **Gale, C., Juszczak, E.**, on behalf of CONSORT-ROUTINE steering committee. CONSORT Extension for trials conducted using cohorts and routinely-collected health data. International Clinical Trials Methodology Conference, Brighton, UK, October 2019.

Acknowledgements

Funder

This part of the global project was funded by the National Institute for Health Research (NIHR) CTU Support Funding scheme - Supporting efficient/innovative delivery of NIHR research (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.

Contribution of authors

Stephen McCall (NIHR-funded research associate; NPEU Clinical Trials Unit, Nuffield Department of Population Health, University of Oxford; systematic reviews and epidemiologist), Chris Gale (Co-investigator; Imperial College London; Clinical Trialist) and Edmund Juszczak (Principal Investigator; Director NPEU Clinical Trials Unit, Nuffield Department of Population Health, University of Oxford; Associate Professor of Clinical Trials Methodology and Statistics in Medicine). SM contributed to identifying stakeholders, was responsible for the completion of the EHR scoping review, identification of long list items and good examples of reporting, assisted in the administration for the Delphi exercise and

contributed at the face-to-face meeting. EJ/CG secured the funding for this work and contributed to the grant application to the Canadian Institutes of Health Research; identified stakeholders; supervised the completion of the EHR scoping review; contributed to the identification of long list items and good examples of reporting; contributed to the real time interpretation of the Delphi exercise and contributed (EJ co-convened and presented, CG chaired a session and presented) at the face-to-face consensus meeting. EJ/CG/SM presented the findings at the SCT conference session in New Orleans. EJ authored this report with significant contributions from CG and SM. All three authors vouch for the work conducted and have approved this report.

Steering Committee

Ole Fröbert, Chris Gale, Lars Hemkens, Mahrukh Imran, Edmund Juszczak, Linda Kwakkenbos, Sinéad Langan, Stephen McCall, Kimberly A Mc Cord, Clare Relton, Brett Thombs and Merrick Zwarenstein.

CONSORT-ROUTINE extension group

Eric I Benchimol, Isabelle Boutron, Marion K Campbell, David Erlinge, Ole Fröbert, Chris Gale, Lars G Hemkens, Edmund Juszczak, Linda Kwakkenbos, Sinéad M Langan, Kimberly A Mc Cord, David Moher, Philippe Ravaud, Clare Relton, Margaret Sampson, Maureen Sauvé, Tjeerd P van Staa, Lehana Thabane, Brett D Thombs, David Torgerson, Rudolf Uher, Helena M Verkooijen and Merrick Zwarenstein.

Independent screening of titles and abstracts

We would also like to thank Sena Jawad (Imperial College London) for her contribution to the systematic review.

References

1. McDonald AM, Knight RC, Campbell MK, Entwistle VA, Grant AM, Cook JA, et al. What influences recruitment to randomised controlled trials? A review of trials funded by two UK funding agencies. Trials. 2006;7(1):9.
2. Djurisic S, Rath A, Gaber S, Garattini S, Bertele V, Ngwabyt S-N, et al. Barriers to the conduct of randomised clinical trials within all disease areas. Trials. 2017;18(1):360.
3. Mc Cord KA, Ewald H, Ladanie A, Briel M, Speich B, Bucher HC, et al. Current use and costs of electronic health records for clinical trial research: a descriptive study. CMAJ open. 2019;7(1):E23.
4. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux P, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. J Clin Epidemiol. 2010;63(8):e1-e37.
5. Turner L, Shamseer L, Altman DG, Schulz KF, Moher D. Does use of the CONSORT Statement impact the completeness of reporting of randomised controlled trials published in medical journals? A Cochrane review a. Systematic reviews. 2012;1(1):60.
6. Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. Pilot and feasibility studies. 2016;2(1):64.
7. Campbell MK, Piaggio G, Elbourne DR, Altman DG. Consort 2010 statement: extension to cluster randomised trials. BMJ. 2012;345:e5661.
8. Juszczak E, Altman DG, Hopewell S, Schulz KS. Reporting of multi-arm parallel group randomized trials: extension of the CONSORT 2010 statement. JAMA. 2019;321(16):1610-20.
9. Kwakkenbos L, Juszczak E, Hemkens LG, Sampson M, Fröbert O, Relton C, et al. Protocol for the development of a CONSORT extension for RCTs using cohorts and routinely-collected health data. Research integrity and peer review. 2018;3(1):9.
10. Vandenbroucke J, Elm v, Altman D, Gøtzsche P, Mulrow C, Pocock S, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. PLoS Med. 2007;4:e297.
11. Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. PLoS Med. 2015;12(10):e1001885.
12. Kwakkenbos L, Imran M, McCord KA, Sampson M, Fröbert O, Gale C, et al. 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.
13. Distiller S. Data Management Software. Ottawa, ON: Evidence Partners. 2015.

Appendix A

Stakeholders in the Delphi exercise

Trialists, participants/patients and public involvement, epidemiologists, healthcare professionals, journal editors, reviewers, CONSORT steering group, Clinical Trials Unit directors and trial methodologists/statisticians from the United Kingdom Clinical Research Collaboration, funders and newsletter circulations (e.g., to members of the Medical Research Council Clinical Trials Methodology Hub).

Participants in the face-to-face consensus meeting

Cohort, EHR, administrative database and registry RCT trialists, CONSORT steering committee, other trialists, PPI, librarian, journal editor, epidemiologists and routinely-collected data experts.

Conflict of interest declaration

EJ's institution, the University of Oxford, received funding from the National Institute of Health Research during the conduct of the study. CG was funded by the United Kingdom Medical Research Council (MRC) through a Clinician Scientist Fellowship award during the conduct of this work. EJ also declares membership of HTA General Board at that time. SM has nothing to declare.