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Reporting of Cohort and Routinely Collected Data in Randomised Controlled Trial Protocols (SPIRIT-ROUTINE): extension checklist with explanation and elaboration

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Randomised controlled trials that use cohorts or health-and-care systems data, often known as routinely collected data—such as electronic health records, registries, or administrative claims—are becoming increasingly common. These trials have the potential to streamline recruitment, intervention delivery, follow-up (within trial and long term), and to lower costs. The lack of clear information governance pathways, heterogeneous data quality, delays in data recording and acquisition, and regulatory or ethical complexities undermine reproducibility and bias assessment when routinely collected data are used in trials. We introduce the SPIRIT-ROUTINE extension to the SPIRIT 2025 guideline: a checklist and explanation designed to improve the reporting of trial protocols that rely on cohorts or routinely collected data sources. Investigators, funders, ethics committees, journal editors, and peer reviewers can use the SPIRIT-ROUTINE extension to enhance completeness, transparency, and usability of such protocols to support better research, healthcare decisions, and patient outcomes.

SUMMARY POINTS

- Randomised controlled trials that use cohorts or routinely collected data are becoming increasingly common, with the potential to streamline recruitment, intervention delivery, within-trial and long term follow-up, and to lower costs
- The lack of clear information governance pathways, heterogeneous data quality, delays in data recording and acquisition, and regulatory or ethical complexities undermine reproducibility and bias assessment
- The SPIRIT-ROUTINE extension aims to improve the reporting of trial protocols that rely on cohorts or routinely collected data sources
- It enhances completeness, transparency, and usability of such protocols to support better research, healthcare decisions, and patient outcome

High quality, well defined protocols are crucial for the rigorous and transparent conduct and analysis of randomised controlled trials. To enhance trial protocol quality, an international group of interested parties launched the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) initiative in 2013 to provide evidence based guidance on the essential items to include in trial protocols. The main outputs include the SPIRIT 2013 statement,[1] which features a 33 item checklist of minimum recommended protocol items and an explanation and elaboration document.[2] The SPIRIT website offers additional information and resources.[3] Widely endorsed by journals, regulators, industries, trial groups, academic institutions, contract research organisations, and patient groups, SPIRIT guidance encourages high quality and transparent evaluations of interventions. Since 2013, numerous SPIRIT extensions have been developed to consider specific trial contexts and methodologies.[4] Building on this foundation, the SPIRIT and Consolidated Standards of Reporting Trials (CONSORT) executive groups later recognised the need to jointly and simultaneously update their respective guidelines, forming a SPIRIT-CONSORT joint executive group.[5] This joint venture resulted in the publication of the SPIRIT 2025 statement, which includes a 34 item checklist,[6] the CONSORT 2025 statement,[7] and their accompanying explanation and elaboration documents.[8 9]

Clinical guidelines and the delivery of evidence based care rely on evidence from randomised controlled trials. The need for large trials to detect important small or moderate treatment effects has been recognised for the past 30 years.[10] However, challenges (eg, administrative barriers) have increasingly impeded the conduct of informative randomised controlled trials. An urgent need exists to develop trials that are affordable and efficient in participant identification,

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recruitment, and follow-up. The use of health-and-care systems data, often referred to as routinely collected data, has been proposed as a potential solution to this challenge.[11] Routinely collected data refers to a broad range of information gathered mainly for purposes other than research, such as healthcare delivery, administration, or surveillance.[12] Data from cohorts and routinely collected data offer an opportunity for low cost, long term outcome follow-up for trial participants, reducing necessary staff resources and participant burden.[13] In the context of clinical trials, routinely collected data generally refers to routinely collected health data or healthcare systems data, such as electronic health records, administrative databases, and disease registries. Routinely collected data can also include other data sources such as socioeconomic and educational data, or information from wearable devices that provide digital biomarkers.[14]

These sources have the potential to improve trial efficiency by facilitating recruitment and safety monitoring, lowering costs of outcome data collection, and enhancing the relevance of trial results.[15] Use of routinely collected data may also provide detailed information to support more nuanced analytical approaches and trial designs than could be achieved without these data.[16] Another potential use of routinely collected data is in pragmatic trials that embed studies on healthcare interventions within healthcare information technology systems and health insurance plans.[17 18] While few trials provide information on the use of such data,[19] designs for trials conducted using cohorts and routinely collected data are becoming more common. One study found that more than 60 per cent of all publicly funded trials in the UK plan to collect data from sources of routinely collected data .[20]

In 2021, the CONSORT Extension for Trials Conducted Using Cohorts and Routinely Collected Data CONSORT-ROUTINE statement was published to support comprehensive reporting of trials that used cohorts and routinely collected data;[21 22] this SPIRIT-ROUTINE extension aims to broaden the SPIRIT guidance for protocols of these trials. The guidance was developed in consultation with the CONSORT-ROUTINE study team, and the publication of SPIRIT-ROUTINE will encourage trialists to consider the use of cohort and routinely collected data from the outset. While the CONSORT-ROUTINE is a guideline for reporting trial itself, the SPIRIT-ROUTINE will serve as a guideline for reporting trial protocol.

Box 1: Summary of scope and use of the SPIRIT-ROUTINE extension

Eligibility

Protocols of trials and phases that use, or consider using, cohort or routinely collected data in the design, conduct, or analysis of a clinical trial.

Purpose

The extension comprises the minimum set of items to be reported, but authors can provide more information for better transparency and interpretation of findings, or to reflect unique aspects of their trial design.

Scope

Some items may not be applicable to clinical trial protocols wherein the use of cohort or routinely collected data is limited to a specific purpose, such as identification of participants for recruitment, delivery of intervention, or outcome assessment.

Flexibility

Items can be combined or reported in different sections from those suggested in the extension. The specific item sections are recommendations and not requirements.

Extrapolation

Some items could be relevant to non-randomised trials or observational studies conducted using cohort or routinely collected data.

Scope and use of SPIRIT-ROUTINE

Box 1 summarises the scope and purpose of the SPIRIT-ROUTINE extension, which is designed for reporting protocols trials and phases that use cohort and routinely collected data, regardless of the source of the cohort or routinely collected data. The extension also specifies the minimum set of recommended items for reporting. However, authors are encouraged to provide additional information to improve the transparency of the planned trial. This extension does not require trial teams to alter their designs or plans to match the recommended items, but authors should clearly describe the study plan while strongly considering the implementation of all items where possible. Box 1 provides further details regarding the scope and application of the extension.

Development of the SPIRIT-ROUTINE extension

This SPIRIT-ROUTINE extension was developed in five sequential stages, in accordance with the EQUATOR (Enhancing the Quality and Transparency Of health Research) Network methodological framework,[23] and similar to other SPIRIT extensions.[24 25] The development plan was registered on the EQUATOR Network website [23] on 5 May 2021, and the research protocol was published on 29 July 2021.[26] The only substantive change made to the original protocol during the course of the study was the addition of a stage 6, after the publication of the updated SPIRIT guidance in 2025 during the writing up phase, at which time the new and modified items for SPIRIT-ROUTINE were mapped from the 2013 checklist to the 2025 checklist.

Stage 1: Project launch

At the start of the study, a steering group (comprising PRW, MRS, AF, FLW, GD, KA, AWC, LK, BDT, AW, LGH, CG, MZ, SML, LT, EJ, and DM) was established to oversee the conduct and methodology of the project. The group comprised experts in trial methodology (including trials using cohorts and routinely collected data), experts in reporting guidelines (including experts involved in the CONSORT Extension for Trials Conducted Using Cohorts and Routinely collected Data (CONSORT-ROUTINE)),[22] and members of the SPIRIT and Medical Research Council—National Institute for Health and Care Research Trials Methodology Research Partnership Health Informatics and Outcomes working groups.[27] A project team comprising the lead

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investigator (PMK), senior research fellow (LOK), and research assistant (MM) was established to carry out the planned study methodology.

Stage 2: Rapid review

Stage 2 of the study involved creating a list of potential modifications, based on an assessment of the SPIRIT 2013 checklist, incorporating new items and changes from the CONSORT-ROUTINE reporting guideline and supplemented by a rapid review. The rapid review was less comprehensive than a systematic review: we conducted the searches in the US National Library of Medicine's clinical trial registry (ClinicalTrials.gov) and the UK National Institute for Health and Care Research journals library for trial protocols that used cohorts and routinely collected data, using a well established approach.[28] Eligibility for inclusion in the review required an randomised controlled trial design, the use of cohorts or routinely collected data, and protocol availability. We identified 1584 records, of which 24 duplicates were removed. One reviewer conducted the initial title or abstract review for eligibility, resulting in 1049 records being moved to full text review. Two reviewers assessed potentially eligible articles in August 2021, with disagreements resolved by consensus and consultation with a third investigator when disagreement or uncertainty arose. Full text reviews led to the inclusion of 181 trial protocols in the rapid review (fig 1).

We examined eligible protocols to identify potential modifications or new items, based on well illustrated examples and instances of important information being omitted. Data extracted from these protocols were compared with CONSORT-ROUTINE and used to compile a list of potential items. This list was reviewed by the investigators, resulting in 13 modifications of SPIRIT items and the addition of 14 new items advancing for rating in the e-Delphi survey. Combining rapid review findings with expert review to develop preliminary item lists aligns with guidance on developing health research reporting guidelines[29] and with approaches used to create other reporting guideline extensions.[22 24 25]

Stage 3: e-Delphi survey

Stage 3 of the study comprised two rounds of an e-Delphi survey to assess the importance of the long list of potential items and to identify any items not identified in stage 2. The survey employed a nine point Likert scale: 1-3 (not critical, item should not be included in the SPIRIT-ROUTINE extension checklist), 4-6 (important but not critical, item should be discussed), 7-9 (critical to include, item should be part of the SPIRIT-ROUTINE extension checklist).[30] Participants could provide feedback while rating each item and had the option to select "unable to rate" if they believed they lacked sufficient expertise. We also included items from the SPIRIT 2013 statement that initially did not have proposed modifications, allowing participants to provide feedback or recommend changes. At the end of the survey, participants could also propose additional potential items along with their rationale. New items were added for the second round upon participant suggestions, provided they did not duplicate or closely resemble existing items. During registration, demographic and professional background details were collected, such as geographical location, self-identified group membership among interested parties, employment sector, and research experience with trials involving cohorts or routinely collected data.

The e-Delphi survey was conducted using DelphiManager software (version 5.0), maintained by the COMET (Core Outcome Measures in Effectiveness Trials) initiative.[31] The software provided a distribution of scores—including the mean, maximum, and minimum scores, as well as percentage of items ranked 1-9 on the Likert scale—after each round. The first round ran from 7 March 2022 to 21 March 2022, and the second round from 30 May 2022 to 30 June 2022. We recruited participants were recruited through various methods: invitations to participate were sent by email to the steering group, reporting guideline developers, clinical trialists, trials research methodologists, guideline experts, members of the Trial Methodology Research Network, members of the Trials Methodology Research Partnership, and one patient and public involvement contributor. Recipients of the invitation were also encouraged to forward it to other potential interested parties.

After the email invitations were sent, 61 individuals registered for the survey and were invited to participate

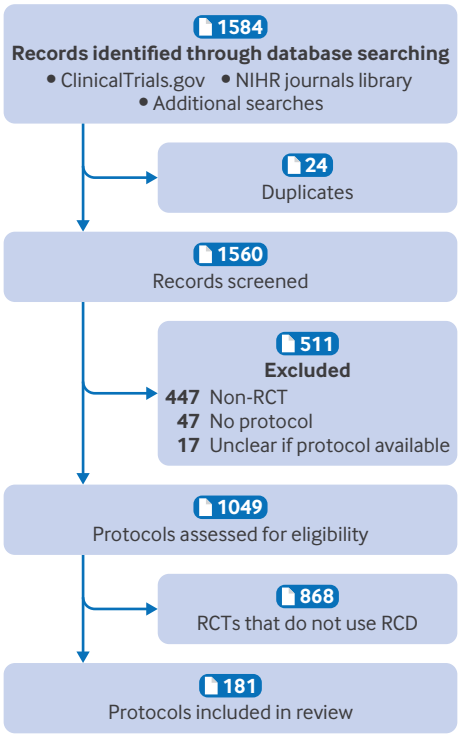


Fig 1 | Inclusion flowchart for trial protocols included in the SPIRIT-ROUTINE extension. NIHR=National Institute for Health and Care Research; RCT=randomised controlled trial; RCD=routinely collected data

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in both rounds. Forty-nine (79%) participants provided ratings in the first round and 34 in the second round. The geographical distribution in the first round was England (n=27), the USA (n=6), Canada (n=4), Wales (n=3), Australia (n=2), Scotland (n=2), Germany (n=1), Italy (n=1), Spain (n=1), Switzerland (n=1), and Sweden (n=1). In the second round, the participants were from England (n=20), the USA (n=5), Canada (n=3), Wales (n=2), Scotland (n=1), Germany (n=1), Italy (n=1), and Spain (n=1). The participants comprised trial investigators, methodologists, clinicians, journal editors, and ethics committee members, among other interested parties. In accordance with CONSORT-ROUTINE, decisions about which items to revise or add were based on whether they addressed elements specific to trials using cohorts or routinely collected data, rather than general items relevant to any trial.

We defined consensus thresholds as consensus for inclusion (a score of 7-9 with at least 75%), consensus for exclusion (a score of 1-3 with at least 75%), and no consensus if neither threshold was reached. In the first round, 27 items were rated for the SPIRIT-ROUTINE extension (14 new items and 13 modifications), and 31 items in the second round (with four additional items suggested by one participant). In the second round, participants received the distribution of scores from the first round, their individual scores, and any comments from the previous round. After completing the second round, the SPIRIT-ROUTINE steering group reviewed the survey results independently before discussing the findings. During this meeting, decisions were made on how to address participant comments by modifying, adding, or combining items.

Box 2: Summary of SPIRIT-ROUTINE items

New items

- SPIRIT-ROUTINE 1: details of the cohort or routinely collected data in the title or summary
- SPIRIT-ROUTINE 2: eligibility criteria for participants in the cohort or routinely collected data and identification of trial participants
- SPIRIT-ROUTINE 3: details of the outcome variables including quality, completeness, and methods used to derive them from cohort or routinely collected data
- SPIRIT-ROUTINE 4: inclusion or exclusion of participants from cohort or routinely collected data
- SPIRIT-ROUTINE 5: sources of cohort or routinely collected data used for the trial
- SPIRIT-ROUTINE 6: participant selection from cohort or routinely collected data

Extended items

- Extended item 1a.1: mention of the cohort or routinely collected data in the title
- Extended item 7a.1: sources of funding for routinely collected data
- Extended item 7b.1: financial and other competing interests extended to data controllers of the cohort or routinely collected data
- Extended item 12.1: role of cohort or routinely collected data in the trial design
- Extended item 14a.1: codes and algorithms used to identify eligible participants from cohort or routinely collected data, and information regarding the data completeness and accuracy
- Extended item 15a.1: implementation of the intervention using cohort or routinely collected data
- Extended item 16.1: ascertaining outcomes using cohort or routinely collected data
- Extended item 17.1: implications of using cohort or routinely collected data
- Extended item 21a.1: use of cohort or routinely collected data in sequence generation
- Extended item 22.1: use of cohort or routinely collected data in the implementation of concealment mechanism
- Extended item 24a.1: risk minimisation in blinding while using cohort or routinely collected data
- Extended item 25a.1: quality improvement measures for cohort or routinely collected data
- Extended item 32.1: consent or assent for using cohort or routinely collected data

Stage 4: Consensus meeting

This stage of the study involved an online consensus meeting with 18 members held on 15 November 2022. The meeting attendees included project team members, the SPIRIT-ROUTINE steering group, and other key interested parties including guideline experts, clinical trialists, trial methodologists, and a public and patient involvement contributor (SM).

All participants in the e-Delphi survey received a report of the results and were invited to attend the consensus meeting, during which the chair presented individual items and a group discussion was held. Firstly, items that met the consensus thresholds in the e-Delphi survey were presented briefly and discussed. Next, each item that did not reach consensus was discussed in detail. After the discussion of each item among the attendees, the chair sought consensus verbally by providing a summary to accept or reject and then checked whether everyone agreed. This process led to consensus on implementing proposed modifications to 13 SPIRIT 2013 items, plus adding six new items. After the meeting, the SPIRIT-ROUTINE steering committee members refined the content and wording of the items.

In line with previous SPIRIT extensions and CONSORT-ROUTINE, many of the recommended changes end with "if applicable," to show that some information that authors are asked to report might not be relevant or applicable to their randomised controlled trial or data.

Stage 5: Knowledge translation and dissemination

This stage has been ongoing since the start of the project and involves knowledge translation, which includes the dissemination and implementation of the extension. Dissemination efforts comprise publishing the project protocol[26] and giving presentations at various meetings, such as a lightning talk at the Health Informatics Working Group of the Trials Methodology Research Partnership in January 2021, an online presentation at the Trials Methodology Research Partnership Webinar in September 2021, and a presentation at the Open Meeting of the Health Informatics Working Group of the Trials Methodology Research Partnership in September 2022. Ongoing and future dissemination plans include publication of the SPIRIT-ROUTINE extension in journals and on the SPIRIT group and EQUATOR network website.

Stage 6: Adaptation to SPIRIT 2025

Following completion of the SPIRIT 2013 based consensus process,[1] the SPIRIT-ROUTINE extension

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was revised to align with the updated SPIRIT 2025 checklist.[6] This revision involved reviewing each item in the SPIRIT-ROUTINE extension against the corresponding items in SPIRIT 2025 and making necessary adjustments to ensure consistency in formatting, numbering, and terminology, while maintaining the original intent and content of the modifications specific to SPIRIT-ROUTINE.

Structure of SPIRIT-ROUTINE extension

The extension consists of a checklist, an explanation section, and elaborations section to clarify modified items and provide examples of their use in published protocols. When items remain unmodified, readers should refer to the SPIRIT 2025 checklist. We draw from 12 published protocols to offer at least one example of reporting for each of the 13 modifications and six new items. The project team identified these protocols through their experience of trials using routinely collected data. A summary of SPIRIT-ROUTINE items is presented in box 2.

SPIRIT-ROUTINE extension

Table 1 compares the SPIRIT 2025 checklist with the extension items in the SPIRIT-ROUTINE checklist. A combined SPIRIT 2025 and SPIRIT-ROUTINE checklist is available in the supplementary appendix, and table can be downloaded as a fillable document.

Section: Administrative information (extended)

Title and structured summary (extended)

SPIRIT 2025 item 1a: Title stating the trial design, population, and interventions, with identification as a protocol.

SPIRIT-ROUTINE 2025 extension item 1a.1: Specify that a cohort or routinely collected data will be used to conduct the trial and, if applicable, provide the name of the cohort or source of routinely collected data.

Example

"Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia (TASTE trial). A multicenter, prospective, randomized, controlled clinical reg-

Table 1 | Comparison of the SPIRIT 2025 items and SPIRIT-ROUTINE extension items

Section/item	Item No	SPIRIT 2025 items	SPIRIT-ROUTINE items
Administrative information			
Title and structured summary	1a	Title stating the trial design, population, and interventions, with identification as a protocol	1a.1 Specify that a cohort or routinely collected data will be used to conduct the trial and, if applicable, provide the name of the cohort or the routinely collected data source(s)
	1b	Structured summary of trial design and methods, including items from the World Health Organization Trial Registration Data Set	—
Protocol version	2	Version date and identifier	—
Roles and responsibilities	3a	Names, affiliations, and roles of protocol contributors	—
	3b	Name and contact information for the trial sponsor	—
	3c	Role of trial sponsor and funders in design, conduct, analysis, and reporting of trial; including any authority over these activities	—
	3d	Composition, roles, and responsibilities of the coordinating site, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable	—
Open science			
Trial registration	4	Name of trial registry, identifying number (with URL), and date of registration. If not yet registered, name of intended registry	—
Protocol and statistical analysis plan	5	Where the trial protocol and statistical analysis plan can be accessed	—
Data sharing	6	Where and how the individual de-identified participant data (including data dictionary), statistical code, and any other materials will be accessible	—
Funding and conflicts of interest	7a	Sources of funding and other support (eg, supply of drugs)	7a.1 State sources and types of financial, material, and other support for both the trial and the cohort or routinely collected data
	7b	Financial and other conflicts of interest for principal investigators and steering committee members	7b.1 Financial and other competing interests for principal investigators for the overall trial, each study site, and the data controllers of the cohort or routinely collected data
Dissemination policy	8	Plans to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, reporting in trial registry, plain language summary, publication)	—
Introduction			
Background and rationale	9a	Scientific background and rationale, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	—
	9b	Explanation for choice of comparator	—
Objectives	10	Specific objectives related to benefits and harms	—
Methods: Patient and public involvement, trial design			
Patient and public involvement	11	Details of, or plans for, patient or public involvement in the design, conduct, and reporting of the trial	—

(Continued)

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Table 1 | Continued

Section/item	Item No	SPIRIT 2025 items	SPIRIT-ROUTINE items
Trial design	12	Description of trial design including type of trial (eg, parallel group, crossover), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	12.1 State that a cohort or routinely collected data was used to conduct the trial (such as electronic health record; registry) and how the data were used within the trial (eg, identification of potentially eligible trial participants, trial outcomes, or other aspects)
Methods: Participants, interventions, and outcome			
Trial setting	13	Settings (eg, community, hospital) and locations (eg, countries, sites) where the trial will be conducted	—
SPIRIT-ROUTINE: Description of routinely collected data component	SPIRIT-ROUTINE 1		Name, if applicable, and a description of the cohort or routinely collected data used to conduct the trial; including the person or role responsible for populating the routinely collected data, as well as information on the setting (such as primary care), locations, and dates (such as periods of recruitment, follow-up, and data collection)
SPIRIT-ROUTINE: Eligibility	SPIRIT-ROUTINE - 2		Eligibility criteria for participants in the cohort or routinely collected data and details of how eligible trial participants will be identified from the source(s) of routine data used to conduct the trial, if applicable
Eligibility criteria	14a	Eligibility criteria for participants	14a.1 State how to access the list of specific codes (eg, ICD-10; SNOMED) and algorithms used to identify potentially eligible participants; information on accuracy and completeness of data used to ascertain eligibility; and methods used to validate accuracy and completeness (eg, monitoring; adjudication)
	14b	If applicable, eligibility criteria for sites and for individuals who will deliver the interventions (eg, surgeons, physiotherapists)	—
Intervention and comparator	15a	Intervention and comparator with sufficient details to allow replication including how, when, and by whom they will be administered. If relevant, where additional materials describing the intervention and comparator (eg, intervention manual) can be accessed	15a.1 Describe how the data sources will be utilised to deliver the intervention; if relevant, for example, a risk-based intervention where an individual's risk is determined using a cohort or routinely collected data
	15b	Criteria for discontinuing or modifying allocated intervention/comparator for a trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	—
	15c	Strategies to improve adherence to intervention/comparator protocols, if applicable, and any procedures for monitoring adherence (eg, drug tablet return, sessions attended)	—
	15d	Concomitant care that is permitted or prohibited during the trial	—
Outcomes	16	Primary and secondary outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome	16.1 Specify how and when outcome details will be determined and identify the cohort or routinely collected data used to establish each outcome
SPIRIT-ROUTINE: Codes and algorithms to define or derive the outcome	SPIRIT-ROUTINE 3		Provide information on how to access the list of codes and algorithms used to define or derive the outcomes from the cohort or routinely collected data that will be used to conduct the trial; information on the accuracy and completeness of outcome variables; and methods that will be employed to validate their accuracy and completeness (eg, monitoring adjudication), if applicable
SPIRIT-ROUTINE: Number of participants in the routinely collected data	SPIRIT-ROUTINE 4		For each group, specify the number of participants in the cohort or routinely collected data available to conduct the trial (if applicable), including (if available) the numbers screened for eligibility, randomly assigned, offered, and accepted interventions (eg, cohort multiple randomised controlled trials), received the intended treatment, and analysed for the primary outcome
SPIRIT-ROUTINE: Sources of data	SPIRIT-ROUTINE 5		The sources of data used to conduct the trial should be specified in the methods section
SPIRIT-ROUTINE: Method to select patients within routinely collected data	SPIRIT-ROUTINE 6		Method for selecting patients within routinely collected data (eg, all, random, etc.)
Harms	17	How harms are defined and will be assessed (eg, systematically, non-systematically)	17.1 Include implications of using data not collected to answer the specific research question
Participant timeline	18	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended	—
Sample size	19	How sample size was determined, including all assumptions supporting the sample size calculation	—
Recruitment	20	Strategies for achieving adequate participant enrolment to reach target sample size	—

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Table 1 | Continued

Section/item	Item No	SPIRIT 2025 items	SPIRIT-ROUTINE items
Methods: Assignment of interventions			
Randomisation:			
Sequence generation	21a	Who will generate the random allocation sequence and the method used	21a.1 Method of generating the allocation sequence (eg, computer-generated random numbers); including whether this is directly within the cohort or from a routinely collected healthcare data system
	21b	Type of randomisation (simple or restricted) and details of any factors for stratification. To reduce predictability of a random sequence, other details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	—
Allocation concealment mechanism	22	Mechanism used to implement the random allocation sequence (eg, central computer/telephone; sequentially numbered, opaque, sealed containers), describing any steps to conceal the sequence until interventions are assigned	22.1 Mechanism of implementing the allocation sequence (such as embedding the random allocation sequence within; or integrating it with the cohort or routinely collected data); (including any steps to conceal the sequence until interventions are assigned)
Implementation	23	Whether the personnel who will enrol and those who will assign participants to the interventions will have access to the random allocation sequence	—
Blinding	24a	Who will be blinded after assignment to interventions (eg, participants, care providers, outcome assessors, data analysts)	24a.1 Who will be blinded after assignment to interventions (eg, trial participants; care providers; outcome assessors; data analysts), how they will be blinded, and, where applicable, outline any precautions taken to reduce the risk of unblinding from the use of routinely collected data
	24b	If blinded, how blinding will be achieved and description of the similarity of interventions	—
	24c	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	—
Methods: Data collection, management, and analysis			
Data collection methods	25a	Plans for assessment and collection of trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of trial instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be accessed, if not in the protocol	25a.1 Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to enhance data quality (eg, duplicate measurements; training of assessors), and a description of study instruments (eg, questionnaires; laboratory tests) along with their reliability and validity, if known. Where applicable, outline the role of quality improvement processes implemented for the cohort or routinely collected data sources. Reference where data collection forms can be found, if not detailed in the protocol
	25b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	—
Data management	26	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be accessed, if not in the protocol	—
Statistical methods	27a	Statistical methods used to compare groups for primary and secondary outcomes, including harms	—
	27b	Definition of who will be included in each analysis (eg, all randomised participants), and in which group	—
	27c	How missing data will be handled in the analysis	—
	27d	Methods for any additional analyses (eg, subgroup and sensitivity analyses)	—
Methods: Monitoring			
Data monitoring	28a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and funder; conflicts of interest and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	—
	28b	Explanation of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	—
Trial monitoring	29	Frequency and procedures for monitoring trial conduct. If there is no monitoring, give explanation	—
Ethics			
Research ethics approval	30	Plans for seeking research ethics committee/institutional review board approval	—
Protocol amendments	31	Plans for communicating important protocol modifications to relevant parties	—

(Continued)

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Table 1 | Continued

Section/item	Item No	SPIRIT 2025 items	SPIRIT-ROUTINE items
Consent or assent	32a	Who will obtain informed consent or assent from potential trial participants or authorized proxies, and how	—
	32b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	32b.1 Describe how participants were informed about the potential/planned use of their data in randomised trials
Confidentiality	33	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	—
Ancillary and post-trial care	34	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	—

istry trial based on the Swedish angiography and angioplasty registry (SCAAR) platform. Study design and rationale"[32]

Explanation

This item is designed to assist in indexing and identifying randomised controlled trial articles in electronic databases. At a minimum, the title should include recognisable terminology indicating the study as a randomised trial. Although it would be more informative to specify that a cohort or routinely collected data are used to conduct the trial, this level of detail may not always be feasible due to typical word count restrictions for titles. The name of the cohort or routinely collected data should be reported, if applicable, either in the title or structured summary. If data are unnamed, authors should state the type of database used (eg, electronic health record). Clarifying the purpose for which the cohort or routinely collected data is being used (eg, to identify or contact eligible participants, deliver the intervention, and/or assess outcomes) is important to described in the structured summary if not included in the title.

SPIRIT 2025 item 1b (no change): Structured summary of trial design and methods, including items from the World Health Organization Trial Registration Data Set.

Protocol version

SPIRIT 2025 item 2 (no change): Version date and identifier.

Roles and responsibilities

SPIRIT 2025 item 3a (no change): Names, affiliations, and roles of protocol contributors.

SPIRIT 2025 item 3b (no change): Name and contact information for the trial sponsor.

SPIRIT 2025 item 3c (no change): Role of trial sponsor and funders in design, conduct, analysis, and reporting of trial, plus any authority over these activities.

SPIRIT 2025 item 3d (no change): Composition, roles, and responsibilities of the coordinating site, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable.

Section: Open science (extended)

Trial registration

SPIRIT 2025 item 4 (no change): Name of trial registry, identifying number (with URL), and date of registration. If not yet registered, name of intended registry.

Protocol and statistical analysis plan

SPIRIT 2025 item 5 (no change): Where the trial protocol and statistical analysis plan can be accessed.

Data sharing

SPIRIT 2025 item 6 (no change): Where and how the individual de-identified participant data (including data dictionary), statistical code, and any other materials will be accessible.

Funding and conflicts of interest (extended)

SPIRIT 2025 item 7a: Sources and types of funding and other support (eg, supply of drugs).

SPIRIT-ROUTINE extension item 7a.1: State sources and types of financial, material, and other support for both the trial and the cohort or routinely collected data.

Example

"The study will be supported from the following foundations: The Swedish Research Council, the Swedish Society of Medicine, Deltofs foundation, Uppsala-Örebro Regional Research Council, The Geriatric Fund, and the regional agreement on medical training and clinical research (ALF) between Västerbotten and Uppsala County Councils and the Universities in Umeå and Uppsala and the Visare Norr Fund, Northern County Councils."

Acknowledgments thank "the Swedish Fracture Register (SFR) technical team and the Center of Registers, Western Healthcare Region" for hosting and maintaining the RCD [routinely collected data] platform used for eligibility screening, randomisation and outcome linkage."[33]

Explanation

This item extends the standard SPIRIT requirement to include funding information specific to trials using cohorts or routinely collected data. Many such trials require support for the trial intervention itself and separate funding for the data infrastructure that enables, for example, the collection and analysis of

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outcome data. However, our assessment of published registry based protocol papers for the examples and elaborations suggests that explicit disclosure of both remains uncommon. In trials relying on cohorts or routinely collected data, researchers often depend on cohorts, administrative health databases, or registries that have their own funding sources and operational costs. Transparency here helps readers understand the full financial context of the study and may be important for assessing potential conflicts of interest related to data sources.

SPIRIT 2025 item 7b: Financial and other conflicts of interest for principal investigators and steering committee members.

SPIRIT-ROUTINE extension item 7b.1: Financial and other competing interests for principal investigators for the overall trial, each study site, and the data controllers of the cohort or routinely collected data.

Example

"Competing interests: NDB's employing organisation provides IT support to GlaxoSmithKline. He has received educational grants and speaker's fees from GlaxoSmithKline and Novartis, and support for attending educational conferences from Boehringer Ingelheim, GlaxoSmithKline and Novartis. AW has acted on advisory boards and provided consultancy for Almirall, Chiesi, Cytos and GlaxoSmithKline. He has received travel support to speak at an international meeting from Boehringer Ingelheim and GlaxoSmithKline. He is an investigator on cough and asthma studies for Afferent and GlaxoSmithKline. JPN has received consulting and speaker's fees, and an educational grant from GlaxoSmithKline. MG's institution has received funding from GlaxoSmithKline as the SLS study sponsor. WW is an employee of, and holds shares/stock options in, GlaxoSmithKline. DL is an employee of, and holds shares/stock options in, GlaxoSmithKline. JV has received travel support and consultancy fees from GlaxoSmithKline (related to the SLS [Salford lung study] study); in addition, he has received consultancy fees from Almirall, AstraZeneca, Bioxydyn, Chiesi, GlaxoSmithKline (outside the SLS study), Novartis, Syntaxin and Takeda (Nycomed), and speaker's fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis and Takeda (Nycomed). His wife has previously worked for AstraZeneca, Ferring and GlaxoSmithKline (until 2009)." [34]

Explanation

This extension item considers the complex network of financial relationships in trials using cohorts or routinely collected data, requiring disclosure beyond traditional trial investigator conflicts. The Salford Lung Study example above demonstrates reporting across three key levels: overall trial principal investigators, individual site investigators, and data controller relationships. At the trial level, investigators disclosed employment and shareholdings with the sponsor, as well as consulting with competitors. Site level disclosures included educational grants, speaker fees, and institutional funding that could influence local study conduct. Importantly, the example covers data controller relationships, including institutional sponsor funding and IT support for the electronic medical record system used for outcomes. Such comprehensive disclosure is particularly important in pragmatic trials using electronic health records, where boundaries between investigators, healthcare providers, and data custodians may be unclear. However, full details across all sites and data controller relationships are often unavailable in current protocols, which highlights the need for this SPIRIT-ROUTINE extension. Many trials only provide partial disclosure, making it difficult to fully assess the range of potential conflicts that could impact patient recruitment, data quality, or data interpretation.

Dissemination policy

SPIRIT 2025 item 8 (no change): Plans to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, reporting in trial registry, a plain language summary, publication).

Section: Introduction (no change)

Background and rationale

SPIRIT 2025 item 9a (no change): Scientific background and rationale, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention.

SPIRIT 2025 item 9b (no change): Explanation for choice of comparator.

Objectives

SPIRIT 2025 item 10 (no change): Specific objectives related to benefits and harms.

Section: Methods: patient and public involvement, trial design (extended)

Patient and public involvement

SPIRIT 2025 item 11 (no change): Details of, or plans for, patient or public involvement in the design, conduct, and reporting of the trial.

Trial design (extended)

SPIRIT 2025 item 12: Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory).

SPIRIT-ROUTINE extension item 12.1: State that a cohort or routinely collected data (eg, electronic health record, registry) was used to conduct the trial and how the data were used within the trial (eg, identification of potentially eligible trial participants, trial outcomes, or other aspects).

Example

"The ASYMPTOMATIC trial is a pragmatic non-inferiority open label RCT [randomised controlled trial] with a 1:1 participant allocation ratio, in general

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practices across the UK that are registered with the Clinical Practice Research Datalink (CPRD). Data will be obtained from EHR [electronic health record] and approved linked datasets, using routinely-collected health information, direct patient report using electronic case report form (eCRF) (accessed via CPRD's Interventional Research Services Platform, IRSP) and an eCRF for Investigators (also accessed via IRSP)."[35]

Explanation

This extension discusses how cohorts or routinely collected data are incorporated into trial methodology. While standard SPIRIT covers basic trial design, it does not specify the role of existing data infrastructure in conducting trials. Trials using routinely collected data leverage these resources in various ways, including identifying eligible participants, collecting baseline data, delivering an intervention, measuring outcomes, or enabling follow-up. The specific role influences the trial's methodology and interpretation. For example, using electronic health records for outcome measurement presents different validity considerations compared to using the same routinely collected data for participant recruitment. Explicit description allows readers to understand the trial's operational framework, assess limitations related to data quality, and evaluate methodological appropriateness.

Trial setting

SPIRIT 2025 item 13 (no change): Settings (eg, community, hospital) and locations (eg, countries, sites) where the trial will be conducted.

SPIRIT-ROUTINE 1: Description of routinely collected data component (new): Name, if applicable, and a description of the cohort or routinely collected data used to conduct the trial, including the person or role responsible for populating the routinely collected data, as well as information on the setting (such as primary care), locations, and dates (such as periods of recruitment, follow-up, and data collection).

Example

"HipSTHeR is a multicentre register-based RCT of 1440 older patients . . . carried out from 2019 to 2029 (inclusion period 2019-2022)"

"Eligible patients will be identified by the Swedish Fracture Register (SFR) platform . . ."

"Seventy-five percent of the hospitals in Sweden that manage fractures on a regular basis participate in the SFR"[33].

Explanation

This extension focuses on trials that use existing data infrastructure rather than newly created data collection systems. While standard SPIRIT assumes prospective data collection, trials that use cohorts or databases depend on pre-existing systems with established governance and operational features. The item requires the data source name, who inputs the data (eg, healthcare providers, clerks, or automated systems), setting (eg, primary care, hospitals), geographical coverage, and temporal aspects (such as the establishment date and collection periods). This information helps readers evaluate data quality, completeness, potential biases, and overall generalisability. For example, knowing that a registry covers 75% of relevant hospitals (HipSTHeR example above) compared with limited coverage can influence the assessment of validity. Similarly, data entered by clinicians versus administrative staff may have different implications for data quality.

SPIRIT-ROUTINE 2: Eligibility (new): Eligibility criteria for participants in the cohort or routinely collected data and details of how eligible trial participants will be identified from the source(s) of routine data used to conduct the trial, if applicable.

Example

"Simple eligibility criteria were based on data available in SwedeHF: heart failure recorded as an outpatient visit or at discharge from hospital; left-ventricular ejection fraction ≥ 40%; NT-proBNP > 300 ng/L (sinus rhythm) or > 750 ng/L (atrial fibrillation), with BMI [body mass index]-adjusted thresholds; and chronic loop-diuretic use."

"Pre-screening occurs ... systematically from two sources:[reference] 'retrospective' pre-screening of patients who were previously enrolled in SwedeHF and are currently alive and meet eligibility criteria[reference]; prospective pre-screening of patients enrolled in SwedeHF in routine care during the trial."[36]

Explanation

This extension considers the two levels of eligibility criteria in trials using routinely collected data, eligibility for inclusion in the original cohort or database and eligibility for the specific trial being conducted. Traditional trials define eligibility criteria and recruit participants directly. However, trials that use existing data sources must operate within the constraints of pre-established cohort inclusion criteria or database coverage. This creates a two step process: understanding who and what is captured in the data source, then identifying eligible participants from that population. The item requires describing the original cohort or database eligibility criteria as well as the specific methods used to identify trial participants. This description is important because the original data source's inclusion criteria may introduce selection biases or limit the generalisability of the findings. For example, a heart failure registry may only include patients with specific diagnostic codes or severity levels, affecting who can be identified for trial participation. Transparency allows readers to understand potential selection biases, assess the representativeness of the trial population, and evaluate whether findings are generalisable beyond the specific database population.

Eligibility criteria (extended)

SPIRIT 2025 item 14a: Eligibility criteria for participants.

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SPIRIT-ROUTINE extension item 14a.1: Describe how to access the list of specific codes (eg, ICD10, SNOMED) and algorithms used to identify potentially eligible participants. Details on the accuracy and completeness of data used to determine eligibility are included, and methods employed to validate data accuracy and completeness are outlined (such as monitoring and adjudication).

Example

"DaRe2THINK will operate using a system of automated patient pre-screening using coded Primary Care health records across the >12 million patients registered in CPRD [Clinical Practice Research Datalink] GP [general practice] surgeries across England. The trial adopts a pragmatic approach to the screening criteria, aiming to display to Investigators only those patients who are likely to fulfil enrolment criteria. Investigators who are medical practitioners are still required to approve automated selection criteria, and are able to exclude potential participants on review of the medical record (see section 3.4 for further details, and section 5 for information about data processing and coding). Automated pre-screening exclusion criteria for medical conditions are based on secure definitions (presence of coding for that condition plus recent prescription of relevant medical therapy) to avoid exclusion where an unsubstantiated or transient code is present in the medical record. This trial will recruit participants from GP practices in England that contribute to CPRD; as of September 2020, 1,337 practices in England (15%) are part of CPRD. Centres that use the Egton Medical Information Systems (EMIS) web software platform will be included first, with practices using TPP SystmOne and InPS Vision software used to supplement recruitment if required. Practices that are participating in any anticoagulant intervention studies where there is potential to confound or modify the effects in DaRe2THINK will be excluded. The selection criteria will be applied within the CPRD IRSP [Interventional Research Services Platform] at study start, based on the predefined code list. A pseudonymised patient list is generated specific to each Primary Care practice. Following the site approval process, a delegated health professional at each practice will access the list, and re-identify the patients. The patient list is then reviewed by the health professional who also responds to a specified set of screening questions. Recruitment will be focused on practices with multiple potential participants for cost efficiency, targeting up to 600 GP surgeries across England. A further update will be performed for patients meeting the trial selection criteria at each participating practice on a weekly basis. The IRSP maintains confidentiality of all patient data according to CPRD internal governance and in line with the Data Protection Act 2018 (see section 9: Data Security)."[37]

Explanation

This extension addresses the complexity of identifying eligible participants from large databases using coded data. Unlike traditional trials, wherein investigators manually review patient records, trials using routinely collected data often rely on automated algorithms using diagnostic codes, prescription data, and other structured information. This item requires transparency about the specific coding systems and algorithms used, their accuracy limitations, and validation methods. This is because coded data quality varies substantially across healthcare systems, with issues such as miscoding, incomplete coding, and temporal inconsistencies reported. Different code sets and versions may capture the same conditions differently. The DaRe2THINK example demonstrates comprehensive reporting by describing the automated pre-screening system using Clinical Practice Research Datalink data, the pragmatic approach to screening criteria, validation through physician review, and methods to avoid exclusion based on spurious codes. However, our assessment of published registry based protocol papers for the examples and elaborations (including the example above) suggests that explicit code lists or a reference to where the lists can be found are not provided. Access options to the lists should be included: such transparency allows readers to assess potential selection biases, understand the reliability of participant identification, and evaluate whether similar approaches could be applied in other settings.

SPIRIT 2025 item 14b (Eligibility criteria) (no change): If applicable, eligibility criteria for sites and for individuals who will deliver the interventions (eg, surgeons, physiotherapists).

Interventions and comparator (extended)

SPIRIT 2025 item 15a: Intervention and comparator with sufficient details to allow replication, including how, when, and by whom they will be given. If relevant, provide links to additional materials that describe the intervention and comparator (eg, intervention manual).

SPIRIT-ROUTINE extension item 15a.1: Describe how the data sources will be utilised to deliver the intervention, if relevant. For example, a risk based intervention where an individual's risk is determined using a cohort or routinely collected data.

Example

"Fast Healthcare Interoperability Resources (FHIR) webservices (a combination of FHIR and Epic web services are being used at one site) pull data from the EHR [electronic health record] backend into the CONCERN CDS engine.[reference] The patients' demographics, clinical notes, and app logging information are retrieved, and the CONCERN score is computed in the engine and pushed back to the EHR backend using a Simple Object Access Protocol (SOAP) service.[reference] Then, the CONCERN level, corresponding color, and description to CONCERN score are displayed to the clinicians in their EHR's patient list and to nursing directors in their EHR's unit dashboard.[reference] Double-clicking the CONCERN level icon in the EHR front end will seamlessly bring

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the user to the CONCERN web app, which provides detailed information about the CONCERN model, including factors that contribute to each patient's specific CONCERN level and CONCERN level trendline over 72 hours."[38]

Explanation

Some trials use existing data infrastructure not only as a source of information but to deliver the intervention itself. The CONCERN example demonstrates advanced data use where electronic health record data feeds into a clinical decision support engine that calculates risk scores and displays them to clinicians in real time. The intervention depends entirely on the data infrastructure, which involves extracting patient data, processing it through algorithms, and providing actionable information to healthcare providers through existing workflow systems. Readers need to understand how data is processed through the system, potential failure points, and technical dependencies. This information helps evaluate intervention fidelity, potential barriers to implementation, and whether similar approaches could be adapted for other healthcare systems with different data infrastructure capabilities.

Intervention and comparator

SPIRIT 2025 item 15b (no change): Criteria for discontinuing or modifying allocated intervention/comparator for a trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease).

SPIRIT 2025 item 15c (no change): Strategies to improve adherence to intervention/comparator protocols, if applicable, and any procedures for monitoring adherence (eg, drug tablet return, sessions attended).

SPIRIT 2025 item 15d (no change): Concomitant care that is permitted or prohibited during the trial.

Outcomes (extended)

SPIRIT 2025 item 16: Primary and secondary outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome.

SPIRIT-ROUTINE extension item 16.1: Specify how and when outcome details will be determined and identify the cohort or routinely collected data used to establish each outcome.

Example

"Outcome measures will be captured at patient level, using data routinely-collected by the National Cancer Registration and Analysis Service (NCRAS). The primary outcome is whether a patient is diagnosed at stage 1 or 2 (early) or stage 3 or 4 (advanced)."[39]

Explanation

This extension considers how routinely collected data sources are used to derive trial outcomes. Standard SPIRIT requires defining which outcomes to measure, but trials using existing databases must also specify how these outcomes will be captured from existing data systems. This item requires transparency about the data source used for each outcome, timing of data availability, and methods for outcome determination. This is because routine data collection varies in accuracy, completeness, and timeliness across different databases and types of outcomes.[40] For example, mortality data may be highly accurate but delayed, while symptom based outcomes may be poorly captured in routine records. The NCRAS example demonstrates clear reporting. Transparency in this aspect allows readers to evaluate potential outcome misclassification, understand data lag times that might affect analysis timing, and assess whether outcome definitions align with clinical standards.

SPIRIT-ROUTINE 3: Codes and algorithms to define or derive the outcome (new): Provide information on how to access the list of codes and algorithms used to define or derive the outcomes from the cohort or routinely collected data that will be used to conduct the trial; information on the accuracy and completeness of outcome variables; and methods that will be employed to validate their accuracy and completeness (eg, monitoring adjudication), if applicable.

Example

"Routine queries will be applied to the PCORnet CDM, Medicare data, and health plan data to capture and classify nonfatal endpoints (hospitalization for MI [myocardial infarction], hospitalization for stroke, or hospitalization for major bleeding) using validated coding algorithms that will be applied to hospitalizations for each randomized participant."

"Deaths occurring in-hospital at participating network hospitals will be captured with CDM queries, but deaths are often not well represented in EHR [electronic health record] data sources, especially out-of-hospital deaths, that are expected to be the majority of the accrued death events during the trial. Medicare data do include information about death events regardless of the location of death, but only for patients enrolled in and eligible for Medicare (Medicare gathers this information from claims, reports from family members, and benefit information collected from the Social Security Administration)."[41]

Explanation

This extension explains how clinical outcomes are converted into database queries using coded data. Unlike traditional trials with standardised outcome assessments, trials using routine data must translate clinical definitions into specific diagnostic or procedural codes and algorithms. However, our assessment of published registry based protocol papers suggests that details on how to access the list of codes and algorithms are not typically provided. This section requires transparency about coding methods, algorithm validation, and accuracy limitations. This is essential because different code combinations for the

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same outcome (eg, myocardial infarction) can have varying sensitivity and specificity, which can influence trial validity. Moreover, investigators may select different individual diagnoses to form an outcome. Transparency allows readers to assess the risk of misclassification, understand biases in data capture, and evaluate the clinical significance of outcome definitions. This item also helps other researchers recognise the challenges in translating clinical endpoints into database queries and underscores the importance of validated algorithms.

SPIRIT-ROUTINE 4: Number of participants in the routinely collected data (new): For each group, specify the number of participants in the cohort or routinely collected data available to conduct the trial (if applicable), including (if available) the numbers screened for eligibility, randomly assigned, offered, and accepted interventions (eg, cohort multiple randomised controlled trials), received the intended treatment, and analysed for the primary outcome.

Example

"The patient population will be drawn from UK primary care. We have chosen a patient population who we can be confident have COPD [chronic obstructive pulmonary disease] by including those who have a previous spirometry indicative of COPD, and who are at risk of hospital admissions by including a prior history of frequent exacerbations . . . We have selected a population at risk of admissions, as delineated by data from UK primary care. The clinical practice research datalink (CPRD) has been linked to hospital episode statistics (HES) for 44201 patients and the annual AECOPD [acute exacerbation of chronic obstructive pulmonary disease] rate per person per year assessed according to COPD severity [Reference]. We have used hospitalisation rates from the clinical practice research database (CPRD) to determine event rate for our primary outcome [Reference]. Assuming a 1-sided significance level of 2.5% and a rate of admission in each group of 65% of that in the referenced data, with a non-inferiority margin of 6 percentage points, we would need to enrol 1329 patients in each of the intervention and control groups (2658 in total) to have 90% power for determining whether the results in the usual care group were non-inferior to those in the intervention group. Assuming dropout/lost to follow-up/non-adherence rate of 10% we therefore need to recruit 2954 patients. We have selected the 6% non-inferiority margin on the basis of clinical judgment that this was a reasonable threshold for a trade-off between a decrease in hospital admissions and other desired outcomes (reduced antibiotic use and resistance) whilst also being feasible to recruit to relatively quickly. To show non-inferiority the two-sided 95% CI [confidence interval] of the difference between hospitalisation rates should not exceed the pre-specified non-inferiority margin of 6%; the significance level set for this non-inferiority test is set at 0.025 (one-sided). A 5% or 4% non-inferiority threshold would require >4200 and >6500 patients respectively; these margins necessitate large numbers of sites which lowers feasibility unless trial duration is extended. This is undesirable as changes in [chronic obstructive pulmonary disease] management and/or health service design might affect our outcomes. With our chosen non-inferiority threshold we require around 80 GP [general practice] practices, assuming that we target larger practices whose list sizes are likely to have >70 eligible patients, and thus around 35 recruits."[42]

Explanation

This extension recognises that trials using routinely collected data operate within existing populations with defined characteristics and size limits. Unlike traditional trials, these trials must operate within the boundaries of established cohorts or databases, which affects sample size planning and recruitment strategies. The item requires reporting the source population size, screening numbers, and recruitment flow, specifically related to the database limits. This is because the available population in routine data sources may be too small for adequate statistical power, or conversely, may provide access to much larger populations than traditional recruitment could achieve. Transparency here allows readers to assess the feasibility of the proposed recruitment strategy, understand how database limitations influenced study design decisions, and evaluate whether the available population is representative of the broader target population.

SPIRIT-ROUTINE 5: sources of data (new): The sources of data used to conduct the trial should be specified in the methods section.

Example

"The UK CF [Cystic Fibrosis] Registry is the primary data collection instrument for the trial. Data entered routinely in the UK CF Registry will be used alongside CF STORM specific data fields in order to collect the data required. The UK CF Registry is a web based remote data entry system that captures information for each CF visit (encounter). Data should be entered on an encounter basis, clinics should aim to enter data on the UK CF Registry and manually transfer the data over to the CF STORM module within three weeks of an encounter and certainly no later than six weeks after the encounter and manually transferred over to the CF STORM Module."[43]

"All hospital admissions, outpatient and emergency department visits are identified from the EMR [electronic medical records] database (whenever and wherever they occur). From primary care, all healthcare contacts, out-of-hours activity and prescriptions of antibiotics or oral steroids can be identified. These events are reviewed by the study research team and classified as asthma or non-asthma related. Furthermore, the EMR captures suspected unexpected serious adverse reactions (eg, reduced kidney function or elevated liver function tests) and, for the purposes of SLS [Salford lung study], includes data from external sources to identify, for example, deaths or National

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Health Service (NHS) hospital admissions outside Salford. Northwest EHealth [reference] manages the EMRs, enabling data on study endpoints and patient safety to be collected continuously and remotely in near-real time."[34]

"The primary efficacy outcome is the occurrence of at least one asthma attack requiring treatment with OCS [oral corticosteroids] in the 12-months after randomisation. Information on this outcome will be obtained from prescription records and through linkage with Hospital Episode Statistic (HES) data.... Data on hospitalisations will be extracted from the EHR [electronic health record] or via linkage with HES data. In around 70-75% of practices included in CPRD, hospitalisation is linked to GP [general practice] data. Data on patients' use of primary care services will be extracted from CPRD [clinical practice research datalink]. The cost of community-dispensed medicines will be derived from linked NHSBSA [NHS business services authority] data . . . No follow-up visits are required as data linkage will occur through CPRD [clinical practice research datalink] of primary care data, secondary care data (via HES) and data from the Office for National Statistics (ONS). Efficacy and safety outcomes will be collated from these sources based on a pre-specified clinical code set supplemented, where required, with a safety reporting process via IRSP [Interventional Research Services Platform]. The code lists will be published and made available via Health Data Research UK (HDRUK). "[35]

Explanation

This extension emphasises identifying all data sources used in trials relying on routinely collected data, which often involve multiple interconnected databases with different governance and quality standards. By incorporating these elements, readers can better understand the complete data ecosystem. Trials may use primary databases (main registry), supplementary sources for additional data, and linkage systems for follow-up. The CF STORM example identifies the UK CF Registry as the primary source while noting additional trial specific data fields collected within the same system, including operational details about data entry and transfer procedures. In the Salford Lung study[34] example, the trial relies on electronic medical records from multiple healthcare systems that are managed by a single platform (NorthWest EHealth). The ASYMPTOMATIC trial[35] uses linked data from multiple sources. However, these examples do not explicitly discuss the quality and completeness of these data sources.

Transparency in reporting is necessary because data quality and completeness may not only vary across sources but also within a single source if the data are collected from multiple networks or systems. Therefore, it is important to specify the details of the underlying networks or systems from which the data are collected. Any changes to the routinely collected data source over the trial period such as changes in data collection platforms and/or updates to the coding system should be reported as they could potentially impact trial conduct and results. For trials using linkage systems, the quality and type of variables used for linkage, any validation procedures and results, and the proportion of records successfully linked, as these factors directly influence the potential for linkage bias. Trials using routinely collected data risk excluding data from underserved groups and underrepresented settings, as they have limited access to healthcare facilities. In all cases, the integrity and provenance of the data should be clearly understood and communicated.

Understanding the data ecosystem enables readers to assess potential biases, evaluate reliability, and comprehend operational complexities.

SPIRIT-ROUTINE 6: Method to select patients within routinely collected data (new): Method for selecting patients within routinely collected data (eg, all, random).

Example

"Potentially eligible patients admitted (or accepted for admission) to the participating PICU [paediatric intensive care unit] will be screened against the inclusion/exclusion criteria by the local clinical team, supported by the site research team. Screening Logs will record the reason patients are eligible but are subsequently not enrolled. All patients on vasoactive drugs should be recorded in the screening log."[44]

Explanation

This extension deals with how investigators choose which patients to include when the database contains more potentially eligible participants than are needed for the trial. Unlike traditional recruitment, where all eligible patients are approached sequentially, routine databases may contain large populations that require systematic selection methods. This item clarifies whether all eligible patients will be included, a random sample will be drawn, consecutive patients will be selected, or other sampling strategies will be used. This is important because selection methods can introduce bias and affect generalisability. Transparency in this aspect helps readers understand potential selection biases, assess representativeness of the study population, and evaluate external validity.

Harms

SPIRIT 2025 item 17: How harms are defined and will be assessed (eg, systematically, non-systematically).

SPIRIT-Routine extension item 17.1: Include implications of using data not collected to answer the specific research question.

Example

"Due to the virtual method of data collection for this study, there will be 2 types of adverse event data collection. One will be done by participants instructed to self-report any adverse events from the study intervention to a call center, and the other by an analysis of medical claims

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data from the participant's provider to their insurance system. Self-reported events will be captured from the date of the first dose of study intervention through the end of treatment (Month 3) plus 30 days. Medical claims data will be reviewed and evaluated in aggregate at the end of the 3-month, double-blind treatment period when the unblinded data are available."[45]

Explanation

This extension addresses the challenges of evaluating harms when using data originally collected for routine clinical care rather than research purposes. Routinely collected data may systematically underreport certain adverse events, overrepresent others, or lack the detail necessary for proper causality assessment with potential implications for use of routinely collected data in licensing trials. The item recognises these limitations and explains how they might influence harm detection and interpretation. Routine databases are very effective at capturing serious events requiring healthcare contact but may miss patient reported symptoms, mild adverse events, or events managed outside the healthcare system.

The example illustrates a hybrid approach that deals with routinely collected data limitations by combining medical claims analysis with participant self-reporting. This transparency helps readers understand potential underestimations of harm rates, assess the reliability of safety conclusions, and determine whether additional safety monitoring may be required.

Moreover, protocols should also describe planned approaches to address other biases specific to routinely collected data, such as the immortal time bias.

Participant timeline

SPIRIT 2025 item 18 (no change): Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended.

Sample size

SPIRIT 2025 item 19 (no change): How sample size was determined, including all assumptions supporting the sample size calculation.

Recruitment

SPIRIT 2025 item 20 (no change): Strategies for achieving adequate participant enrolment to reach target sample size.

Section: Methods: assignment of interventions (extended)

Randomisation

Sequence generation (extended)

SPIRIT 2025 item 21a: Who will generate the random allocation sequence and the method used.

SPIRIT-ROUTINE extension item 21a.1: Method of generating the allocation sequence (eg, computer-generated random numbers), including whether this is done directly within the cohort or from a routinely collected healthcare data system.

Example

"Method: A simple randomisation will allocate the participants 1:1 to either DOAC [direct oral anticoagulant] therapy (intervention group) or to continue without oral anticoagulation (control; standard of care). Implementation: The trial platform includes a module for randomisation once informed consent and selection criteria have been confirmed. The patient is assigned a unique randomisation number which is automatically generated by the IRSP [Interventional Research Services Platform]. Where the participant is allocated to the DOAC arm, the resulting prescription will be logged both on the trial platform and the electronic health record as per usual clinical practice. Statistical software: The randomisation sequence will be generated using Stata version 15.1(StataCorp LP, Texas)." [37]

Explanation

This extension explains how randomisation procedures are incorporated into existing data systems instead of using separate trial infrastructure. Traditional trials usually rely on independent randomisation systems, but trials integrated into routine care may embed randomisation directly into clinical databases, registries, or electronic health records. The item should specify whether randomisation takes place within the current data ecosystem and how this integration influences allocation procedures. The example illustrates a scenario where randomisation occurs within the trial platform which is linked to routine care systems. This transparency allows readers to identify potential vulnerabilities in allocation concealment, judge the reliability of the randomisation process, and consider whether technical failures might compromise trial integrity.

Type of randomisation

SPIRIT 2025 item 21b (no change): Type of randomisation (simple or restricted) and details of any factors for stratification. To reduce predictability of a random sequence, other details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions.

Allocation concealment mechanism (extended)

SPIRIT 2025 item 22: Mechanism used to implement the random allocation sequence (eg, central computer/telephone; sequentially numbered, opaque, sealed containers), describing any steps to conceal the sequence until interventions are assigned.

SPIRIT-ROUTINE extension item 22.1: Mechanism of implementing the allocation sequence (eg, embedding the random allocation sequence within, or integrating it with the cohort or routinely collected database(s), including any steps to conceal the sequence until interventions are assigned.

Examples

"Allocation concealment

Infants will be randomised using an online secure central randomisation system which will be

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embedded into the existing neonatal EPR [electronic patient record] systems (BadgerNet and BadgerEPR). Randomisation will occur within the EPR to ensure allocation concealment."[46]

Explanation

This extension explains how allocation concealment is maintained when randomisation systems are embedded within routine healthcare databases or clinical systems. Traditional trials rely on separate randomisation services, but trials integrated with routine care must balance allocation concealment with system integration needs. The item requires authors to detail the technical mechanisms for implementing randomisation within existing data infrastructure while ensuring proper concealment (because integrating with clinical systems risks compromising allocation security if not carefully designed). This transparency enables readers to assess whether allocation concealment is sufficiently protected when randomisation is embedded in routine systems, understand potential technical vulnerabilities, and evaluate the risk of selection bias.

Implementation

SPIRIT 2025 item 23 (no change): Whether the personnel who will enrol participants and those who will assign participants to interventions will have access to the random allocation sequence.

Blinding (extended)

SPIRIT 2025 item 24a: Who will be blinded after assignment to interventions (eg, participants, care providers, outcome assessors, data analysts).

SPIRIT-ROUTINE elaboration item 24a.1: Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), how they will be blinded, and, where applicable, outline any precautions taken to reduce the risk of unblinding from the use of routinely collected data.

Example

"The trial is open-label and therefore trial participants and their care providers will not be blinded or masked with respect to intervention allocation. Outcome assessment is based on coded health outcomes and therefore less susceptible to assessment bias on the part of the research team; nonetheless, the Trial Management Group will remain blinded to intervention allocation from an analysis standpoint. The exception to this is where knowledge of allocation in individual participants is needed to facilitate communication with patients/GPs [general practitioners], or in cases of valid medical or safety reasons."[37]

Explanation

This extension deals with unique challenges around blinding when using routinely collected data, which can inadvertently reveal treatment allocation through data patterns or clinical care documentation.[47] Unlike traditional trials with separate research assessments, routine data may contain clinical notes, prescription records, or monitoring data that could unblind investigators. The item requires describing specific precautions to maintain blinding when using routinely collected data. Challenges include prescription data revealing allocated treatments, clinical notes mentioning study participation, or monitoring patterns that differ between treatment arms. Transparency here, as in the example, helps readers understand potential risks of unblinding specific to routine data use, assess whether sufficient precautions are in place, and assess the validity of outcome assessment.

SPIRIT 2025 item 24b (no change): If blinded, how blinding will be achieved and description of the similarity of interventions.

SPIRIT 2025 item 24c (no change): If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial.

Section: Methods: data collection, management, and analysis (extended)

Data collection methods (extended)

SPIRIT 2025 item 25a: Plans for the assessment and collection of trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of trial instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be accessed, if not in the protocol.

SPIRIT-ROUTINE extension item 25a.1: Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to enhance data quality (eg, duplicate measurements, training of assessors), and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Where applicable, outline the role of quality improvement processes implemented for the cohort or routinely collected data sources. Reference where data collection forms can be found, if not detailed in the protocol.

Example

"To determine practicality of hospital episode statistic HES data. We will do this by reviewing incidence of hospitalisations for AECOPD [acute exacerbation of chronic obstructive pulmonary disease] and AECOPD rate (including unreported events in the e-diary study) in the HES record and compare to self- reported events by the patient. Timeliness of obtaining data and degree of alignment to patient reported events will be used to determine if HES should continue to be used, as determined by the trial steering committee. HES has been shown to pick up more events in other respiratory conditions (specifically pneumonia) but whether this will apply in COPD [chronic obstructive pulmonary disease] is not yet clear."[42]

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Explanation

This extension considers data quality assurance when trials rely on existing data infrastructure rather than custom data collection systems. Unlike traditional trials, wherein researchers seek to control data collection procedures, trials using routinely collected data have to work within existing quality frameworks while potentially implementing additional validation measures. The item requires describing both routine data quality processes (built into the existing system) and any trial specific enhancements, including understanding baseline data quality in the source system, implementing additional validation procedures, and addressing potential data gaps or inconsistencies. Transparency in this area helps readers understand data reliability limitations, assess the adequacy of quality assurance measures, and evaluate whether findings are likely to be valid. It also helps other researchers understand the importance of validating routine data sources for specific research purposes.

SPIRIT 2025 item 25b (Data collection methods) (no change): Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols.

SPIRIT 2025 item 26 (Data management) (no change): Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry, range checks for data values). Reference to where details of data management procedures can be accessed, if not in the protocol.

Statistical methods

SPIRIT 2025 item 27a (no change): Statistical methods used to compare groups for primary and secondary outcomes, including harms.

SPIRIT 2025 item 27b (no change): Definition of who will be included in each analysis (eg, all randomised participants), and in which group.

SPIRIT 2025 item 27c (no change): How missing data will be handled in the analysis.

SPIRIT 2025 item 27d (no change): Methods for any additional analyses (eg, subgroup and sensitivity analyses).

Section: Methods: monitoring (no change)

Data monitoring

SPIRIT 2025 item 28a (no change): Composition of data monitoring committee, a summary of its role and reporting structure, a statement of whether it is independent from the sponsor and funder, conflicts of interest and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a data monitoring committee is not needed.

SPIRIT 2025 item 28b (no change): Explanation of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial.

Trial monitoring

SPIRIT 2025 item 29 (no change): Frequency and procedures for monitoring trial conduct. If there is no monitoring, give an explanation.

Section: Ethics (extended)

Research ethics approval

SPIRIT 2025 item 30 (no change): Plans for seeking research ethics committee/institutional review board approval.

Protocol amendments

SPIRIT 2025 item 31 (no change): Plans for communicating important protocol modifications to relevant parties.

Consent or assent (extended)

SPIRIT 2025 item 32a (no change): Who will obtain informed consent or assent from potential trial participants or authorised proxies, and how.

SPIRIT 2025 item 32b: Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable.

SPIRIT-ROUTINE extension item 32b.1: Describe how participants were informed about the potential/planned use of their data in randomised trials.

Example

"SwedeHF is used for extensive observational clinical research as described in previous publications [reference] but prior to SPIRRIT-HFpEF, had never been used as a platform or for pre-screening for interventional trials. Patients do not provide written informed consent for entry into SwedeHF, but at all clinical encounters, patients in Sweden are informed of data entry into national quality registries and are allowed to opt out."[36]

Explanation

This extension deals with the unique consent challenges when participants' routine healthcare data may be used for research without their explicit awareness at the time of data collection. Unlike traditional trials, where participants explicitly consent to research participation, routinely collected data are collected during normal clinical care and may later be used for trials. The item requires describing how participants are informed about potential or actual use of their routine data in randomised trials, including an explanation as to whether participants were aware that their data might be used for research when it was originally collected, and how they are informed about specific trial participation. In the SPIRRIT-HFpEF example, although participants can opt out of data collection for the registry, there is no mention of consent to contact them for research purposes. This transparency is essential because routinely collected data use raises different ethical considerations than prospective research participation. Participants may not have anticipated research use when their data were originally collected, requiring clear communication

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about how their information will be used, stored, and protected.

Confidentiality

SPIRIT 2025 item 33 (no change): How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial.

Ancillary and post-trial care

SPIRIT 2025 item 34 (no change): Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation.

Conclusion

The SPIRIT-ROUTINE extension provides a practical minimum reporting standard for protocols using, or considering using, cohorts or other routinely collected data. When paired with SPIRIT 2025, the extension enhances transparency around data sources and governance, clarifies planned analysis and validation methods, improves reviewers' and regulators' ability to evaluate bias risk, and facilitates quicker replication of key trials through openly shared code sets and algorithms.

Some limitations to our approach exist; firstly, the limited scope of this extension poses a potential risk of missing relevant protocols during rapid reviews and we did not conduct a formal assessment of interrater reliability during the review screening process. However, we focused on National Institute of Health (NIH) and National Institute for Health and Care Research (NIHR) databases, which are among the largest health research funders in the world to provide a broad sample of relevant protocols. We ensured that the rapid review remained systematic by adhering to the core principles, aiming to minimise bias in the screening and inclusion of protocols. Although a moderate attrition rate is expected for Delphi studies of this kind, we acknowledge that this might affect generalisability. There is a possibility of missed perspectives: the online consensus meeting might have limited in-depth discussion compared to in-person meetings, of low-income and middle-income countries were underrepresented. Despite the limited quantity of patient and public involvement, the quality of engagement was maintained through active participation in consensus discussions, providing feedback on the checklist items and review of the final manuscript. The checklist is not a panacea, and cannot, on its own, overcome governance barriers specific to certain jurisdictions that can restrict access to health system data (eg, overly stringent ethics and data governance procedures), and several items, such as validating complex electronic phenotypes, will need refinement as data science methods evolve. Real impact will therefore depend on regular updates to the extension and, importantly, on active endorsement and enforcement by funders, research ethics committees, journals, and data custodian groups. Moreover, only a small number of trials currently use cohort data or routinely collected data,[49] which means that there is limited expertise in this area. This first iteration of a SPIRIT extension for trials using routinely collected data represents a useful starting point. A revision should be developed, by which time more trialists with relevant experience will likely be available to contribute and further strengthen the checklist.

We encourage all these interested parties—and trialists themselves—to incorporate SPIRIT-ROUTINE into grant templates, protocol registries, and journal submission systems. Consistent application will lessen unnecessary research waste and promote the safe, efficient, and trustworthy use of real world data to enhance patient outcomes.

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