How do trial teams plan for retention during the design stage of the trial? A scoping review protocol.

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Abstract

Background

Retention remains a major challenge for many clinical trials. The SPIRIT guidelines state the following information on retention should be included in the trial protocol “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”. This guidance shows the importance of planning retention methods and handling missing data as this can impact how the results of the trial are analysed and interpreted. The most recent Cochrane review of strategies to improve retention in clinical trials highlighted that some trials implemented multiple retention strategies and we questioned whether the use of multiple strategies was planned at the design stage and included in the protocol or are strategies implemented when retention becomes an issue within the trial. The purpose of our scoping review is to establish how trial teams prepare for retention at the design phase of clinical trials.

Methods and analysis

We will follow the methodological framework and guidelines for scoping reviews outlined by the Joanna Briggs Institute. We will search MEDLINE/PubMed**,** Scopus, EMBASE, CINAHL (EBSCO) and Web of Science. A comprehensive search strategy for PubMed was developed in collaboration with an experienced research librarian and the search will be adapted to each database. The screening process will involve two reviewers. EM will independently screen all titles, abstracts, and where necessary full protocol texts to determine eligibility. FS will screen 10% of the overall search output. We may purposively sample eligible protocols to ensure the protocols represent a variety of trial and intervention types. Next, data will be extracted from each protocol using the data extraction form. Once the data has been extracted the results will be synthesized. The analysis will be qualitative using a narrative summary and descriptive statistics where appropriate.

Discussion

The scoping review will help trial methodologists better understand when/if retention strategies are planned for during the design stage of the trial contributing to the PRioRiTy II unanswered question “How should people who run trial plan for retention during their funding application and creation of the trial (protocol development)?”.

Background/rationale

Randomised controlled trials (RCTs) are conducted in accordance with a trial protocol. Having a protocol that is incomplete and non-transparent makes it difficult to critically appraise the trial (1). Protocols are needed for the readers of the corresponding paper to be able to fully appraise and interpret the results of the trial (2). As per the 2013 SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) definition, a protocol is “a document that provides sufficient detail to enable understanding of the

background, rationale, objectives, study population, interventions, methods, statistical analyses, ethical considerations, dissemination plans, and administration of the trial, replication of key aspects of trial methods and conduct; and appraisal of the trial's scientific and ethical rigor from ethics approval to dissemination of results" (3;202). Prior to the introduction of SPIRIT, the content and quality of protocols differed greatly (3, 4) but the 33-item SPIRIT checklist for the minimum recommended protocol items improved this. Having a clearly written protocol increases transparency in trial conduct and they are usually published prior to the trial paper publication (5). However, this is not always the case and some publications will require payment for access. For example, of the cancer clinical trials published in January of 2020 (n=113), only 11.3% had a publicly accessible protocol that was not behind a paywall (2).

Retention remains a major challenge for many clinical trials (6). The SPIRIT guidelines recommend the following information on retention be included in the trial protocol in section 18b "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" (7;3). These of course are minimum requirements but the information can impact how missing data is dealt with and interpreted in the analysis of the trial (7).

A recent Cochrane systematic review of strategies to improve retention in clinical trials found that there were none for which the quality of evidence was high that showed improved retention. The review also highlighted that some trials implement multiple retention strategies (8), and we question thus whether the use of multiple strategies is planned at the design stage and included in the protocol, or are strategies implemented when retention becomes an issue within the trial. Evidence from a small number of interviews with trial staff is variable (9). Prospective retention planning informs appropriate costing and implementation of retention strategies but also increases transparency in trial conduct.

Objective

The purpose of our scoping review is to establish how trial teams prepare for retention at the design phase of clinical trials. This will contribute to the evidence base for the PRioRiTy II unanswered question "How should people who run trials plan for retention during their funding application and creation of the trial (protocol development)?" (10).

Methods

The scoping review will be conducted in accordance with the guidelines and framework outlined by the Joanna Briggs Institute (JBI) (11), the most recent framework for scoping reviews which builds on prior work (12-14). The framework consists of the following nine steps:

1. Defining and aligning the objective/s and question/s,
2. Developing and aligning the inclusion criteria with the objective/s and question/s

3. Describing the planned approach to evidence searching, selection, data extraction and presentation of the evidence
4. Searching for the evidence
5. Selecting the evidence
6. Extracting the evidence
7. Analysis of the evidence
8. Presentation of the results
9. Summarising the evidence in relation to the purpose of the review, making conclusions and noting any implications of the findings

The guidance from the Joanna Briggs Institute (11) along with the newly developed reporting guidelines for scoping reviews: the Preferred Reporting Items for a Systematic Review and Meta-Analysis Protocols Extension for Scoping Reviews (PRISMA-ScR)(15) have been consulted in the development of this protocol(Additional File 1).

Data sources and search strategy

A comprehensive search strategy for PubMed was developed in collaboration with an experienced research librarian at University College Cork and is shown below. The following electronic databases will be searched for relevant protocols, MEDLINE/PubMed, Scopus, EMBASE, CINAHL (EBSCO), and Web of Science. The search will be adapted as appropriate for each database using the software Polyglot which translates search strategies across databases. The search and screening process will take place over a six-week period. No other limits will be applied to the search.

Inclusion Criteria

Population: Protocols of RCTs that include adults and/or children of any age.

Concepts: Protocols of RCTs investigating any treatment/intervention type for any disease area. Randomisation can be at the cluster or individual level. Protocols of RCTs investigating any comparator including placebo and examining any outcome.

Context: The context of this scoping review is open sources of evidence pertaining to any contextual setting.

Types of evidence sources: We will include trial protocols published in the English language. We will include protocols for a 5-year period from 2014-2019, sufficient time to see the effect of the SPIRIT guidelines, which were published in 2013. We will include protocols for Phase 2, 3, and 4 RCTs as well as pilot and feasibility studies.

Example of PubMed search

This is the full search strategy developed for PubMed. The limits that were applied include published in the English language between the years of 2014-2019

Screening and selection process: EM will systematically collate and import titles and abstracts of all electronically sourced search results to EndNote, grouping results separately for each database. Duplicates will be removed, and the remaining results will be exported to Rayyan QCRI software for screening. The screening process will involve two reviewers (EM and FS). EM will independently screen all titles, abstracts, and where necessary full protocol texts to determine eligibility. FS will screen a random selection of 10% of the overall search output. If disagreement arises between these two reviewers regarding the eligibility of a protocol a third reviewer KG will be consulted. The protocol screening and selection process will be presented both narratively and graphically using a PRISMA (Transparent Reporting of Systematic Reviews and Meta-Analyses) flow diagram. Details of excluded sources at full-text review will be outlined and included in the review with reasons for the protocol exclusion.

Sampling: If the search produces a very large number of eligible protocols, we will use purposive sampling to reduce this number and ensure that the protocols selected represent a wide variety of trial types (academic, commercial), and intervention types (investigational medicinal product, licensed drug, surgical technique, medical device, and behavioural interventions), conducted in different disease areas, among different populations, in different countries, and from a range of funders (private, public, third parties).

Data management and data charting (extraction) process: Following screening for eligibility all data on retention plans will be extracted. Data to be extracted is outlined in Table 1. Where there is ambiguity on the purpose of specific actions, i.e., if they are for participant retention or not, the protocol authors will be contacted. Where contact is not possible/a reply is not received the ambiguous information will be highlighted and included in the data extraction. Prior to the full data charting process, the data extraction form will be piloted using a sample of 10 protocols as the variables to be extracted may need to be refined and improved to best meet the objectives of the scoping review. Data charting will be carried out by one reviewer (EM) and a random sample (10%) of the protocols will be double extracted and checked for consistency by (FS) to ensure consistency and improve the reliability of the data extraction process. Data charting will be conducted, and information will be entered into a Microsoft Excel file.

Data Items

Table 1. Variables to be extracted

Variables to be extracted
1. Protocol title, author and year, source of funding
2. Trial characteristics (disease area, patient population, duration of the trial, intervention and comparator, outcome)
3. Planned sample size
4. Mention of using the SPIRIT guidelines in the development of the protocol (“yes” or “no”)
5. Description of retention strategies outlined in the protocol
6. Does the description of the retention strategy include all the information recommended by the SPIRIT guidelines section 18b (“yes” or “no”) “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” (7;3)
7. Mode of follow up e.g., questionnaire, clinic visit, telephone call etc.
8. Mention of Patient and Public Involvement (PPI) in relation to retention
9. Mention of cost associated with retention strategy

Data synthesis: We will synthesise the data in a narrative synthesis with descriptive statistics where appropriate. The content will be analysedto determine if the protocol complies with the SPIRIT guidelines for retention strategies section 18b- “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” (7;3). This will be recorded as either “yes” or “no”. If the protocols include information regarding planned retention strategies this information will be analysed in the narrative synthesis. The narrative synthesis approach will be based on the Guidance on the Conduct of Narrative Synthesis in Systematic Reviews (16).

Presentation of findings

We will present the search results in a PRISMA flow diagram illustrating the total number of protocols generated by the search strategy, and the number of protocols excluded following the application of the inclusion/exclusion criteria and ultimately the number of protocols included in the scoping review. Summary tables will depict the study characteristics described in the included protocols. Additional tables, figures and narrative descriptions will illustrate the data addressing our research question. The findings of the scoping review will be disseminated via publication in a peer-reviewed journal.

Discussion

Conducting a scoping review of randomised controlled trial protocols to investigate when and if retention strategies are planned by trial teams during the design stage of the trial will contribute to the PRioRiTy II unanswered question “How should people who run trial plan for retention during their funding application

and creation of the trial (protocol development)?" (10). The strength of this review is that the intention to include a variety of trial types as described in the methods section. The review will highlight the gaps that exist in the planning and communication of retention strategies in clinical trials. The findings of this review have the potential to make trials more efficient and assist trial teams to consider the issue of retention as early as possible in the trial design.

Abbreviations

Randomised controlled trials (RCTs)

Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)

Prioritising Retention in Randomised Controlled Trials (PRioRity)

Preferred Reporting Items for a Systematic Review and Meta-Analysis Protocols Extension for Scoping Reviews (PRISMA-ScR)

Transparent Reporting of Systematic Reviews and Meta-Analyses (PRISMA)

Declarations

Ethics approval and consent to participate

As this will be a scoping review of previously published protocols no ethical approval or consent to participate is required.

Consent for publication

Not applicable as this protocol does not contain any individual persons' data.

Availability of data and materials

Not applicable as this is a protocol for a scoping review.

Competing interests

All authors confirm that they have no competing interests.

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Authors' contributions

All authors contributed to developing the review question and the review design. EM designed and drafted the protocol and is the guarantor of this protocol. FS and KG reviewed the protocol. All authors read and approved the final version of the protocol.

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Not applicable

Patient and Public Involvement

No patient or public involvement.

Amendments

The protocol will be closely followed during the scoping review, due to the iterative nature of scoping reviews any amendments that are made to the published protocol will be reported in the final publication.

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Supplementary Files

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- AdditionalFile1.docx