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Methodological letter

How to start and develop a multicenter, prospective, randomized, controlled trial

Cómo poner en marcha y desarrollar un estudio multicéntrico, prospectivo, controlado y aleatorizado

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Prospective, randomised, controlled studies (PCRS) are the studies with the highest scientific evidence and internal validity, specifically with a level 1a-b according to the Oxford Centre for Evidence-Based Medicine.[1] The steps involved in their development are summarised here (Fig. 1).[2]

Identification and development of an idea

What problem am I trying to answer? This is the question every study should start with. Example: Is intracorporeal anastomosis in right hemicolectomy more beneficial for the patient in colon cancer surgery?

From this question, a working hypothesis is generated. To do this, we must determine a main variable that can provide an answer to our question. Example: *Intracorporeal anastomosis in right hemicolectomy in colon cancer surgery reduces the risk of suture dehiscence.*

The hypothesis is then translated into the main objective of the study. Example: To determine whether intracorporeal anastomosis in right hemicolectomy in colon cancer surgery reduces the risk of suture dehiscence.

Bibliographic search

Steps to carry out a correct bibliographic search in the main bibliographic databases (Medline, Cochrane, Scopus…):

A Identification of the key words of our hypothesis. We recommend using English as the search language and, in the case of the Medline database, using its controlled vocabulary called MeSH.
B Combine these words using logical or "Boolean" operators: AND, OR, NOT.
C Evaluate the search result and select the articles of greatest interest.

Creation of the protocol

The protocol is the basis for planning, executing, publishing and evaluating the study and its results. The 3013 SPIRIT declaration (Standard Protocol items: Recommendations for Interventionals Trials[3] represents a common guideline for the different types of clincial trials in which the minimum content that the protocol should have is established.

Depending on the response sought, different PCRS designs exist.

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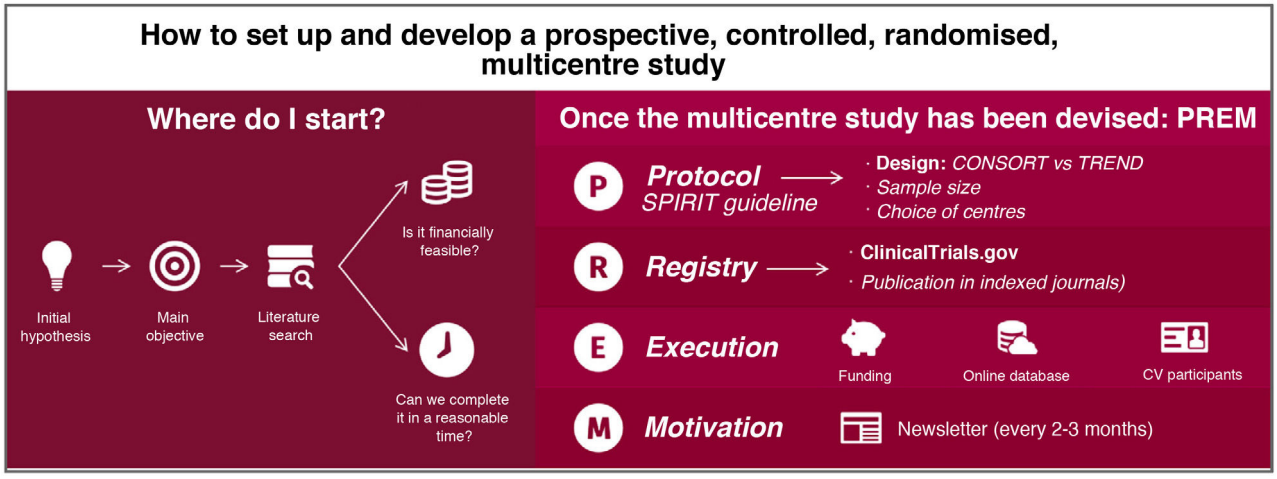

Fig. 1 – Graphical summary of the development of a prospective, randomised, controlled, multicentre study.

"Superiority" PCRS design

The purpose of superiority studies is to demonstrate that one treatment is better than another or better than no treatment.

The CONSORT (Consolidated Standards of Reporting Trials[4,5] guide is used in the design of PCRSs to make the results as rigorous as possible given the potential significance of their conclusions.

"Non-inferiority PCRS design

The purpose of non-inferiority studies is to demonstrate that one treatment is similar to another, with particularities (e.g. cost, safety, tolerability) that may make it more suitable in certain clinical scenarios.

As with superiority studies, there is the CONSORT guideline adapted to non-inferiority studies[6] with the recommendation for protocol development.

"Non-randomised PCRS design of superiority or non-inferiority. Is it always ethical to randomise?

Randomisation is a tool that contributes to the homogenisation of the groups to be compared and avoids selection bias.

However, there are certain exceptions where non-randomisation is acceptable[7]:

A When one of the research groups thinks that one of the two treatments is clearly worse.
B When the objective is to evaluate the cost-effectiveness of a therapeutic intervention.
C When the objective is to analyse the effectiveness of the treatments under conditions of routine clinical practice, having more experience with one of them.

The TREND Statement,[8] published in 2004, is the current guideline recommended for the creation of this type of study.

Sample estimation

The importance of the sample size is due to the fact that without a sufficient number of patients, we can give inconclusive results with an impeccable design. For its calculation, it is necessary to determine a number of variables depending on the study design.

Sample estimation in PCA superiority studies

For this type of study, it is necessary to determine:

- The value of the main variable with the standard treatment.
- The value of the main variable to be obtained with the experimental treatment.
- Risk α: the default value is given as .05–.025.
- Risk β: a power of 90–80% or β risk of .1–.2 is considered prudent.
- Allow for a 10% loss.

There are many online calculators to calculate the sample size from all the data discussed above. One of the best known in our environment is the GRANMO[9] sample size calculator.

Sample estimation in non-inferiority PCA studies

For this type of study, it is necessary to determine:

- The value of the main variable with the standard treatment.
- The non-inferiority margin accepted as valid (delta [δ]). This margin is determined by the research team and is interpreted as the decrease in efficacy of one treatment relative to another that is accepted as valid.
- Risks α and β.
- Allow for a 10% loss.

Viability

Once the protocol design and the required number of patients to be included have been determined, consideration should be given to whether the project is feasible from an infrastructural, economic and duration point of view.

Why conduct multicentre studies?

The answer is twofold. On the one hand, it allows a larger number of patients to be enrolled in a shorter period of time. On the other hand, it gives the study greater external validity since it adds reproducibility in several hospitals, bringing the results even closer to real clinical practice and diluting the effect of possible particularities of each centre.

Search for funding

Another crucial point for the feasibility of the project is to calculate the costs and look for possible sources of funding.

The hiring of a data manager is highly recommended for the smooth running of the trial, because he or she will be responsible not only for data entry, but also for the coordination of all patient tests and any problems that may arise at any of the centres.

Finally, it is also advisable, for grant applications, to have the curriculum vitae in standardised format (CVN[10] of all investigators available from the outset. This is usually a standard requirement and will save time.

Centre selection

It is advisable to choose related centres, if possible with previous successful collaborations and which show a clear commitment to the study.

Registration

Creation of an online database

For proper data management and randomisation, the creation of an online database is essential. This can be done through a Contract Research Organisation (CRO): a company that provides all clinical trial management services.

Clinical Research Ethics Committee (CREC)

Prospective, controlled, multicentre studies must be approved by the CREC of the sponsoring centre.

International clinical trials registry (ClinicalTrials.gov)

All indexed journals with a high impact factor request, prior to the start of the study, their registration in international clinical trial websites. One of the best known is ClinicalTrials.gov.[11]

Study insurance

Its function is to respond to possible complications or adverse effects. The research ethics committee itself will decide whether it is necessary to take out insurance for the study.

Execution and motivation

The final challenge is to develop and complete the study. It is therefore the obligation of the principal investigator and the promoter group to maintain the motivation of the rest of the collaborating centres. Having an online database showing the current status of the study and creating a newsletter every 2–3 months are two highly recommended tools.

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