Editorial

Randomic clinical trial pilot: what do we need to know?

Piloto de ensaios clínicos randômicos: o que precisamos saber?

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Randomized clinical trials (RCTs) have been considered the most robust type of research design to test the efficacy, effectiveness and safety of a health intervention. They are essential to guide decision-making in clinical practice.[1-3]

Efficacy clinical trials are designed to obtain answers regarding the effect of the intervention under ideal circumstances, described as those in which participants accept the interventions that are offered, follow instructions rigorously, receive the best care for the outcome being investigated, and are not treated for other outcomes.[4] This type of RCT is carried out in a highly controlled environment.

In turn, clinical effectiveness trials answer questions that address the effect of the intervention under circumstances of clinical practice, understood as those in which participants may not follow the treatment designated by randomization; some may drop out of the study and others may find ways to receive treatment for which they were not allocated. These RCTs describe results as most participants would experience them in real-world conditions.[4]

To obtain answers to the objective of the RCT and to guarantee its internal and external validity, it is essential to adequately select participants, use properly calibrated measuring instruments, uniform application of the research protocol in the compared groups, adherence to the interventions tested, measurement correct outcome of the investigated outcomes and sufficient sample size.

Once the outcome is defined, researchers who conduct RCTs seek to establish a significant difference between the compared groups, thus establishing the magnitude of the investigated effect. To this end, the sample must be sufficient to achieve adequate statistical power for the research and detect statistical differences between the groups.[5]

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Thus, in order to verify the viability of an RCT[6], test its eligibility criteria, protocol and obtain data to be able to carry out the sample calculation, it is recommended to carry out a pilot, characterized by being a small-scale test of methods and procedures to be used on a larger scale.

Given this fact, researchers must correctly identify the study as an RCT pilot and clearly explain the feasibility objective[7], and be clear that this type of study does not measure the efficacy or effectiveness of the intervention tested.[7-9]

These studies are considered merit studies, that is, carried out before the start of clinical research.[7-13] This type of study often has complex objectives related to the feasibility of carrying out the future RCT, and may not be clear to participants.[6] Therefore, researchers must clearly present what they intend to achieve with the pilot results and present them to the people recruited.

The pilot plays an exceptionally important role in preparing for larger-scale trials, examining beyond feasibility the acceptability of interventions and the methods used to test them.[14] It is also important to highlight that the pilot provides an excellent opportunity to evaluate vital information to ensure the acceptability participation of recruited people, their caregivers and the clinical team[15] who will apply the interventions in the groups studied, in addition to checking whether the variables of interest will be easily collected, evaluating the inclusion of other variables not thought of by the researcher, calibrating and standardizing the application of the data collection instrument and verifying the adherence of participants (patients and those responsible for implementing the interventions).

However, its possible applications for planning a future trial are not always fully realized[8-9], being limited to obtaining data to acquire the sample estimate, due to lack of knowledge about its purposes. Thus, in many cases, RCT pilots are conducted solely to generate data for sample size calculations. This seems especially sensible in situations where there is no previous research data that could contribute to this process.

The sample size of a pilot is a decision that has statistical implications for the future RCT in relation to the number of participants that will need to be recruited.[5] As the pilot has different objectives from the future RCT, in this type of pilot it is not recommended to apply formal tests regarding the hypotheses for the efficacy or effectiveness of the intervention, which is the objective of the main RCT. This fact is due to the small sample size, with little power to verify significant statistical differences between the groups compared. Therefore, it is not necessary to define the sample size in the same way, using formal power considerations.

In this context, it becomes essential to justify the pilot sample size, even when the reasons for choosing a certain size are pragmatic, as if not carried out with caution, studies of this nature can potentially lead to errors in sample size calculations of the future ECR.

From a statistical point of view, when the investigated outcome is a continuous variable, the pilot size must consider the desired level of confidence for the standard deviation, the chosen power and the level of statistical significance of the analysis in the future RCT. With a high level of confidence, piloting with at least 50 to 70 participants (25 to 35 per group) is advisable in many circumstances to estimate the standard deviation of this type of variable.[16,17]

If the objective of the pilot is to estimate the percentage of qualitative outcomes, a total of 60 to 100 individuals will be needed. Furthermore, in research whose primary outcome is binary, a total of at least 120 individuals (60 in each group) may be needed for the pilot. It is noteworthy that it is more efficient to use a larger number of participants in order to avoid the occurrence of lack of precision with inadequate samples[17] , in relation to estimating the sample size of the future RCT.

Feasibility needs to be fully tested and demonstrated before committing the considerable human and monetary resources involved in the study.[8] To this end, researchers must establish predetermined thresholds for feasibility results and thus decide whether a larger trial will be feasible.[13,18,19]

Among these limits of RCT pilots are recruitment, randomization, non-adherence, loss to follow-up, retention/discontinuation, and number of participants analyzed.[13] Other criteria can be added to the feasibility assessment such as eligibility, protocol fidelity, missing data and satisfaction of patients/participants with the tested intervention.[18,19]

The viability criteria and limits can be determined as follows: eligibility (>80% of screened patients who meet all inclusion criteria and no exclusion criteria); recruitment (>80% of eligible patients providing informed consent); protocol fidelity (>90% randomized patients receiving allocated intervention); retention (<5% of recruited patients were lost to follow-up or withdrew consent); missing data (<5% of total clinical outcomes data that cannot be collected); and patient satisfaction with the tested intervention (>80% continued using the intervention until the end of data collection).[18,19]

Many RCT pilots are not conducted with the intention of evaluating feasibility, much less establishing progression criteria, and few report the intention to proceed to a future clinical trial,[11] which may be due to lack of knowledge regarding their possible purposes, which adds value to this editorial.

It is therefore recommended to clearly report the results and criteria for determining feasibility success, justify the sample size, and appropriately interpret and report the implications of feasibility results for future RCT, as poor planning can subsequently compromise research efforts.[7]

Therefore, authors, editorial boards, editors and reviewers must ensure the appropriate use of the CONSORT 2016 extension to report RCT pilots[9,20,21], in order to report them with greater clarity and facilitate the understanding of their implementation.[22]

Concerns are frequent regarding the quality of RCTs and their potential to contribute to the collective evidence base. Although there has been progress in standardizing guidelines for this type of research, guidelines for carrying out pilots remain limited, potentially contributing to the lack of exploratory studies in this area and deficient evidence for the effective conduct of future clinical trials.[23]

Pilots represent a good opportunity to increase the probability of success and avoid failures in future RCTs, therefore, they must be well planned, with well-defined objectives, clear analytical plans, and explicit criteria to determine the success of viability, configuring themselves as an almost essential prerequisite.

Therefore, given the above, it is recommended that researchers who wish to conduct RCTs carry out pilot tests when necessary, given the contributions these types of research offer to future trials, in addition to sample estimates.

Author contributions

The authors declared that they have made substantial contributions to the work in terms of the conception or design of the research; the acquisition, analysis or interpretation of data for the work; and the writing or critical review for relevant intellectual content. All authors approved the final version to be published and agreed to take public responsibility for all aspects of the study.

Conflicts of interest

No financial, legal, or political conflicts involving third parties (government, private corporations and foundations, etc.) have been declared for any aspect of the submitted work (including, but not limited to, grants and financing, advisory board participation, study design, preparation manuscript, statistical analysis, etc.).

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