Symbiosis

www.symbiosisonlinepublishing.com
ISSN Online: 2374-6866

Review Article | SOJ Pharmacy & Pharmaceutical Sciences | Open Access

# Specific Requirements of the Multicenter Trial

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**Received: March 1, 2019; Accepted: March 21, 2019; Published: March 22, 2019**

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## Abstract

The golden rules of multicenter studies are that protocol design be kept relatively simple and the same at all centers, that careful planning of the initiation, conduct, and analysis of the study is mandatory and that statisticians be involved in the process, and that communications problems be minimized through all possible techniques.

**Keywords:** clinical trials; methodology; multicenter controlled trial;

## Introduction

The multicenter trial has a common protocol conducted by several centers (hospitals or individual physicians) and leading to an overall analysis. Whenever a clinical trial is to be performed for a rare disease or in a very limited category of patients, or when a large number of patients is involved, it is not sufficient to recruit a single investigator. Several participants are necessary (several physicians or several hospital departments). This not only allows a broader recruitment of patients but also a greater representativeness because of the peculiarities of each center. The generalization of the results will thus be more valid. Current clinical trials are increasingly multicenter, with implementation problems due to the heterogeneity of diseases recruited if the methodology and organization fail. The purpose of this article is to specify the constraints of such tests.

### Special Requirements

The centers must be comparable in their equipment, staff, timetables and recruitment. Only examinations performed in identical conditions and providing results of similar reliability can serve as a criterion for the evaluation of a multicenter trial [1]. The equipment used to assess the results should be standardized and easily available. The availability of staff and their training in conducting therapeutic trials should be similar for each center. The schedules for meal distribution, examinations and drug administration should not differ greatly. The recruitment of patients should be uniform in all centers. To do this, it is necessary to organize meetings of coordinators and investigators, most often using video tapes of patients such as recruitment.

### A common protocol

The recruitment, the way of assessing results and the assay methods for biological studies should be identical. As any difference in the interpretation of the protocol can lead to a defect in homogeneity, it should be considerably more detailed than when applied by a single center. In-depth discussions with all of the staff in each center involved in the trial are highly desirable. To increase the chances of a successful trial, the protocol should be written clearly and be as simple as possible [2].

### A coordinating center

The composition of the coordinating center team varies according to the trial but generally includes one or two clinicians not participating in the performance of the trial, a statistician, a pharmacologist and a representative of the organization that has requested the trial. There should be sufficient facilities such as secretarial services, means of calculation and easily accessible telephone lines.

The role of a coordinating team may differ from one trial to another but generally includes the following:

- Elaboration of the protocol and discussion with interested parties.
- Organization of preliminary meetings.
- Drafting of the definitive protocol.
- Motivation of the participants:
  - Legitimate desire for scientific renown, which can be satisfied by an equitable listing of the authors of a publication;
  - Equitable distribution of credits among the participants at all levels based on the portion of the work performed;
  - Advantage of belonging to a work group allowing participation in training events.
- Preparation or control of the randomization procedure, the packaging of products intended for the trial, and the binders or sheets for observations.
- Informing participants about the trial procedure.
- Centralization of data for each patient.
- Checking adherence to the protocol and noting any deviation from patient selection criteria, conduct of the treatment, dates of examinations, etc.
- Checking the recording of individual observations.
- Rejection of inadequate observations.
- In an extreme case, exclusion of a participating center because of a lack of reliable data.

### Particular situations encountered during international trials

In international trials there can be a diversity of languages and concepts. It is essential to use translations of protocols, but a reference version should exist in a language understood by all participants. Differences in nosology are sometimes involved. It is also necessary that the assessment tools be translated into the language of the investigator and that this translation be validated to be sure that it corresponds to the original. It is necessary that the intensity of the pathology studied is close to one country to another and does not depend on variations in cultural appreciation. This is the case of studies in generalized anxiety where some countries only treat severe forms with drugs.

### A wise precaution: the pre-trial

It is desirable to request each center to conduct a pre-trial relative to a few cases. This provides an idea of the recruitment of each center, the feasibility of the study as planned, the quality of the information collected, the comparability of the centers, the acceptability of the treatments and their tolerance, and, if possible, the variability of the results [3]. The great inconvenience of the pre-trial is the "consumption" of patients before the real trial begins. It is important to determine whether the expected number of patients to be enrolled at each site of a multicenter study will be sufficient for the data to stand alone statically, since data obtained from various sites may only be combined to be compatible [4].

## Analysis of the Results

Several special problems of multicenter trials should be considered [5]:

A particular element known as the center factor should be taken into account when the results are analyzed by a suitable statistical method. This factor allows intercenter variability to be deducted from residual variability, thereby improving sensitivity in the detection of differences between treatments.

It is also important to check whether differences between treatments (other than random variations) have been found in all the centers. If important differences exist, they can be revealed by a significant "treatment per center" interaction test. The cause of such discrepancies could be a difference in the initial characteristics of subjects from one center to another; an abnormal proportion of drop-outs or non-observers in one or more centers, which could be due to laxity in interpretation of the protocol or inadequate motivation of investigators in these centers; and/or a real variation in differences between treatments in one or more centers.

In practice, the "treatment by center" interaction is especially disturbing if the difference between treatments detected for the trial as a whole is actually due to a single center, or if there is a "crossover" interaction, with distinct differences and contrary findings among the centers (one treatment better than another in some centers, and the opposite for other centers). In the latter case, it is also necessary to take the number of centers into account. Finally, the number of patients recruited by each center must to be taken into consideration. Ideally, the contribution of the centers should be uniform.

### Ensuring the good functioning of clinical trials

The responsibility for the good functioning of the study is shared between the organization requesting the trial (represented by a coordinating group or a supervisor) and the team(s) involved. First of all, it is necessary to keep all the investigators participating in the trial informed by meetings, periodic visits, telephone calls, letters and mailings. The investigator should in turn inform the patients through explanations about the trial and by providing them with reminders, lists of dates and appointment times, and examination programs. The protocol must also be explained to the care staff that should be made aware of the interest of obtaining the data. The family doctor of the patient should also be informed.

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