

## Phase III Clinical trials: what methodology?

Michel Bourin\*

*Neurobiology of mood disorders University of Nantes*

Received: June 27, 2017; Accepted: August 22, 2017; Published: August 26, 2017

\*Corresponding author: Michel Bourin, Neurobiology of mood disorders University of Nantes, 98, rue Joseph Blanchart, 44100, Nantes, France, E-mail: michel.bourin@univ-nantes.fr

### Abstract

The main objective of Phase III clinical trials of medicinal products in humans is to confirm the therapeutic efficacy observed in Phase II on a large number of patients in a given disease. This is the phase from chemical to drug status.

In this article, the basis of the methodology is reviewed; in particular the choice of the experimental scheme, the calculation of the number of subjects necessary to demonstrate certain efficiency in the pathology concerned. The risk benefit ratio is considered as well as the collection of undesirable effects

**Key words:** Phase III Clinical Trials; Methodology; Risk Benefit Ratio; Drug Registration

### Introduction

Most phase II clinical trials ending with a positive outcome do not succeed in phase III, often due to serious adverse effects or lack of therapeutic efficacy, so it is necessary to perform widest trials. The main objective of phase III trials is to verify the therapeutic action of a new substance in a large number of patients, essentially to determine the risk/benefit ratio. Before phase III, the substance is not regarded as a drug, but after a positive phase III trial it becomes a drug. In fact, the drug may then be approved for registration and accepted by the authorities concerned. It can subsequently be offered to prescribing physicians on the basis of valid arguments. Phase III is thus the logical continuation of the previous phases of the drug trial in man. Its purpose is to confirm the therapeutic effects of the drug. In this respect, the notion of minimal benefit must be considered.

The objectives of phase III are the confirmation and extension of the results relative to efficacy and safe use, evaluation of efficacy and safety in the medium- and long-term, consideration of the most frequent adverse effects, and observation of other specific characteristics of the drug (e.g. drug interactions of clinical importance and factors such as age and sex that could modify the results). Phase III trials thus require a greater number of patients and often a longer treatment period.

### Methodological bases of phase III trials

These methodological bases are the classical ones for a clinical trial, insofar as it is generally controlled, with random double-blind assignments between the treatment and control groups, and includes a sufficient number of correctly analyzed patients. Although the modalities

differ depending on the substance studied, the protocol must generally satisfy certain demands:

#### **Choice of experimental scheme**

The choice of scheme depends on several factors such as the objectives of the study, the number of participants and the number of stages in the study. The scheme allows the comparison of two or more groups of patients, including a treatment group and a group receiving a placebo or treatment with a reference drug. In fact, correct evaluation of the drug effect requires comparison [1].

Among the various types of experimental schemes, the most common ones involve a study in parallel groups. In this method, the patients are randomly divided into two groups which by definition receive the planned treatment throughout the trial period. The treatment of each group is different, except in the case of crossover trials when each patient receives both compared treatments [2].

#### **Randomization**

Randomization, the method of assigning a patient to a given treatment by chance, is intended to reduce bias in the choice of treatments. If a difference is to be found between treated and untreated groups, it is essential that both be strictly comparable, except for the treatment received. Randomization is necessary, and there are several methods for performing it. However, two limitations may be noted in therapeutic trials: differences between groups are not necessarily eliminated, and the choice of a suitable method can be complicated. Randomized clinical trials serve as the standard for clinical research and have contributed immensely to advances in patient care. Nevertheless, several shortcomings of randomized clinical trials have been noted, including the need for a large sample size and long study duration, the lack of power to evaluate efficacy overall or in important subgroup [3].

#### **Blind studies**

The efficacy of treatments can be assessed differently depending on whether or not the patient knows that he belongs to the treatment or control group. To eliminate this major difficulty and maintain comparable groups throughout the study, it is necessary to implement a blind procedure: either simple blind (generally the patient does not know) or double-blind (the patient and the physician do not know).

## Statistics

The contribution of the statistician is essential. In fact, the groups represent only a sampling of the general population which can vary. Only statistical tests (with risks of first and second order) can ensure that the differences observed are meaningful. It is desirable that the power of comparison be high, so that the probability of detecting a difference between the treatments is maximal [4].

## Key elements of phase III trial

Several key points may be noted for these phase III protocols:

### **Inclusion criteria**

The inclusion criteria define the requirements for entering a patient into the trial. If the definition of these criteria is too vague, the patients included may compose a heterogeneous group, therefore making interpretation of the results difficult and thus compromising the objectives of the study. Conversely, if the inclusion criteria are too restrictive, it is sometimes impossible to find a sufficient number of patients for the study, and thus the results will be difficult to extrapolate to a larger population. Depending on the substances studied, several trials are generally conducted during phase III. During each of these different trials, a specific population can be studied (e.g. elderly persons, patients with renal failure, etc.) [5].

### **Exclusion (and non-inclusion) criteria**

Exclusion as well as inclusion criteria must be indicated in order to eliminate patients for whom the trial represents an excessive clinical risk, or those whose follow-up is uncertain, or those who would make the group too heterogeneous.

### **Evaluation (Judgment) criteria**

Evaluation criteria include outcome measurements and assessment tools designed to evaluate the efficacy, safety and tolerability of a new treatment. The choice of an evaluation criterion or criteria is fundamental to attain the objective of the study. Such criteria should be chosen in a judicious manner depending on the pathology studied. In fact, evaluation criteria are often intermediary choices [6].

### **Adverse (clinical and biological) effects**

Adverse effects should be determined by means of a questionnaire composed of closed questions organized systematically with respect to possible symptoms indicated on a pre-established list, or of open questions soliciting spontaneous complaints, or of standardized questions.

### **Number of subjects required**

The number of subjects required is decided before the trial begins and determines its length. In some cases, a multicenter study is necessary because of the large number of subjects required. However, this quite essential calculation is restrictive and complicates the trial. Studies are being conducted to try to reduce the number of subjects needed, which would be of interest to patients (the drug would be available sooner), registration authorities and manufacturers [7].

## Other information provided by phase III trials

Although the benefit-risk estimation is the major objective of phase III trials, other secondary objectives allow useful knowledge to be obtained for the prescribing physician. These include the conditions for monitoring treatment, patient characteristics requiring an adjustment of dosage, length of treatment, modalities for discontinuing treatment, the profile of the responding patient (i.e. the target of the treatment), interferences with other drugs, and optimal conditions for the dose. It is also necessary to define the criteria of efficacy. The main criterion corresponds best to what the patient expects in terms of the prognosis for survival, good health or quality of life.

## General conditions for phase III trials

### **Choice of key elements for the phase III trial**

It is essential to recognize that a very large number of evaluation criteria can apply to the same patient and the same pathologic situation. Thus, in evaluating the efficacy of an antithrombotic treatment, the main criterion could be one of the following: a change in the biological data for blood coagulation; a change in imaging data, e.g. for Doppler ultrasound; a change in phlebography data; a change in clinical data, e.g. clinical diagnosis of phlebitis; a search for complications, e.g. clinical diagnosis of pulmonary embolism or of the beginning of post-phlebitis trophic disorders; systematic imaging for pulmonary embolism, e.g. lung scintigraphy or angiography; occurrence of death by pulmonary embolism; etc.

These criteria relate to the same disease but are obviously quite different in their significance. Moreover, some can be easily demonstrated in all patients without great expense, whereas others are invasive, raise ethical problems, involve considerable expense or are only observed in a few patients. As a result, large series of patients are required. The choice of the "level" of proof provided by the main evaluation criterion is crucial. It is evident that the different key elements are directly related, since the inclusion criteria should help determine the main evaluation criterion. The number of subjects required is related to the frequency of occurrence of the event searched for and the difference expected between the groups.

The drafting of a phase III protocol should aim at obtaining total coherence among the different key elements. This coherence depends on the question which the trial is intended to answer.

### **Phase III: an "experimental situation"**

The main objective of managers concerned with drug development in the pharmaceutical industry is to convince the registration authorities in the different countries of the efficacy and safety of their new product. Phase III trials, which are important since they occupy a large part (often 3 to 5 years) of the clinical development period, should be designed to demonstrate the qualities of the new drug as clearly as possible. The experimental plan and the monitoring of patients should be conducive to this purpose. The techniques of the clinical trial (which will be described later on) constitute an "experimental situation." It is often useful to choose a very homogeneous group of patients and to establish monitoring conditions which "oblige" the patient to follow his treatment faithfully and perform the essential examinations. No patients should be included

who are likely not to respond favorably to the treatment: those who are too young or too old, sometimes those who are too severely or too slightly affected, and often those with several diseases or using several drugs, etc. In fact, the results of these trials are only valid for the population chosen and the monitoring conditions defined.

### **Other questions to be raised**

When the results are favorable for the drug studied, a series of questions still remains unanswered: Will the results observed in experimental conditions prove valid in routine therapeutic conditions?

Will the results observed in highly selected patients be similar in ordinary ones (for example, patients with an associated disease or taking a combination of drugs)?

Can the results observed during a very special type of monitoring be corroborated in routine therapeutic conditions?

Recent experiments have shown that undesirable effects observed during treatments in uninformed, non-volunteer patients, who were sometimes taking several drugs or had defects, could be much more intense than during therapeutic trials. For example, this was the case with hypoglycemic episodes in elderly subjects and gastrointestinal disturbances in subjects receiving non-steroidal anti-inflammatory drugs when the customary precautions applied in therapeutic trials were not used in routine therapeutic conditions. The safety data for certain groups at risk (elderly or very elderly subjects, persons with hepatic, renal and sometimes respiratory failure, etc.) should be evaluated in separate studies if such patients have not been included in the main trials [8].

### **Approval for drug registration**

After the phase III trial, the efficacy and the safety data of the new drug should be defined. A file, including pharmaceutical data and the results of preclinical studies and the three phases of clinical trials, should be prepared and submitted to the registration authorities of the different countries. This file should establish the major criteria: pharmaceutical quality, efficacy and safety. It should also provide answers to all possible questions concerning the choice of patients to be treated and the modalities of prescription. In practice, the file should provide all the data for the "summary of product characteristics" which appears in the official information sent to all health professionals [9].

## Conclusion

The risk of selection bias could not be ascertained for most trials due to poor reporting. Many trials which did provide details on the randomization procedure were at risk of selection bias due to a poorly chosen randomization methods. Techniques to reduce the risk of selection bias should be more widely implemented [10].

Phase III clinical trials act as more intensive extensions of the first phases of research, testing the ultimate safety, efficacy and dosage of drugs as compared to the current gold standard treatment or placebo. Dosage levels will be modified to determine the dosage that provides the most beneficial effects while offering the least negative side effects. During Phase III research, the efficacy of the drug on various levels of the disease is also tested.

## References

1. Avallone A, Piccirillo MC, Aloj L, Nasti G, Delrio P, Izzo F, et al. A randomized phase 3 study on the optimization of the combination of bevacizumab with FOLFOX/OXXEL in the treatment of patients with metastatic colorectal cancer-OBELICS (Optimization of BEvacizumab scheduLIng within Chemotherapy Scheme). *BMC Cancer*. 2016;16:69. doi: 10.1186/s12885-016-2102-y
2. Skoog G, Edlund C, Giske CG, Mölsted S, Norman C, Sundvall PD, et al. A randomized controlled study of 5 and 10 days treatment with phenoxymethylpenicillin for pharyngotonsillitis caused by streptococcus group A - a protocol study. *BMC Infect Dis*. 2016;16:484. doi: 10.1186/s12879-016-1813-7
3. Turner EL, Li F, Gallis JA, Prague M, Murray DM. Review of Recent Methodological Developments in Group-Randomized Trials: Part 1-Design. *Am J Public Health*. 2017;107(6):907-915. doi: 10.2105/AJPH.2017.303706
4. Kane RC. The clinical significance of statistical significance. *Oncologist*. 2008;13(11):1129-1133.
5. Bourin M. Criteria of patient selection in a clinical trial. *SOJ Pharm Pharm Sci*. 2017;4(3):1-4.
6. Bourin M, Garay RP. Choice of Evaluation Criteria in a Clinical Trial? *SOJ Pharm Pharm Sci*. 2016;3(3):1-4.
7. Weinberg SH, Butchart AT, Davis MM. Size of clinical trials and introductory prices of prophylactic vaccine series. *Hum Vaccin Immunother*. 2012;8(8):1066-1070. Doi: 10.4161/hv.20506
8. Bhatt DL, Mehta C. Adaptive Designs for Clinical Trials. *N Engl J Med*. 2016;375:65-74. DOI: 10.1056/NEJMr1510061
9. Vieta E, Bourin M, Sanchez R, Marcus R, Stock E, McQuade R, et al. Aripiprazole Study Group. Effectiveness of aripiprazole v. haloperidol in acute bipolar mania: double-blind, randomised, comparative 12-week trial. *Br J Psychiatry*. 2005;187:235-42.
10. Kahan BC, Rehal S, Cro S. Risk of selection bias in randomised trials. *Trials*. 2015;16:405. Doi: 10.1186/s13063-015-0920-X