Editorial comment
To stop or not to stop a clinical trial: that is the problem

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The randomized controlled trial (RCT) is currently the best method to confirm the value or to test the efficacy of a treatment, to prevent the propagation of worthless treatments or to document the harm caused by a conventionally and widely used therapy. This is the reason why we need to continue developing well conducted clinical trials to solve therapeutic uncertainty and to improve the treatment of patients. However, the design and the conduction of RCT elicit two major ethical questions: 1) the decision to enroll a patient in an RCT, and 2) the need to guarantee the safety of patients followed up for weeks, months, or even several years in a double blind condition.

Ethics of enrollment

All physicians have to deal with two conflicting duties: first, to bear in mind what is medically most beneficial for the patient and therefore to prescribe the best treatment available, and second, to support studies that will improve the treatment for his/her patient and for future generations. There is no doubt that the primary duty of a physician is to prescribe the best treatment for the patient. Nevertheless in many circumstances physicians are uncertain about the intrinsic value of a treatment, because they have no data to distinguish the relative efficacy of certain drugs. In this case they are ethically obliged not to use those drugs on the basis of non-documented information or of commercial pressure by drug companies but to promote a suitable RCT which can distinguish the relative value of the drugs in question.

Ethics of conducting a clinical trial

Since it is impossible for patients and physicians involved in a clinical study to have sufficient, updated information regarding the studied product, and they cannot personally monitor the study, they both have to rely on the knowledge and experience of someone else conducting the study. All medical research is primarily committed to safeguarding the patient's health but ethical questions can subsequently arise during the study by *interim* analyses or from emerging evidence derived from other concomitant trials. Who should assume the responsibility for patient safety?

The decision whether to interrupt a trial cannot be taken by the principal investigators leading the study (Steering Committee) since they have a personal interest in a favorable conclusion and because of the amount of time, work and credibility invested. Neither can the sponsoring company decide to interrupt a trial given that it has already invested a fair amount of human and economic resources. To protect patients from unexpected adverse effects it is common practice to establish a group of independent investigators who are neither involved in the research project nor in the sponsor company. This committee is usually called the Data and Safety Monitoring Board (DSMB) and it is responsible for the safety of current and future patients in the trial, and for patients who might otherwise use the treatment being tested[1]. In the United States DSMBs were initially recommended by the National Heart, Lung, and Blood Institute Task Force[2] while the Coronary Drug Project[3] was being designed. The

aim was to rely on an external independent committee and give advice to both the trial Steering Committee and the sponsor about many aspects regarding the progress of the trial. In order to carefully and periodically monitor the study of long-term clinical trials (4-6 years) *interim* analyses are usually conducted every 6 months to assess if any beneficial or harmful effects have emerged in each treatment arm. These data should not be available to the Steering Committee or to the sponsor, since they could redesign and adjust the protocol to conceal negative results or to enhance small beneficial effects on the basis of intermediate information. Since the primary responsibility of the DSMB is to protect the patient's interest, all its members must maintain independence from both the sponsor and the investigators and should have no financial investment in the sponsoring company. Outcome and safety data from the *interim* analyses should be reviewed in closed sessions exclusively by DSMB members, and the DSMB has the power to recommend early trial termination or protocol modifications[4,5] based on the *interim* analyses. A treatment should be discontinued as soon as an inferior efficacy/toxicity profile has been established.

To stop or not to stop

Premature interruption of a clinical trial is a general rule that can be applied to safeguard patients enrolled in the study who are blinded to the treatment and who are unable by themselves to decide whether to continue or stop the treatment. The decision should be based on two major reasons: 1) outcome data collected during the *interim* analysis showing a better or worse outcome in one of the study arms, 2) external information threatening the safety of patients followed in one of the study arms.

Regarding the first reason, trials can be stopped due to emerging beneficial or negative effects. In this case convincing evidence is required and restrictive statistical boundaries should be adopted to avoid the demonstration of a therapeutic effect based on only a few patients who benefited from the treatment simply by chance.

We have several examples in the literature of premature interruption of a trial due to manifest efficacy or harm of the study drug. The Beta-Blocker Heart Attack Trial[6] was designed to compare the effectiveness of propranolol versus placebo in reducing mortality in 3837 hospital survival cases of acute myocardial infarction. The trial was terminated 9 months before the scheduled closing date because at that time 7.2% of the propranolol treated patients had died compared to 9.8% of the placebo group (with a relative mortality reduction of 26%). The Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF)[7] was discontinued in April 1990 because of strong evidence favoring warfarin over placebo in the treatment of 420 patients with non-rheumatic atrial fibrillation.

On the other hand the Cardiac Arrhythmias Suppression Trial (CAST)[8], aimed at evaluating the effect of three antiarrhythmic drugs (flecainide, encainide, and moricizine) in patients with asymptomatic ventricular arrhythmias, was terminated because of emerging harm in the flecainide group. After 2 years the *interim* analysis revealed an excess of mortality (7.7% in the flecainide group and 3.0% in the placebo group). Very recently, the arm of patients treated with doxazosin was interrupted in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[9], which evaluated four types of drugs (chlorthalidone, doxazosin, amlodipine, and lisinopril) as first line treatment for hypertension in 24 335 patients with hypertension and at least one other coronary heart disease risk factor. Mortality rate was similar in the doxazosin and chlorthalidone group but the incidence of congestive heart failure had doubled (relative risk 2.04; 95% confidence interval 1.79 to 2.32). Since no other differences emerged among the other treatments the trial is still ongoing to evaluate the relative efficacy of the three remaining drugs.

Sometimes trials are stopped improperly. For example, the Cardiac Arrest Study Hamburg (CASH)[10] was aimed at comparing the incidence of sudden death, cardiac mortality, and total mortality among four treatments (amiodarone, propafenone, metoprolol, and implantable cardioverter defibrillator). The study was stopped because in the propafenone group the mortality rate was similar, but an excess of non-fatal ventricular fibrillation and of ventricular tachycardia was observed. Since not enough strict criteria were adopted to evaluate the statistically significant level uncorrected by multiple comparisons, the conclusion that propafenone is less effective could be regarded as a false positive result. Based on the partial data obtained from the trial there is no proof that propafenone is less safe than the other treatments; the completion of the trial would have probably led to a better understanding of the relative effect of the studied drugs.

Sometimes sponsoring companies put pressure on the DSMB to stop a trial on commercial rather than scientific grounds[11] when they feel that the results are unlikely to reach a statistical and demonstrable conclusion. Unfortunately sponsor decision is increasing rapidly because long-term clinical trials are becoming much more expensive and the sponsor tries to avoid further investments in studies unlikely to produce positive results. In similar cases the DSMB has the right and the duty to continue the trial to the predefined end because it is not infrequent that only after an adequate follow-up the survival curves of treated and placebo patients diverge.

To stop due to external evidence

Finally, a study can be stopped because of external evidence which emerged during the study. This is the

case for the second part of the GISSI Prevenzione study published in this issue of the *Italian Heart Journal*[12] in which 4271 patients 6 months after acute myocardial infarction with total cholesterol levels > 200 mg/dl were randomized to low-dose cholesterol treatment (pravastatin 20 mg daily) or no treatment. When the GISSI Prevenzione study started in 1993 there were several data demonstrating the effectiveness of HMG-CoA reductase inhibitors to reduce high levels of serum cholesterol, but no strong evidence that in the long term they could reduce mortality and ischemic events. Thus, it was ethical to randomize patients with cholesterol levels > 200 mg/dl to pravastatin or placebo. The following year the results of the 4S study were published[13]. The study was conducted in middle-aged patients with coronary artery disease and cholesterol levels between 210 and 310 mg/dl. After 5.4 years of treatment total death decreased from 12% in the placebo group to 8% in the simvastatin group (30% relative risk reduction) and the combination of major coronary events decreased from 28 to 19% respectively (34% relative risk reduction). At that time it was unethical to continue to treat high serum cholesterol patients with placebo and a first amendment was suggested by the DSMB and approved by the Steering Committee: only patients with cholesterol levels < 250 mg/dl could be randomized and each cardiologist was free to decide whether or not to treat a patient with higher cholesterol values. In 1996 the results of another large and well conducted clinical trial which enrolled patients with previous myocardial infarction randomly assigned to receive 40 mg daily of pravastatin were published[14]. In this study also patients with low-moderate blood cholesterol levels (< 240 mg/dl) were included and the frequency of fatal coronary events plus non-fatal infarctions was reduced by 24% in the pravastatin treated patients. At that point many GISSI investigators felt no longer ethically uncertain as they knew that pravastatin was more effective than placebo and thus they were unwilling to continue treating half of the patients with placebo. The DSMB and the Steering Committee decided to close the second randomization of the study. In this issue of the *Italian Heart Journal* the data collected up to the interruption of the hypocholesterol treatment are presented and the description of the motivations that led the Steering Committee to stop the trial are fully described. There is no doubt that both decisions were correct because the trial was conducted during three different periods in which the knowledge of the effect of lipid-lowering therapy varied. The investigators modulated the trial in accordance with the available growing evidence based on published information.

Conclusion

From the examples discussed in this article it is clear that an independent DSMB is an essential mechanism to safeguard the health of patients and to guarantee patients and physicians on the ethical conduction of a clinical trial. In many circumstances the decision to stop or not to stop a trial due to its efficacy or harmful effects is a very difficult task. External scientific interests and economic pressures can forcibly bring about an independent resolution but the interest of present and future patients, of physicians and of developing science should become the foundation of any decision. Any other interference should be banned.

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