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Review

Ethics in clinical research☆

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R&D of new drugs is driven by pharmaceutical companies that invest considerable amounts of money for this purpose. This may introduce bias, to emphasize the clinical value of drugs to be allowed onto the market. Bias is caused by methodological flaws including the population under study, the choice of inadequate comparators or of their dosage, the adoption of surrogate or composite endpoints, the decision to publish mainly positive findings or to overlook some safety concerns, etc. All this happens in a legal context that requires no added value for new drugs to be approved for the market. This encourages the use of placebo even when active comparators are available, or the search for non-inferiority of new products in comparison with active comparators. Superiority over placebo and non-inferiority to active comparators may allow drugs onto the market that are in fact less active (or safe, tolerable, convenient, etc.) than those already available, usually with consolidated properties and lower costs. In addition, they do not meet patients' or physicians' needs of defining the place in therapy and respective roles of new and available treatments. The current legislative and regulatory setting seems designed to meet commercial interests rather than public health needs.

***Keywords*: Clinical research; Clinical trials; Ethics; Clinical methodology**

1. Introduction

Planning, conducting and concluding clinical trials has always been a matter for ethical discussion because patients may risk receiving treatments that are not always potentially in their interest. A vast amount of literature deals with the principles for recruiting patients for clinical studies, who are free to participate and can withdraw at any time. Trials with patients such as prisoners who were obliged to participate, or studies done in developing countries without adequate external control have been condemned. Although there is always a need for active vigilance the ethics of clinical trials today is essentially confined to the preparation and conduct of the protocol because the results can be considerably influenced by apparently minor details. These details require attention considering that most clinical trials are supported, executed and analyzed by pharmaceutical companies which have an obvious conflict of interest in testing new drugs whose development has incurred considerable expenditure. Clinical trials that require thousands of patients have a high cost, sometimes running to hundreds of millions of euros. Possibly unintentionally, this may introduce bias that affects the outcome of the study. There is also a substantial gap between the capacity of industry to utilize experts in clinical trial methodology and the specific knowledge of the members of the ethical committees responsible in many countries for approval of the protocols. This article underlines some of the biases in the scientific literature concerning phase 3 randomized controlled trials (RCT).

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Abbreviations: RCT, randomized clinical trial; EMEA, European Medicines Agency; EU, European Union; DMARD, disease modifying anti-rheumatic drugs; Hb A1c, glycosylated hemoglobin; FDA, Food and Drug Administration; HDL, high-density lipoprotein; SSRI, selective serotonin reuptake inhibitors.

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The present European legislation works in favour of the pharmaceutical industry for several reasons. The European Medicines Agency (EMEA), which approves new drugs and follows them on the market for all the Member States of the European Union (EU) depends – unlike most single countries – on the Directorate of Industry and Enterprise, suggesting that drugs are considered more as consumer goods than tools to cure diseases. Perhaps it is in relation to this link that the EU legislation establishes that new drugs must be required only to prove quality, efficacy and safety, as if they were in a therapeutic vacuum. It is therefore not required to make comparisons with drugs already available for the same indication [1]. In other words new drugs may well be less useful than the ones already on the market because the legislation does not ask for any "added value". Finally, the entire dossier for the approval of new drugs or for the extension of indications is assembled by the industry, which has a direct interest in predominantly stressing favourable effects. The public or its representatives have no chance to consult the dossier because the entire procedure is secret, thus penalizing the rights of the patients who have made themselves available – even with some risk – for clinical trials. This and other aspects of the EU legislation are responsible for several biases that have come to light in phase 3 RCT.

2. The excessive use of placebo

The Helsinki declaration states that placebo should be used only when there are no effective drugs for a given indication. However, this ethical requirement is not followed in many conditions. For instance in trials with an add-on design one of the two arms receives the new drug and the other a placebo, while both are given an effective drug that is already available which, as such, cannot be omitted; this is acceptable if there is no previous study showing that another drug has already shown a beneficial effect for the same indication with the same design. The RCTs of new anti-TNFα or other so-called disease modifying anti-rheumatic drugs (DMARD) is paradigmatic: they are added to methotrexate in comparison with placebo even though other drugs are already known to act synergistically with methotrexate [2]. Another example is in diabetes. Exenatide has been found to be more active than placebo in patients treated with a glitazone and metformin in lowering fasting plasma glucose and glycosylated hemoglobin (Hb A_{1c}) [3]. This design has exposed diabetic patients treated with placebo to useless risk. A fair comparison would have been to use one of the many antidiabetic agents available on the market instead of placebo.

It is warrying that the FDA has recently refused to accept the Helsinki declaration, stating that placebo is necessary for scientific reasons even if comparators are available [4], arousing protest from clinical investigators [5]. Practically, the EMEA is on the same line even if there are no official statements. This attitude, which is ethically unacceptable, is essentially dictated by the refusal to consider added value as mandatory for all new drugs. In fact only if the design of a RCT is based on superiority is there no need for a placebo arm.

3. Design of clinical trials

There is an increasing tendency to utilize non-inferiority designs for RCT. In a recent analysis of anticancer agents approved by the EMEA, out of 21 approvals for a new indication only nine cases had a phase 3 RCT but in six cases the design was of non-inferiority [6]. This design cannot establish the drug's real role in the therapeutic armamentarium [7] and therefore it is ethically questionable to exploit patients when the sole purpose is to obtain a slice of the market [8]. Those supporting non-inferiority trials argue that patients do not always respond to the same drug and therefore it is useful to have other drugs even if they are less active. However, the answer to this is to select patients unresponsive to a given drug and then to carry out a superiority trial with the new drug versus placebo.

Others consider that a drug may have a better toxicological profile while being non-inferior in terms of efficacy. This could be clarified better by a superiority trial addressing safety, although the real toxic profile of a drug only becomes evident once it is on the market. Others consider that non-inferiority trials may be justified when a drug could lead to better compliance. However, better compliance has less meaning if does not result in a better outcome, to be tested by a superiority trial. A discussion of the ethical aspects of non-inferiority trials is available [9].

In addition, what is presented as equivalent is frequently an excuse not to look for a difference [10,11]. Moher et al. [12] reported that in 64 percent of 383 RCTs a difference in efficacy could be detected only if it was more than 50 percent more or less than the comparator and in 84 percent of cases only if the gap was more than 25 percent.

Fortunately, there have been some reactions from the regulatory agencies in respect to non-inferiority trials recently. The FDA declared that antibiotics studied with non-inferiority designs will not be accepted for approval [13]. EMEA in its guidelines advises that non-inferiority trials will not be accepted anymore for anti-Parkinson and anti-Alzheimer indications [14,15].

4. Inclusion and exclusion criteria

The inclusion criteria for most RCT give priority to young males. Women, children and the elderly are

frequently excluded from RCT because they pose problems in terms of their sensitivity to adverse reactions [16]. However, older patients in particular are the ones receiving the majority of drug prescriptions. Rochon et al. [17] found that out of 9664 patients in RCT dealing with osteoarthritis and rheumatoid arthritis only 2.1 percent were over 65 years and only 14 patients were older than 75 years. In a Health Technologic Assessment report [18] concerning the use of bevacizumab and cetuximab in metastatic colorectal cancer, patients included were 5–10 years younger than the UK population bearing this disease, raising doubts about the generalizability of the results. Similar considerations hold for children, who are usually treated with doses adjusted according to the body weight established in trials in adults, ignoring the fact that a growing body has reactions that are likely to be different from adults. It is worrying to consider that about 50 percent of drugs currently prescribed to children or adolescents have never been studied in a RCT [19].

5. Inadequate comparators

When new drugs are compared with drugs already available for the same indication the ethical requirement is that the selected comparator must be the best available and must be utilized at an optimal dosage and schedule. This is not always the case. A well known example of the choice of comparator was the new cyclooxygenase-2 specific inhibitors, studied as anti-inflammatory agents. The selection of diclofenac as a comparator masked the cardiotoxicity of rofecoxib while the choice of naproxen would have revealed this important adverse reaction [20].

Mycophenolate, presented as a considerable improvement for the treatment of organ rejection [21], was recently found to be comparable to the older drug azathioprine in terms of efficacy and safety, though not price [22]. For the same indications tacrolimus was found more active than ciclosporin [23] but, on measuring the trough concentration of ciclosporin, Schieppati et al. [24] found that the doses utilized were not able to reach what is considered the optimal concentration.

The new atypical or second-generation antipsychotic agents are usually considered to show an advantage over haloperidol in terms of extrapyramidal effects, but Geddes et al. [25] found this happened only when the dose of haloperidol exceeded 12 mg a day. The claimed superiority of atypical or second-generation antipsychotic drugs over the older drugs of this class is no longer true in the light of a meta-analysis of 150 randomized trials [26].

This analysis found that as a group the second-generation antipsychotics were no more effective, did not improve specific symptoms, and had no clearly different side-effect profiles from the first-generation drugs, and were also less cost-effective. Therefore, the ''atypical'' antipsychotics are now regarded as an ''invention only'', manipulated by the drug industry for marketing purposes [27].

These examples illustrate vividly how the choice of comparator and its dosage can considerably influence the outcome of a test drug in terms of toxicity or efficacy.

6. Surrogate end-points

Quality of life, morbidity and mortality should always be the primary hard end-points for evaluating new drugs because these outcomes reflect significant therapeutic benefits. However, in some cases an end-point that closely correlates with a hard end-point can be used as a surrogate although the therapeutic efficacy must always be proved.

Because of the long duration and the consequent cost of a therapeutic RCT there is a tendency to abuse surrogate end-points, which may be misleading. For instance encainide and flecainide decrease arrhythmias but increase mortality [28]. Estrogens were supposed to be cardioprotective in menopausal women because they increased the surrogate end-point high-density lipoprotein (HDL) cholesterol [29]. However, large RCT have not been able to demonstrate any prevention of cardiovascular events [30]. Torcetrapib was also quite active in raising HDL-cholesterol but unfortunately the drug increased mortality [31]. Sulfonylureas lower glycosylated hemoglobin but increase the risk of myocardial infarction [32].

In these cases an effect on a surrogate end-point does not result in a therapeutic advantage. Similarly, an effect of anticancer agents on tumour size is not always predictive of an increase in overall survival, because of the possibility of adverse reactions. This is because a drug does not have merely a single beneficial effect but a number of side effects too which may counteract the benefits.

Finally, the use of surrogate end-points as an outcome for drug approval is unethical when there are already drugs on the market for the same indication which have already proven their clinical efficacy. A case in point is the approval of atorvastatin and rosuvastatin on the basis of cholesterol-lowering activity when simvastatin and pravastatin were already known to have beneficial effects on cardiovascular events and mortality.

7. Composite end-points

Since the efficacy of some drugs has already reached a high level, proving that a new drug is superior would require too large a population and too many years so

it is becoming current practice in RCT to utilize composite end-points [33], meaning adding in different events as outcome measures. For example, in the cardiovascular area it is possible to add myocardial infarction and revascularization procedures to mortality. However, it would be misleading to claim this composite end-point if revascularization procedures were more common outcomes than death or infarction or – even more – if the new drugs had a large effect on revascularization but not on death or infarction.

A typical example is a trial on clopidogrel where the composite end-point was significant only for coronary artery occlusion, but not for recurrent ischemia or death [34]. Ferreira-Gonzales et al. [35] analyzed a number of cardiovascular studies where composite end-points represented the outcome. By stratifying the component of the composite end-points on the basis of their importance for patients it was found that the contributions of minor or moderate categories were driving the significance of the composite end-points.

The DREAM trial of rosiglitazone in the prevention of diabetes in patients with impaired fasting glucose or glucose tolerance (or both), adopted the composite primary outcome of diabetes or death [36]. The primary outcome was statistically highly significant, although there was no difference in deaths in the groups (1.1 percent in the rosiglitazone group and 1.3 percent in the placebo group). Following standard practice, the FDA would react to an application for extension of the marketing authorization by granting authorization for the composite outcome but this would wrongly endorse the idea that mortality was reduced.

8. Selective publication

The perception of drug efficacy is misled by publication selectivity because positive trials have about three times more chance of being published than negative ones [37]. Melander et al. [38] found that out of 42 studies evaluating antidepressant agents acting on serotonin (SSRI) only 25 were published and of these 19 reported positive results and only six negative ones. It is clearly difficult to obtain objective information if negative data are not reported.

Melander's findings were indirectly confirmed by a recent analysis by Kirsch et al. [39]. These authors had access to all the studies deposited at the FDA, published and unpublished, showing that SSRI are active only on severe depression and not in mild depressive conditions, though this is not evident from the scientific literature.

Selective reporting of RCT may bias meta-analyses, creating a favourable impression of drug efficacy, and may misdirect guidelines based on published results. There is also selective reporting on the outcome of clinical trials [40] as shown by an analysis of 122 journal articles concerning 3736 outcomes; 50 percent of efficacy and 65 percent of harmful outcomes were reported incompletely.

9. Selective reporting of adverse reactions

Atypical antipsychotics were presented as an improvement over phenothiazines and butyrophenones because they were less likely to induce extrapyramidal effects. This was the basis for the rapid increase in their prescriptions. However, subsequent independent investigations provided evidence that atypical antipsychotics cause weight gain and can raise blood cholesterol and glucose and glycosylated hemoglobin – all important risk factors for cardiovascular diseases and diabetes [41].

In another field coxibs were considered better anti-inflammatory agents because of their lower gastrotoxicity [42]. It took several years for it to become clear that coxibs caused increases in myocardial infarction and heart failure [43]. Even the reduced gastrotoxicity could not be confirmed. Ironically, because of physicians' confidence in coxibs, English hospitals saw an increase in cases with gastrointestinal bleeding. Eventually these drugs were withdrawn by the industry, not by the FDA or EMEA.

10. Conflict of interest

There is no need to stress this point because conflict of interest is a source of other biases. It is sometimes worrying to see that most papers include long lists of disclosure of possible conflicts of interest, sometimes longer than the abstract. Kjaergard and Als-Nielsen [44] pointed out that RCT significantly favoured experimental interventions if financial competing interests were declared; other competing interests were not significantly associated with their conclusions. Cho and Bero [45] and Baker et al. [46] reached similar conclusions. Wilcock et al. [47] found that galantamine was better than donepezil in alleviating symptoms of Alzheimer disease, while Jones et al. [48] found the opposite. The superiority of one drug or the other corresponded to the producer that supported the study. However, an independent RCT (AD2000) questioned the activity of donepezil in Alzheimer disease [49].

The independent ALLHAT study on antihypertensive agents showed that α-adrenergic inhibitors had a less favourable benefit-risk ratio than other anti-hypertensive drugs, and the old diuretics proved better than more recent drugs [50].

11. Concluding remarks

RCTs are still the best way to assess the efficacy and safety of new drugs in order to find their place in

therapy. The huge profits from the sales of pharmaceutical products and the dominance of marketing in "big pharma" tend to introduce biases in planning, conducting and evaluating new drugs, with the complicity of the European legislation. It is therefore important to change the location of EMEA which should be under the umbrella of the General Direction of Health and Consumers, to abolish the confidentiality of pharmacological and clinical data and to introduce the concept of added value in approving the marketing of new drugs. More independent research is needed, supported by public resources, to challenge results of industry promoted trials. Drug approval should not rely solely on data produced by the pharmaceutical industry. A recent BMJ editorial suggested that at least one pivotal phase 3 study should be carried out by clinicians independent of pharmaceutical companies [51].

Measures are needed to encourage physicians to look critically at papers with long lists of possible conflict of interest, and to pick up signs of bias in RCT. Similarly, ethics committees should be more critical in evaluating protocols, not approving those designed purely to support commercial interests rather than the needs of patients. Scientific societies should also pay more care when issuing guidelines to the problem of selective publication. RCTs should be required to ask important clinical questions which cannot be answered by surrogate end-points or non-inferiority designs. With a more critical approach industry would be obliged to produce new drugs with added value while National Health Services with a better understanding of biases will be able to gauge the value of drugs better and will have a broader base for deciding on their reimbursability.

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