DOI:10.1111/j.1365-2125.2004.02184.x

Editors' view

What is a clinical trial?

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Defining clinical trials

What is a clinical trial? Here's a definition from section 31 of the Medicines Act of 1968:

> An investigation or series of investigations consisting of the administration of one or more medicinal products of a particular description . . . to one or more patients . . . where . . . there is evidence that medicinal products of that description have effects which may be beneficial to the patient or patients in question and the administration of the product or products is for the purpose of ascertaining whether, or to what extent, the product has, or the products have, those or any other effects, whether beneficial or harmful.

But, as Abraham Lincoln said in his State of the Union message to Congress in 1862, the dogmas of the quiet past are inadequate to the stormy present. He was talking about slavery, but his remarks could equally apply to clinical trials, in view of the new definition in the Clinical Trials Directive of the EC [1, 2]:

> 'clinical trial': any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy.

An unsatisfactory definition. But before considering why, and its implications for academic medicine, consider two other definitions in the Directive:

> 'non-interventional trial': a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorization.

> 'investigational medicinal product': a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.

So, what types of studies are encompassed by these definitions?

Randomized controlled trials

The Directive covers all randomized controlled trials (RCTs), whether placebo-controlled or comparative, designed to determine the beneficial and adverse effects of a drug, whether in patients or healthy subjects. Healthy subjects were not mentioned in the Medicines Act definition; under the old rules, doctors and dentists conducting clinical trials on their own patients, and not on behalf of a third party, were exempt from the requirement to have a clinical trials certificate for an investigational product. However, studies in healthy subjects do come under the banner of the new Directive and are not exempt from its strictures.

Studies in which drugs are used to probe physiological or pathological systems

Suppose I want to study the sodium–lithium countertransport system in patients with hypertension, by measuring the disposition of an oral dose of lithium chloride

[3]; does that count as a clinical trial? Well, fortunately it doesn't, since the use of a drug to probe pathophysiology is different from discovering or verifying a pharmacokinetic or pharmacodynamic effect. But suppose I want to use an inhaled leukotriene with and without pretreatment with a new leukotriene receptor antagonist as part of a study on airways pathophysiology in asthma. That could be interpreted as a clinical trial under the new definition.

Observational studies

Case-control studies, cohort studies, and other types of observational study are non-interventional and should not be covered by the Directive. But the Directive's definition of a 'non-interventional trial' specifies authorized indications. So, if I want to study the use of amitriptyline in depression, that's all right. But if I want to carry out a case-control study in nocturnal enuresis, for which amitriptyline is not licensed, that's a clinical trial as defined by the Directive and is not covered by the definition of 'non-interventional'. Actually, the term 'non-interventional' in the Directive doesn't mean non-interventional at all; it refers to an intervention with a licensed medicinal product. It would be ludicrous if non-interventional studies of unlicensed uses of drugs were classed as clinical trials for the purposes of the Directive, but that seems to be the case. Will other types of epidemiological studies also be covered if they involve patients who have taken drugs for unlicensed indications? That would hit record linkage studies, studies involving databases such as the General Practice Research Database, and Prescription Event Monitoring.

N-of-one studies

An n-of-one study is a randomized, controlled, crossover comparison of different treatments, in principle no different from any other RCT. Now, some patients taking SSRIs experience electric shock sensations in the head [4]. Suppose I hypothesize that this symptom, which has also occasionally been reported by patients taking monoamine oxidase inhibitors [5], can be relieved by pyridoxine [6]. This is an uncommon adverse effect; if I have only one patient who complains of it, I can give that patient pyridoxine in an uncontrolled study and see what happens. But a placebo-controlled n-of-one study would have to comply with the Directive.

Pharmacokinetic and pharmacodynamic studies

The Directive specifically covers such studies, and the wording suggests that drug interaction studies are included. Suppose I'm interested in the interaction of two licensed products, and want to perform a randomized controlled study in healthy subjects. Although the products will be licensed, I shall not be using them for their licensed purposes – it will be as if they were 'investigational medicinal products'. So it seems that all drug interaction studies will be covered by the Directive.

Reporting clinical trials

Which brings me to a paper in this month's *Journal*. Mills *et al.* (pp. 61–5) have studied the extent to which RCTs published in four clinical pharmacology journals adhered to the criteria of CONSORT – the Consolidated Standards of Reporting Trials [7, 8]. But, surprisingly, they did not define the term 'randomized controlled trial'. They simply picked all the published reports that included the word 'random' or its variants. Thus, they included studies for which the CONSORT criteria were not designed, such as pharmacokinetic, pharmacodynamic, and drug interaction studies – when reporting the results of such studies some of the CONSORT criteria are otiose, such as analysis by intention to treat and flow diagrams.

Equally surprisingly, there is no definition of RCTs in CONSORT itself. Mills *et al.* call for clinical pharmacology journals to sign up to CONSORT, but that cannot happen until the studies to which CONSORT applies have been defined.

However, they do make an important point. If not CONSORT, then there should be some criteria for studies that we publish. We have already adopted PHARMA, a proposed set of criteria for publishing case reports of suspected adverse drug reactions (see the instructions to authors). We now hope to make a start on developing criteria for publishing population pharmacokinetic studies.

The definitions cited above from the Clinical Trials Directive are unsatisfactory and will adversely affect academic studies, although it is not yet clear how the Directive will be interpreted in the UK by the Department of Health and the MHRA. The definitions need to be revised; in particular we need to decide what is meant by a clinical trial. Perhaps we should have stuck to the dogmas of the quiet past.

References

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