Statistics in Question

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ASSESSING CLINICAL TRIALS— TRIAL DISCIPLINE

In this article several questions about trial discipline are raised that must be answered satisfactorily before the clinical study begins. It is important to decide whether a fixed-dose or a variable-dose regimen is appropriate—they are different treatments—to realise that including a vehicle treatment (or placebo) may be unethical and is not a necessary part of clinical trial methodology. Consideration should be given to ways of enhancing or monitoring compliance with treatment and follow-up of patients. The routine for examining patients should be carefully determined and, when appropriate, a time table drawn up. Intraocular pressure, for example, shows diurnal variation and so should be measured at fixed times by one tonometrist. Blood pressure should also be recorded under standard conditions—for example, sitting blood pressure after two minutes' sitting and specified cut-off for diastolic pressure.

Fixed or variable dose

(33) *Investigators are tempted to compare fixed-dose regimens merely to facilitate double-blind comparison of treatments. When should this temptation be resisted?*

—when there is considerable variation between patients in the dosage required to produce a therapeutic effect

—to avoid getting answers to clinically trivial questions

COMMENT

This temptation should be resisted when a considerable variation in the dosage between patients is required to produce a pharmacological effect. For example, in diabetes the dose is tailored to the patient's need, and so should it be also in a clinical trial; otherwise, as Ritter¹ suggests, we risk getting "highly reliable answers to inherently trivial questions." For practical purposes in clinical trials comparisons should be made between treatments that are optimally prescribed.² Only then is the relevant clinical problem tackled. It will not do to alter the prescription of one drug to bring it in line with another to force double-blind comparison if by modifying the regimen you interfere with the drug's effectiveness. In such circumstances double-blind comparison must be abandoned, and clinical importance takes priority. Arrange for an independent blind assessment when the differences between treatments cannot realistically be concealed from the patient. Fixed regimen has been criticised in electroconvulsive treatment³ and in the use of

beta-blocking drugs¹: investigators valued double-blind comparison too highly, perhaps with the loss of therapeutic activity.

Placebo treatment

(34) *When is the inclusion in a clinical trial of a placebo treatment justified?*

—when there is no recognised proved management for the disease, and in addition a non-specific psychological effect is suspected or observer bias is likely

COMMENT

The pragmatic view of a clinical trial is that the control arm should be an accepted treatment for the disease in question. Only then do the results of the trial answer the relevant clinical question: "Does the new treatment improve on a standard method?" The explanation that a new drug is better than no treatment may interest drug regulatory authorities but has no practical implication for the treatment of patients.⁴

To include an untreated group or a sham or inactive treatment group, or both, in trials that ask a practical question about how to treat—that is, in pragmatic trials—is warranted only if there is no recognised proved management for the disease. If so, and a non-specific psychological or psychophysiological effect is

suspected or observer bias is likely, a group treated with placebo should be included as well as or instead of untreated patients. Schwartz *et al*⁶ referred to an example that showed how readily a doctor's expectation was translated into "fact." An astonishing response to a new drug was noted in a patient with asthma for whom other treatments had been tried without success. There was a consistently poor response when a placebo was substituted for the new drug. No one was more surprised than the doctor who, having written to congratulate the drug firm, was informed that they had supplied him only with placebo.

Deliberate denial of an effective treatment is wrong unless patients give fully informed consent to it and there is also ethical

approval (conditions which are rarely met). The accusation that the only justification for many of the placebo trials that are reported is the speed with which the statisticians can be satisfied is equally wrong!

Although much ingenuity is channelled into preparing sham inert treatments occasionally there is an unfortunate error, as when lactose powder—"a nutrient substrate eminently utilisable by large-bowel organisms"⁶—was chosen as a placebo in a trial to compare methods for reducing postoperative wound infection.

Order of examination

(35) *What is wrong with the procedure illustrated?*

—the same doctor first interviews the patient and then performs an endoscopy

—the second assessment may be biased by the information he has got from the interview

COMMENT

The same doctor first interviews the patient and then performs an endoscopy. The information about symptoms and the patient's perception of how successful treatment has been may thus prejudice the endoscopic findings. The doctor may see what he expects to see. A better arrangement is for one doctor to take the patient's history and a second doctor, who has not read these clinical notes, perform the endoscopy, so that the second assessment is independent of the first.

In a study⁷ of symptoms in middle life special care was taken not to mention menopause in the first questionnaire, which asked about whether some 40 different symptoms had occurred. The covering letter said merely that the study was concerned with the health problems of men and women of working age. The second questionnaire, sent about eight weeks later, investigated family, social, and gynaecological matters and treatment and so contained material that might have biased responses to the first questionnaire if the two had not been separated. Bias was the eighth of 13 mortal sins of clinical assessment.⁸

Two other faults are change of assessor and change in the time of assessment. The first, and usually also the second, should be determined in the list of the trial procedures. In the Northwick Park trial of electroconvulsive treatment (ECT)⁹ treatments were given on Tuesdays and Fridays. Patients who began their course of ECT on a Tuesday were rated on five consecutive Mondays, and those who began their course on a Friday were rated on five consecutive Thursdays. In a trial on essential hypertension¹⁰ patients were examined at a fixed time of day and instructed to take their tablets at the same time each day. In such studies blood pressure should be measured by the same observer throughout and the procedure carefully defined.

Compliance

(36) *What steps can be taken to enhance treatment compliance or to monitor it, or both?*

—simplify instructions

—use a calendar pack (for example, oral contraceptives)

—practice (for example, how to use inhalers)

—use a diary card as a reminder

—return unused drugs

—observe (spectacles worn?)

—analyse blood or urine samples (spot checks)

COMMENT

Simplifying the regimen, provided that this is consistent with pharmacological activity, minimises errors of comprehension and errors of memory. Prescribing medication once daily or timing doses to correspond with mealtimes or other regular activities helps¹¹; training patients before discharging them how to use their medicines—for example, inhalers—providing labels that are easy to read and convenient packaging—for example, calendar packs—and providing a diary card make it simpler for the patient to adhere to the prescribed routine. Unpleasant taste or smell may inhibit compliance. Liquid and tablet De-Nol were compared¹² for efficacy and acceptability in the treatment of duodenal ulcer.

In an explanatory clinical trial, which is devised to answer a question about the therapeutic activity of a particular regimen,

Diary card			
Day	Time	Dose	Check
Mon (18.5.81)	8am	2 tablets	✓
	6pm	1 tablet	✓
Tues (19.5.81)	8am	2 tablets	✓
	6pm	1 tablet	
"	"	"	
Sun (24.5.81)	8am	2 tablets	
	6pm	1 tablet	

compliance with that regimen is important and should be checked. A different question is whether the regimen is efficient in practice, when inevitably patients vary in compliance. This second pragmatic study does not differentiate at analysis between those patients who comply strictly and those who lapse, though it still may be important to measure the degree of compliance and observe the disease and other characteristics of patients who fail to follow instructions.

Treatment compliance may be monitored by asking patients to bring their medicines with them for inspection when they attend the clinic, and by asking them to return all unused trial drugs. Patients may easily dispose of an incriminating surplus if they have a mind to, of course. But the results of even such a naive check may be startlingly informative—for instance, the patient who knows that the doctor has changed the tablets because they don't float when they are flushed down the lavatory. Peckham *et al*¹³ found that 17% of children who had been prescribed and needed spectacles were not wearing them when they attended for an eye examination. The true proportion of non-users is likely to be even higher.

A more reliable monitor is the analysis of blood or urine samples. Elwood and Sweetnam¹⁴ compared aspirin versus placebo in preventing secondary mortality after myocardial infarction. Additional home visits were made without warning and a urine sample requested to measure salicylate. The results suggested that the compliance rate was at least 72% (due consideration was given to false-positive and false-negative rates).

Lionel and Herxheimer have produced a check-list for assessing reports of therapeutic trials¹⁵ in which they include monitoring of compliance.

(37) *What can be done to minimise the loss to follow-up of patients in a clinical trial?*

—careful definition of the study population in the first instance

—issue reminders when appointments are missed

—avoid unnecessarily lengthy or complicated forms

—maintain enthusiasm for the trial

COMMENT

The proportion of studies in which patients are lost to follow-up or withdrawn in retrospect is high. In 20 out of 38 clinical trials reported in the *Lancet* from July to December 1977 patients were withdrawn or excluded because follow-up had lapsed. Loss to follow-up and withdrawal of patients from a clinical trial may be minimised by (a) a careful check on the eligibility of the patient to enter the trial before registration; (b)

restriction of the study population (and hence also restriction of the implications of the trial) to patients for whom examinations for the clinical trial are not a serious imposition either domestically or physically; (c) the diligent issue of reminders when appointments are missed. It is also the responsibility of the trial co-ordinator to know as early as possible about lapses in the trial procedures and to report these at meetings of trial participants so that corrections may be made. Nothing is more destructive of enthusiastic collaboration than for doctors to be faced with unnecessarily lengthy or complicated recording forms, which are time consuming to complete. Simplified trial procedures that are discussed and agreed before the trial starts and verified in pilot studies do much to ensure co-operation and follow-up. In multicentre trials visits to the centres by the trial co-ordinator are more effective than sending impersonal progress reports.

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