Statistics in Question

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ASSESSING CLINICAL TRIALS— PROTOCOL AND MONITORING

The question of whether a patient is eligible for a clinical trial is resolved by the doctor checking through the list of entrance requirements to be met—diagnostic tests, clinical state, previous treatment, other disease. The doctor should also ensure that there is no reason specifically to exclude the patient because of treatment preference, contraindications, or possibly biased response (see question 42). A good practice is to keep a log of all patients who satisfy the trial diagnosis, and against each name register either clinical trial number or the entrance requirement or exclusion clause that debarred the individual patient. In this way the investigators define the class of patients about whose treatment inferences will be made from the trial results and also estimate the proportion of patients that this class represents of all the patients who satisfy the diagnostic criteria.

As a general rule entrance criteria should be less restrictive when the aim is to compare treatment policies and so reach a practical decision about how to treat than if the trial has an explanatory purpose, such as discovering how treatments work. A good discussion on this point is given by Mosteller *et al.*¹ Moreover, in practice the entrance requirements will usually be tailored to ensure that patients are followed up completely and considerately. Thus there may be an age barrier, or patients may be excluded because they have other disease, because their life expectancy is shorter than the study period (except, of course, when survival is the endpoint of the trial), because they are not mobile, or because their families cannot cope adequately. The rules should be simply defined, agreed by the participating doctors and interpreted uniformly by them. Investigators should recognise that limiting the study population also limits the generality of their findings.

Besides defining the entrance criteria the trial protocol gives details of design, randomisation, checks that will be made on how the study is being conducted, and how data will be handled. But the protocol is important for another—sometimes forgotten—reason. It sets down the comparisons between treatments that the investigation has been designed to make, thereby setting them apart from hypotheses that are suggested after the trial results are known. The analysis should be thought through when the design of the clinical trial is being considered. This outline analysis is then written into the protocol and computer programs prepared in advance, as necessary.

Specific exclusions

(42) Describe three types of patients who should be specifically excluded from randomised comparison of treatments.

—patients for whom a trial treatment is contraindicated

—patients whose response to particular treatments may be biased

—patients for whom the doctor has a definite treatment preference

COMMENT

Patients for whom one of the trial treatments is contraindicated differ in respect of that contraindication—and perhaps also in other respects related to outcome—from patients who may receive any one of the rival treatments without harm. Therefore patients for whom a trial treatment is contraindicated should be specifically excluded. Treatment with beta-blockers, for example, is not advised for patients with asthma; such patients were ineligible for the trial in which Wilcox *et al.*² compared propranolol, atenolol, and placebo in the immediate treatment of myocardial infarction. Also ineligible, but for a different reason, were patients who were already taking a beta-blocker. In this case the specific exclusion was necessary because synergism (or antagonism) of drugs could not be ruled out. Patients whose response to particular treatments may be biased should be excluded. A second example comes from a study in neuropsychology about which I was consulted. It compared “reality orientation schemes” for geriatric patients. In two of the schemes patients were instructed how to make things. Group instruction was practicable only if patients could hear well. Elderly patients who were deaf were therefore excluded because their response to two of the treatments would be impaired. As a consequence the conclusions applied also only to patients who had an adequate level of hearing. Thirdly, exclude any patient for whom the doctor has a definite treatment preference. As described in the introduction a log should be kept of patients

Entrance criteria	
Example	Double-blind randomised controlled trial to compare topical antiglaucoma agents, one of which is a beta-blocker
Entrance criteria	Previously untreated patients who have simple open-angle glaucoma or ocular hypertension [unilateral or bilateral] Patients must be well enough to attend hospital for all day tonometry on four study days at intervals of one week
Specific exclusions	Specifically exclude patients with cardiovascular disease Specifically exclude patients who are being treated with a systemic beta-blocker Specifically exclude patients for whom the ophthalmologist has a definite treatment preference

who are specifically excluded with the reason for their ineligibility.

Protocol

(43) *An orderly presentation of the details of the design, organisation, and outline analysis for a clinical trial is shown below. Why is full documentation important?*

—the protocol is a record not only of decisions made but also of the reasoning or calculation that led to those decisions

—trial procedures should be fully described

—documentation should be sufficiently detailed for the statistician to pick up quickly the threads of the study

COMMENT

Careful documentation is important because the report on a clinical trial is usually written months or years after the first patient is entered. The protocol stands as a record for the authors—of the decisions made and also of the reasoning or calculation that led to those decisions. The protocol will, of course, be incomplete as a reference unless any modifications that were made to the trial procedure during accrual or follow-up are described in an appendix, noting the date, nature of, and reason for changing the procedure.

The second reason for full documentation is the inevitability that clinical investigators will change. New participants must become familiar with the trial procedures, which are described in the protocol. Lastly, documentation should be sufficiently detailed for the statistician quickly to pick up the threads of the study when the time comes for interim or final analysis. Otherwise, important comparisons may be overlooked or a less sensitive analysis reported because the critical features of the study design have been forgotten.

Indeed the protocol should be written clearly enough for the

trial to be repeated elsewhere and analysed in a similar fashion. An aide-memoire for preparing clinical trial protocols is useful.³

Protocol

- (1) Title, list of centres entering patients, job description of trial organisers, date of trial starting
- (2) Aim of investigation
- (3) Ethical consideration, pilot studies
- (4) Entrance criteria
- (5) Criteria for withdrawal or exclusion
- (6) Response variables (and priority if there is more than one measure of response)
- (7) Covariates, recording sheets as appendix
- (8) Trial organisation
treatment assignment (locally or centrally, sealed envelopes. . .), treatment details (fixed or variable dose, administration (qid)), observers, time of visits, timing of assessments, order of assessments
- (9) Design
historical data (referenced), size of clinically important difference and power requirements, fixed or sequential design, size of clinical trial (calculation as appendix), between- or within-patient study, method of randomisation (randomisation list is held in camera)
- (10) Plan of analysis
treatment comparisons of interest, assumptions about response distribution, handling of missing observations, withdrawal, exclusions, loss to follow-up, reversed treatments, frequency of interim analyses and their formality

JUSTIFY DECISIONS MADE

Checks on trial conduct

(44) *Checks on trial conduct are particularly important in long-term studies. What type of check should be made, and why?*

For ethical reasons:

—toxicity

—excess mortality from a particular cause

—important treatment difference

For stable trial conditions:

—rate of patient entry

—rate of withdrawal

—change in distribution of baseline patient characteristics (age, tumour stage . . .)

—change over time in level of response to all treatments

—change in level of response to a particular treatment

COMMENT

Ethical considerations oblige the statistician to review periodically accumulating data from long-term studies for evidence of toxicity, excessive mortality from a particular cause (as in the University Group Diabetes Program⁴), or important treatment difference. To account properly for repeated significance testing the trial design should specify the number of such interim analyses and when they will be performed.

Most other checks are made to detect instability in the trial

conditions. Thus a tailing off in the rate of patient accrual is often the first sign that investigators have lost enthusiasm for the trial and a progress report is urgently called for. A change in the rate of patient withdrawal from the study is a warning that entrance criteria have been relaxed to admit patients who would have been deemed unsuitable before or that there has been a systematic change in the assessment of how severe the side effects of treatment are. Other indications of a subtle alteration in the type of patient admitted to the study are change in the distribution of baseline patient characteristics—such as age at diagnosis, tumour stage, histology—or in the level of response to all treatments. Change in the overall level of response could also be accounted for by a drift in the measurement of response. A change in the level of response to a particular treatment is equally alarming. Possible explanations are a leak in the assignment scheme so that selection bias operates, a change in drug formulation (batch number, for example) or biased assessment because the observer is no longer blind to the assigned treatment.

The execution of a clinical trial is the most exacting phase for

doctors; it should not be a period of quiescence for the statistician.

References

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- 4 Cornfield J. The University Group Diabetes Program: a further statistical analysis of mortality findings. *JAMA* 1971;217:1676-87.

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Lesson of the Week

Dental health in patients susceptible to infective endocarditis

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Despite the availability of antibiotics infective endocarditis is still a dangerous disease. The mortality is about 30%, and there is considerable morbidity owing to valve destruction, systemic embolism, and renal impairment.¹ For many years infective endocarditis has been the target of preventive measures based on the strong link between endocarditis and dental status. Two preventive approaches have been recommended²: (1) giving prophylactic antibiotics to susceptible patients before performing dental procedures that are known to produce a bacteraemia (also before surgery or before using instruments in the upper respiratory, genitourinary, and lower gastrointestinal tracts); (2) maintaining good dental health in patients who are vulnerable to endocarditis.

To study the extent to which the second recommendation has been successfully put into practice we examined the teeth of a group of patients attending a cardiac clinic.

Patients and methods

One hundred patients (29 men and 71 women) underwent a dental examination. They were a consecutive series of patients who had a cardiac lesion that was susceptible to endocarditis.² Their ages ranged from 20 to 76 years, mean 50.8 years (SD 12.9). Sixty-five patients had mitral or aortic valvular disease,

Although good dental hygiene will help to prevent infective endocarditis, many patients with cardiac lesions susceptible to infection have poor dental health

or both; 34 had a prosthetic valve; and one patient had pulmonary valve stenosis. Six patients had a history of endocarditis. Dental examinations were conducted by WPH. The examination consisted of a mirror and probe survey of the teeth and soft tissues.

Results

The results of the dental examination are given in the table. None of the edentulous patients had attended a dentist in the preceding year, but 28 had ill-fitting dentures and 15 had disease of the mouth that could produce bacteraemia. Dental infection was common in the dentate patients: 25 (60%) had either chronic periodontal inflammation or an abscess, or both. Only 17 of the 42 patients with teeth could be regarded as having satisfactory dental health. In this group of dentate patients 17 (77%) out of 22 without caries had seen a dentist in the past year, while only seven (35%) of the 20 patients with caries had seen their dentist during this period ($p < 0.05$, χ^2 test). Only nine patients with teeth knew of their special need to maintain good dental health.

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