essential that such trials have adequate power to provide both negative and positive answers about the efficacy of the treatments tested within the time of the trial. The Bart's-Windsor study provides one of the longest periods of prospective follow-up of a cohort of subjects with ICA. From our risk estimates (table II) it can be calculated that to achieve 90% power to detect a 50% reduction in development of IDDM in subjects with peak ICA levels above 80 JDF units, 118 subjects would have to be followed for 3 years, 73 subjects for 5 years, or 23 subjects for 7 years in each group.[12] Among the 719 first-degree relatives followed for over 4000 subject-years in the Bart's-Windsor family study IDDM has developed in only 16, so the confidence intervals for the risk estimates are wide and, clearly, the numbers are not sufficient for clinical trials. The accuracy of the risk estimates can only be improved further by studying more subjects. It is unlikely that any single centre could achieve a larger study group, but it would be possible by pooling data from comparable studies.

The value of information derived from prospective studies in high-risk groups can be greatly increased by the measurement of ICA in international reference units. Quantification of ICA above a low detection threshold allows stratification of risk in subjects with detectable antibodies, and standardised quantification of ICA means that large-scale collaborative studies are now possible. Pooling of data, standardisation of follow-up, perhaps with the establishment of an international registry of non-diabetic subjects positive for ICA, should clarify the natural history of the IDDM prodrome, and prepare the way for statistically ethical intervention studies.

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Randomisation and baseline comparisons in clinical trials

DOUGLAS G. ALTMAN CAROLINE J. DORÉ

80 reports of randomised clinical trials in four leading general medical journals were reviewed. The reporting of the methodology of randomisation was inadequate. In 30% of trials there was no clear evidence that the groups had been randomised. Among trials that used simple randomisation the sample sizes in the two groups were too often similar, and there was an unexpected small bias in favour of there being fewer patients in the experimental group. The handling of comparisons of baseline characteristics was inadequate in 41% of the trials. Suggestions are made for improving standards.

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Introduction

Many papers published in medical journals contain statistical errors.[1] For example, in 86 controlled trials in four obstetrics and paediatrics journals, the conclusions were justified in only 10%, while in a further 71% insufficient information was supplied.[2] Clinical trial reports in four general journals described, on average, only 56% of eleven aspects of methodology; in particular, the method of randomisation was stated for only a fifth of trials.[3] A properly conducted, randomised controlled trial is the most reliable way of comparing treatments. However, there are many aspects of design and analysis that require careful handling for the conclusions to be reliable. Unless methodology is described the conclusions must be suspect. Randomisation allocates treatments without bias, but does not necessarily produce groups that are similar in important prognostic factors. The similarity of baseline characteristics must be established, but not by hypothesis tests.[4–6] We have

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reviewed randomised clinical trials published in four general journals. We looked at the method of treatment assignment and the presentation and interpretation of baseline information. Because we suspected that the numbers of patients in the treatment groups were often too similar we examined group sizes in relation to the method of randomisation.

Methods

We selected the first 20 randomised clinical trials published after Jan 1, 1987, in each of the *Annals of Internal Medicine*, *British Medical Journal*, *The Lancet*, and *New England Journal of Medicine*. (Details of the 80 trials are obtainable from D. G. A.). These samples spanned 19, 13, 5, and 10 months, respectively. Our study was restricted to parallel group trials of two treatments where allocation was stated to be randomised. Initial selection was based on the abstract and cursory inspection of the main text. A few papers were subsequently excluded because detailed reading showed they did not meet our criteria. In particular, in 1 trial[7] that was said to be randomised, allocation was according to odd or even birth date. We also excluded 2 papers because they were not the first publications relating to those trials.

The 80 papers were reviewed with a standard form that had been tested in a small pilot. Randomisation and the assessment of baseline equivalence were examined independently by each of us, with any disagreements resolved by discussion. Other aspects were assessed by only one of us, but each item of information was obtained by the same reviewer for all 80 trials. There was little disagreement between us about the type of randomisation, the few disagreements arising from vague information on the possible use of stratified randomisation. In simple randomisation a single sequence of random numbers is used to decide which treatment a patient receives, while in stratified randomisation separate sequences are used for subsets of patients, defined by prognostic factors or study centres. Blocking can be used with either type of randomisation, whereby the numbers receiving each treatment are balanced in small blocks of fixed or variable size, such as every 6 patients. Minimisation can be used to make small groups closely similar with respect to several characteristics.[8] The mechanism of treatment allocation should be designed to avoid bias: suitable methods are central randomisation, coded drugs prepared by the pharmacy, and the use of a series of numbered opaque sealed envelopes. Judging the adequacy of the assessment of baseline similarity was subjective and led to 19 joint reviews. To investigate the numbers assigned, the two treatments were designated as experimental or control from information given.

Results

Randomisation

Information about the type of randomisation was missing in 60% of the papers (table I). A third of the trials were stratified, while only 1 mentioned simple randomisation. Most of the others probably used simple randomisation. Nearly 30% of the trials used blocking, but including only 16 of the 31 stratified trials (52%). The size of blocks was not stated in 8 trials (35%). 1 trial of 30 patients used inappropriately large blocks of 20. When blocking is used without stratification the maximum difference between the numbers in the two groups should be half the block size; this was not the case in 2 trials. Only 1 trial used weighted randomisation to give an unequal split in numbers, although in another the numbers allocated to the two groups (40 and 78) suggest weighting. Information about the method of generating random numbers gives clear evidence that the trial was randomised. Only half the trials stated the method used: 16 trials used random number tables, 19 a computer, 3 a "random arrangement", and 1 minimisation. Nearly half of the trials (45%) gave no information about the mechanism used to allocate treatments. Of the other 44 studies, 16 reported the use of envelopes but only 2 of these mentioned that they were numbered, sealed, and opaque, all of which are important.[9] 4 studies used central randomisation. We assumed that the 15 trials reporting the use of numbered or coded bottles had had these prepared in a pharmacy. Even so, only 21 studies (26%) reported the use of a system to reduce bias. Only 27 trials (34%) included information on both the method used to generate random numbers and the mechanism used to allocate treatment.

TABLE I—RANDOMISATION

—	Ann Intern Med	Br Med J	Lancet	N Engl J Med	Total
Type of randomisation					
Simple	0	0	1	0	1 (1%)
Stratified	12	5	4	10	31 (39%)
Not stated	8	15	15	10	48 (60%)
Blocked	6	6	4*	7	23 (29%)
Stratified and blocked	5	3	3*	5	16 (20%)
Method of generation specified	10	10	7	12	39 (49%)
Bias-reducing allocation					
Yes	7	3	2	9	21 (26%)
No	6	7	5	5	23 (29%)
Not specified	7	10	13	6	36 (45%)
Both generation and allocation specified	9	5	6	7	27 (34%)

*1 used modified minimisation.[8]

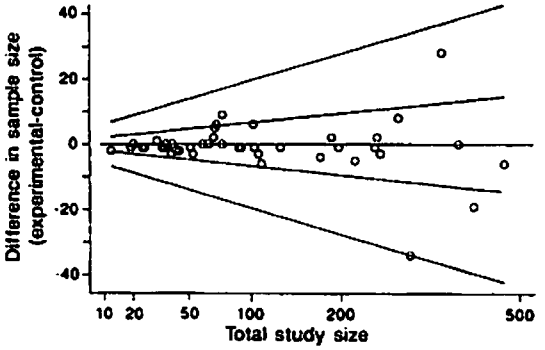
Sample size

The sample size was based on prior statistical power calculations in 31 (39%) of trials (table II). In a further 26% the time span of the study was stated, although only rarely was it stated that the sample was based on the number of patients recruited in a prespecified period. 1 trial was sequential. For a third of trials the sample size used was not explained. There were pretreatment exclusions in 27 (34%) of the trials; only 9 of these papers specified the numbers randomised—ie, a quarter of the 80 reports did not state the numbers initially allocated to each treatment. In the 9 trials that gave full information, about 10% of patients had been excluded before treatment, and in 8 of these trials there were more exclusions in the controls ($p = 0{\cdot}04$, sign test). Most of the trials with mention of exclusions did not report the number of exclusions per group and only 7 gave reasons for those exclusions for each group.

For the 62 trials giving numbers randomised, there were 12 trials with an equal number of patients in each group; of these only 5 were blocked. Of the 19 studies that used blocking, 7 had more patients in the control group and 7 had more in the experimental group. Among the 43 unblocked trials there was a clear bias, with 26 (72%) of the 36 trials with unequal samples having more patients in the control

TABLE II—SAMPLE SIZE AND EXCLUSIONS

—	Ann Intern Med	Br Med J	Lancet	N Engl J Med	Total
Reason given for size used					
Power calculation	6	8	7	10	31 (39%)
Time period	5	2	6	8	21 (26%)
Group sequential	0	0	0	1	1 (1%)
None	9	10	7	1	27 (34%)
Exclusions					
None	12	12	14	15	53 (66%)
As randomised	3	4	2	0	9 (11%)
As analysed	5	4	4	5	18 (23%)



Relation between difference in numbers in experimental and control groups and total study size for 43 unblocked trials.

Straight lines indicate expected distribution. Sample size is shown on square root scale to make confidence intervals straight. The 95% interval is approximately $\pm 2\sqrt{\text{total study size}}$

group ($p = 0.01$, sign test). However, the difference in sample sizes was usually small (figure). 5% of trials should fall outside the outer pair of straight lines—none did. Furthermore, half of the 43 trials should be outside the inner pair—only 5 were. For the 18 trials giving only the numbers analysed a similar pattern was seen.

Baseline characteristics

The median number of baseline characteristics presented was 9, with 39% of trials giving data for more than ten variables. 6 studies gave no information. Continuous baseline variables were reported in 69 papers. 19 reports used the SE to describe the variability of baseline data, and 1 used confidence intervals. In 13 papers no measure of variability was given. Thus the presentation of baseline data was unsatisfactory for 39 trials (49%). Hypothesis tests were used to compare baseline variables in 46 trials (58%), but the methods were specified in only 34 (74%) of these. More than ten variables were tested in 18 trials (39%). For 17 (37%) of the trials one or more of the baseline variables tested was significantly different ($p < 0.05$) between the two groups. Overall there were six hundred hypothesis tests in the 46 trials, of which 24 (4%) were significant at the 5% level. These figures are based on the published analyses; we did not test data for which the authors had not presented test results.

Almost half of the trials made no adjustment for differences in baseline characteristics, while a quarter used some form of statistical modelling (table III). 12 trials analysed changes from baseline. In 8 trials analyses were done only within treatment groups. Nearly all reports (91%) included some comment on baseline similarity. We assessed how reasonably the authors handled these comparisons, taking into consideration the information presented, the magnitude of differences between groups, the method of analysis, and the amount of discussion. Handling was reasonable in 47 trials (59%). Of these, 20 trials used modelling or changes from baseline and another 20 had adequate discussion or design. In 7 trials the groups were so similar that discussion was not required. Among the 33 trials that did not deal adequately with baseline comparisons, most either gave insufficient information (17) or failed to adjust for major differences (13). Here "major" indicates a subjective substantial difference in means or proportions, regardless of statistical significance. We assumed that any

TABLE III—HANDLING OF BASELINE CHARACTERISTICS

—	*Ann Intern Med*	*Br Med J*	*Lancet*	*N Engl J Med*	Total
Method used					
Statistical modelling	8	2	4	7	21 (26%)
Changes from baseline	3	5	1	3	12 (15%)
No adjustment	5	12	13	9	39 (49%)
Within groups	4	1	2	1	8 (10%)
Reasonable handling	15	12	8	12	47 (59%)

baseline variable presented was potentially prognostic. In 3 trials where there were some substantial observable differences between the groups, there was no comment other than the reporting of no significant differences.

Discussion

Randomisation

Although guidelines recommend that the method of randomisation be specified,[10,11] the type of randomisation, source of random numbers, and mechanism of allocation are not generally distinguished, although Zelen's advice[12] is an exception. Also the blindness of treatment allocation is important in assuring that the trial is unbiased.[9] Few reports mentioned the type of randomisation, unless to note that it was stratified. Blocking was said to have been used in 29% of trials, but in only 16 of the 31 stratified trials. Stratification serves no purpose without blocking, although it is likely that more trials used blocking than mentioned the fact. The method of generation of random numbers and the mechanism for allocating treatment were poorly reported, with no information in about half the studies. In nearly a third of the papers neither was described, so there was no evidence that the trial had been randomised. 5–10% of "randomised" trials have been found to use non-random methods of allocation[13,14] so some of the 24 trials that gave no information may have been non-random. A dramatic example of the bias that can occur with systematic allocation is given by Keirse.[15] Bias can also arise from non-blind treatment allocation. Only 26% of trials used a system designed to reduce bias.

Sample size

Pocock et al[16] found that sample size was based on prior statistical power calculations in only 5 of 45 trials published in three general medical journals in 1985. Our study of the same journals plus one other 18 months later found 39% of the 80 trials reported power calculations. For the three journals common to both reviews, the increase was from 11% to 42% ($p = 0.001$, χ^2 test). Our figure of 39% is the largest we are aware of in any review, although it still means that in about two-thirds of the reports no reason was given for the termination of recruitment.

Unless a trial is small there is no need for similar numbers of patients in the groups. With simple randomisation, there may be some discrepancy, but this will not have an important effect on the power of the study. We considered the distribution of the difference in group sizes as randomised in relation to the stated method of allocation. The differences were much as would be expected among the 19 trials that used blocking. For the 43 unblocked trials, however, the sample sizes in the two groups tended to be much too similar, with only 5 trials outside the inner lines in the figure compared with the expected 50%. This finding

supports our prior hypothesis. The clustering around equal sample sizes may be due to failure to report: (A) the use of blocking, (B) the use of a deterministic method such as alternation or odd/even date allocation, or (C) the rectification of an unsatisfactory imbalance by adding extra patients to one treatment. The size of the effect makes it unlikely that chance is the sole cause. We believe that both (A) and (B) are not uncommon, but have no evidence that (C), which is far more serious, actually occurs.

The sample size tended to be slightly higher in the control group. This statistically significant asymmetry, which was seen in all four journals, was unexpected and is harder to explain. The differences in sample size were generally so small that deliberate manipulation is unlikely; it is more likely that patients who were withdrawn after the start of the study were excluded from the report. Withdrawals are often for side-effects, which are more likely in the experimental group. When we looked at the 47 trials reviewed by Lavori et al,[4] there were only 15 unblocked randomised trials, but among these we found a similar asymmetry. In 2 trials the sample sizes were the same in the two groups, and 8 of the other 13 trials (62%) had more patients in the control group.

Baseline characteristics

Because random allocation can lead to chance fluctuations between groups, the degree of similarity achieved should be demonstrated. The number of baseline comparisons presented varied widely, with two-thirds of trials giving information for more than five variables and 6 trials giving none. For continuous variables it is important to have information about variability (eg, SD, range, selected centiles, or, occasionally, all the data) as well as the mean or median, but measures of variability were missing or inappropriate in 33 trials (48%). The SE is not a descriptive measure, but rather indicates the uncertainty of an estimate such as a mean.[17] As such it should not be used when presenting baseline information, and nor should the closely related confidence interval. Use of hypothesis tests was common, but the methods used were not always specified. Hypothesis tests are not a valid way of assessing similarity; such an assessment should be based on consideration of the prognostic strength of the variables and the magnitude of the imbalance.[4,6] If randomisation has been done fairly, the null hypothesis that the two groups come from the same population is by definition true; so we would expect 5% of such comparisons to be significant at the 5% level. Thus these tests assess, indirectly, whether randomisation was fair, not whether the two groups have similar characteristics. Taking all such tests together 4% of six hundred comparisons were significant at the 5% level, so there was no evidence that these were due to other than chance variation. We looked for some indication that authors had considered whether differences between the groups could have affected the treatment comparison. If groups are similar with respect to prognostic variables, the analysis can be simple. If, however, there are differences that might be important, the analysis should be modified by, for instance, regression modelling or analysis of changes from initial values. Overall only about 60% of the trials dealt reasonably with this topic.

Recommendations

When an item is absent from a paper it is usually not possible to distinguish whether a procedure was not done or whether it was not reported. Liberati et al[18] examined the information published in 63 randomised trials of primary treatment of breast cancer and also telephoned the principal investigators to clarify some aspects. With the benefit of this information, the proportion of trials deemed to have had adequately blind randomisation rose from 25% to 43%, and those having used power calculations to determine the sample size of the trial from 32% to 52%. These findings suggest that while a fair proportion of trials sell themselves short in their reports, the bulk of missing items are due to failure to do procedures rather than under-reporting. In our study, important information about methodology was commonly omitted in all four journals.

There have been many adverse reports on the quality of reporting in medical journals, especially for clinical trials.[1,3,13,14,16,18-20] Our study showed that some aspects remained poor in 1987. A report of a randomised clinical trial should give the following statistical information: (A) a description of the trial design (including type of randomisation); (B) evidence that the allocation was randomised (the method of generation of random numbers); (C) how the allocation was done, including whether or not it was blinded; (D) how the sample size was determined; and (E) baseline comparisons, and satisfactory handling of any differences. Also important are whether the patient, the person giving the treatment, and the assessor were blinded. The term double-blind requires amplification. Of course, all papers should adequately describe the statistical methods of analysis and should reasonably interpret the results. Authors should be provided with a list of items that are required. Existing check lists[9,11,21,22] do not cover treatment allocation and baseline comparisons as comprehensively as we have suggested. Even if a check list is given to authors there is no guarantee that all items will be dealt with. The same list can be used editorially, but this is time-consuming and inefficient. It would be better for authors to be required to complete a check list that indicates for each item the page and paragraph where the information is supplied. This would encourage better reporting and aid editorial assessment, thus raising the quality of published clinical trials.

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VIEWPOINT

Central America: the cost of war

CÉSAR A. CHELALA

Central America, an area of tremendous agricultural potential, has undergone a decade of upheaval and destruction that has adversely affected the health and well being of its population.[1] With the exception of Costa Rica, the other countries in the region have endured the consequences of both internal and external conflicts. There is increasing poverty, and in the past decade more than 2 million people, mostly women and children, have been displaced from their homes; about half have left the region, many of whom have become refugees in the US.[2] Partly because of the state of war, the Central American countries have had very low or negative rates of economic growth; so governmental allocation of money to social and health programmes has suffered. Between 1980 and 1987, per caput income in the region decreased on average more than 15%. The decrease has been even greater in Nicaragua and El Salvador, which are the countries most affected by the war.[3] The United Nations Economic Commission for Latin America and the Caribbean estimates that Central America is in the deepest economic recession of the past half century.

According to the Pan American Health Organisation, of 850 000 children born every year in Central America, more than 100 000 will be low-birth-weight babies, and 100 000 will die before they are five years old. In addition, almost two-thirds of those who survive will have some degree of malnutrition, of whom 10% will have disorders of physical or mental development.[4] Average infant mortality rates for El Salvador, Guatemala, Nicaragua, and Honduras are 75 per 1000 live births. These rates are much higher (about 200/1000) in rural areas, especially among the uneducated poor. The main causes of infant mortality in the region are intestinal and respiratory infections.[5] In all countries affected by the conflicts, thousands of people have been killed and maimed, and a huge number of children (about 100 000–120 000 in Guatemala alone[6]) have been orphaned. Additionally, hundreds of medical facilities—from basic health posts in rural areas to more complex medical facilities in towns and cities—have been completely or partly destroyed.

A regional disaster

El Salvador

Even though it is the fifth largest recipient of US aid in the world (more than US $3·3 thousand million in the last eight years), El Salvador continues to have a very high infant mortality rate. 27% of Salvadorean children under the age of five are malnourished. A recent American medical delegation to the country found that 43% of child deaths in the "repopulated" village of San Jose Las Flores were due to violence from the army.[7] 70 000 people have been killed since 1979—ie, 1% of the total population. During the same period, over 1 million Salvadoreans have become refugees.

Guatemala

Between 50 000 and 75 000 people have been killed in Guatemala since the late 1970s.[6] Although most of the deaths were attributed to war-related violence, many were due to malnutrition and sickness. Data from nutritional surveys indicate that the nutritional status of rural children under five years of age has not improved over the past twenty years. According to UNICEF, 75% of the population have no potable water services, and 60% have no access to health care. Immunisation programmes are not conducted regularly, and most health posts lack adequate refrigeration systems for vaccine storage. While real salaries have gone down, the cost of medicines has increased by about 300% in the past three years.[8]

No sector of Guatemalan society has been unaffected by the violence. In the case of health professionals, 130 possible violations of medical neutrality have been recorded between

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