Drop-out in the VenUS III trial

Presented to the VenUS III collaborators meeting, 24 July 2008.

For those who don't know, VenUS III (Venous Ulcer Study 3) is a trial comparing low dose ultrasound to promote healing with usual care in the treatment of venous leg ulcers. The outcome variable is time to heal. This time is measured in months rather than days.

Randomisation

VenUS III is a randomised controlled trial. Why do we randomise patients to treatment, allocating them to treatment groups by chance? We do this to get comparable groups which are similar in every way, including both things we know about and the things we do not know about. The only differences between them should be the treatment and those which arise by chance.

Well, what else could we do to compare two treatments?

We could compare the results of the new treatment on new patients with records of previous results using the old treatment. This is seldom convincing. There may be many differences between the patients who received the old treatment and the patients who will receive the new. As time passes, the general population from which patients come may become healthier, standards of nursing care improve, the social mix in the catchment area may change.

For an example, Christie (1979) described an analysis of data to evaluate the introduction of a C-T head scanner. Christie took the records of patients treated in 1978, who received a scan, and matched each of them with a patient treated in 1974 (before the scanner was introduced) of the same age, diagnosis and level of consciousness on admission. Table 1 shows the results for these patients. This looks good, the 1978 patients did better. Christie also took the records of patients treated in 1978, who ***did not*** receive a scan, and matched each of them with a patient treated in 1974 of the same age, diagnosis and level of consciousness on admission. The 1978 patients did better again! Indeed, the 1978 patients did better whether they had a scan or not. So comparing patients seen after the scanner was introduced with those seen before the scanner is not a good way to see whether using the scanner improved patients' outcome. Controls at a different time don't work.

Table 1. Difference in survival for matched pairs of stroke patients (Christie (1979)

	Scan in 1978	No scan in 1978
Pairs with 1978 better than 1974	31%	38%
Pairs with same outcome	62%	43%
Pairs with 1978 worse than 1974	7%	19%

Table 2. Result of the field trial of Salk poliomyelitis vaccine

Study group	Number in group	Paralytic Polio Number of cases	Rate per 100000
Randomized control:			
Vaccinated	200745	33	16
Placebo control	201229	115	57
Not inoculated	338778	121	36
Observed control:			
Vaccinated 2nd grade	221998	38	17
Control 1st and 3rd grade	725173	330	46
Unvaccinated 2nd grade	123605	43	35

We could ask people to volunteer for the new treatment and give the standard treatment to those who do not volunteer. People who volunteer and people who do not volunteer are likely to be different in many ways apart from the treatments we give them. For an example, we shall look at the 1954 field trial of Salk poliomyelitis vaccine (Meier 1977). We can often learn a lot from trials carried out before the modern method was established.

This was an unusual trial. Jonas Salk didn't believe in randomisation or statistical analysis and wanted to do a study where all second grade children were offered vaccination and the first and third grade left unvaccinated as controls. Not everyone agreed, and the trial was carried out using two different designs simultaneously. In some districts, second grade school-children were invited to participate in the trial, and randomly allocated to receive vaccine or an inert saline injection (placebo). Table 2 shows the results. We can see that in the placebo control areas, the placebo control children (volunteers) and the children who were not inoculated (refusers) are very different. (Of course, it was their parents who volunteered or declined on their behalf.) The control groups are the only ones which differ between the two types of area. This is because we compare volunteers in the placebo area with unselected children in the observed control areas. We cannot compare volunteers with any group apart from other volunteers (the children given the vaccine).

We could allocate patients to the new treatment or the standard treatment and observe the outcome. However, the way in which patients are allocated to treatments can influence the results enormously. For example, Hill (1962) presented the results of a series of trials of BCG vaccine in New York (Levine and Sackett 1946). Children from families where there was a case of tuberculosis were allocated to receive BCG vaccine or to a control group who were not vaccinated. The studies fell into two parts. Between 1927 and 1932 physicians chose which children to vaccinate. From 1933 alternate allocation to treatment or control was done centrally. Table 3 shows some of the results.

Table 3. Results of BCG vaccine trials in children from tuberculosis families (Hill 1962)

Period of trial	Death rate per year		Average no. of visits to clinic during 1st year of follow-up		Proportion of parents giving good co-operation (nurses)	
	BCG	Contrl	BCG	Contrl	BCG	Contrl
1927–32 Selection made by physician:	0.7%	3.3%	3.6	1.7	43%	24%
1933–44 Alternate allocation:	1.4%	1.5%	2.8	2.4	40%	34%

When the physician allocated children to groups, the mortality rate was much lower in vaccinated children than in controls. When there was central alternate allocation, the difference was much smaller. We can see a possible explanation from Table 3. In the first period, the families of the vaccinated children were more compliant with prevention methods than were the controls. They came to the clinic more often and more of them were seen as giving good cooperation with TB control measures by visiting nurses. In the second period these differences are much smaller.

Different methods of allocation to treatment can produce different results. This is because the method of allocation may not produce groups of subjects which are comparable, similar in every respect except the treatment.

We need a method of allocation to treatments in which the characteristics of subjects will not affect their chance of being put into any particular group. This can be done using random allocation. We allow chance to decide into which treatment group the patient falls. We also separate the allocation from the clinician recruiting the patient, so that we can avoid well-meaning bias from the clinician. Patients are recruited by the clinician then allocated by a central randomising service.

Analysis by intention to treat.

We allocate subjects randomly so that we will have comparable groups which differ only in intervention and randomly. When we have randomised, the two groups are samples of the same population, because the allocated group depends only on chance.

Trials are carried out by fallible people and mistakes in treatment can occur, where patients do not get their allocation. Sometimes we even have deliberate sabotage, where clinicians change the treatment in what they perceive as the best interest of the patient. Patients sometimes refuse to continue when they find out their allocation. Sometimes patients begin treatment, but then decide that they do not want to go on and drop out of the trial. Mistakes, sabotage, refusal, and drop-out can all lead to non-comparable groups.

Our solution is to analyse subjects in the comparable groups to which they were originally allocated. We call this analysis by intention to treat.

For an example, consider the observed control areas of the Salk trial (Table 2). The vaccinated children and the control group of first and third grades are not comparable. How could we analyse the trial? We can compare all second grade children, both

vaccinated and refusers, to the control group. The first and third grade combined should be roughly comparable to the second grade children. They are certainly in the same place at the same time. Because they are unselected, the only difference should be the small age discrepancy. The paralytic polio rate in the second grade children can be found by (38 + 43) / (221998 + 123605) = 23 per 100,000. Compare this to the 46 per 100,000 for the 1st and 3rd grade children, shown in Table 2. This difference of 23 per 100,000 in the children offered the vaccine and 46 per 100,000 in the children who were not offered the vaccine demonstrates the effectiveness of the vaccine. The "treatment" which we are evaluating is not vaccination itself, but a policy of offering vaccination and treating those who accept. This is analysis by intention to treat.

The random allocation procedure produces comparable groups and it is these we must compare, whatever selection may be made within them. We therefore analyse the data according to the way we intended to treat subjects, not the way in which they were actually treated.

Drop-out from a trial

What happens when participants drop out of a trial? In clinical trials, this almost always happens for some patients. We no longer have the groups which were randomised. The problem is that groups may become less comparable. This is particularly a problem if withdrawal is because:

- the patient doesn't like the treatment,
- the patient is doing badly on the treatment.

This will make the groups not comparable. However, it won't matter much if we can do an intention to treat analysis.

We cannot do this if we do not have the data on every participant. When a participant drops out of a trial, we need to keep collecting data if possible. We should ask a patient who wants to withdraw from treatment whether they would be willing to provide data. Even if the patient declines to receive any more questionnaires, we should ask whether we can use the clinical data, such as the date of healing. If we have data on patients who drop out from treatment, we can still analyse the trial according to the intention to treat.

The message

When a participant drops out of a trial, we should ask whether they would be willing to provide data. Even if the patient declines questionnaires etc., we should ask whether we can use the date of healing. ***The clinician will have this anyway, whether the patient is continuing in the trial or not.*** If we have data on patients who drop out from treatment, we can still analyse the trial according to the intention to treat.

Keep collecting data on patients who drop-out!

Martin Bland

Prof. of Health Statistics
University of York

References

Christie, D. (1979) Before-and-after comparisons: a cautionary tale *British Medical Journal* **2**, 1629-30.

Hill, A.B. (1962) *Statistical Methods in Clinical and Preventive Medicine* Churchill Livingstone, Edinburgh.

Levine, M.I. and Sackett, M.F. (1946) Results of BCG immunization in New York City. *American Review of Tuberculosis* **53**, 517-32.

Meier P. The biggest health experiment ever: the 1954 field trial of the Salk poliomyelitis vaccine. in Tanur JM *et al.* (eds.) *Statistics: a Guide to the Biological and Health Sciences* San Francisco: Holden-Day, 1977.