

# Essential statistics for the pharmaceutical sciences

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Publisher: John Wiley & Sons Ltd (<http://eu.wiley.com>)

Published: 2007

ISBN: 978-0-470-03468-2

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Additional topics as supplements to the book:

**Fixed and random factors**

# Fixed and random factors

## Two contrasting scenarios

### First scenario. A test of a general theory.

A rare eye condition is treated with an expensive ointment dispensed in tubes of 5 grams. The amount being consumed seems excessive and there is a suspicion that patients are just squeezing the tubes in the middle, leaving much of the medicine in the lower end of the container (à la toothpaste). This is confirmed when a couple of patients return some of their 'empties'.

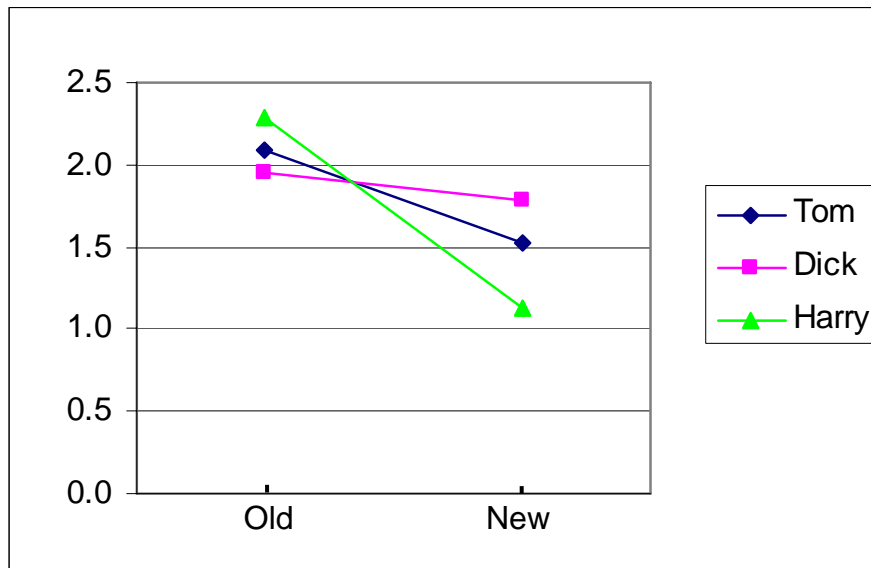
An alternative design of tube is available which is claimed to be less wasteful, although it's not immediately obvious that this would be so. An experiment is designed to test whether there should be a general policy to change to the alternative tubes. Three patients are randomly selected from a national register of sufferers and asked to return their used tubes. Initially they continue using the original design, but then a switch is made to the alternative. All returned tubes are analysed for residual ointment.

The results, including mean wastage for each patient, are shown in Table 1 and the mean values are also represented in Figure 1.

**Table 1. Ointment wastage (g) with old and new designs of tube.**

Patient	Tom	Dick	Harry	
Old design	1.92	1.93	2.26	
	1.74	1.52	2.53	
	2.24	2.17	2.16	
	2.74	2.44	2.27	
	1.80	1.68	2.40	
		1.91	2.29	
		1.76	2.09	
		2.20		
		-----	-----	-----
		Mean = 2.088	Mean = 1.950	Mean = 2.284
New design	1.95	1.42	0.62	
	2.35	1.54	1.13	
	1.14	1.77	1.61	
	1.32	1.81	1.11	
	1.04	1.77	1.68	
	1.69	1.89	0.53	
	1.16	1.59	1.09	
		1.93	1.21	
		2.38	1.24	
		-----	-----	-----
	Mean = 1.521	Mean = 1.790	Mean = 1.135	

**Figure 1. Ointment wastage dispensed in old or new designs of tube**



It is pretty obvious that wastage for Harry declined when he switched to the new tubes and Tom also shows a reasonably convincing reduction. For Dick, the outcome is less clear cut (Slight reduction or no change?).

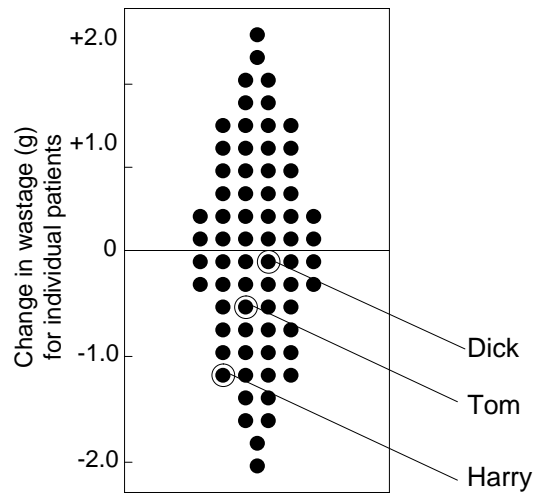
**Using commonsense, what would we conclude from these results?**

Note that the question to be answered is:

*Should there be a general switch to the new tubes?*

We need to keep in mind that these three randomly selected patients are intended to represent a wider population of patients. Our null hypothesis will be that within the general population, the overall effect of switching to the new container would be no change in wastage. The assumption behind the null hypothesis is that some patients would increase and others decrease their wastage and that these gains and losses would cancel out. It would also have to be assumed that our sample happened to over-represent those patients who showed reduced wastage. Fig 2 shows this diagrammatically.

Fig 2 Null hypothesis that changing tube design will not change average wastage



If the effects of changing tube design were as suggested in Fig 2, it would not be especially unlikely that a sample would include two individuals showing definite reductions and one who was little changed. On the flimsy basis of just three patients, we really cannot be confident that a general switch to the new tubes would improve matters.

### **Second scenario. A test of a much more limited theory.**

A clinic has just three patients with the disease condition mentioned previously. This clinic has also noticed apparent wastage and wants to know whether they should switch to the new tubes. The clinic carries out essentially the same experiment as that described above, but using the three patients under their care. The results are exactly the same as those in Table 1.

### **Using commonsense, what would we conclude from these results?**

In this case the question being asked is:

*Should this clinic, with these specific patients, switch to the new tubes?*

Our null hypothesis is now that there would be no change in average wastage if these three patients switched tubes. We are no longer using the three subjects to represent a wider population; we are specifically and exclusively interested in these three. Two of the patients showed clear reductions in wastage and the other certainly showed no signs of increased wastage. That is all we need to know; this clinic should change to the new tubes.

# A formal statistical approach for the two scenarios

## Distinguish fixed from random factors

In both scenarios the end-point is wastage which is a measured (Interval) value and there are two factors that may influence the extent of wastage:

- The individual patients
- The different designs of tube.

The natural statistical test would therefore be a two-way analysis of variance. The method of calculating analyses of variance can be modified to suit the two scenarios considered.

The key is to recognise that factors may be 'fixed' or 'random'. With fixed factors, the levels studied are planned and represent the full set of possibilities that are of interest, whereas with a random factor, the levels are a random selection from a wider range of possibilities. The distinction will probably be clearer in the context of our two scenarios.

- Tube design: In both scenarios, the design of tube is a fixed factor. The two designs studied were the two in which we were specifically interested. They were not some random selection from a catalogue of products.
- Patients: In the first scenario, the patients studied were a random selection and therefore constitute a random factor. However, in the second situation, the three patients were precisely the ones of interest and were not randomly selected. In the latter case the patients constitute a fixed factor.

If you are still unclear about the distinction, ask yourself the following question:

*If the results of your experiment were lost in a disastrous fire and you had to repeat the work, would you use the same levels of the factor as previously?*

- In both scenarios we would use the same designs of tube as previously – a fixed factor.
- In the first scenario, Tom, Dick and Harry were just a random choice and there is absolutely no reason to use them again. Any randomly chosen subjects will do, so this is a random factor. In the second case, Tom, Dick and Harry are the only patients in our clinic and we would definitely use them again – now a fixed factor.



## Fixed and random factors

- Fixed – you knew in advance what you wanted to study. You were specifically interested in Tom, Dick and Harry.
- Random – you randomly selected from a wider group. Any old Tom Dick or Harry would have done.

### Using statistical packages to perform the analyses

Most statistical packages make a default assumption that all factors are fixed and then there is a mechanism to allow factors to be declared as random when appropriate. Specific instructions for Minitab and SPSS are given at the end of this document. Generic output from two-way analyses of variance are shown in Tables 2 and 3.

Table 2 shows the results when the patients were declared as a random factor which is appropriate for the first scenario. Our common-sense analysis suggested that within such a context, the results were unconvincing. Happily, the formal analysis produces a non-significant P value of 0.174 for the design of tube. The commonsense assessment and formal analysis are consistent.

**Table 2. Analysis of effect of patient and tube design on ointment wastage. Patient treated as a random factor.**

Analysis of Variance for Waste  
Factors: Tube - fixed  
Patient - random

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Tube	1	4.3222	4.2392	4.2392	4.29	0.174
Patient	2	0.3555	0.2086	0.1043	0.10	0.906
Tube*Patient	2	2.0020	2.0020	1.0010	8.32	0.001
Error	39	4.6937	4.6937	0.1204		
Total	44	11.3735				

Table 3 shows an analysis of exactly the same data, but the patients have now been treated as a fixed factor as is appropriate for the second scenario. Commonsense suggested that the data were convincing in this setting and the formal analysis supports this with a clearly significant P value for tube design of less than 0.001.

**Table 3. Analysis of effect of patient and tube design on ointment wastage. Patient treated as a fixed factor.**

Analysis of Variance for Waste  
 Factors: Tube - fixed  
 Patient - fixed

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Tube	1	4.3222	4.2392	4.2392	35.22	0.000
Patient	2	0.3555	0.2086	0.1043	0.87	0.428
Tube*Patient	2	2.0020	2.0020	1.0010	8.32	0.001
Error	39	4.6937	4.6937	0.1204		
Total	44	11.3735				

### One and two way analyses of variance

It is only with two (or more) way analyses of variance where we really need to worry about whether factors are fixed or random. For experimental designs studying only one factor, that factor may be fixed or random, but this will not affect the result of the analysis.



When does it actually matter?

- The distinction between fixed and random factors is only relevant for two (or more) way analyses of variance. There is no need to distinguish them for one way analyses.

## Differences between the two approaches to analysis

### Greater power when analyses treat factors as fixed.

It is generally the case that a two-way ANOVA is more likely to produce a significant result when both factors are analysed as fixed than when one or both are treated as random. Notice that if we change the way in which we analyse one factor, it is the other factor that shows a change in significance. In our examples, changing our opinion as to whether the patients constitute a fixed or random factor, changes the significance of the tube design.

The reason why the form of the analysis affects the chances of a significant result are obvious enough if we consider our two scenarios.

In the first scenario, there were two levels of random sampling; we randomly selected three patients and then randomly selected a set of used tubes from each of those individuals. Each level of random sampling is subject to sampling error (The three patients may not be exactly representative of the whole population of patients and each set of tubes may not perfectly

represent wastage by that particular patient.) Both of these sources of imprecision have to be taken into account in the analysis, reducing the chances of statistical significance. In this case, the very small sample of patients ( $n=3$ ) is hopelessly lacking in precision.

In the second scenario, there is only the one level of random sampling (The random set of used tubes from each patient.) There is no longer any additional sampling error from the patients. With only the one source of random sampling error, the result is more likely to be judged significant.

### **Confusing the two forms of analysis and the danger of over-generalisation**

The two scenarios considered above were both internally consistent and perfectly sound.

- In the first case, we were testing whether changing our dispensing method would be beneficial for a whole population (Effectively all patients receiving the ointment). To tackle that question, we selected some patients randomly and treated them as random in the subsequent analysis.
- In the second case, we were only interested in three specific patients, so they were a fixed factor and were analysed as such.

Investigators who do not appreciate the characteristics of fixed and random factors are in danger of drawing sweeping conclusions that go way beyond anything justified by the data. Because most stats packages default to an assumption that factors are fixed, the danger is that a factor will be analysed unthinkingly as fixed, but then the outcome will be interpreted in an unjustifiably general manner. Typically, we might take the analysis from the second scenario with its clearly significant result and then claim that we have proved that patients *in general* would benefit, instead of restricting ourselves to a conclusion about these three specific individuals.



#### **Generalise (when you shouldn't)**

Given the widespread ignorance of the distinction between fixed and random factors, you've got a fair chance of getting away with this one, but if you push it too far, it will be obvious that something's not quite right.

You have multiple observations from a small number of individuals or institutions. Analyse the results treating the people/institutions as a fixed factor to increase your chances of a significant result and then insinuate that your finding applies to all patients/institutions rather than restricting your conclusion to the specific cases studied.

## Efficient use of data

In the first scenario, there are two levels of random sampling. We selected a sample of patients and then collected a sample of used tubes from each of them. With a chain of randomisation, the strength of the chain is heavily dependent upon the first or 'Primary' level of sampling (In this case the patients). The first level of sampling (Just three patients) was inadequate and the damage was done. At the second level of sampling we have done a pretty thorough job (Five to nine tubes for each combination of patient and tube type), but this can't compensate for the inadequate number of patients .

Table 1 shows that we did a fair amount of work (46 tubes analysed) but our pattern of working was seriously imbalanced and wasteful. We could have done almost exactly the same amount of analytical work and given ourselves a far better chance of achieving statistical significance if we had recruited (say) eight patients but restricted ourselves to analysing sets of three tubes.



### Collect data efficiently

When a random factor is involved, balance your data collection so that there are ...

- Enough examples of the random factor to represent the population adequately and
- Enough data from each individual to give reasonably precise estimates for each of them.

The primary level of sampling is especially important. If this is done inadequately, it will not be possible to compensate by collecting large amounts of data from each individual.

## Other examples

The examples of two-way analyses of variance quoted in the book are restricted to fixed factors. Section 13.3 described the effects of different types of catalyst and methods of mixing on the efficiency of a chemical synthesis. The catalysts investigated were not randomly chosen. (We could have made a random selection of metals by throwing darts at a copy of the periodic table, but it would make little sense!) A limited number of metals were likely to be any use and these were precisely the ones studied. Similarly, the methods of mixing were the only two practical alternatives, not a random assortment.

It is the same story with the tableting experiment. The punches and pressures used were those likely to be of practical use.

In the first scenario in this document, the patients were randomly selected. Individual subjects frequently constitute a random factor. It is only in rare instances (such as the second scenario) that we want to investigate specific

individuals; it is much more likely that individuals are selected to represent a larger population.

Another factor that is likely to be random is a sample of institutions. If you are going to study the effect of a change in some procedure in (say) hospitals, you may study several. If these are selected randomly to represent all such institutions, they must be analysed as a random factor. If they are not declared as random then a significant outcome should only lead to a claim that the change in procedure had an effect in those particular hospitals rather than in all hospitals.

## **Details for carrying out analyses using specific statistical packages.**

### Minitab:

If you follow the menus Stat / ANOVA and then select either 'Balanced ANOVA...' or 'General Linear Model...' you will see a box labelled 'Random factors'. Any factor that you enter into this box will be treated as random; factors not listed will remain as the default – fixed.

### SPSS:

If you follow the menus Analyze / General Linear Model / Univariate... you will see a box labelled 'Random Factors(s)'. Any factor that you enter into this box will be treated as random; factors not listed will remain as the default – fixed.