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Paper Celebrating the 25th Anniversary of *Statistics in Medicine*

Cross-over trials in *Statistics in Medicine*: The first '25' years

Stephen Senn*, †

Department of Statistics, University of Glasgow, Glasgow G12 8QQ, U.K.

SUMMARY

Papers on cross-over trials that have appeared in the first 25 years of *Statistics in Medicine* are reviewed. Papers on bioequivalence are also considered. After a brief statistical summary, individual papers are discussed under seven headings: 1. The two-stage analysis of AB/BA trials, 2. Baselines, 3. Binary and categorical data, 4. Survival data, 5. Modelling carry-over, 6. Bioequivalence and 7. Components of variation. Finally, a brief assessment of the importance in this field of *Statistics in Medicine* is given. Copyright © 2006 John Wiley & Sons, Ltd.

KEY WORDS: baselines; bioequivalence; binary data; carry-over; survival analysis

1. INTRODUCTION

Readers of a journal with a title *Statistics in Medicine* will surely expect that in addition to pulling out the cherries from the delectable dessert, so to speak, of the cross-over trial papers in this journal, some taste will also be given of the general flavour and that account should be suitably bolstered by *statistics*. Unfortunately, I labour in this respect under several difficulties, as I shall now explain.

The first difficulty is to do with the variety of bewildering names that are used for the trials in question. In the statistical literature in general one may encounter the following: cross-over, crossover, change-over, changeover, within-patient, within-subject, repeated-measures and even test–retest. Patient preference trials, sometimes referred to as Baskerville designs, after a paper in this journal [1], and so-called 'n-of-1' studies [2] are also forms of cross-over trial.

The second difficulty is that the term 'cross-over' is not uniquely reserved for cross-over trials. For example, one may have case-crossover studies as in the paper by Marshall and Jackson [3] or the phenomenon may be studied in connection with non-compliance in clinical trials whereby patients 'cross over' in an unplanned way from one treatment to another as in Heitjan [4], to take examples from this journal. In my search of the literature I excluded 'case-crossover' studies

*Correspondence to: Stephen Senn, Department of Statistics, University of Glasgow, Glasgow G12 8QQ, U.K.
†E-mail: stephen@stats.gla.ac.uk

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deliberately as part of the search strategy and used (crossover OR cross-over OR changeover OR change-over OR Baskerville OR *n*-of-1 OR *n* of 1) AND (journal = *Statistics in Medicine*) NOT case-crossover NOT case cross-over. The papers that remained were checked to ensure that non-compliant cross-over was not the subject of the paper.

The third difficulty is that it is partially a matter of judgement as to what should be classified as a paper on cross-over trials. Excluded by the strategy above would be some papers that made points of relevance and importance to cross-over trials simply because their authors did not feel it was worth including this in the keywords. Such exclusion may be reasonable enough but one cannot guarantee that the reverse does not occur and some authors may include *cross-over* as a key word even though the concept only gets a fleeting mention. Furthermore, there is one particular field, that of bioequivalence, in which papers frequently appear and for which cross-over trials are highly relevant but where it is possible that this fact is made neither explicit in title nor keywords. I have in the end decided to make a separate provision for such papers in my survey as will be explained below.

The fourth difficulty is that what may be defined as a paper is somewhat arbitrary. Some authors despise that short communication known as a 'Letter to the Editor' as being a form of publication not worth noting. For personal reasons I find this attitude distressing and I have decided to count in my statistical reckoning anything that would get a separate citation in PubMed MEDLINE.

The fifth difficulty is that ideally my review should be of the first 25 years of *Statistics in Medicine*. The timetable of writing, reviewing, editing and producing a paper in time to meet an anniversary edition however, means that I am struggling to cover the first 24 years in order to be able to produce a paper in time to celebrate the first 25. It sounds so much better, however, to refer

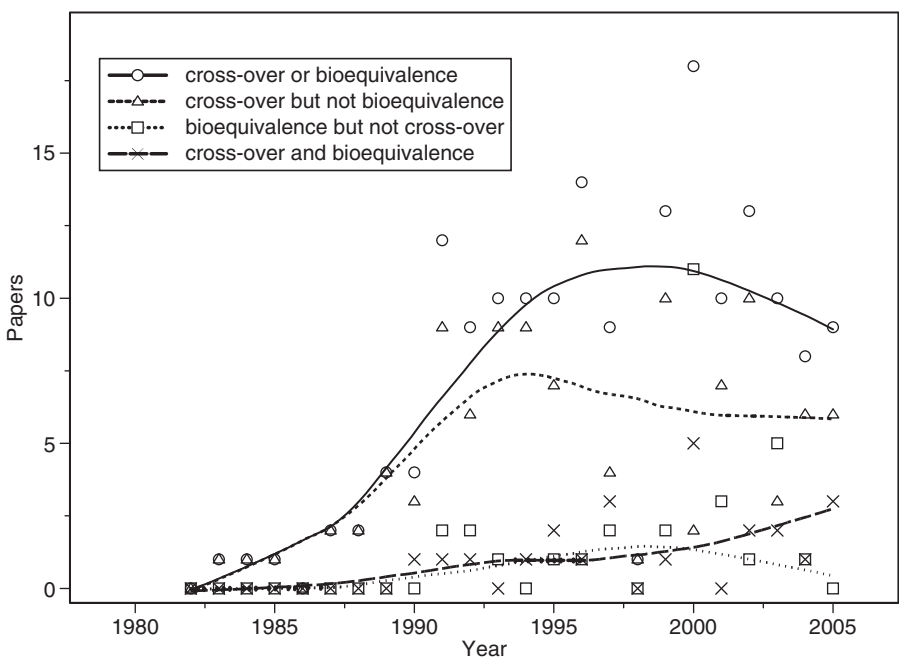

Figure 1. Number of papers on cross-over trials in *Statistics in Medicine* by year and type.

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to 25 rather than 24 years, that in what follows I will often use the larger figure. I am keeping my fingers crossed (-over) that no paper appears in 2006 that is so important that it renders all prior history of the cross-over in *Statistics in Medicine* irrelevant.

So accepting these limitations I can report that I have found some 171 papers in *Statistics in Medicine* about cross-over trials or bioequivalence or both. Of these 32 appear to be about bioequivalence only and 115 not about bioequivalence, the remaining 24 being about both topics, at least to the extent that title, keywords or abstracts are any guide.

At this point, I feel that some definition of cross-over trials is required and so I shall use one I like. 'A cross-over trial is one in which subjects are given sequences of treatments with the object of studying differences between individual treatments' [5, p. 3].

Figure 1 shows a scatter plot by year of the number of papers in the three categories, as well as the totals. Also included are LOESS fits. Readers should bear in mind that during its history *Statistics in Medicine* has moved from being a journal with four issues a year (1982–1985) to six (1986), then eight (1987), 12 (1988–1991), 16 (1992) and then 24 (1993–2005).

Accepting my definition of paper, just over 4000 have been published in *Statistics in Medicine* since its beginning but the annual rate has risen from 39 in the first year to a mean of over 250 since 2000.

2. REVIEWS OF INDIVIDUAL PAPERS

I shall review these under the following headings: 1. The two-stage analysis of AB/BA trials, 2. Baselines, 3. Binary and categorical data, 4. Survival data, 5. Modelling carry-over, 6. Bioequivalence and 7. Components of variation. In doing so, I shall not attempt a comprehensive review of all papers but pick out those that I feel are important. Although I have tried to say something about matters others think are important, even where I do not share their opinion, inevitably my selection is influenced by my personal tastes although it has also been guided by the number of times a paper has been cited. Where I have quoted this figure it is for citations until the end of 2005. A further limitation is that I have made no general assessment of the relative contribution (compared to other journals) of *Statistics in Medicine* in this field. This would have required a much more ambitious survey including other journals. However, a brief personal assessment of the contribution of *Statistics in Medicine* is made at the very end.

2.1. The two-stage analysis of AB/BA trials

In my opinion the most important paper on cross-over trials in the 25 years of *Statistics in Medicine* is Peter Freeman's paper [6] of 1989 (72 citations). However, this was not only the most important paper on cross-over trials in *Statistics in Medicine*, but also the most important paper on this theme anywhere. To understand its importance one has to appreciate what the 'accepted' approach to analysing AB/BA cross-over trials was when the paper appeared. That approach had been established by Grizzle [7] in 1964, nearly a quarter of a century earlier and it was to compare the means over both periods between sequences in order to test for carry-over and, if significant use an analysis based on the first period data only. This procedure had been endorsed by Hills and Armitage [8] in a very fine expository paper on the AB/BA cross-over (in which the two-stage procedure was only a minor feature) and there had been working papers on it produced both by the Food and Drug Administration (FDA) and by Statisticians in the Pharmaceutical Industry (PSI).

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I can perhaps best illustrate how pervasive the view was within the pharmaceutical industry that this was the 'right' approach to analysing such trials by the fact that when I started work in the pharmaceutical industry in 1987, one of the analysis tools available to me, was a SAS® macro that had been written by the programming support group and which would perform the test for carry-over and automatically select the 'correct' test to follow, documenting everything that had been done.

This automatic analysis gives a clue to the way that statisticians should have been looking at the two stage, but, prior to Freeman were not. However, many stages are involved, in the end a decision is made to accept or reject the null hypothesis just as surely as if only one stage were used. To the extent that they rely on clearly defined algorithms, all such procedures lead to a definite partition of the sample space into two regions: one in which the null hypothesis is accepted and one in which it is rejected. For the algorithm to be valid it should not lead to a greater rejection rate under the null than that claimed for it. It is this point that Freeman's paper examines as regards the null hypothesis. By considering the joint distribution of the test for carry-over and that of the within-patient test on the one hand (trivial, because independent), and the first period test and the test for carry-over and the first period test on the other (which are not independent), he was able to show that the two-stage procedure had a size well in excess of its nominal value.

A subsequent examination by Jones and Lewis some years later in *Statistics in Medicine* [9] attempted to show that the two-stage procedure was not in fact as bad as Freeman had painted it. The demonstration was based on power considerations but was not valid as the main point of Freeman's paper was that the procedure did not maintain the correct size [10]. It is possible to correct the two-stage procedure so that correct size is maintained [10–12] but it then loses its power advantage and for this and other reasons this cannot be recommended. Now I think it is more or less accepted by all who research in this field that Freeman's conclusion 'the two-stage analysis is too potentially misleading to be of practical use' is correct and but for the fact that medical statistics textbooks have been much slower to catch on, we could safely relegate the procedure to a historical curiosity.

2.2. Baselines

A thorough investigation of the use of baselines was made by Mike Kenward and Byron Jones [13] (29 citations). In fact, various 'baseline' measurements can be taken in an AB/BA cross-over trial: before the trial starts, after the first period and before the second and at the end of the trial [14]. In discussing the paper by Kenward and Jones, I consider the case with two baselines only (without the final baseline). Kenward and Jones made two important points. The first is that the strategy of subtracting the baseline values from the outcome values to create change scores, as is sometimes done, can only deal with the problem of carry-over if one assumes, which is usually implausible, that the carry-over from the first active treatment into the second is the same as the carry-over into the baseline. The second point is that under the most simple plausible correlation structures an analysis of such change scores will actually be less efficient than the analysis of raw outcomes. This is an important point and the reason that this is so is worth explaining.

For a parallel group trial, as has often been pointed out (an excellent discussion is given by Hills and Armitage [8]), then the change score has a lower variance than the outcome provided that twice the covariance between baseline and outcome is greater than the variance of the baseline. If the variances at outcome and baseline are equal then this implies that the correlation between them must be greater than 0.5 for the change score to be more efficient. Of course, in practice,

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most medical statisticians agree that an appropriate way to use the information in the baselines is not by simple subtraction but by conditioning on them in an analysis of covariance [15].

Nevertheless, simple analysis of change scores is frequently encountered in the medical literature and has even received some support (misguidedly so, in my opinion) from statisticians [16]. However, the origin of the correlation in a parallel group trial can only be the between-patient variation. If this is at least as great as the within-patient variation, the correlation will exceed 0.5. However, in an AB/BA cross-over design the standard analysis proceeds using within-patient contrasts and these already completely eliminate the between-patient component of variance. Thus, no further reduction of this component is possible. The only reduction that is possible by comparing change scores is thus from the within-patient element. If we write Y_1, Y_2, Y_3, Y_4 for period 1 baseline, period 2 outcome, period 3 baseline and period 4 outcome, then the analysis will be based on

$$(Y_4 - Y_3) - (Y_2 - Y_1) = (Y_4 - Y_2) - (Y_3 - Y_1)$$

rather than

$$(Y_4 - Y_2)$$

The condition for greater efficiency is now that twice the covariance between baseline and outcome *differences* is greater than the variance of the baseline *difference*. For the homoscedastic case this reduces to the condition that

$$2(1 - \rho_{13}) < 2(\rho_{12} + \rho_{34} - \rho_{23} - \rho_{14})$$

$$1 < \rho_{12} + \rho_{34} - \rho_{23} - \rho_{14} + \rho_{13}$$

where ρ_{ij} is the correlation between Y_i, Y_j. It is far from obvious that this condition is likely to be satisfied in practice.

To understand its implications further we can consider an AR1 process for the within-patient error but allowing for the fact that not all time intervals are equal. For example, the wash-out interval between observation Y_2 and Y_3 need not be the same as the intervals between Y_1, Y_2 and Y_3, Y_4 which ought, however, to be equal to each other, since corresponding to the length of a treatment period. Thus, we have $\rho_{12} = \rho_{34} = \theta$ (say) but $\rho_{23} = \phi$ (say). The AR1 process would imply $\rho_{13} = \rho_{24} = \theta\phi$ and $\rho_{14} = \theta^2\phi$. Hence, if this applies we have as our condition

$$1 < \theta + \theta - \phi - \theta^2\phi + \theta\phi$$

$$1 < 2\theta + \phi(\theta - \theta^2 - 1)$$

Since $0 \leqslant \theta \leqslant 1$ then the second term on the right-hand side must be negative. Hence, a minimal requirement for the analysis of change scores to be more efficient is that $2\theta > 1$. If the wash-out interval is very long compared to the treatment period, then it is possible that ϕ will be close to zero but that $\theta > 0.5$ so that the condition may be satisfied. This is most plausible for single-dose pharmacodynamic studies in which the wash-out period is frequently many times the length of the treatment follow-up period [17]. Under other circumstances the condition is unlikely to be satisfied.

2.3. Binary and categorical data

Mike Kenward and Byron Jones, both of whom have been frequent authors, both separately and together, in *Statistics in Medicine*, also published, in the same year as their baselines paper, an

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extremely important paper on binary and categorical data [18] (27 citations). In fact, both of these papers were substantially incorporated in the well-received monograph that they wrote together [19]. However, the paper on binary data did not appear in *Statistics in Medicine* but in *Applied Statistics* and so does not form a proper subject for this review. The most important paper on this topic to appear in this journal was, in my view, that of Ezzet and Whitehead [20] (31 citations). In fact, the paper concerns ordinal data and not binary data, but the latter is a special case of the former and the paper is of greater interest because it deals with the more difficult general case. In fact, logically it would form a follow-on paper to the joint paper of Ezzet and Whitehead in *Applied Statistics* [21] dealing specifically with binary data but the paper in *Statistics in Medicine* appeared in the preceding year and so has priority.

What Ezzet and Whitehead achieved in the paper was the generalization of McCullagh's proportional odds model [22] to a repeated-measures context by adding a random Normally distributed effect on the logit scale. The resulting formulation is elegant, flexible and appealing but in practice, not so easy to implement as both the authors, who wrote 'Interpretation of parameters is easy, though with a complicated fitting procedure' and others noted [23].

However, developments in statistical computing since the paper appeared, for example, Russ Wolfinger's proc nlmixed® in SAS® have made it much easier, at least as regards the binary case, to implement the Ezzet and Whitehead approach and for such data this is the one I now recommend [5]. Also useful is the Mainland–Gart test [24, 25]. However, the most-cited paper from *Statistics in Medicine* treating cross-over trials is that of Zeger and Liang [26] (209 citations) and this also covers binary data. The reason I have not given space to discuss this is that this is a general paper on repeated-measures modelling with illustration of the methodology on cross-over trials.

2.4. Time-to-event analysis

This topic is most often associated with survival analysis, for which cross-over trials are unsuitable, but for re-occurring events they may be applied. For example, patients can be given exercise tests in angina, the outcome being the amount of exercise tolerated before pain occurs. Similarly, in asthma, patients may be given provocation tests and the amount of methacholine inhaled that produces a given reduction in forced expiratory volume in one second (FEV_1) noted [27]. Such measures may be censored if the manoeuvre stops before the target outcome is reached. Hence, techniques generally used in survival analysis are relevant.

An important early paper on this topic in this journal was that of France *et al*. [28] (25 citations). They used a proportional hazards formulation to derive a conditional test that was effectively a version of the sign test allowing for censoring. The advice they gave regarding estimation, however, was rather controversial. In fact, it was an important paper in *Statistics in Medicine* a few year later by Ford *et al*. [29] (24 citations) that showed that there are problems of model consistency when comparing estimates from proportional hazards models with and without covariates. Although their paper does not address the issue of cross-over trials, the problems they describe apply *a fortiori* in that context.

A subsequent paper also in this journal was that of Feingold and Gillespie [30], whose development of survival analysis for cross-over trials led to a modified form of the Wilcoxon test. This is the approach I now recommend for analysing survival data for AB/BA cross-over trials. However, such methods do not readily generalize to more complex designs and it may be worth studying Philip Hougaard's magnificent book on multivariate survival analysis [31] for alternatives.

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2.5. *Modelling carry-over*

Cross-over trials in two or more periods appear to offer more possibilities for modelling carry-over than the AB/BA design. Hence, modelling carry-over has been a topic particularly associated with design of cross-over trials in more than two periods.

A fine example of the genre is the paper by Fletcher *et al*. [32]. This develops a toolkit for building cross-over trials using 'bricks' which have known efficiencies for estimating direct effects of main effects and interactions. (A 'direct effect' in this context means the effect of a treatment or treatments in the period in which they are administered as opposed to 'residual effects' appearing in subsequent periods, which are forms of carry-over.) The bricks can then be put together to build a design in a way that is reasonably efficient given the practical constraints of the number of periods available.

Nevertheless, the formulation in the paper is not without problems as it pre-supposes a form of carry-over, which has been referred to as 'simple carry-over' [33], that is not realistic. In simple carry-over the carry-over is assumed to last for one period only and to depend only on the engendering treatment and not the perturbed treatment. This means that in modelling effects, for any patient, for every period except the first, there is a carry-over parameter that is analogous to the direct treatment effect parameter in the preceding period. Thus, in the case of factorial cross-over designs, since the direct effect model is factorial, there is a direct parameter for the interaction of two treatments and there must also be a carry-over parameter for this interaction. This carry-over of an interaction can be formally equivalently modelled in terms of an interaction of carry-overs. In fact, in terms of pharmacokinetic and phamacodynamic modelling, this interpretation makes more sense. Yet if the model allows for the interaction of two residual effects why does it not allow for the interaction of residual and direct effects?

Similar contradictions abound in the literature. For instance, dose-finding cross-over trials with several doses are considered, which only make sense if the possibility of non-linearity of the dose–response cannot be excluded, whereas the simple carry-over model only makes sense if it can.

One can argue that some sort of simplification in modelling is required if progress is to be made but if that is the defence of such models, then it is puzzling as to why the even simpler and plausibly more efficient approach of assuming that whatever carry-over there is so modest that it may be ignored altogether is eschewed. The suspicion naturally arises that the real purpose of such models is not to contribute to the search for new remedies but to produce publishable mathematics. For example, papers that have appeared in *Statistics in Medicine* on this particular topic have been so divorced from clinical reality that they have even implicitly assumed that patients are recruited simultaneously onto clinical trials [34–36]!

It has been rather disappointing that little has appeared in *Statistics in Medicine* on the subject of modelling for carry-over that is more grounded in clinical and pharmacological reality. A notable exception is a paper on dose-finding by the late Lewis Sheiner [37] and colleagues, that appeared in 1991 (44 citations). They considered an integrated non-linear mixed effects model for dose–response and carry-over in the context of repeated dose trials (that is to say where patients are given a treatment schedule of several weeks), as follows. First, the drug effect DE_{ij} for the jth period for the ith individual is

$$\mathrm{DE}_{ij} = \frac{E_{\max i} d_{ij}}{D_{50i} + d_{ij}}$$

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where d_{ij} is the actual cumulative dose (taking account of dose history, time and pharmacokinetic elimination). Second, a pharmacokinetic model links d_{ij} to D_{ij} the nominal dose (that is to say the dose administered in that period) by

$$d_{ij} = \sum_{l=1}^{j} D_{il}(1 - \mathrm{e}^{-tk_i})\,\mathrm{e}^{-k_i(T_j - T_l)}$$

Here k_i is the weekly elimination rate for patient i, T_j is the time in weeks since the beginning of the trial to the end of treatment period j and t is the length of a treatment period in weeks.

This model may seem rather crude but is, in fact, much more sophisticated than those commonly employed by statisticians working on optimal design and it is used to make a number of penetrating observations by the authors.

First, they point out that it implies that to the extent that carry-over applies, steady-state has not been reached by the end of a standard treatment period. Hence, parallel group trials will also be biased as a means of studying the steady-state effect of treatment. Second, they point out that although the model is adopted for convenience it 'is simply one way of causing current drug effect to depend on all past doses in direct proportion to their magnitude, but in inverse proportion to their remoteness in time' (p. 307). In the particular context of dose–response, this is a brilliant solution to the problem of carry-over since two arbitrary and implausible elements of the simple-carry-over model, that the effect last for one period only and (more seriously) is not perturbed by the current treatment, are replaced by a more plausible one at the cost of no extra parameters.

Otherwise, in my view, the most important papers on carry-over did not appear in *Statistics in Medicine* but were published in *Biometrics* [38] and *Controlled Clinical Trials* [39] (13 and 42 citations, respectively) by the late Joe Fleiss who argued vigorously that models and designs relying on the assumption that the carry-over from one drug into another was the same as from a drug into itself were not credible. This work did, however, receive an echo in this journal [33, 40].

2.6. Bioequivalence

Some of the key names in this field, one thinks of Anderson, Chow, Endrenyi, Gould, Hauck, Hauschke, Liu, Schall, Steinijens, Vuorinen and Wellek have published on bioequivalence in *Statistics in Medicine* over the years. Of the 56 or so papers on bioequivalence, at least 35 have been (at least partly) on the subject of individual bioequivalence. The figure of 35 is a lower bound because there is at least one instance, Lewis Sheiner's much-cited (71 citations) paper [41] of 1992, where the word 'individual' does not appear in title, abstract or amongst the keywords although that is what the paper is about. This is not the most-cited paper on the topic of bioequivalence in *Statistics in Medicine*. It is beaten by a whisker by Schall and Luus's paper [42] of the following year (72 citations). I shall look briefly at these papers in due course. However, it would be unreasonable to survey the field of individual bioequivalence without mentioning the work of Hauck and Anderson, since it is ultimately responsible for so much that has appeared in this journal. They *have* published on this topic in *Statistics in Medicine* on a number of occasions, for example, a brief note in 1991 [43], but it is their innovating earlier paper of 1990 in the *Journal of Pharmacokinetics and Biopharmaceutics* [44] which has been most influential (113 citations) and, indeed, has been the reference point for much of the debate in this journal. Also important is their paper of 1992 in the International *Journal of Clinical Pharmacology and Therapeutics* [45] in which they developed these ideas further.

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What Anderson and Hauck did was raise two practical issues that might affect judgements of equivalence, namely prescribability and switchability, and which might not be guaranteed to have been achieved simply by proving that in an average sense two formulations were the same. For example, one of the formulations might be much more variable with greater potential for over- and under-dosing. I agree that this is a relevant concern. However, addressing it is as much an issue of design as analysis. For example, if it occurs as a result of inferior manufacturing it would seem to imply some strategy for *sampling* from production with a plan for selecting batches [46, 47]. If, on the other hand, it is not a question of simple generic substitution but because different routes of administration are being compared, as say when a pill is compared to a suppository, then the issue may be affected by the physiology of patients, implying that care must be taken how they are chosen. This would call into question the general practice of using healthy volunteers. This field of comparing formulations in terms of marginal distributions (conveniently summarized by means and variances) is now referred to as *population* bioequivalence.

A rather different issue, however, is that of 'switchability' [45]. Hauck and Anderson pointed out that even if the two formulations had identical means and variances as regards bioavailability it could be still be the case that there were given patients for which one or the other was more bioavailable. Such patients might notice a difference in effect when switched from one formulations to the other. Although I agree that this is a technical (if rather implausible) possibility I do not accept that it is important [48]. This view, I have to report, seems to be a minority one, else there would not have been so many papers on the subject in this journal. My argument is, however, that authors have forgotten what the end purpose of bioequivalence studies is and this is not, strange as it may seem, to prove that a new formulation is equivalent to an existing one, it is to show that it is sufficiently similar to be granted a license.

Imagine a thought experiment in which we have shown to everybody's satisfaction that a generic drug G is equivalent to a brand-name B in terms of mean and variance of bioavailability. We suppose that drug B has a license but that G does not. If we refuse to grant a license to the generic manufacturer we must nevertheless believe that if exactly the same full development programme that led to B's registration were repeated by G there would be a good chance that G would get a license [48]. Indeed if we doubt that this programme would be successful, it calls into question also the grounds on which B has been granted a license. It is thus absurd to refuse to grant G a license on the grounds of failure to demonstrate switchability when such a demonstration is neither relevant to the general prescribability of the drug nor a requirement we impose on products that go through full drug development. After all, when a new statin is put on the market some physicians will switch patients on rival statins, with different molecular structures, without the regulator having demanded studies to show that this is harmless. The risk in switching a patient from one formulation to another of the same drug must be less than this. However, these practical and philosophical considerations do not seem to have deterred authors from continuing to research in this area and, as promised, I now look, briefly, at the two most-cited papers in *Statistics in Medicine* in this field.

Sheiner's paper [41] reviews and builds on many of the ideas in Anderson and Hauck but gives them a typical (for Sheiner) biological twist. He mentions right away in Section 1 that a minimal requirement that standard approaches to bioequivalence omit is a consideration of the variances of the formulations. In Section 2 he proceeds to consider what physiological and pharmacokinetic considerations lead us to consider that equality in terms of measured concentration of two formulations implies equivalence of the formulations themselves. Further discussion in Section 3 leads to two moment-based measures of equality. If F is a univariate measure of bioavailability with T and R standing for test and reference i, indexing individuals and k indexing 'drug/preparation

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exposure within individuals', the first measure is for 'relative population risk'

$$\mathrm{RPR} = \frac{E[(F_{\mathrm{T}ik} - \overline{F}_{\mathrm{R}})^2]}{E[(F_{\mathrm{R}ik} - \overline{F}_{\mathrm{R}})^2]} = \frac{[\overline{F}_{\mathrm{R}} - \overline{F}_{\mathrm{T}}]^2 + \omega_{\mathrm{T}}^2 + \sigma_{\mathrm{T}}^2}{\omega_{\mathrm{R}}^2 + \sigma_{\mathrm{R}}^2}$$

Here it is assumed that the reference product is being given at the optimal dose, which leads to expected concentration $\overline{F}_{\mathrm{R}}$ and that any prescribing physician faced with a new patient has no choice but to use the dose that is expected to lead to the supposed optimal concentration. By definition for the reference product on average this will be obtained but for the test product on average the value is obtained is $\overline{F}_{\mathrm{T}}$. If a quadratic loss is assumed and Normally distributed values, then for any given patient, the expected loss in being prescribed the test formulation is the sum of the three terms in the numerator on the extreme right-hand side of the expression: the square of the difference in means, plus the inherent variation ω_{T}^2 between patients from the ideal when given T plus any remaining variation in giving the formulation σ_{T}^2. However, analogous terms to the last two cannot be avoided by giving the patient the reference formulation and so terms ω_{R}^2 and σ_{R}^2 appear in the denominator.

The second expression is for 'relative individual risk',

$$\mathrm{RIR} = \frac{E[(F_{\mathrm{T}ik} - \overline{F}_{\mathrm{R}i})^2]}{E[(F_{\mathrm{R}ik} - \overline{F}_{\mathrm{R}i})^2]} = \frac{[\overline{F}_{\mathrm{R}} - \overline{F}_{\mathrm{T}}]^2 + (\omega_{\mathrm{T}}^2 + \omega_{\mathrm{R}}^2 - 2\omega_{\mathrm{TR}}) + \sigma_{\mathrm{T}}^2}{\sigma_{\mathrm{R}}^2}$$

Here the loss for any patient is by comparison to the best expected value for him or her in applying the reference product. The denominator eliminates the pure between subject variability. Here ω_{TR} is a sort of covariance of bioavailability measure and the numerator, however, reflects the fact that only if the means are the same and the variances ω_{T}^2, ω_{R}^2 are equal to each other and the covariance, implying perfect correlation, will a patient be expected to suffer no loss in switching from his or her perfectly adjusted test dose to the suppose equivalent reference.

Much as I admire Lewis Sheiner's work in general, for reasons given above, I am not of the opinion, although conceding its theoretical interest, that the RIR measure is particularly useful in particular because the assumption that the reference product is being given at an optimal dose for a given individual seems unrealistic. However, further sections of Sheiner's paper including discussions of suitable experiments and various practical considerations will repay careful study.

Without in any way wishing to diminish the importance of Schall and Luus's paper [42] it is perhaps fair to note, as they do themselves, that there are many similarities in their approach to that of Sheiner's. However, in addition to proposing various approaches to estimation and considering these in some detail, in particular a bootstrap approach, they also consider explicitly the relationship between moment-based criteria of equivalence and probability-based criteria. For example, they consider measures such as

$$P_{\mathrm{W}}(T, R) = \Pr[|F_{\mathrm{T}} - F_{\mathrm{R}}| \leqslant r]$$

$$P_{\mathrm{W}}(R, R') = \Pr[|F_{\mathrm{R}} - F_{\mathrm{R}'}| \leqslant r]$$

where the first of these is the probability of a within-subject difference between formulations less than or equal to some target quantity and the second the analogous quantity for a subject given the same formulation on two occasions. Next, they propose the bioequivalence criterion

$$P_{\mathrm{W}}(T, R) - P_{\mathrm{W}}(R, R') \geqslant \Delta$$

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Table I. Degrees of freedom in a cross-over trial.

Source	Degrees of freedom
Patients	$n-1$
Periods	$p-1$
Treatments	$t-1$
Residuals	$np-n-p-t+2$
Total	$np-1$

An analogous approach is outlined for population bioequivalence. It is the relationship between the development of probability- and moment-based criteria in Schalland Luus's paper that is particularly interesting and which has led to its popularity in citation.

2.7. Components of variation

Consider a complete blocks cross-over design with n patients, p periods and t treatments $t \leqslant p$. A conventional linear model fitting patient, period and treatment as fixed effects is employed. Assume for simplicity that carry-over will not be modelled. The degrees of freedom from a linear model will then be as in Table I. Since $t \leqslant p$ then for any n and p the residual degrees of freedom will be a minimum when $t = p$, when they will be equal to $np-2p-n+2=(n-2)(p-1)$. Thus, for any trial with three or more periods the degrees of freedom for error exceed $2(n-2)$ and provided that the number of patients is at least 5 will exceed the number of patients. This implies that for a valid analysis of treatment contrasts from such designs strong assumptions are required [49]. In the context of bioequivalence a great deal of work on this topic has been carried out (as should have been clear from the discussion in Section 2.6). This is rather ironic since the formulation-by-subject interaction may be expected to be much smaller in bioequivalence studies than the corresponding treatment-by-patient interaction in other trials and not surprisingly the component of variation has been found on occasion to be zero [50]. Outside of bioequivalence there appears to have been little work in this journal on this topic though papers by Brown and Kempton [51] and Putt and Chinchilli [52] and perhaps my paper with Hartwig Hildebrand [49] might be mentioned.

The fact that more generally the formal study of patient by treatment interaction has received little attention is rather a pity since to the extent that we do think, as the subject of pharmacogenomics invites us to, that individual response to treatment is important, then cross-over trials in which patients are treated repeatedly with the same treatment (n-of-1 trials are an example) would have great potential in investigating this issue [53, 54].

3. SUMMING UP

So what can be said about the contribution of *Statistics in Medicine* in its first 25 years to the literature on the cross-over trial? On the whole I think it is one of which the editors can be proud. The most important paper on cross-over trials during the period was Freeman's paper in the journal [6]. Baskerville designs [1] were first introduced in *Statistics in Medicine* and the debate on bioequivalence was given a vigorous airing, not just in the two papers I have considered in detail [41, 42] but in others also. (See Reference [48] for a review of some issues.) Important papers on survival analysis [28], baselines [13] and binary and ordinal data [20] as well as one of

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the most original and realistic approaches to modelling carry-over [37] appeared in *Statistics in Medicine*.

However, the record is not without blemishes. Some very silly work on design has been published in which the authors, for example, were unaware of the simple fact that patients are treated when they fall ill. It must be counted as a black mark against the refereeing and editorial process that these papers got through. However, with more than 4000 papers in total published in *Statistics in Medicine* since the start this is perhaps understandable.

It is also perhaps to be regretted that despite its seminal importance to researchers in methodology, Freeman's paper [6] has not had the impact it should on practice. Grizzle [7] and Hills and Armitage [8] continue to be cited at a higher rate [55] and textbooks advising their readers on how to perform a two-stage analysis continue to appear [56]. Once started, nonsense is difficult to stamp out.

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