Guernsey carries on

Guernsey McPearson

At Panacea Pharmaceuticals we actually have two statistics groups, clinical and methodology. As I often put it, 'we have a group with lots to do and no time to think and another with lots of time to think and nothing to do'. The trouble is that the time to think group, that is to say the methodology group, don't actually think very well and in particular seem to get very confused about the difference between mathematics and science. I think it was the great George Box who said, I quote from memory, 'statisticians have the opportunity to become first class scientists but generally prefer to be second class mathematicians'. Well, I wouldn't go so far as to describe the statisticians in clinical as first class scientists, with perhaps one or two exceptions, or maybe just one, now I come to think of it, but then I am not sure that our statisticians in methodology make it to being second class mathematicians either. Perhaps third class would be nearer the mark.

Don't get me wrong. There are plenty of posturing nincompoops in every profession at Panacea. All of them, of course are expensive in terms of salaries but many of them are also very costly in terms of consequences, in particular some of the morons we have working in our marketing department cause endless trouble for the company. Now, although the statisticians in our methodology group don't work for free, being statisticians, of course, they don't get paid a fortune and further more since nothing they ever do has the slightest effect on anything anybody else does, they are largely harmless and we in clinical don't lose any sleep over them, in fact we generally don't think about them at all. They might as well exist on another planet. (We are on planet pharmy and they are on planet barmy.) So on the whole, I look upon our methodology group as an affordable luxury and, if I am perfectly honest, it has occurred to me that it might be a possible sideways move for myself to switch to the methodology group and pass some quiet years out of sight doing largely what I want while collecting my monthly pay check and whiling away the years to retirement.

So until recently, I had no cause to worry about the methodology group. Unfortunately however, conditions have changed, and there is now a serious danger that somebody might actually start paying attention to them. Sir Lancelot Pastit is becoming ever more desperate about the lack of molecules in the pipeline and, as anybody with any years' experience in the industry knows, as the number of projects declines, the number of management initiatives increases. One of the latest is the so called IDEA initiative. I hated it even before I knew it meant, *Innovation in Design and Excellence in Analysis*, at which point I graduated to utter loathing. The saddest thing about this, I thought, was that some moron in the marketing department actually thought that he was having an idea in naming this, 'IDEA'. I was reminded of Ambrose Bierce's definition of a platitude: *a jellyfish withering upon the shores of the sea of thought.*

Imagine my horror, therefore at hearing the following words emerge from Harvey Puffer's mouth, when discussing work on an early development cross-over trial in asthma for our would be once daily long acting beta-agonist (or *LABA* to use the jargon), Fairbreeze®.

‘So Guernsey, you do remember, don’t you, that we need to justify the trial design in terms of the IDEA initiative.’
‘What?’ I said, ‘it’s not enough to justify the design as being suitable for the job, we actually have to refer to the IDEA slogan: *millennial methods for millennial medicine*?’
‘It’s more than that Guernsey, we have to show that we have consulted the methodology group about possible alternatives.’
‘What!!!!?’
‘Yes. I feared that might be the reaction. I know that you are never very keen on management initiatives, so I took the liberty of passing our protocol outline to the methodology group and have received some comments from them.’
‘Harvey,’ I said, ‘these morons are a bunch of mathematicians manqué. They wouldn’t know whether you swallow a metered dose inhaler or shove it up your,’ I paused, ’nose. How do you expect to get sensible advice from them?’
‘Now, now, Guernsey, why don’t we look at what they came up with. In fact, I have invited one of them, David Sign, to come and give us a brief presentation.’
‘What, here, now?’
‘Yes.’
‘Well, I think the least you could have done is told me. I would have arranged to have a prior engagement or taken the day off.’
‘Ah here he is. David, I believe you know, Guernsey.’
‘Hi Guernsey. How’s the philosophy going? Written any more papers on concepts recently?’
‘Quite a few,’ I replied. ‘Defrosted any patients recently?’
David turned pale. I was referring to a recent paper of his, ‘Optimal adaptive cross-overs,’ in which he had described how you might adjust the treatments given to patients in subsequent periods of a cross-over design based on results from period one and two. This of course, brought a letter to the editor from GMcP pointing out how difficult this was to achieve in practice in view of the time-honoured tradition that you treated patients when they presented, which made it quite hard to start everybody off at the same time. I think I referred to the approach favoured by Sign et al as the *deep-freeze microwave theory* of clinical trials. Some at Panacea protested that this wasn’t a very nice way to treat a colleague but I believe it was Popper who said that science is the process of hostile-friendly criticism and in the words of Meatloaf, ‘two out of three ain’t bad’
‘Well,’ he said, ‘you will be pleased to learn that I have found a simple way to improve your design.’
‘Don’t tell me,’ I said, ‘you are going to tell us how to balance for first order carry-over.’
‘Yes. You have a very inefficient design. In fact it isn’t even uniform on the periods.’
‘What does that mean?’ said Harvey
‘It means balanced for period effects,’ I replied.
David’s lips curled into a sneer. ‘In the design community we reserved the word balanced for a technical meaning,’ he replied.
‘Or *meanings*,’ I said. ‘You know, *balanced incomplete blocks*, *balanced for carry-over*. I sympathise,’ I continued, ‘we reserve *period* in clinical trials for a technical meaning that reflects the fact that patients are treated when, but generally not before, they fall ill.’
David shot me a look that would have curdled milk. ‘You see,’ he said, writing on the board , ‘you have sequences as follows:

0	1	1	1
1	0	2	2
2	2	0	3
3	3	3	0

'What does that mean?' said Harvey, 'We have treatments P, D_1, D_2, D_3 in our protocol.' (I mean he didn't actually say the subscripts as subscripts but that's what he meant.)
I answered his question, '0 is P, 1 is D_1 and so forth. They often use numbers for treatments in the design world.'
'Ah well,' said Harvey, 'there's obviously a misunderstanding. You have the patients being given dose 1 three times in the first sequence.'
'They also write the sequences down the page,' I said, 'Sequence 1 is the first column not the first row.'
'They write sequences down the page!' repeated Harvey in a voice of utter amazement, 'Why?'
'It's a tradition in the design community,' replied David.
Harvey looked flabbergasted.
'Anyway,' repeated David, 'I have a very standard simple alternative. It looks like this,' and he wrote:

0	1	2	3
1	3	0	2
2	0	3	1
3	2	1	0

'Now, not only does this permit efficient adjustment for the period effect but it is highly efficient as regards adjustment for the carry-over effect since every treatment follows every other.'
Harvey nodded and fixed his features to produce the sort of face a man tries to produce who wishes to let the world know he is following when in fact he is still struggling to open the front door.
'*Simple* carry-over effect,' I corrected. 'You are assuming that the carry-over from a given treatment is the same whatever follows'
'Well, why shouldn't it be?' replied David.
'Careful', I said, 'this could involve some conceptual thinking. I don't often find myself quoting Sir Lancelot, but we might have to *push the envelope*, *think outside the box* and possibly do some *reverse engineering* whilst thinking about the *ownership* of the problem'. I nodded in the direction of Harvey, who was perking up at the sound of some familiar phrases.
'Permit me to restore some context,' I answered, writing

P	D_1	D_2	D_3
D_1	D_3	P	D_2
D_2	P	D_3	D_1
D_3	D_2	D_1	P

'and', I added, 'because of the proposed design we don't even need to argue as to whether rows or columns are sequences. Now in the third period of the second sequence the simple carry-over model has a carry-over due to D_3, which is the highest

dose and the same is true for the second period of sequence four and these carry-overs are assumed identical.'
'Yes. What's wrong with that?'
'Well,' I said 'let me put it in a way you might understand,' and I wrote on the board.

$$\Delta Y = f\left(X + \delta\right) - f\left(X\right), 0 \le X \le D_3$$

'Here X is the current dose, δ is the fraction of the *dose* given in the previous period, $f(\ )$ is the dose response function and ΔY is the difference in the response, Y, brought about by the phenomenon of carry-over that is to say the carry-over of effect. This is what the simple carry-over model implies'
'So?'
'So what can we say about $f(\ )$?

(Gentle reader, I should point out that you have to make allowances, *mutatis mutandis*, for the difference between a scientific discussion as it takes place and the way it is reported. When I write $f(\ )$, I didn't actually say 'start italics f open bracket blank close bracket end italics' still less proceed in the style of Victor Borge's phonetic punctuation, http://www.kor.dk/borge/b-mus-1.htm.)

'Well. Clearly it's linear,' said David.

'Yes,' I replied 'in fact linear between 0 and D_3 and even beyond and how many doses does one need to estimate a linear dose response?'

'Two, of course.'

'And how many doses do we have?'

'Three.'

'Well actually four, since placebo may be regarded as dose zero' I said. 'And why have we chosen four doses if we think the dose response is linear?' I carried on.

'Because you haven't thought about it!,' said David triumphantly.

'On the contrary, we have thought about it a great deal. We don't believe the dose response has to be linear and so we don't believe your carry-over model but then we don't consider it likely that there will be appreciable carry-over at all.'

'OK. So you don't like the carry-over model. But what about your design not being uniform on the periods?'

'It's an ethical constraint. This is the first repeated-dose study in patients. We suspect that the highest dose will be tolerated but we aren't absolutely sure. We are very confident that the D_1 dose will be tolerated but we would really like to go as high as D_3 in case D_1 is not efficacious but we can't risk giving the patients that first without trying them on the lower doses.'

‘I am just wasting my time,’ said David bitterly.

‘Not just yours,’ I wanted to say, but uncharacteristically bit my tongue.
After he had gone Harvey said, ‘this is all very well, Guernsey, but how are we going to square this with IDEA?’

‘That’s easy,’ I said. ‘I’ll write the justification’.

And so I did:

The team members considered the standard solution of employing a Williams square but inspired by the IDEA philosophy and being encouraged to push the envelope and think outside the box, used some pharmacokinetic pharmacodynamic insights as well as exploiting bias variance trade-offs to choose a bold solution of a dose-escalation design with intervening placebo, thereby recognising ethical constraints as well.

Some time later I met Harvey.

‘That David Sign character,’ he opined, referring to our previous meeting, ‘He made even less sense than you usually do. I can’t imagine why you got him involved.’

For once, I was speechless.

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