



## A subject requiring great patience

by Alistair Reeves

Elise Langdon-Neuner recently provided *TWS* readers with a useful table of terms for animals and people in nonclinical and clinical trials (What takes part in a clinical trial—subjects, individuals, controls, or even people? *TWS* 2005;14(4):118).

Let's take a closer look at the options. And at the same time, I'd like to give you my opinion on each.

Before that, however, a typical scenario for us medical writers when writing a protocol or study report:

- I am given a template and instructions at the kick-off meeting that says 'use patient', even though the official title of the report says 'subjects'.
- I prepare a draft with 'patient', and during the first review cycle, one reviewer crosses out 'patient' and scribbles 'Company terminology is "subject"; please use'. I try once to point out that the template and instructions say use 'patient'. No response.
- I change everything to 'subject' for the next review cycle (I have learned to check for 'insubject(s)' and 'outsubject(s)' after using search and replace!). During this cycle, one reviewer writes in the margin 'I thought we were supposed to use "patient", please change'.
- I check with the report coordinator who says he will have to contact the line manager to ask about this one. The line manager says she 'knows the template says "patient" but actually prefers "subject", and that she'll discuss this with colleagues'. Answer: use 'patient'.
- I change everything back to 'patient'.
- The report goes to the US subsidiary for review. One of the reviewers asserts: 'FDA says we have to use "subject"! Please change!'
- I am told by the European Head Office to ignore this and stick with patient.
- The report goes into wider review, including Regulatory Affairs. Someone in Regulatory Affairs says that ICH says you 'have to say "subject" so we have to change it back'. I change everything and check for 'insubject(s)' and 'outsubject(s)' again.
- OK, but when the report goes to QC, they say 'our template says "patient" so we have to use patient'.
- At the report finalisation meeting, I ask the report manager what we should do. I sit back while several very highly paid people once again discuss the merits of each term for about 10 minutes and then decide that they will have to address this with line management.

- Line management, QC and Regulatory Affairs have various telephone conversations and tell me to stick with patient.
- I change everything back to patient.

**Moral of the story: this is a subject requiring great patience.**

### People in clinical trials

#### Patients and subjects

For me, the term for people in clinical trials is **subjects**, and **patients** are a subgroup of subjects. And that is basically it.

Elise pointed out that 'many physicians were dismayed by the FDA's suggestion that trial participants be called subjects rather than patients. They considered such a label to be hurtful to the physician-patient relationship'. Maybe it's because I am not a physician (although I am a patient from time to time), but I see nothing wrong with the word 'subject'. In fact, I think it is a good, neutral word, and I prefer it to 'participant' or 'volunteer' (see below). In our field, we use many words with a specific meaning that they do not have in general usage, because it is expedient and, as long as abuse or denigration of people is not evident, I don't think this means we are seeing the thin end of the wedge with the term 'subject'. It is quite different, of course, if you use the verb 'to subject to': then the word 'subject' has very different connotations. Also, I am not really happy about being a *subject* of Queen Elizabeth II, although it is actually still quite legitimate to describe me as such!

My basic approach: **Subjects** are enrolled into Phase I–IV trials; **patients** are enrolled into Phase II–IV trials. You decide which to use and remain consistent.

Of course, there is a grey area with Phase I and IIa trials:

- Pharmacodynamic (PD) investigations in persons with a target disorder: **patients** or **subjects**.
- Pharmacokinetic (PK) investigations in persons with renal or hepatic impairment: **subjects**. Even though the people/persons enrolled have renal or hepatic impairment and are therefore not healthy, the aim of the study is not to establish whether the drug has any effect on the renal or hepatic impairment (although this may be an incidental finding), but whether the absorption, distribution, metabolism and excretion pattern is different from in healthy **subjects**.
- PD and PK investigations: **subjects**.

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### Participant

I am always for brevity, so why use a four-syllable word when you have shorter alternatives: men, women, subjects, patients? 'Participant' also does not work so well used adjectivally (consider 'participant diary' instead of 'patient diary', for example).

### Volunteer

My objections to volunteer are: i) it is also longer than alternatives; and ii) all people in all clinical studies, regardless of the phase, are volunteers. Using volunteer only for healthy subjects in Phase I studies does not seem correct since it suggests a different quality of participation, as if patients are not volunteers, whereas, in fact, both healthy subjects and patients have to give informed consent, have to meet inclusion criteria and not violate exclusion criteria, and may withdraw from the study at any time without giving reasons. But it would be ridiculous to talk about 'healthy and patient volunteers', for example ('unhealthy volunteers' would be a possible formulation, but 'unhealthy' has negative connotations, includes almost a 'moral' component, and often means more than just the opposite of 'healthy'). Back to: healthy subjects and patients!

### Individual, male and female

You should never have cause to describe a person as a 'male', a 'female' or an 'individual'. To me, 'individual' as a noun smacks of a comic police report ("*I was proceeding down Grey Street in Newcastle when I was approached by an individual in a flat cap.*") and it is not commonly used in spoken and written British English. I appreciate that those more used to American English may feel differently about this, as I think it enjoys wider currency in the American English-speaking world.

I agree with Elise that 'male(s)' and 'female(s)' as nouns should be reserved for animals and that 'individual' should only be used adjectivally, and even then should be used sparingly, because 'single' or 'isolated' is often better.

Wherever possible, I also always prefer to use 'girl', 'boy', 'man', 'woman' or the plural. For example, if you are writing a patient narrative, in almost all cases it will be obvious that you are talking about a patient. Why not start with 'A 26-year-old man was admitted ...' rather than 'A 26-year-old male patient ...'? In your inclusion criteria, why not put 'Men and women aged 18 years' instead of 'Male and female patients/subjects ...', or worse 'Patients of both genders ...' or worse still 'Patients of either gender ...'? 'Adolescent' can be a problem if it needs to be qualified to indicate the sex of the young person: 'adolescent boy(s)' or 'adolescent girl(s)' is certainly preferable to 'male/female adolescents'. The same goes for 'teenage(r)'. Do not use 'juveniles' or 'youths' for young people in our context. 'Juvenile' is used almost exclusively adjectivally: in common parlance, it is frequently collocated with the words 'delinquent' and 'offender' in British English and therefore has a negative connotation, and also often means 'immature' in the negative sense. 'Juvenile neutrophils' and

'juvenile diabetes sufferers' are quite different: here it just means 'not yet adult or mature'. 'Youth' used as a **concrete (countable) noun** is used to refer **only** to young men (at least in British English) and is also not generally used in a positive context. 'Youth' used as an **abstract (uncountable) noun** is used for men and women and can have a romantic touch: 'She may be 69 years old, but she has such youth and vitality!' The adjectival use of 'youth' (youth projects, youth organisations, youth studies) is usually positive and applies to both sexes.

### Untreated people in studies or people who receive placebo or vehicles

Control subject(s), untreated subject(s) or healthy subject(s), whatever is appropriate (be consistent). However tempting it may be to write, people are never just plain 'controls'—it makes them sound like rats or contact persons in a spy ring.

### Other designations

What about terms like 'diabetic(s)' and 'hypertensive(s)'? Such terms are linguistically interesting because they are actually—wait for it—adjectival nouns, a device used much less frequently in English than in other languages. This is a familiar concept to speakers of languages other than English, because in many languages they are inflected (are gender-, number- and case-dependent) in some way (and are a difficult aspect of foreign languages for native English speakers to master). They are therefore often sex-specific without a modifying adjective in such languages.

When you are speaking, I think no-one could take exception to your saying 'Diabetics have a hard life because they have to stick to a very rigid diet'. As a 'hypertensive' myself, I have no problem in being referred to as just that in spoken English: 'a hypertensive'. But I think writers of English in our field should make it a general rule that they say 'diabetic girls/boys/men/women/children/patients' even sometimes 'people', perhaps 'persons' or 'the diabetic population', for example. 'Epilepsy sufferers' should also always be used in preference to 'epileptics'. This does not mean you shouldn't write 'She is epileptic' (adjective): it is 'she is **an** epileptic' (adjectival noun) which is objectionable.

I have done very little work in the psychiatric field, but I have learned from a relative of mine who works in this area in England that the accepted term for a person under treatment for psychiatric illness is now a 'client', at least in the non-hospital setting: again, a specific use of a word in our field that is different from its meaning in general usage. The problem I see here in English for us writers is how to make this sex-specific without saying 'female/male client'. This is just about the only option in this case. 'A woman client' does not sound strange, but 'a man client' does. Maybe you just have to use it often enough to make it sound all right.

### Animals in nonclinical trials

Here it is much simpler. Use the name of the species in common usage (e.g. mice, rabbits, pigs, guinea pigs [use a capital 'G' if you want], stump-tailed Macaque monkey) or just

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'animals' after having mentioned the species, qualified by 'female' or 'male' for sex-specificity. It is quite acceptable, and indeed usual, to refer to animals as 'females', 'males' or 'controls'. If you object to this, then use 'female animals', 'male animals', 'control animals' or 'control group'.

Let me also get something off my chest here: 'Groups of 6 beagle dogs (each with 3 males and 3 females)' is a contradiction in terms and sounds strange. As we all know, beagles are dogs, but within the dog species, when you add the word 'dog' to the name of the subspecies (beagle, labrador, poodle) it means 'male' and when you add the word 'bitch' it means female. The latter is perfectly legitimate when used in this way ('Do you have a dog or a bitch?')—really—even though it does have a negative meaning in vulgar use. The correct general term is just 'beagle': the use of 'dog' and 'bitch' in this way, however, is usually limited to private pet ownership; in scientific investigations, the qualifying adjective that indicates the sex is 'female' or 'male', hence 'female/male beagles' and not 'female/male beagle dogs'.

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**Sorting out Word's document properties**

A valuable contribution was made by John Carpenter (JohnCarpenter21@aol.com) to the Ghostwriting Forum at the EMWA Spring conference in May this year. John suggested that medical writers who work on manuscripts for journals should make a habit of checking the information given in Word's document properties. In this way you can avoid wrong information being attached to the document. For example, if you are preparing a document using a template that has been sent to you, it will appear with the name of whoever drew up the template. As a medical writer you should ensure that your own name appears there, rather than the agency's or the pharmaceutical company's.

The document details can be checked as follows: with the document open, click on File (Alt F on an English keyboard), select Properties (i on an English keyboard), then select Summary (no hot key as far as John knows). Click in the field you want to change and delete or type in whatever you want.

Three of the other buttons (General, Statistics & Contents) give useful information (especially Statistics) but there's nothing you can change by overtyping. The other area (Custom) can be used to attach any information you like to the file (e.g. about other authors, agency, contributors, whether it supports product claims, whether it's been submitted, rejected, who last reviewed it, whether it's in the public domain, etc.).

**Reply: Words say a lot**

I thank Alistair for his useful commentary and expansion on terms for animals and people partaking in nonclinical and clinical trials.

But I join issue with him on referring to people as subjects. As I stated in the box on the topic<sup>1</sup> many physicians were dismayed by the FDA's suggestion that trial participants should be referred to as subjects. Why should a mere word move physicians to 'dismay'? Words carry connotations. When we use the word 'subject' for another person, whether that person minds or not, it says something about how *we* consider other human beings.

Subject has a passive connotation—something is done to subjects. They are used. Participant has an active connotation implying the person of his/her freewill has agreed to experiments being conducted on his or her body—a partner in the enterprise. Put another way it is a question of where the emphasis lies, as explained by Michael Sly in his editorial urging authors to avoid 'asthmatic' as a noun. Substitution of 'asthmatic patients' places more emphasis on the patient as a person<sup>2</sup>.

You could argue that our aim in clinical trials is to help humanity but the importance of the individual should not be lost. Thus I am also worried about the attempts by the FDA to make it more difficult for a person to bring legal action against a drug manufacturer for harm caused by one of its products<sup>3</sup>. Likewise I was concerned when 'permanent brain damage' was listed as a 'drawback' in a drug development document that I read. This is a little more than a drawback for the individual person who suffers it, although it could be a drawback in getting the product to market.

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<sup>1</sup> *TWS* 2005;14(4):118.

<sup>2</sup> *Annals of Allergy, Asthma & Immunology* 1996;(6)77:435–7.

<sup>3</sup> *NEJM* 2006;354:2409–11.

**Some useful words for tight word limits**

Some useful words that mean two things (albeit two different things):

Iradake =	ripe and unripe	(Tulu, India)
Sitoshna =	cold and hot	(Tulu, India)
Merripan =	life and death	(Romani, Gypsy)
Gift =	poison and married	(Norwegian)
Danh t =	a church and a brothel	(Vietnamese)
Magazinschik =	a shopkeeper and a shoplifter	(Russian)

Source: *The meaning of Tingo* by Adam Jacot de Boindod, Penguin Books 2005