



Commentary on 'The world of medical devices: Serving two masters'

by Helen Colquhoun

I read with interest the article comparing the International Organisation for Standardization (ISO) 14155 and International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidance, written by Art Gertel and Nancy Stark and published in *The Write Stuff*, 17 (2), 2008. There are two ways to approach subjects like this: one is to emphasise the differences, which is what Gertel and Stark did, and one is to emphasise the similarities. In response to the original article, I would like to offer the alternative approach of highlighting similarities.

In my view the two guidance documents (ISO 14155 and ICH GCP) are almost interchangeable, based as they are on the principles of protecting the rights of study participants; documenting the study procedures to be conducted and obtaining ethics approval for these; adequately assessing the risk-benefit of conducting the trial at the outset; assessing safety on an ongoing basis; ensuring the validity of the data so that decisions can reliably be made based on the results. It seems to me that there should be no difference in the protection afforded to participants in a study of a simple, non-invasive medical device compared to that afforded to participants in a trial of an experimental pharmaceutical product with a high risk profile.

So the two guidance documents ought to be very similar—of course, the language may differ a little, but in general their instructions result in very similar courses of action. To suggest, as Gertel and Stark do, that data collected in Europe according to ISO 14155 would not be acceptable to the Food and Drug Administration (FDA) in the United States of America (USA) is an over-statement—for example, data for a Pre-Market Approval (PMA) must be collected according to the Declaration of Helsinki, applicable to the population of the USA, gathered by investigators who are competent, and verifiable by the FDA if necessary. All of these criteria would be met if ISO 14155 is followed.

I agree with Gertel and Stark regarding harmonisation of sponsors' operating procedures—it is possible! My company has one set of harmonised standard operating procedures (SOPs) that cover the whole range of tasks involved in setting up and managing a clinical study, whether that study uses a medical device or a pharmaceutical product, and whether the study is conducted in the USA or in the European Union (EU).

Each SOP has an associated set of working practice documents (WPDs), which describe the 'how to do' based on

the SOPs' 'what to do'. Out of around 55 SOPs, the WPDs differ for device trials and drugs trials for only a handful of SOPs. Most of the differences are related to simple semantics such as counting devices or counting drugs to complete accountability: in some cases we keep it generic by referring to investigational product, although that can sound a little clumsy at times.

The one area where there are significant differences, as pointed out by Gertel and Stark, is adverse event reporting. The rules are different for device and drug trials in the USA and EU with regard to definitions and expedited reporting rules, and they differ for pre- versus post-market devices and drugs. We have advised our clients - and this approach is increasingly being adopted by the major medical device manufacturers - to use the pharmaceutical definitions of a serious adverse event (SAE) as the basis for what the sites report to the sponsor or contract research organisation (CRO) on an expedited basis in both pre- and post-market trials. These definitions are actually very close to the ISO 14155 definitions, but differ from the FDA 'medical device' expedited reporting language.

In theory, there is the possibility of missing an unanticipated adverse device effect (UADE), which would be reportable to the FDA on an expedited basis for an investigational device. In practice we have never seen a UADE that did not also comply with at least one of the six criteria for serious under the pharmaceutical definitions, particularly the general 'catch-all' of 'medically serious'. To ensure that we do not miss any, a rigorous review of adverse events is conducted on at least a monthly basis during the trials.

This approach works well with investigators, even surgeons, whom arguably may have had little or no exposure to drug trials. Almost all investigators seem very familiar with the pharmaceutical SAE definitions and that ensures good compliance with reporting to the sponsor (who then has to work out what is reportable where and in what timescale). We have not found that European investigators struggle at all with adopting the ICH GCP guidance.

One area that Gertel and Stark did not touch on at all was the Global Harmonization Task Force, an organisation devoted to harmonising medical device trial standards and regulatory guidance, in much the same way that ICH does for the pharmaceutical industry. Harmonisation of standards and guidance between territories will eventually

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facilitate appropriate harmonisation of standards and guidance between medical devices and drugs. The FDA has in some ways led the way, since its own monitoring guidance (for example) does not distinguish between clinical trials of medical devices or drugs. Similarly in the United Kingdom, any trial conducted with the National Health Service (NHS) must be conducted in compliance with the ICH GCP guidance whether it uses a drug or a medical device. What a fuss there was when this was first introduced—until everyone realised that it was not going to make any significant difference!

In conclusion, I would emphasise the similarities rather than the differences between the GCP guidance for medical device trials conducted in the USA and EU, and between the GCP guidance for medical device and drugs trials. By doing so, I suggest that the chances of harmonisation are enhanced—a sensible goal since the underlying principles of conducting any kind of clinical research should be the same.

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Vital signs

Dear TWS,

I've just had the latest copy of *The Write Stuff* delivered, as usual, it's been a very good read.

As a medical writer who makes part of his income as a photographer, I was very interested in Irene Hames' article on digital manipulation [*TWS* 2008 17;(4):164-67]. Although I fully agree with what was said regarding establishing the digital equivalent of a paper trail and the need for full archiving, there are a couple of caveats.

Firstly, just because an original image is film-based doesn't mean that we should be too confident about it. Image manipulation goes back almost as far as photography its self. Oscar Rejlander and Alexander Rodchenko are just two examples of people who used constructed/manipulated images in support of their theories (ideology).

Secondly, the digital format that stores most data, the RAW format needs some "tweaking" to give the correct rendition as a file for printing, this involves some push to contrast and sharpening. Files recorded as jpg already have that push to contrast, sharpening and colour saturation done in-camera and the image data is subject to compression, causing a loss of data.

Thirdly, to be truly good at image manipulation is no trivial matter, it takes a lot of work and if over done, or under done makes an easily spotted mess.

So yes, let's have standards for images and let's be no less thorough with our handling of photographic data than we are with any other form of scientific data, but let's not get too worried about the validity of photographic material just because it's from a digital original.

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Author's reply:

I'm very glad that Peter Meade was interested in my article on the problem of inappropriate manipulation of digital images, and I in return was very interested to see his comments.

I agree that image manipulation isn't a new phenomenon, and also occurred in scientific reporting when image capture was only via photographic film. It was, however, much more difficult to alter images then (and I speak as someone who used to spend many hours in the darkroom in my cell biology research days before digital image capture existed). Most researchers didn't have the expertise to do this, or even if they did, they didn't necessarily have access to a darkroom and the equipment and materials required. Today, virtually every research scientist has access to a computer—it's impossible to work in many areas without one—and the software packages for image storage and manipulation are widely available and affordable. Significant changes to images can result from just a few keystrokes or mouse clicks. There is also, I suspect, a general acceptance that the 'beautification' type of change is all right. This, coupled with the lack of realisation that some changes are wrong, makes the practice potentially widespread and, so, very worrying.

Yes, to make sophisticated alterations takes a lot of work and expertise. But many of the sorts of inappropriate image manipulations editors see aren't "an easily spotted mess". They often look absolutely fine, and only come to light because of the vigilant eye of a reviewer, sometimes coupled with their knowledge of the literature, or because a journal routinely screens images for manipulation—all, a certain proportion randomly, or just those that have raised suspicions. In molecular biology, things such as duplications, rotations, elimination of background features because of excessive contrast adjustment don't leap out of the page/screen until they are subjected to checking.

There will always be those individuals who knowingly act in a way that is fraudulent in both film-based and digital image capture (we can even extend this to artists who fake old masters). As in any other type of fraud, there will be some very skilled practitioners. Our aim when any new technology is introduced is to play a role in trying to educate the research community on what is good practice and where reliable guidelines can be found.

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