

Medical device clinical trials: the changing scene

Improvements in communication and transportation technologies mean that the traditional locations for R&D are being challenged by new sites. *Gerard Dunne* lays out the advantages of conducting clinical trials in non-traditional countries.

Traditionally, most medical device clinical trials have been run “close to home”. However, the definition of the terms “close” and “home” is changing rapidly; the device trial landscape is shifting.

Modern communications allow researchers to collaborate much more easily around the world. Not only are they able to find like-minded individuals – people with a similar interest in their field – more easily, they are also able to exchange information quickly as they work towards a common goal. Thus, “close” is increasingly used to mean “closeness of interests”, rather than geographic proximity.

Similarly, the term “home” is no longer restricted to meaning the place where the technology or company originated. In the past, most initial development of medical devices has happened in North America and Europe. However, with other countries now developing their strengths in medicine, engineering, economics and other areas, “home” for device development can occur all over the world.

For example, at the recent conference in the US run by US medtech industry association AdvaMed, the delegation from New Zealand included a variety of device companies working on everything from exoskeletons to physiological status monitoring (a technique used in the recent rescue of Chilean miners).

Of course Europe and North America still have the lion's share of device trials, but it is this very popularity that means that initiating new trials in those geographic regions – particularly as a start-up – can be difficult. Many other regions with high standards of healthcare, notably New Zealand and Australia, as well as other Asia Pacific countries, are able to do similar device trial work and have advantages over Europe and North America. They often have greater capacity for device trial work, they do not have so many competing trials, and the speed at which trial work is initiated is particularly advantageous with early phase proof-of-concept trials.

New Zealand and Australia

Both countries have been running clinical trials for over 20 years and their expertise has increased substantially over that time. In a 2005 Economist Intelligence Unit report, Australia was placed number one out of six key destinations to carry out clinical trials, beating the US, UK,

Germany and several Asian countries.

At the end of October 2010, there were slightly fewer than 4,600 trials on the Australian New Zealand Clinical Trials Registry^{1,2} (the register includes trials being undertaken in Australia, New Zealand and elsewhere involving pharmaceuticals, medical devices, surgical procedures, preventive measures, lifestyle, treatment and rehabilitation strategies and complementary therapies). However, the main advantage of this region is not numbers – the combined population of both countries is just 27 million people – but speed, with small proof-of-concept trials typically completed within six months of a finalised protocol.

Australia and New Zealand have a valuable community of global key opinion leaders

Both countries have pragmatic ethics and regulatory regimes, and these allow proof-of-concept device trials to get up and running quickly and achieve rapid data turnaround. This means a company could “kill it fast, kill it cheap” if a device fails to perform. If it does come through, the company would gain an early data set that can be used to obtain the next round of funding for device development in target markets.

In New Zealand, device trials do not have to gain regulatory approval. They just need to obtain the go-ahead from an ethics committee, which typically takes between six and eight weeks.

Moreover, only one ethics committee approval is required regardless of how many sites in the country are involved in the trial.

Australia does its scientific review through its ethics committees and it only requires a notification process to the regulatory authority before you initiate your trial. Again, the time it takes to initiate a trial is between six and eight weeks.

In the US, clinical evaluation of devices that have not been cleared for marketing requires an investigational device exemption (IDE) approved by an institutional review board (IRB); if the study involves a significant risk device, the IDE must also be approved by Food and Drug Administration³. In Australia and New Zealand, in a nutshell, while an IDE is not required to conduct the trial, the device should be IDE-ready.

Sponsor companies

Another advantage that Australia and New Zealand have is their community of global key

opinion leaders in areas including cardiovascular disease, diabetes and orthopaedics.

For example, a considerable amount of bench testing of stents is undertaken in Auckland, New Zealand, by John Ormiston, a world-leading investigator.

Many offshore start-ups look to New Zealand and Australia to find investigators interested in their field, and who are willing to assist with proof-of-concept trials and contribute their trial experience to the device's development.

Because the countries are a manageable size and have a known number of quality sites, an assessment can be made fairly quickly as to whether a device is ready and able to undergo clinical trials in the region.

Case study

The following case study illustrates the process for a US company initiating clinical trials in New Zealand.

A US cardiovascular device company approached New Zealand's Auckland Hospital looking to run initial human clinical trials with their device. The principal investigator discussed the design of the trial with the company's staff and agreed to recruit an initial five subjects.

The trial was approved by the ethics committee and several of the company's team flew in to instruct physicians at the site in the procedure, and oversee the first cases. These were done in a couple of tranches and the data remitted to the company. The whole procedure, from the company first approaching the hospital, to the first data being remitted to the company, took around six months. Pleased with the results, the company initiated a further trial at the hospital.

This is not an uncommon outcome. On one hand, it reflects how one of the main hurdles for North American and European device companies is getting over the concept of running their trials at a distance. Conversely, once they have successfully run one trial in the region, they come back again and again; the repeat rate for client studies runs at between 80 and 90%.

Limitations

One key limitation of doing your clinical trials in Australia and New Zealand is the size of its population. With just 27 million people, trials are typically of the order of 25-250 subjects (with some exceptions). Thus, companies that carry out device and diagnostic trials in these countries would

typically be looking for rapid proof-of-concept data for investors. They may come back and do several trials as they improve the device, before going for the IDE (in the US) or CE mark (for sale in the EU). Safety, of course, is paramount and the ethics committees will want to see pre-clinical data in animals, depending on the device.

Once proof-of-concept is achieved, devices are typically trialled in their target markets with larger populations, although at times, Australia and New Zealand will be included in these trials as well, as part of a global study. Certainly many of the top ten device companies include both countries in their ongoing global trials.

Other regions

A number of countries in the Asia Pacific region have woken up to the opportunities for their patient populations and medical staff in having access to clinical trials and are also doing what they can to remove barriers. Such competition, where moderated by maintaining high standards

as well as a pragmatic approach, should assist the future globalisation of device and diagnostic trials.

The rise of India and China with their large populations is likely to affect clinical trials in the region. While these two countries, and others, are expected to continue to grow rapidly in research, with their large scale and developing infrastructure, they are seen as more a destination for later phase research. Thus, there is little direct impact on the type or number of trials in the foreseeable future.

New Zealand and Australia have usually contributed only a small portion of the patients to global late phase studies, unless it has been in an indication particularly prevalent in the region. This is expected to continue to be the case. So, these two countries are aiming to remain at the forefront of rapid, quality early phase proof-of-concept trials while other Asia Pacific countries develop into large later phase trial and market destinations for products as they move beyond this stage.

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References

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Egypt's new committee clarifies medical device regulations

Gihan Taha describes recent efforts aimed at encouraging companies to register their devices ahead of mandatory procedures due to come into effect in 2012.

The committee that is now responsible for the registration of medical devices in Egypt has issued a number of decisions aimed at clarifying unclear rules and encouraging companies to register and list their products ahead of mandatory procedures that will come into effect in August 2012 for certain classes of devices^{1,2}.

Among other things, the Committee for Regulating Medical Devices, Medical Instruments, Cosmetics, Household Pesticides and Disinfectants has eased the import procedures with regard to the submission of information on country of origin and manufacturer/representative details. It has also introduced new requirements relating to stability, sterility and releasing imported products onto the Egyptian market.

These decisions, which were made over the past several months, were published by the Ministry of Health and Population on 10 November 2010. They will be referenced in

the regulation that introduces the mandatory registration requirements, which is currently in draft form and is expected to be finalised before August 2012. Egypt's current registration and listing requirements are set out in Table 1.

Importation requirements

A decision made at the committee's 17 August session explicitly states that it is possible to add a new country of origin to a registered medical device's marketing authorisation, provided that a corresponding Free Sale Certificate is submitted. Previously, the rules were not clear and thus officers at the ministry's Central Administration of Pharmaceutical Affairs were left to make decisions on a case-by-case basis.

The new country can be a reference or non-reference country as long as the product is registered in at least one reference country. (The reference countries are: Australia, Austria, Belgium, Canada, Denmark, Finland, France,

Germany, Iceland, Ireland, Italy Japan, Luxembourg, New Zealand, Norway, Portugal, Spain, Sweden, Switzerland, the Netherlands, the UK and the US.)

If the added country is the US, the importing company must submit a Certificate to Foreign Government issued by the Food and Drug Administration that clearly states the name of the medical device and the name of the manufacturer. The committee's decision lists the documentation that must be included with the submission.

Furthermore, the committee is now permitting the registration of a product with more than one country of origin, provided that at least one of these countries is a reference country. A corresponding Free Sale Certificate endorsed by both the Chamber of Commerce and the Egyptian Embassy or consulate in the country of origin must be submitted.

Table 1. Current Egyptian registration and listing requirements for medical devices

| Device class | Registration/listing requirements |
|--|---|
| Class I, IIa, IIb, III sterile single-use devices | registration obligatory |
| Class III non-sterile devices | registration obligatory |
| Class IIa, IIb, III non-sterile single-use devices | registration obligatory with two-year grace period (starting from 17 August 2010) |
| Class I non-sterile, non-measuring | listing optional |
| Class IIa, IIb non-sterile | registration optional |