Killing the goose

The regulatory framework for implanted medical devices is preventing severely impaired people from benefitting from rehabilitation research. Consequently, research effort is wasted and we are unable to use implants to reduce the costs of healthcare. The framework should be altered so that it is economically possible to get new devices for small patient groups into widespread use.

For clinicians who treat patients with spinal cord injury, establishing satisfactory bladder management is a priority. At present, at discharge from hospital, the commonest methods are either anticholinergic drugs or botulinum toxin to prevent incontinence, combined with intermittent catheterisation to drain the bladder. In a recent British study, the annual cost per patient to the National Health Service of these methods was calculated as £7,000 and £8,700 respectively (Hamid, 2015), which may continue for the remaining decades of the patients' lives. The side effects of anticholinergics are unpleasant and typically patients get many urinary tract infections (UTIs). Is this satisfactory when the healthcare budget is so stretched?

A neuroprosthesis was developed by Brindley in the 1970s for complete-lesion spinal cord-injured patients. It allows the user to empty the bladder when convenient by stimulating the sacral motor nerve fibres. Implantation of the device is usually accompanied by cutting the sensory fibres because this deafferentation prevents incontinence and facilitates stimulator-voiding. The device is very simple and very reliable: some patients have implants that are still working well after 30 years. The device means that routine use of drugs is unnecessary, the frequency of UTIs is much reduced and there are many other urological benefits (Brindley, 1994). Although about 4000 of these devices have been implanted world-wide, only a few hospitals now routinely carry out the procedure.

These implants have been and remain very important to many patients. For example, Sir Philip Craven wrote the following. "I have been paraplegic since I was 16, but I have been very active as an international wheelchair basketball player and I have been the President of the International Paralympic Committee for 14 years. I decided to have a Brindley implant because I used to have so many UTIs and it has been brilliant for the past 26 years. It has been absolutely fundamental in enabling me to do a lot of long distance air travel which has been essential in order to be an effective president. Without the implant I would have probably been dead now!"

The reason it has fallen out of favour has been understood for years – it is the other effects of the deafferentation, mainly loss of reflex sexual function in men. Obviously there is a need for a new type of neuroprosthesis which does not require concomitant deafferentation but is still reliable and inexpensive. As a result of research in many labs into methods for suppressing reflex bladder contractions, temporarily blocking nerve conduction, and detecting specific afferent nerve traffic (Kirkham, 2002; Tai, 2004; Bhadra, 2006; Kilgore, 2014; Metcalfe, 2017), I think that we are now close to being able to specify such a device. The aims would be to improve quality of life and also reduce healthcare costs for complete-lesion patients. However, there is a new problem. The technical difficulties may have almost been overcome but the commercial difficulty of producing such devices has increased enormously in the past 30 years. Then it was only necessary to show the company how to make the devices in the same way as those made for the first ten patients, and to write documents to explain to the surgeons and to the patients respectively what to do with them. That was all – the company started selling devices immediately.

Now, within the EU, companies cannot sell until they have a CE Mark, and that is only awarded after a clinical trial has shown efficacy. The trial is not allowed to start until the government agency (MHRA in Britain) has been persuaded that the device is safe, which requires a comprehensive Technical File with a risk assessment and data showing that the device complies with requisite

standards. I do not know what the least cost could be for producing an adequate Technical File from scratch but it seems likely to be in the range £1-10M. In 2014, Torax Medical, an American start-up company reported (Demarchi J, 2014) that half way through their 100-subject European trial they had spent $50M, this expenditure against a loan by investors. The product has now been 'discontinued' due to a 'business decision' (www.toraxmediacl.com/fenix).

After completing the trial the company can apply for a CE Mark. This requires further expense, now making an application to a different organisation (a *Notified Body*) which is neither limited in the time it is allowed to make a decision nor the amount that it charges before reaching a decision. Clearly this pathway takes years to travel, with uncertain cost but at the end, having a CE Mark allows sales on the *open market*. If the company could immediately start selling 1000s of devices per year, maybe such a large loan might be paid off but for devices that treat complex disabilities like spinal cord injury and stroke, the number of patients treated will be much fewer, initially at least. Clinicians must learn the surgical and therapeutic methods, as well, one hopes, as gaining confidence that it is a good treatment for appropriate patients. In the UK (population 65M), the total number of spinal injuries is about 1000 per year so an implant for treating incontinence in complete-lesion patients is unlikely to be suitable for more than 200 recent injuries per year and, however well the device worked, it is unlikely that one could reach this rate for, perhaps, ten years. It is very hard to see how a business case can be made. The interest payable on a loan of £10M will be at least £250k per year and if, for example, £2.5k of the sales prices of each device were paid back to the lender, one would have to sell 100 per year just to cover interest on the loan. Essentially the commercial problem is that the cost of regulatory process is so high that companies cannot reach a point where they break even. The device never gets past the so-called *Valley of Death.*

As researchers, we can do something to help: we can look for grant funding with device development and preparation of the Technical File before the clinical trial; we can look for grant funding for the clinical trial; and we can study the benefits of the device after it is on the market in order to show clinicians at other centres that it is a good treatment, because this will advertise it to the customers. However, most companies that have tried to put neurological prostheses for small patient groups on the market have failed; I think that this is not because the technology was generally inadequate, nor because many patients have not liked them, but because of commercial difficulty which is getting worse as the regulations are tightened year by year. In the EU, the medical device *Directives* have just been superseded by the *Medical Device Regulations* which are generally expected to raise the bar even further[1].

Currently there are many research projects running for new types of implant for treating small patient groups: millions of pounds have been committed in research grants. These projects have great potential for improving quality of life, allowing disabled people greater freedom and ability to work, as well as reducing healthcare costs. But it is hard to see how they can get far beyond the research labs. The point of the regulations is consumer protection, to avoid risk to the patient, but the effect, I believe, has been to deprive severely impaired people of devices that we know were effective and this effect will continue in the EU in the future unless something is done.

[1] In the annual prospectus for regulation, the BSI Director of Information Services wrote the following. "The changes … are likely to have considerable impact. With every single medical device currently on the market having to be evaluated for its suitability, manufacturers may decide that not every device in their portfolio is worth the time and expense this will take. Others may decide to pull out of the medical device market altogether." (Bailey-Wood S, 2016)

Deregulation of devices for small patient groups is urgently needed to avoid further disappointment and wasted research effort and money. One way to do this would recognize that the *open market* is not a realistic description of sales for the first few hundred patients, or perhaps ever. The company is likely to supply only a small number of specialised rehabilitation centres, maintaining contact between the manufacturer and the clinicians. Patients can be followed closely, looking out for adverse effects. If such an arrangement were defined by agreement with the *Competent Authority* (MHRA), it seems reasonable that the company should be able to sell devices before getting a CE Mark. No doubt there are other possibilities. We should start by recognizing that the current system is economically unrealistic for small patient groups, which is bad for the patients and expensive for everybody.

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References

Hamid R, Loveman C, Millen J, Globe D, Corbell C, Colayco D, Stanisic S & Gultyaev D, 2015, "Cost-Effectiveness Analysis of OnabotulinumtoxinA (BOTOX) for the Management of Urinary Incontinence in Adults with Neurogenic Detrusor Overactivity: A UK Perspective." Pharmacoeconomics, 33:381-393.

Brindley GS, 1994, "The first 500 patients with sacral anterior root stimulator implants: general description" Paraplegia, 32, 795-805.

Demarchi J., IMPRESS Workshop, Leeds, October 2014.

Kirkham APS, Knight SL, Craggs MD, Casey ATM, & Shah PJR (2002) "Neuromodulation through sacral nerve roots 2 and 4 with a Finetech-Brindley sacral posterior and anterior root stimulator" Spinal Cord, 40(6), 272-282.

Tai CF, Roppolo JR, & De Groat WC (2004) "Block of external urethral sphincter contraction by high frequency electrical stimulation of pudendal nerve", J. Urol., 172(5), 2069-2072.

Bhadra N, Bhadra N & Kilgore K (2006) "High frequency electrical conduction block of the pudendal nerve" J. Neural Eng., 3(2), 180-186.

Kilgore K & Bhadra N (2014) "Reversible Nerve Conduction Block Using Kilohertz Frequency Alternating Current" Neuromod., 17(3), 242-255.

Metcalfe BW, Nielsen TN, Donaldson NdeN, Hunter AJ & Taylor JT "First Demonstration of Velocity Selective Recording from the Pig Vagus using a Nerve Cuff shows Respiration Afferents" Submitted 2017.

Bailey-Wood S, BSI Standards Outlook, 2016.