Abstract
43 microstimulators were implanted in a feasibility study of rehabilitation of arm function in subjects with stroke. Results of safety, reliability, and efficacy of the system are presented. It was shown that microstimulators could be implanted safely with only minor side effects. The system proved reliable. The motor thresholds showed to be low and stable.

1. INTRODUCTION
85% of stroke survivors regain the ability to walk but less than 14% of those who have upper limb problems regain useful function. Many subjects have difficulty in reaching and have ineffective grip. Electrical stimulation therapy was shown to improve function especially when voluntary activated.

This communication presents the safety outcome of a feasibility study designed to improve recovery of upper limb function following stroke using implantable microstimulators.

2. METHODS
2.1. Subjects
Seven subjects have been included with a chronic stroke causing a hemiplegia, at least 3 months post stroke. These subjects have an impaired hand function due to poor control and weakness of wrist extension and elbow extension. They have some voluntary control of finger flexors and proximal arm and shoulder muscles. Subjects have given written informed consent, and the protocol was approved by the Thames Valley multicentre research ethics committee (04/12/021), and by the Medicines and Healthcare products Regulatory Agency (CI/2004/0027). This study was conducted following the guidelines of good clinical practices.

2.2. Microstimulator system
The microstimulator is a miniature (cylinder 2.4 mm x 17 mm), single-channel, implantable stimulator that produces capacitively-coupled, charge balanced, asymmetric, biphasic, constant-current pulses. In this study 5 to 7 devices have been implanted in each subject (with 2 additional devices in one revised subject), for a total of 43 devices. Each device is implanted adjacent to a target muscle motor point or the nerve using the surgical insertion tools. Once implanted, the devices receive power and stimulation commands via a 2 MHz RF inductive link provided by an external coil, connected to a Control Unit (See Figure 1). The stimulation parameters are set by a laptop based fitting system, and can be programmed to respond to triggers issued by sensors (e.g. elbow angle).

Figure 1 External System

2.3. Surgical procedure
The implant surgery involved a microstimulator inserted onto the nerve/motor-point (N/MP) of each of the medial and lateral triceps muscles for elbow extension. For wrist extension, a microstimulator was positioned on each of the N/MP of the extensor carpi radialis longus and ulnaris. For finger and thumb extension, 1-2 microstimulators were inserted onto the posterior interosseous nerve.
Insertion is done under local anaesthesia through a 5mm skin incision. First, the N/MP is identified using a 0.7mm rounded-tip stimulation probe. Prior to implantation, the devices are tested, a dissolvable suture is tied to an eyelet attached to the anode, and the devices are stored temporarily in sterile saline solution with antibiotic (colomycin 1,000,000 units in 500 ml 0.9% saline). The devices are then inserted using a #7 Gage cannula introducer and ejection tools.

Once the devices are inserted in the position that elicits acceptable motor response, motor thresholds are measured, the incision is irrigated with antibiotic saline, and the skin is closed. Final verification of the device placement is done with the RF coil positioned over the arm.

Cefuroxime 1.5 g was given at commencement of the procedure and an additional dose of 0.750 g was given six hours later, before subjects were discharged home. Subjects were given a prescription for a ten day supply of Cefalexin 0.250 g.

2.4. Follow up and evaluation

The subjects were followed up at 7 days, 15 days, 30 days and 90 days post surgery. Stitches were removed after 15 days. During each follow up session, implant sites were examined, operation of the devices was verified, and motor thresholds were measured.

Motor thresholds were measured at 30 Hz repetition rate. The pulse width was set at a fixed pulse width (0.2 ms) and the pulse current was increased to get a coarse value of threshold. Then the pulse amplitude was set at a specific value (generally 1.62 mA) and the pulse width was varied to get the exact value of motor threshold.

Subjects were asked about the performance of the system, and to report any side effects of the stimulation. Subjects were also tested to evaluate the therapeutic outcome of the procedure.

3. RESULTS

ADVERSE EVENTS

There were no serious adverse events to report following 43 device implantations. No sign of infection has been observed. No sign of allergic reaction has been observed.

Minor post operative adverse events include moderate post operative pain in 2 subjects for 1 week, and in 1 subject for 4 weeks. 3 subjects showed signs of swelling for 2 weeks after surgery in the forearm. 2 subjects showed mild tenderness on one of the implant sites. 1 subject showed moderate bruising. 1 subject had a small amount of bleeding at one implant site after 1 week, which required early dressing replacement. 1 subject reported digestive problems associated with antibiotics after 1 week.

Minor side effects of the stimulation have been observed. 1 subject reported cramps following one therapeutic session. 1 subject reported shoulder pain following one therapeutic session, judged as unrelated to therapy. 1 subject reported light tickling sensations with one device.

RELIABILITY OF THE SYSTEM

The microstimulators performed reliably and consistently during the study.

The power coupling between the microstimulators and the external system was reliable.

The external elements of the system performed reliably. Three minor mechanical problems have been reported, which had no consequence in the efficacy of the treatment, or to safety. Two control units have been replaced because of loose power connection; one coil has been replaced because of loose connection. Corrective and preventative action were initiated to mitigate the issues.

MOTOR THRESHOLDS

Longitudinal motor thresholds are displayed in Figure 2 on the day of the surgery and up to 3 months after surgery. The left ordinate scale shows the charge per phase of the stimulation pulses. The right ordinate scale shows the computed equivalent current of 0.2 ms pulses. Dotted grey lines show the individual thresholds for all devices. Bold black line shows the value of the median and error bars displaying the 10th and 90th percentile of thresholds.

All thresholds (97%) but one remained stable over time, allowing for test – retest repeatability. The motor threshold of the device targeted at the medial head of the triceps of subject #4 had changed significantly immediately after the surgery. This threshold is highlighted as the black dashed line.

3 months following implantation, the average charge per phase at thresholds were 0.12 µC and 90% of thresholds had a charge per phase below 0.22 micro Coulombs (8.4 µC/cm² with an area of 0.026 cm²) which is 1.1% of the maximum output of the microstimulator.
4. DISCUSSION AND CONCLUSIONS

The follow up review of 43 microstimulators implanted show that the surgeries could be completed safely with only minor side effects.

Infection is always a risk with implantable medical devices, and as yet no such adverse event has been reported. Our recommendation is constant attention to strict aseptic surgical procedures, use of preventive antibiotics, and careful post operative follow up of implant sites.

All side effects related with the surgical procedure were minor and had transitory effects. The most prevalent side effect was moderate post operative pain, relieved with oral paracetamol/acetaminophen.

The system proved reliable and the minor issues did not interrupt the subject’s therapeutic stimulation regimen.

The follow-up of the motor thresholds showed that they were stable and that they had a level very low (1.1%) compared with the available range of stimulation of the device. The average thresholds were 0.12 µC and 90% percent of the thresholds were below 0.22 µC (charge density 8.4 µC/cm²).

This data may be put in perspective referring to preclinical data⁴ where distances between nerve and microstimulator electrode were recorded and associated with motor thresholds (See Figure 3). This analysis would suggest that 90% of devices were placed 7 mm from their target location or closer.

The motor threshold of the device targeted at the medial head of the triceps (MHT) of subject #4 increased significantly after surgery (See Figure 2, dashed line).

This finding indicates that this device moved from its target location during the first week after surgery. When the stimulation level of this device was set above motor threshold, the contraction of the medial head of triceps was found to be satisfactory, despite the higher stimulation level required. Note that the dissolvable suture attached to the microstimulator would have allowed retrieval of the device at up to 8 days after implant. Later the triceps muscle was showing signs of early fatigue, and stimulation of the lateral head (LHT) was not sufficient to extend the elbow alone. This led to the subject having a revision surgery in which two additional microstimulators were implanted, one on the MHT and the other on the LHT. With the two new devices, satisfactory contractions of the triceps were achieved to extend the elbow.

In conclusion, it was shown that microstimulators can be implanted safely with only minor side effects. The system proved reliable. The low level and the stability of the thresholds indicate that the electrical stimulation delivered by microstimulators was effective and stable in 95% of cases. In subject #4, 2 microstimulators were revised, demonstrating the flexibility of the approach.

References

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