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Improving Patient Safety During Introduction Of Novel Medical Devices Through Cumulative Summation Analysis

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Abstract

Objective—To implement cumulative summation analysis (CUSUM) as an early warning detection and quality assurance system for the pre-clinical testing of the iSYS1 novel robotic trajectory guidance system.

Methods—Anatomically accurate 3D printed skull phantoms were created for three patients that had previously undergone implantation of 21 stereoelectroencephalography (SEEG) electrodes using the current standard of care (frameless technique). Implantation schema were recreated using the iSYS1 system and paired accuracy measures were compared with the previous frameless implantations. Entry point, target point and implantation angle accuracy were measured from post-implantation CT scans. CUSUM analysis was undertaken prospectively.

Results—The iSYS1 trajectory guidance system significantly improved electrode entry point accuracies from 1.90+/-0.96 mm (Mean+/-SD) to 0.76+/-0.57 mm (Mean+/-SD) without increasing implantation risk. CUSUM analysis was successful as a continuous measure of surgical performance and acted as an early warning detection system. The surgical learning curve, although minimal, showed improvement after insertion of the 8th electrode.

Conclusions—The iSYS1 trajectory guidance system did not show any increased risk during phantom preclinical testing when performed by neurosurgeons who had no previous experience of its use. CUSUM analysis is a simple technique that can be applied to all stages of the IDEAL framework as an extra patient safety mechanism. Further clinical trials are required to prove the efficacy of the device.

Keywords

Stereoelectroencephalography; Robotic surgery; CUSUM; Medical device; iSYS1

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1 Introduction

Novel surgical procedures and devices have the potential to improve patient outcomes and safety through the translation of technological advancements to healthcare. The introduction of robotic devices to a number of surgical specialities over the last decade has seen them become applied to numerous procedures⁶. Novel medical devices or procedures are associated with a learning curve and patients are exposed to potential risks until efficacy can be proven and long-term outcome data is acquired^{4,15}. Surgical device trials have the added complication of user dependent outcomes and the learning curve / surgeon contribution to outcome is difficult to predict, especially when trying to assess the external validity of a particular device or procedure. The regulation with regards to approval of devices is varied in different countries and a recent cross sectional study showed less than half of the devices in which clinical studies are undertaken go on to achieve regulatory (FDA) approval¹⁰. Of the devices that are cleared for regulatory approval, 43% were found to have been cleared without the publication of a single clinical study under the 510(k) clearance, where only substantial equivalence to another approved device is necessary. Alarming, a study of medical devices for orthopaedic surgery revealed that those approved using the 510(k) clearance were 11.5 times more likely to be recalled than devices that underwent clinical studies prior to pre-market approval⁵. The IDEAL framework is a collaborative approach between surgeons and trial methodologists to provide structured guidance, similar to that employed for drug trials, for the transition of medical devices from ideas (stage 1) to long term outcome studies (stage 4)¹¹. The IDEAL framework, however, does not provide a continuous method for surgical vigilance towards the early detection of harm or the potentially negative effect of learning curves. Cumulative summation analysis (CUSUM) is a simple early warning system that compares outcomes of a new intervention or procedure against an established risk or failure rate that can be used longitudinally to monitor outcome and surgical performance^{9,20,21}. CUSUM analysis has been used in prospective robot-assisted randomised control trials⁹ and case control studies in which historical outcome data is used to provide an baseline for comparison. The latter use has been successfully applied to assess learning curves of particular surgical^{8,24,25} and non-surgical interventions^{2,26}. CUSUM analysis acts as an early warning mechanism to inform investigators if an intervention is exposing patients to a higher than expected risk of adverse events, but does not replace conventional statistical methods.

Stereoelectroencephalography (SEEG) is a neurosurgical procedure in which multiple electrodes (usually 8-14) are placed within the brain to identify the seizure onset zone in patients with drug refractory focal epilepsy, to determine if a resection would be feasible. To date four techniques have been described to implant multiple intracerebral electrodes, including stereotactic frame-based¹⁹, frameless¹⁶, robotic^{3,12,14} and custom 3D printed fixture methods¹. Electrode trajectories are pre-planned to ensure that electrodes are a safe distance from intracranial arteries and veins^{18,22,27}, as damage to these vessels could result in a life-threatening haemorrhage that caused mortality or significant morbidity¹³. The accuracy with which the electrode conforms to the pre-planned trajectory is therefore dependent on the implantation method. We have previously carried out a meta-analysis of accuracy related to the surgical implantation methodology and found a paucity of evidence

within the literature comparing implantation techniques²³. Studies to date have been of poor quality amounting to Level 3 evidence. There have been no prospective comparisons of different implantation techniques. Here we provide an example in which CUSUM analysis has been used as an early warning tool to compare a novel robotic device for the insertion of intracerebral Stereoelectroencephalography (SEEG) electrodes with the currently used frameless technique¹⁶.

2 Methods

2.1 Stereoelectroencephalography technique

The frameless implantation technique used as the standard of care at the study institution has been described previously¹⁶. In brief, the technique involves the use of a mechanical arm in combination with a precision aiming device and Stealth S7 neuronavigation system (Medtronic Inc). After registration of the patient to the neuronavigation system, using bone fiducials as registration points, pre-planned trajectories on the Stealth station are used to align the mechanical arm and precision aiming device. Using a series of reduction tubes the trajectory is then drilled through the skull and the electrode bolt is screwed into the skull. A stylet is then passed through the bolt and following this the electrode is inserted to the target point. In a similar fashion the novel iSYS1 trajectory guidance system (Medizintechnik GmbH) is a small device that interfaces with the S7 Stealth neuronavigation system and through a series of iterative steps aligns to the pre-planned trajectory. Similar to the precision aiming device the iSYS1 has a working channel through which reduction tubes are placed to allow drilling and insertion of the skull bolt followed by the electrode. Both procedures are performed with the same two neurosurgeons working together.

2.2 Phantom generation

Three patients who previously had a total of 21 electrode implantations using the conventional frameless method were selected on the basis of a power calculation, representative range of anatomical targets and drilling angles to the skull. The skull models for each of the patients were 3D printed (3D Systems Inc., High Wycombe, UK) with bone fiducials in-situ using a commercially available realistic bone-like substitute (Duraform PA) and covered with a synthetic skin substitute (See figure 1). The two neurosurgeons who had previously undertaken the implantation on the patients then repeated the implantation procedure on these phantoms, using the iSYS1 robotic trajectory guidance system. All equipment including the drill, and electrode bolts were kept consistent for both implantation techniques. The two neurosurgeons had previously seen a demonstration of the iSYS1 system and were aware of the instructions for use but had not received any previous practical training.

Following implantation the 3D printed skulls underwent a CT scan and the planned and actual (implanted) bolt trajectories were compared using a lateral deviation method (see figure 2) for both the entry point, projected target point and angle error¹⁶. The results were compared to the actual post-operative patient implantation for the same planned trajectories using EpiNav™¹⁷.

2.3 Cumulative summation analysis

Cumulative summation analysis is calculated using the following equation:

$$\sigma_n = (\sigma_{n-1} + X_{i_n}) - X_{o_n}$$

where, σ_n is the cumulative summation after n attempts, X_{i_n} is the result of the intervention following the n th attempt and X_o is the established risk or failure rate of the control to which the on-going attempts are compared. X_o can be calculated either on a case by case basis (X_{o_n}) as with paired control trials in this case, or as an overall frequency if this is known. When σ_n is plotted for subsequent attempts the gradient of the graph provides information regarding whether the intervention is performing better (negative gradient) or worse (positive gradient) than the control intervention. A change in the gradient from negative to positive following the introduction of a new intervention therefore serves as an early warning that outcomes are worse than in the control group, even though this may not yet have reached statistical significance. Each of the electrode bolt insertion accuracies using the iSYS1 on the phantom (X_{i_n}) were compared with the patient insertions using the frameless technique (X_{o_n}). Analysis was also undertaken using a 3 mm accuracy safety margin based on the accuracy data provided by Cardinale et al³.

2.4 Statistical analysis

The power calculation assumed a significance level of $\alpha = 0.05$, power of $1-\beta = 0.95$ to detect a 0.8 mm improvement in entry point accuracy with an estimated standard deviation of 0.7 mm based on previously published data⁷. Based on this paired results from 20 electrodes would therefore be required. Following implantation paired electrode bolt insertion accuracies for the entry point, projected target point and angle error were tested using both the Kolmogorov-Smirnov and Shapiro-Wilk tests to confirm a Gaussian distribution. A student's paired t-test (2-tailed) was then performed using SPSS 24.

3 Results

3.1 Phantom testing accuracy

Figure 3: Accuracy data

Comparison of the frameless insertion of the SEEG electrodes in the patients with the iSYS1 system on the 3D phantoms resulted in a statistically significant ($p < 0.01$) improvement in the entry point accuracy from 1.90 ± 0.96 mm (Mean $\pm$ -SD) to 0.76 ± 0.57 mm (Mean $\pm$ -SD) respectively. Projected target point accuracy improved from 1.72 ± 0.98 mm (Mean $\pm$ -SD) to 1.34 ± 0.86 mm (Mean $\pm$ -SD) but was not statistically significant ($p = 0.17$). Angle error from the plan non-significantly improved from 0.95 ± 0.39 degrees (Mean $\pm$ -SD) to 0.88 ± 0.55 degrees (Mean $\pm$ -SD) ($p = 0.59$).

3.2 Cumulative summation analysis results

The CUSUM analyses for Entry point, Target point and Angle error are shown in Figure 4. The Entry point and Target point plots reveal a negative trend line with high correlation (R^2

= 0.98 and 0.69 respectively) indicating that the iSYS1 implantation technique is beneficial and does not increase risk. The angle error CUSUM however shows wide variation with poor correlation ($R^2 = 0.15$) suggesting that the implantation method had little or no effect on this.

3.3 Learning curve assessment

The end of the learning process is where the positive gradient of the curve becomes negative or the region in which the gradient becomes most negative. The CUSUM analysis curves (Figure 4), suggest that the overall learning effect was minimal and the maximal improvement with iSYS1 as compared to the frameless technique occurred after the 8th electrode.

4 Discussion

The transition of medical devices to the clinical setting through use by early adopters of technology has the potential to cause patient harm before the long term risks and benefits can be determined through methodologically sound clinical trials. In contrast to drug trials, where Phase 1 and 2 trials are performed on small numbers of patients to prevent harm, only 60% of devices were found to have published clinical trials prior to attaining regulatory approval. The IDEAL collaboration is an attempt to provide a framework for device trials analogous to that of a drug trial, in which small scale studies are performed using few patients to determine the device safety and efficacy prior to larger comparative studies in which long-term data can be gathered. During this period robust early warning mechanisms are required that will detect any potentially deleterious effects of the device and thereby prevent patient harm. Here we have utilised a CUSUM Analysis to compare paired electrode insertions in an anatomically accurate phantom using the iSYS1 robotic trajectory guidance system with a previous frameless implantation in patients.

4.1 Comparison with other studies

CUSUM analysis has been used in a number of surgical and non-surgical fields to assess the learning curve of operators and as a continuous quality assurance indicator. Through the collection of prospective outcomes real time comparisons can be undertaken between prospective control groups, retrospective cohorts or previously established risk / failure rates. The main use of CUSUM analysis currently is to assess surgeon learning curves and training for new techniques, but it also has the potential to be applied as a quality assurance indicator, to surgeon revalidation and as an early warning detector in clinical trials.

To date there have been no prospective control trials comparing SEEG insertion techniques. This is likely due to the requirement for a single unit to have a surgeon or group of surgeons who are capable of performing more than one implantation technique. There is some evidence from studies in which one technique has replaced another. Cardinale et al³, compared historical SEEG electrode implantation accuracy using the Talarach frame with the Neuromate (Renishaw) robot. No prospective controlled trial data are available to suggest superiority of one over the other. Given that the Neuromate (Renishaw) robot is now the standard of care in that unit, it would be ethically challenging to perform a prospective

trial comparing it to the previous technique. The scenario of a single neurosurgical unit not having the surgical expertise to use more than one technique could be overcome through multi-centre trials, but individual surgeon specific performance is difficult to account for methodologically. Furthermore, comparison of techniques between different units may introduce a systematic bias. Another important consideration is how the learning effect will be overcome when comparing a new technique with less surgeon familiarity to a previously established one. CUSUM analysis may overcome this. Using paired electrode data we showed that performance of a novel device can be continuously monitored and any change in safety performance over time detected. By recreating an anatomically accurate phantom replica of a patient's skull using 3D printing technology the same electrode trajectories could be implemented by the same surgeons to control for any systemic bias. During clinical trials, data monitoring committees are established to preside over serious adverse events and have the power to close trials prematurely when one arm of the trial shows significant benefit over another. For an adverse event to reach statistical significance a significant number of patients are exposed to risk. Our prospective power calculation revealed that 20 electrodes would be needed to statistically detect a 0.8 mm improvement in entry point accuracy. CUSUM analysis cannot replace statistical tests but does allow trends in beneficial or adverse events to be monitored closely and could potentially alert investigators to deleterious outcomes before they become statistically significant. We found that using the iSYS1 trajectory guidance system implantation entry point accuracies were significantly improved ($p < 0.01$) from 1.90 ± 0.96 mm (Mean $\pm$ -SD) to 0.76 ± 0.57 mm (Mean $\pm$ -SD). These results are consistent with a study by Dorfer et al⁷, in which preclinical testing of the iSYS1 device improved entry point accuracy to 0.6 ± 0.4 mm (Mean $\pm$ -SD) from 1.4 ± 0.5 mm (Mean $\pm$ -SD) with the frameless technique. The same group also reported entry point accuracy of 1.18 ± 0.5 mm (Mean $\pm$ -SD) in 93 electrodes in 16 patients, after slight modification of the technique. Cardinale et al³ have found a mean entry point accuracy of 0.78 mm using the Neuromate (Renishaw) for SEEG and Mullin et al¹⁴ found a mean entry point accuracy of 1.2 mm using the ROSA system.

Based on these accuracy data Cardinale et al recommended the institution of a safety margin of 3mm based on the following:

$$\text{Safety margin} = \text{bolt diameter} + \text{mean error} + 3 \text{ S.D.}$$

1% of electrodes would deviate outside a 3 S.D. safety margin, which was deemed acceptable. When the CUSUM analysis is repeated on the basis of a 3 mm entry point safety margin and an accepted 1% violation rate, the iSYS1 device performed within this threshold for all implanted electrodes.

4.2 Study Limitations

- 4.2.1** Limitations of our study include the small study size (21 electrodes) and differences in the use of a 3D printed phantom compared to a patient. We tried to use a material that had similar properties to real bone, but the bone substitute was slightly harder.

- 4.2.2** The control group was derived from *in vivo* frameless implantations and we accept it may have been methodologically better if the frameless implantation method was also used on the phantoms. We compared the same surgeons to prevent inter-surgeon variability, but they have more experience with the frameless technique than with the iSYS1 robotic device. We found there was a very minimal learning curve associated with first time use of the iSYS1 device and at all times entry point accuracy was found to be more accurate than the frameless technique. We do not feel that previous experience through implantation of electrodes in the patient using the frameless method would have resulted in an increase in the accuracy of the iSYS1 phantom implantation because the robotic implantations were performed on retrospectively implanted patients many months after the patient implantations. Furthermore, given that the iSYS1 trajectory guidance system performs the alignment automatically we cannot envisage how prior experience with the skulls can improve the accuracy of the implantation.
- 4.2.3** We focussed on entry point accuracy over target point accuracy. The reason for this is that entry point accuracy and angle are the main factors that can be controlled by the surgeon. Given that the electrodes are flexible and inserted in a blind fashion, there is a potential for them to deviate within the brain. Our phantoms did not have a brain material within them and as such we could not accurately compare actual target points. To account for this we calculated projected target points based on the bolt tip and extrapolated this to a uniform distance for both manual and iSYS1 implantations. The majority of intracranial haemorrhages following SEEG implantation are extra-axial, most likely as a result of damage to cortical veins. Although there does remain a risk of haemorrhage along the entire intracranial length of the electrode small inaccuracies at the target are unlikely to prevent measurement of the inter-ictal and ictal electrophysiology from the target structure of interest.

5 Conclusion

The introduction of novel medical devices to clinical practice is associated with an inherent risk. A large proportion of devices are approved without rigorous clinical trial data or long term follow up. Here we have shown that CUSUM analysis is an effective tool in the assessment of a novel robotic device for SEEG electrode insertion. As part of the preclinical testing we recreated implantation schemes and implemented these using an anatomically accurate skull phantom. Entry point accuracy was statistically improved using the iSYS1 robotic trajectory guidance system. CUSUM analysis can be used as an early warning tool in conjunction with all stages of the IDEAL framework to enhance patient safety. A thorough independent appraisal of both the clinical and economic factors is required before medical devices can be widely adopted. Even with the use of methodologically sound clinical trials patients are exposed to potential risks and it is an ethical obligation incumbent on all trial investigators to mitigate this risk as far as possible through early complication detection.

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Abbreviations

3D	Three dimensional
CUSUM	Cumulative summation
FDA	Food and drug administration
IDEAL	Idea, Development, Exploration, Assessment, Long-term follow-up
S.D.	Standard deviation
SEEG	Stereoelectroencephalography

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Figure 1.
Implantation using iSYS1 robotic trajectory guidance system on phantom head recreated to replicate the patient SEEG implantation.

Figure 2.

Schematic of implantation accuracy metrics include entry point, projected target point and angle error to skull. Solid line (diamond) indicates planned electrode and dashed line (circle) indicates bolt axis trajectory. Entry point (a) and projected target point (b) error measured as lateral deviation from plan. Image modified from Nowell et al (ref 16) with permission.

Figure 3.

a) Comparison of entry point, target point and entry angle deviation from plan with manual patient and iSYS phantom implantations. b) Suggested grading system for clinical relevance of implantation error and proportion of manual patient and iSYS phantom electrodes within error tolerances.

Figure 4.

a) CUSUM for entry point error b) target point error and c) angle error. A negative gradient implies the intervention (iSYS1) is more beneficial than the control (frameless) implantation. Any change to a positive gradient should alert the investigators to an increase in the potential risk of the implantation (as can be seen between electrodes 6-8 in figure 4b). The end of the learning curve is taken as the point where the positive gradient becomes negative or where the gradient is most negative. In figure 4a, the learning curve for entry point error becomes most negative after electrode 8. In figure 4b, the target point error

becomes negative after electrode 8. In figure 4c, angle error learning curve becomes negative after electrode 10, but there is poor correlation between intervention and angle error.