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Feasibility studies, clinical trials and multicentre collaboration

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Dear Editor

The COXIBRAIN study published in the September issue of Acta Neurochirurgica [5] was designed to determine the effects of a selective COX-2 inhibitor (Celecoxib) on the recurrence rate of chronic subdural haematomas. Unfortunately, despite a good design, it was terminated prematurely, due to low recruitment. Despite the relative common occurrence of chronic subdural haematoma, the COXIBRAIN study only managed to enrol 23 patients despite screening 246 (9.4%). The major cause for the low enrolment was due to contraindications to selective COX-2 inhibition and contra-indicated pre-existing therapy. Of note a neurosurgical trial comparing early surgery versus initial conservative treatment in patients with traumatic intracerebral haemorrhage (STITCH) [4], published in 2015, was also terminated early; although overall recruitment was progressing well, insufficient participants were recruited from UK sites (6 out of 170).

These findings emphasise the importance of performing rigorous feasibility and internal pilot studies, as the accompanying editorial is also pointing out [3]. Engaging neurosurgical trainees who are spread out in several units can help studies reach their sample size faster and may also facilitate the assessment of feasibility of trials. For example, in the UK, the British Neurosurgical Trainee Research Collaborative (BNTRC) [2] completed a prospective observational study of 1205 patients with chronic subdural haematoma from 26 UK neurosurgical units over a period of 8 months (manuscript currently in press with the Journal of Neurosurgery). Subsequently, a funding application to the UK National Institute for Health Research for a trial of dexamethasone in chronic subdural haematoma was successful largely because there was substantial evidence of adequate patient numbers. (www.dexcsdh.org)

Bragge *et al* recently published an overview of randomised controlled trials evaluating acute management of moderate-to-severe traumatic brain injury [1]. 207 randomised controlled trials were identified of which more than two thirds had fewer than 100 participants and almost three-quarters were single centre. For all outcomes of interest measured almost three-quarters of the trials found no differences between the intervention and control groups. The authors correctly pointed out that a substantial investment of resources has resulted in very limited translatable evidence. Two of the main reasons for this, put forward by the authors, are the small sample sizes and the preponderance of single-centre RCTs.

The trend towards conducting multicentre trials, based on high quality feasibility studies, conducted in multiple centres in multiple countries with adequate sample sizes is surely the way forward. With this in mind the Society of British Neurological Surgeons (SBNS) have generated a database of UK neurosurgeons with an interest in research, along with their subspecialty expertise. Furthermore, the SBNS (www.sbns.org.uk/index.php/research/), in collaboration with the European Association of Neurosurgical Societies (EANS, www.eans.org), have initiated a database of multicentre trials with the purpose of promoting wider support. Both of these initiatives will hopefully help with the setup and running of trials.

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REFERENCES

(1) Bragge P, Synnot A, Maas AI, Menon DK, Cooper DJ, Rosenfeld JV, Gruen RL (2016). A state-of-the-science overview of randomised controlled trials evaluating acute management of moderate-to-severe traumatic brain injury. J of Neurotrauma. Aug 5;33(16):1461-78

(2) Kolias AG1, Jones TL, Cowie CJ, Coulter IC, Afshari FT, Tarnaris A, Nelson RJ, Gray WP, Hutchinson PJ, Brennan PM; UK Neurosurgical Research Network; British Neurosurgical Trainee Research Collaborative (2016). A report from the inaugural meeting of the British Neurosurgical Trainee Research Collaborative held in the Royal College of Surgeons of England, 19 October 2012. Br J Neurosurg. Jun;27(3):307-10.5.

(3) Maas AIR. (2016) Clinical trials: do we need criteria for pre-study feasibility assessment? Acta Neurochir. DOI 10.1007/s00701-016-2950-x

(4) Mendelow AD, Gregson BA, Rowan EN, Francis R, McColl E, McNamee P, Chambers IR, Unterberg A, Boyers D, Mitchell PM on behalf of the STITCH(Trauma) Investigators (2015). Early Surgery versus Initial Conservative Treatment in Patients with Traumatic Intracerebral Hemorrhage STITCH [Trauma]): The First Randomized Trial. J of Neurotrauma *.*32: 1312-1323

(5) Schumann A, Klene W, Rosenstengel C, Ringel F, Tüttenberg J, Vajkoczy P (2016) COXIBRAIN; results of the prospective randomised, phase II/III study for the selective COX-2-inhibitoion in chronic subdural hematoma patients. Acta Neurochir. Doi:10.1007/s00701-016-2949-3