Methodological advances in randomized trials

TO THE EDITOR: We enjoyed reading the paper by Mansouri et al., and the accompanying editorial by Barker (Mansouri A, Cooper B, Shin SM, et al: Randomized controlled trials and neurosurgery: the ideal fit or should alternative methodologies be considered? J Neurosurg 124:558–568, February 2016). We entirely agree with their conclusion that “given the role of RCTs [randomized controlled trials] as one of the highest levels of evidence, it is critical to improve on their methodology and reporting.” In this letter, we highlight a number of recent methodological advances that have the potential to improve the quality of neurosurgical randomized trials and clinical research in general.

Firstly, we believe that the IDEAL (Idea, Development, Exploration, Assessment, Long-term study) framework, which describes the 5 stages through which surgical innovation normally passes, is a very useful guide for surgeons interested in evaluating surgical interventions—both new and established. The international IDEAL Collaboration offers recommendations for all stages of surgical innovation, from the initial idea (Stage 1) to the established and accepted procedure subjected to long-term studies (Stage 4), and accepts that different study designs and methods of reporting are needed for the various stages, since each stage has unique characteristics. Importantly, it recognizes that during the development stage (Stage 2a), innovations undergo rapid iterative change in the light of accumulating experience, limiting the usefulness of randomized trials. Hence, it supports prospective development studies at this stage, with “sequential reporting of all cases and outcomes without omissions, and with clear explanations of when and how technique, design, or indications were changed.” Moreover, it recognizes that randomized trials should be used whenever possible to investigate effectiveness (Stage 3) but also suggests a number of solutions for overcoming common issues in surgical trials (that is, surgeon preferences, patient preferences, quality control of intervention) and a number of alternatives when a traditional randomized trial is not feasible.

Secondly, in recent years the importance of using standardized sets of outcomes, known as “core outcome sets” (COSs), in effectiveness trials has been increasingly recognized. Heterogeneity in the outcomes measured is a well-documented phenomenon that leads to considerable difficulties with evidence synthesis. In addition, outcome-reporting bias, which is a “results-based selection for publication of a subset of the original measured outcomes variables,” is a significant problem. The consensus-based development and use of a COS, which as a minimum should be measured and reported in all trials for a specific clinical area, can address these well-known problems. Recent progress in the field of COSs is exemplified by the work undertaken by the COMET (Core Outcome Measures in Effectiveness Trials) Initiative (http://www.comet-initiative.org), an international group that brings together people interested in the development and implementation of agreed-to COSs for clinical research. The initiative conducts methodological work on COS development and supports a COS database that allows developers to register new projects to avoid unnecessary duplication. We consider the involvement of patients and caretakers as stakeholders to be important in COS development. For example, the ongoing CODE-CSDH (Core Outcomes and Common Data Elements in Chronic Subdural Haematoma) project will involve these groups as well as health care practitioners and researchers in the development of a COS for chronic subdural hematoma.

Importantly, the IDEAL framework and the use of COSs are gaining support from funding bodies. The National Institute for Health Research (NIHR) Health Technology Assessment program in the United Kingdom (UK) recently issued, based on the IDEAL framework principles, a call for proposals for prospective collaborative cohort studies of fenestrated endovascular aneurysm repair for juxtarenal abdominal aortic aneurysms. In addition, the same body has added the following statement to its application forms: “Where established Core Outcomes exist they should be included amongst the list of outcomes unless there is good reason to do otherwise.”

Thirdly, in the UK there has also been investment in trials methodology research by the Medical Research Council and the formation of 5 hubs. For example, the ConDuCT-II (Collaboration and Innovation in Difficult and Complex Randomised Controlled Trials in Invasive Procedures) Hub for Trials Methodology Research in Bristol (http://www.bristol.ac.uk/social-community-medicine/centres/conduct2/) has a specific focus on creating new and better methods for the design and conduct of randomized trials in surgery.

Fourthly, a national program for surgical trials has been developed in the UK. In 2012, the Royal College of Sur-
geons of England (RCS) along with partners established a network of surgical trial units across the UK and appointed surgical specialty leads (SSLs) from the various surgical specialties with the “specific remit to develop new trials, establish clinical networks, and work with their patients to develop and deliver innovative trials across the surgical disciplines.”10,11 Trainee research collaborators, networks of trainees working together to design and deliver multicenter trials and high-quality prospective studies, are at the foundation of this national program.2 In neurosurgery, the British Neurosurgical Trainee Research Collaborative (BNTRC; http://www.bntrc.org.uk) was formed in April 2012 with the support of the Society of British Neurological Surgeons (SBNS) and the Neurosurgical RCS SSL.10 More than 1800 patients undergoing 2 of the commonest neurosurgical procedures (evacuation of chronic subdural hematoma and ventriculostomy) have been enrolled in the 2 first prospective, UK-wide, observational cohort studies designed by the BNTRC.5,9 In addition, funding was secured from the NIHR Health Technology Assessment program for 2 randomized trials in collaboration with the SBNS Neurotrauma Group. The RESCUE-ASDH (Randomised Evaluation of Surgery with Cranietomy for Patients Undergoing Evacuation of Acute Subdural Haematoma) trial (craniotomy vs hemicraniectomy for acute subdural hematoma; http://www.rescueasdh.org) has now rolled out to 21 UK units,8 while the Dex-CSDH trial (Dexamethasone for Adult Patients With a Symptomatic Chronic Subdural Haematoma; 2-week tapering course of dexamethasone vs placebo for patients with chronic subdural hematoma treated in neurological units) started recruitment in August 2015.7 All of these studies are recruiting patients to schedule and are supported in all participating units by a consultant (that is, board-certified neurosurgeon) principal investigator and at least 1 trainee (that is, resident) co–principal investigator.

Finally, we would like to endorse Dr. Barker’s statement that “in 2015, no form of medical publication rivals the RCT for academic and ‘real world’ clinical impact.”11 Pragmatic randomized trials—aiming to compare 2 or more treatments in the real world—are a form of comparative effectiveness research (CER), the so-called experimental CER.3 In our view, the latter together with nonexperimental CER (for example, registry-based observational studies) provides neurosurgeons with the necessary tools to evaluate established and novel therapeutic interventions. However, we strongly believe that surgeons should aim to work with multidisciplinary teams to design and conduct pragmatic randomized trials when a research question is sufficiently refined to allow for the design and conduct of such studies.

References
7. ISRCTN Registry: A randomised, double blind, placebo-controlled trial of a two-week course of dexamethasone for adult patients with a symptomatic chronic subdural haematoma (Dex-CSDH trial). (http://www.isrctn.com/ISRCTN80782810) [Accessed January 20, 2016]