The Barrow Ruptured Aneurysm Trial and International Subarachnoid Aneurysm Trial

To The Editor: We were pleased to read the results of the Barrow Ruptured Aneurysm Trial (BRAT) (McDougall CG, Spetzler RF, Zambramski JM, et al: The Barrow Ruptured Aneurysm Trial. Clinical article. J Neurosurg 116:135–144, January 2012) and the accompanying commentary that described it as a “Landmark Trial.” We had been aware of the study and preliminary results, which were announced about 3 years ago at the American Association of Neurological Surgeons meeting in Chicago. While there may be methodological criticism of the trial, particularly its unusual design, the results, whether analyzed by intention to treat or treatment received, show a larger absolute benefit of coiling, in terms of reducing death and dependency at 1 year, than was reported in the International Subarachnoid Aneurysm Trial (ISAT) (10%–13.9% absolute improvements in outcomes with coiling in BRAT compared with 7.4% in ISAT).

The small number of patients enrolled into ISAT, which proved so controversial and for which it was widely criticized after it was published almost 10 years ago, led many neurosurgery colleagues to question the wider applicability of the results. This is discussed at some length in the report of McDougall and colleagues and, in some measure, this consideration drove the design of BRAT and deserves further comment. Those who have drawn attention to this aspect of the ISAT design and reporting misunderstanding the principles and the realities of conducting large multicenter randomized trials. It is a fallacious argument.

During the final 6 months of recruitment into ISAT, a national audit of the outcomes of subarachnoid hemorrhage was conducted in the United Kingdom (UK) and Ireland. This recorded all patients with subarachnoid hemorrhage admitted to neurosurgical units in the UK and Ireland in the period from September 2001 to September 2002, and for a further year to September 2003.

The findings of this audit have been published in Stroke; and the full report is available from the Royal College of Surgeons of England. By chance this period of observation coincided with the premature closure of recruitment into ISAT following the release of the non-blinded outcome data by the independent Data Monitoring Committee to the Trial Steering Committee, which stopped recruitment on May 2, 2002, because of a highly statistically significant benefit observed in the coiling arm of the trial at 1 year.

The national audit recorded whether a patient was treated by either clipping or coiling of the aneurysm, or was untreated. We were able to accurately analyze the proportions of patients in each UK center who were treated by clipping or coiling during the period of recruitment into the trial from September 2001 to April 2002, and in the subsequent period from May 2002 to September 2003.

There were 21 UK centers that recruited patients into ISAT during this period. We divided those UK centers into 2 groups: those that recruited more than 50 patients into the whole trial and those that recruited fewer than 50 patients into the whole trial. We examined the numbers of patients treated by clipping or coiling in those units during the relevant 6-month period of recruitment into ISAT and the subsequent 18 months to observe whether practice changed after trial recruitment was stopped.

In the large recruiting centers (more than 50 patients entered into the whole trial) during the period from September 2001 to April 2002, 52% of the patients were treated with clipping and 48% of the patients were treated with coils, the expected proportions.

In the smaller recruiting centers (fewer than 50 patients enrolled), 82% of the patients were treated with clipping and 18% with coiling during this period. During the same period, 5 UK centers were carrying out coil occlusion of aneurysms but were not signed up to recruit into ISAT. In those centers 25% of patients underwent coil treatment and 75% of patients underwent clip treatment (Fig. 1).

After trial recruitment was stopped, we informed the investigators immediately of the reason for stopping prematurely, namely, the improved clinical outcomes in the coiling group. An immediate change of practice was observed in the subsequent 6 months in the large recruiting centers (Fig. 2), and 80% of patients were treated with coiling in the next 6 months whereas the smaller recruiting centers continued to treat 70% of patients with clipping and only 30% with coiling. The centers that were not participating in ISAT placed coils in 60% of patients over that same 6 months.

This pattern continued between January and September 2003, with large recruiting centers using coils in 83% of patients, low-volume recruiting centers using coils in 46% of patients, and non-ISAT centers using coils in 57% of patients.

As principal investigators of a large pragmatic trial that seeks to recruit a large numbers of patients in many centers and is attempting to answer an important clinical question, we have no control over the behavior of neurosurgeons or neurointerventionists concerning recruitment of individual patients, or whether they make the effort to recruit them into such studies.

It takes considerable time and effort to recruit patients. Some neurosurgical centers and individual neuro-
surgeons paid “lip service” to participation in the trial. They lacked clinical equipoise; that is, they believed that patients did better in their hands with clipping and lacked personal uncertainty. This is not a fault of the trial and is irrelevant to the results. If doctors are not motivated to enroll patients and simply continue their existing surgical practice, such behavior and nonrecruitment cannot be blamed on the trial or its design; ideally one would like all centers and surgeons from a center to fully participate and enroll as many patients as possible. We would have the answer sooner and, as it turns out, ultimately many patients would have been saved from death or disability. Sadly that is not the real world!

It is not well understood in the neurosurgical community that in fact most randomized medical trials, such as cancer trials, recruit only a very small number of patients with the particular disease. This does not invalidate the findings of such randomized trials. All randomized clinical trials examine a selected population with a particular condition. It is not always possible to know in advance the exact population demographic of patients with the condition who will enter a trial. However, when such trials are reported, the population is accurately described and the results are valid for that population.

We are delighted that BRAT has at last been published, but equally, it is sad that we have had to wait so long to show that, even in one of the best neurosurgical units in North America, using coils to treat suitable pa-

**Fig. 1.** Pie charts showing audit data for UK rates of coiling and clipping by center type during recruitment into ISAT (September 2001–April 2002) based on returns to the Royal College of Surgeons. Data are categorized as high-recruiting centers (> 50 patients: 12 centers, 660 patients) and low-recruiting centers (< 50 patients: 9 centers, 297 patients). Five non-ISAT centers treated 196 patients. The total number of patients treated in all centers in 8 months was 1362.

**Fig. 2.** Pie charts showing audit data for UK rates of coiling and clipping by center after ISAT recruitment stopped (May 2002–December 2002) based on returns to the Royal College of Surgeons categorized according to high-recruiting centers (> 50 patients: 12 centers, 530 patients) and low-recruiting centers (< 50 patients: 9 centers, 298 patients). Five non-ISAT centers treated 150 patients. The total number of patients treated in all centers over 8 months was 1153.