Flow Diversion in the Treatment of Intracranial Aneurysm Trial

TO THE EDITOR: We read with interest the recent paper by Raymond et al.8 (Raymond J, Gentric JC, Dursaut TE, et al: Flow diversion in the treatment of aneurysms: a randomized care trial and registry. J Neurosurg [epub ahead of print November 4, 2016; DOI: 10.3171/2016.4.JNS152662]). The authors conclude that “Flow diversion was not as safe and effective as hypothesized. More randomized trials are needed to determine the role of flow diversion in the management of aneurysms.” We respectfully disagree with these conclusions.

Randomized controlled trials (RCTs) are held up as the pinnacle of clinical research. Many previous investigators as well as regulatory agencies have decried the dearth of RCTs evaluating flow diversion. The challenges in conducting RCTs in the setting of emerging technologies are well known to us, and we congratulate the authors on their ability to enroll patients in an RCT. However, not all RCTs are created equal, and a substantial degree of “pushback” has emerged by authors critical of the potential limitations of RCTs. Chief among these critiques is that the gauntlet of selection criteria in many RCTs results in a rarified population that is not representative of usual practice. In order to overcome this specific limitation, many investigators have proposed implementation of “pragmatic RCTs,” which have relatively broad inclusion criteria to encompass a wide array of patients. As a result, most current pragmatic RCTs are very large trials that typically utilize the electronic medical record to sweep up vast amounts of clinical data on large numbers of patients. Granted, the MR CLEAN trial was described by its investigators as “pragmatic,” based on the fact that a wide range of NIHSS (NIH Stroke Scale) scores and endovascular devices were allowed. However, in the MR CLEAN trial inclusion and exclusion criteria were still precisely defined, a factor that was likely responsible for its positive result.

Raymond and colleagues have recently introduced into the medical lexicon the idea of the “randomized care trial.” This term seems new, and both Google and PubMed searches fail to uncover a single prior publication using that specific term. The authors have previously claimed that “care” trials can cure nearly every ill of the RCT. They have written, “Care trials protect present patients from both unverifiable medicine and research performed for extraneous interests. They provide prudent care when evidence is lacking…. Care trials can identify which medical alternative should be standard therapy. In the meantime, they provide optimal care in the presence of uncertainty.” Unfortunately, there is little evidence to substantiate these claims.

The FIAT (Flow Diversion in Intracranial Aneurysm Treatment) trial is a small trial with unclear enrollment criteria that somehow captured a predominance of lesions that have been known, based on much, much larger previous trials, to be of high risk for flow diversion. Indeed, if the FIAT investigators had been in charge prior to regulatory approval of flow diversion we would never have learned that carotid artery aneurysms that were previously very difficult to treat can be easily cured with low complication rates, even with first-generation flow diversion technology. The investigators and regulators who designed and oversaw the PUFS (Pipeline for Uncoilable or Failed Aneurysms) trial understood the critical importance of clear enrollment criteria, unmet clinical needs, and rational design of trials. What were the enrollment criteria for FIAT? As written in the paper, “All patients harboring an aneurysm for which flow diversion was considered a promising treatment were eligible to participate.” Who decided that flow diversion was promising for these patients? What were their specialties? Who are these patients? What was considered “promising?” How many patients were excluded and why? And how did they end up with cohorts of patients known to be at high risk of treatment with any device, with more than one-third of patients randomized to flow diversion harboring aneurysms distant from the internal carotid artery (ICA)? Further, the complications were concentrated in known “high-risk” aneurysms for flow diversion, including ruptured, distal anterior, and posterior circulation aneurysms. Indeed, rather than eliminating bias and providing data on “usual care” patients, FIAT reports on complications in very small cohorts of very rare aneurysms. How does this inform the community on the usual patient with small or medium-sized anterior circulation aneurysms? It doesn’t.

Just as not all RCTs are created equal, not all aneurysms are created equal. The natural history, treatment efficacy, and complication rate vary widely among aneurysms of different size, territory, and presentation. We fully agree
with the FIAT authors’ suggestion that we remain in the early stages of investigation regarding flow diversion. Accordingly, it seems premature to shift from explanatory trials—focused on clearly selected, relatively homogeneous groups of patients—to all-encompassing pragmatic trials. Trials such as PUFS, ASPIRE, and PREMIER have enrolled well-defined groups of patients that likely allow “generalization” to other, similar aneurysms.\textsuperscript{1,3,4} Almost counterintuitively, the results of the “pragmatic” FIAT trial, instead of being “generalizable,” are impossible to apply to any patient group, given unclear enrollment criteria and substantial heterogeneity.

**Response**

We thank the authors for their interest in our study. They acknowledge “the dearth of RCTs evaluating flow diversion” and the “challenges in conducting RCTs in the setting of emerging technologies,” and it is precisely to address these challenges that the care trial methodology was conceived.\textsuperscript{11} In fact, FIAT is the prototype care trial.\textsuperscript{11}

While a received view and the current regulation separate clinical interventions and comparison of patient outcomes, one within the domain of care and the other within the domain of research,\textsuperscript{1,2} care trials assess the outcome of interventions as they are practiced in the best medical interest of participants.\textsuperscript{11} Care trials are pragmatic as opposed to explanatory trials, design concepts introduced in 1967.\textsuperscript{8,14} Kallmes and colleagues appear to think that it is too early for pragmatic trials because of a belief that, in evaluating innovative treatments, there is a proper chronology of methods based on the selection of patients: “it seems premature to shift from explanatory trials—focused on clearly selected, relatively homogeneous groups of patients—to all-encompassing pragmatic trials.”

To discuss this issue, we have ordered various research methods (preclinical, clinical, and epidemiological) according to the selection of research subjects in Fig. 1. Dr. Kallmes participated in PUFS,\textsuperscript{3} which was a case series lacking a comparator group that was used for device approval (Fig. 1B). If, as he and his colleagues assert, “the investigators and regulators who designed and oversaw the PUFS … trial understood the critical importance of … rational design of trials,” we believe that they would have done more than rename their case series, the weakest method, as a clinical trial (Fig. 1C). Ethical care using innovative devices remains research, and the protection of participating patients requires randomized allocation, as we will see shortly.\textsuperscript{5,6,13}

The authors’ approach is to start with the preclinical method, since the idea that you can only learn from the careful selection of identical research subjects (of the same purebred species) comes from the animal laboratory (Fig. 1A). According to this line of thinking, the more selected and homogeneous your research subjects, the more generalizable the results of your experiment. In clinical medicine, the truth is exactly the opposite: the more selective the patient group, the less generalizable the results.\textsuperscript{14} This common mistake confuses the problem of who should be studied in order for the results to be generalizable with the problem of how to re-identify the same patients in the future (to make clinical categories of “natural kinds”).

The authors complain of the “limitations of RCTs.” However, here we are confronted with our own human limitations.\textsuperscript{7} The reasoning that “RCTs are difficult—therefore let’s use an alternative” is common, but not the best solution. The complaint is typically followed by a good idea, like PROS (pragmatic registry-based observational studies), which is only a new name to re-introduce the same old case series and observational studies.\textsuperscript{10}

The authors’ second methodological choice, then, is epidemiological, as we know from past publications.\textsuperscript{4,9,12} However, even there, canons of statistical inference, such as random sampling to validly infer that results from the sample apply to the population, are rarely if ever respected (Fig. 1B).\textsuperscript{5}

The end result of starting with a small case series of selected patients, without a comparison group, followed by observational studies of treatments performed in all other patients, is that innovations are practiced just as if they were standard care and proper RCTs comparing the innovation with standard care are never performed.