The requirement that clinician-investigators need to have equipoise before randomizing patients to clinical trials is widely accepted in the scientific community. Here, we contend that such requirement demands a nuanced and critical interpretation and should not become an obstacle to the conduction and completion of well-conceived clinical trials.

“Do you have equipoise?” The question was simple, yet loaded with challenges. We were being invited to participate in a prospective randomized controlled phase 3 trial testing whether acute endovascular stroke therapy can be beneficial for patients presenting beyond 6 hours from symptom onset (≤6 hours is the currently accepted therapeutic time window for mechanical thrombectomy) when using perfusion brain imaging for selection of candidates. As clinicians, we may have qualms because we are already treating some of these patients with thrombectomy—albeit a minority—in our daily practice. As investigators, we want to participate because we agree with the scientific merit of the study, and we think it has good potential to advance our knowledge and change the standard of care for future patients. So, do we have equipoise? Furthermore, is having equipoise truly an indispensable condition for us to decide whether to participate in this (or any) trial?

To answer this question, we must first understand what we mean when we talk about equipoise. Equipoise is traditionally defined as a state of genuine uncertainty on the relative value of 2 approaches being compared in a trial.1 After its inception, equipoise became rapidly embraced as a necessary condition for randomization in clinical trials. However, the practical application of this ethical concept has proven far from straightforward.

Initially conceived to reflect uncertainty on the part of each individual investigator,1 the concept was subsequently modified by the Canadian Bioethicist Benjamin Freedman2 to instead represent uncertainty within the expert medical community. Freedman convincingly argued that the requirement for uncertainty on the part of each investigator (which he named theoretical equipoise) was impractical and even improbable. Investigators participating in a trial are likely to have personal preferences in favor of one of the approaches being tested, which may stem from their personal, uncontrolled experience, their interpretation of available literature, or simply their clinical attitudes. Yet, Freedman contended that as long as uncertainty remains across experts in the field, the requirement for equipoise is satisfied without equipoise necessarily being present on the part of each participating investigator. Freedman’s concept of equipoise, which he designated as clinical equipoise, considers it to be entirely ethical for individual clinician-investigators with a preference for one of the alternatives being tested to enroll patients for randomization, even if subsequent randomization places a patient in a treatment arm deemed inferior by the randomizing physician.

Clinical equipoise (ie, uncertainty within the clinical community) is unquestionably more practical than theoretical equipoise (ie, uncertainty on the part of each individual investigator). Most experts have strong opinions, which often get into guidelines endorsed by professional organizations that, in turn, influence the opinion of many clinicians. Furthermore, the principal investigators of randomized controlled trials often reach that position after convincing funding agents of the promising value of one of the alternatives being tested. Clearly, demanding each investigator to have complete balance of opinion between the 2 arms of a trial may be setting the bar too high, particularly in placebo-controlled trials that tests a possibly effective treatment for a critical and disabling disease.

The requirement for clinical equipoise has also been criticized as defective. The main argument against it is that it may condone a violation of the principle of therapeutic nonmaleficence by accepting randomization to a placebo arm or an inferior treatment arm in cases when the randomizing clinician-investigator thinks the active arm or one of the two therapeutic alternatives may be superior. In such cases, the critics argue, the treating clinician-investigator would be failing her obligation to provide the patient with the best possible treatment based on her individualized judgment.3 Another criticism is that it is not clear what should be considered a lack of expert consensus. In other words, what degree of disagreement within the professional community should be deemed sufficient to meet the condition of clinical equipoise.4,5 Further complicating this second argument is the absence of reliable information on the divergence of opinion within the medical community about various treatment options.6

Miller and Brody7 have advanced a different approach to this ethical problem. Instead of requiring equipoise, they propose to focus on the principle of nonexploitation of the patient-subject. According to this view, the only essential
preconditions for the ethical conduction of a randomized trial are the scientific merit of the question being asked (ie, having an honest and valid null hypothesis) and the social value of the eventual results of the investigation. Approval by institutional review boards, ongoing monitoring by an independent safety review committee, and adequate use of informed consent would guarantee that the patient-subject is protected from exploitation. Within this formulation, neither theoretical nor clinical equipoise is deemed a necessary ethical requisite. However, reluctance on the part of the enrolling physician may remain problematic in this approach.

Uncertainty about equipoise is more than a scholarly debate. The requirement for equipoise can ruin trials. Some trials may fail to be funded because they are not considered feasible, others may be prematurely stopped because of slow recruitment, and others may be completed but suffer from lack of credibility because of selection bias during recruitment (eg, only the best or the worst cases having been enrolled).

So what is the solution? Trial recruitment can be greatly helped when the only way to get the treatment being tested is by participating in the study. However, this is often easier said than done because political and financial considerations often play a major role on whether a treatment is available and its costs are covered. In comparison to explanatory trials, pragmatic trials are designed to provide more room for clinician-investigators to decide if randomization is appropriate for the individual patient and thus it would be more attuned to the requirement of individual equipoise; however, this may result in too many patients with the condition under investigation being treated outside of the trial. Registries of all screened patients who do not get enrolled in the trial can be useful (when outcomes are collected), but they are rarely mandated. Institutional review board approval, safety monitoring boards, and detailed and transparent informed consents are all good and necessary measures, but they do not solve the problem per se. It remains up to the clinician-investigator to decide whether to invite the patient to participate in the trial, with or without equipoise. Once that decision is made, the investigator should clearly inform the candidate participant of the risks and benefits of both study arms, answer all questions in language that the candidate participant can understand, and do everything possible to help ensure that the candidate participant can fully assess the implications of the voluntary participation in the trial.

Perhaps the problem with equipoise results from our fixation with randomized controlled trials. In fact, these trials have been increasingly criticized because they study cohorts rather than individuals. As the burgeoning field of individualized (precision) medicine keeps growing, it is possible that our research paradigms may change. But for now, randomized controlled trials remain the best way to reach robust conclusions about the comparative value of medical treatments. Thus, we must continue conducting clinical trials.

Reasons to do so abound. First, we really know less than we think we know. History keeps showing us that our individual and collective fallibility cannot be underestimated. Galen was thought to be right for many centuries until many of his authoritative notions were disproven. Much closer in time, strategies that had been broadly but prematurely adopted into clinical practice despite being only supported by single center or methodologically weak studies were subsequently proven unhelpful or even frankly detrimental by adequately powered and rigorous randomized controlled trials (intensive insulin therapy for critically ill patients can be cited as one of many available examples).4 Second, trials protect us from dogmas. Not infrequently we hear competing opinions about 2 treatment options being defended with similar passion and seemingly convincing, yet mutually exclusionary arguments. Once again, in these instances, trials are necessary to provide impartial evidence to guide patient care. Third, trials are beneficial at a societal level. From a social beneficence standpoint, they inform best therapy for future patients. From a utilitarian perspective, they provide the data to support the coverage of effective therapies by public or private payers and approval of novel treatments by regulatory agencies. They can also result in cost savings when showing that an expensive treatment is not more effective than a cheaper one and they can prevent future harm when demonstrating that a treatment is not safe.

Back to the trial that motivated this reflection. The discussion is not new. Several recent trials have conclusively demonstrated that mechanical thrombectomy is highly beneficial for patients with acute stroke from a large intracranial artery occlusion who can be treated within 6 hours of symptom onset.7–11 Yet, these positive trials were preceded by a few negative trials that had questioned the value of acute endovascular stroke therapy.12–14 The initial reaction in the stroke community was generally one of surprise and dismay. However, this was rapidly followed by a concerted effort to conduct new and improved randomized controlled trials and calls to overcome the previous reluctance among clinicians to enroll patients into these types of trials.15,16 We can say with certainty that many of the clinician-investigators who randomized patients to those trials lacked individual equipoise themselves, but they understood that the intervention was not supported by the available evidence and it was therefore essential to contribute to the completion of the new trials to reach a solid answer. The change in standard of care that resulted from these trials represents a sound validation of the scientific merit of the trials but also of the importance of the collective commitment that allowed their completion.

So how do we have equipoise? In the case of an elderly patient found several hours after being last known normal and showing a moderate early hypodensity on the head computed tomographic scan, we would have no preference whether to try endovascular intervention. Conversely, in the case of a young patient with severe neurological deficits present on awakening and a normal computed tomographic scan, we would favor endovascular therapy if a perfusion scan showed a limited ischemic core and a large penumbra (ie, hypoperfused but still viable tissue temporarily preserved by collateral flow). But we would encourage both patients to participate in the trial, highlighting the lack of agreement within the medical community in regard to the value of the intervention and the voluntary nature of their participation. We would try to randomize both patients because only consecutive enrollment of all eligible patients can optimize the external validity of the results. Because we know our therapeutic biases remain unproven. Because failing to challenge our beliefs can render us
dogmatic. And because we are convinced that we have a social responsibility to advance medical knowledge by collaborating to the successful completion of rigorous clinical trials.

Disclosures
Dr Kallmes received research support from Medtronic, MicroVention, Codman, NeuroSigma, Surmodics, Sequent Medical, and Shape Memory Therapeutics. He is a consultant (all money to institution) in Medtronic, GE Healthcare. Patents submitted or anticipated at Mayo Foundation (Spine augmentation, stroke intervention) and UVA Patent Foundation (Spine fusion). Know-how agreements: NeuroSigma.

References

Key Words: equipoise ■ informed consent ■ standard of care ■ stroke ■ thrombectomy
Equipoise in Clinical Trials: Angst and Progress
Alejandro A. Rabinstein, Waleed Brinjikji and David F. Kallmes

Circ Res. 2016;119:798-800
doi: 10.1161/CIRCRESAHA.116.309594

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circres.ahajournals.org/content/119/7/798

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/