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In Reply

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Most of the evidence to date supporting neuroprotection after traumatic brain injury with erythropoietin administration comes from experimental studies. Two case-matched studies in patients with traumatic brain injury and large clinical trials in general trauma patients have found improvements in mortality with erythropoietin treatment.¹⁻³ For patients with traumatic brain injury, however, recovery of neurological function long-term is more important than simple survival and none of these previous studies have adequately addressed long-term outcome.

In their letter, Dr Nichol and colleagues misunderstand the hypotheses being tested in this futility (phase 2) study. The futility study was designed to determine if it would be worth while to conduct a future phase 3 trial. In futility studies, type I error and type II errors are reversed compared with conventional study design errors and a 1-sided test is used.⁴ Supplemental information provided with the article inadvertently omitted the futility hypotheses being tested, and this has been corrected.

Specifically, a type II error in a futility trial would indicate that an ineffective therapy is effective (a false-positive result) and should be tested further in a phase 3 trial. Similarly, a type I error in a futility trial would indicate that an effective therapy is unlikely to be ineffective (a false-negative result) and would not be tested further. To account for this reversal of the error types, we designed the futility study with a 15% probability that the revised erythropoietin dosing regimen (initial regimen of 1 dose within 6 hours) was mistakenly found to be ineffective, and we had 91% power (9% probability that this dosing regimen was mistakenly found to be effective).

Our study found that in the dosing regimens used, a 20% or greater improvement in long-term outcome was not likely. Additional supplementary information on exploratory secondary analyses suggested that the revised dosing regimen remained futile for a 10% absolute improvement in long-term outcome.

In terms of the change in dosing regimen, the original erythropoietin dosing regimen (initial regimen of 1 dose within 6 hours, then 2 additional doses at 24 and 48 hours) was stopped early by the US Food and Drug Administration for a safety concern. This regimen was not

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shown to be futile ($P < .47$, which is greater than the 15% probability level), and the regimen could be considered for a phase 3 trial if this higher dose were found to be safe.

Even though our study did not support use of erythropoietin at the present time using the dosing regimens that we tested, we agree that our results do not exclude the possibility that another dosing regimen or even the original erythropoietin regimen of 3 initial doses might provide a smaller improvement in neurological outcome.

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