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Comment: Ethics and ECMO

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I will address several general issues that the Ware paper raises. These include the use of historical controls, the ethics of randomized trials, the impracticality of Neyman-Pearson inference, and optimal adaptive design. I will also suggest a more ethical and perhaps more scientific approach to medical research than that of randomized clinical trials.

RANDOMIZED CLINICAL TRIALS: THE EMPEROR'S NEW CLOTHES

Randomization has achieved hallowed status in biostatistics. Some biostatisticians and clinicians refuse to believe that a treatment has an effect unless it has been shown in a "properly conducted" randomized clinical trial. A report of a randomized clinical trial takes for granted that the trial provides the conclusive answer: if its conclusion is the same as the prevailing wisdom that is based on historical data, the authors tell us that we can finally believe this wisdom; if it differs, they chide historical data and extol the virtues of randomized studies. In the case of ECMO, there was a substantial amount of historical data that, in my view, not only carry more weight than the Ware study, but suggest that randomizing patients to non-ECMO therapy as in the Ware study was unethical.

Ware refers to several previous studies concerning ECMO. The Bartlett et al. (1985) study included 12 patients in its play-the-winner phase; all 11 ECMO patients survived and the conventional therapy patient died. Bartlett et al. also reported on 10 patients who met their entry criteria but were treated after the study was completed: all 8 patients assigned to ECMO survived and the 2 assigned to conventional therapy died (though the authors do not indicate the reasons for different therapy assignments—one possibility unrelated to prognosis is the availability of ECMO machines). Bartlett et al. say they admitted only patients who had at least an 80% chance of dying on conventional therapy. I am currently examining historical controls provided by Dr. Bartlett to verify this mortality rate, and so far I have no reason to doubt it. The 40% (4 of 10) death rate on CMT in the Ware study is somewhat inconsistent with an 80% mortality rate, but patients in the Bartlett et al. study generally had worse prognoses than those in the Ware study.

Commenting on the Bartlett et al. study, Ware and Epstein (1985) lament its 50% false-positive rate (or type I error level) since "in trials comparing equally effective innovative and standard therapies, the innovation would be identified as superior therapy in 50% of the trials." Type I error levels do not depend on the data; they are unconditional measures of inference. In particular, they average over data that might have occurred but did not. So the significance level of ½ would apply even if it happened that equal numbers had been assigned to the two therapies with all failures on one therapy and all successes on the other (this is unlikely but possible when using randomized play-the-winner assignment). I will return to conditional versus unconditional inference below. Ware and Epstein conclude that "Further randomized clinical trials using concurrent controls and addressing the ethical aspects of consent, randomization, and optimal care will be difficult but remain necessary." Hence the current study.

I disagree with the conclusion of Ware and Epstein: there was ample evidence in the Bartlett et al. study and in other evidence available at the time to conclude that ECMO is beneficial. (And I felt as strongly about this before I became aware of the Ware study.) This is clear if one uses measures of inference that condition on the observed data. For example, a Bayesian analysis that takes into account historical controls and the differing prognoses of the patients shows a dramatic benefit for ECMO (Berry and Hardwick, manuscript in preparation). Historical controls are

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