Every few years, there is a research study that focuses attention on issues and concerns that go far beyond the immediate case. The SUPPORT study, which was conducted at 22 sites with 1300 subjects and tested how much oxygen clinicians should provide to premature infants, has generated enormous controversy. Questions include: how trials that randomize to two or more “standard of care” interventions should be designed and reviewed; how risks should be evaluated; and how or if consent should be obtained. The ongoing debate has broad implications for the conduct of comparative effectiveness research.