One-Sided Versus Two-Sided Testing

8.1 Introduction
The charge of unethical conduct stikes at the heart of every physician who takes his or her oath seriously. Ethical conduct does not play an important role in our work in healthcare— in fact it is preeminent. It is present in every conversation we have with patients, in every treatment plan we formulate, and in each of our research efforts. Decisions concerning test sidedness clearly define the battlelines where a researcher’s deep-seated belief in therapy effectiveness collides with his obligatory prime concern for patient welfare and protection.

The issue of test sidedness in a clinical experiment may be a technical matter for mathematical statisticians, but for healthcare workers it is an ethical issue. Test sidedness goes to the heart of the patient and community protection responsibilities of physicians.

8.2 Attraction of One-Sided Testing
Students instantly gravitate to one-sided (benefit only) testing, and many, after concluding an introductory section in significance testing, come away with the idea that the one-sided (benefit only) testing is efficient, and that two-sided tests are wasteful.

Consider the example of a test statistic that falls on the benefit side of a two sided critical region. Many investigators argue that the evidence seems clear. The test statistic is positive — why continue to insist on placing alpha in the negative, (opposite) side of the distribution? Be adaptive and flexible, they would say. Respond to the persuasive nature of the data before you. Clearly the test statistic falls in the upper tail — the benefit tail — of the probability distribution. That is where the efficacy measure is. That is where the magnitude of the effect will be measured. Place all of your alpha, like a banner in a newly claimed land, with confidence.

8.3 Belief Versus Knowledge in Healthcare
Physicians may have many reasons for conducting research, but a central motivation is the desire to relieve the suffering of patients. We do not like to harbor the
notion that the interventions we have developed for the benefit of our patients can do harm. Nevertheless, harm is often done. Well-meaning physicians, through ignorance, injure their patients commonly. The administration of cutting and bleeding in earlier centuries, and the use of strong purgatives in this century are only two of the most notorious examples. The administration of potent hormone replacement therapy for menstrual symptoms, and the use of surgical lavage and debridement as palliative therapy for osteoarthritic knees are only two of the most recent examples of the well-meaning community of physicians treating patients under mistaken and untested assumptions. What will they say 200 years from now about our current oncologic treatments?

While we must continue to treat our patients with the best combination of intellect, rigor, knowledge, imagination, and discipline, we must also continue to recognize what for us is so difficult to see and accept — the possibility that we may have harmed others.

Physicians often develop strongly held beliefs because of the forces of persuasion we must bring to bear when we discuss options with patients. We find ourselves in the position of advocating therapy choices for patients who rely heavily on our recommendations and opinions. We often must appeal to the better nature of patients who are uncertain in their decisions. We must be persuasive. We educate patients about their options, and then use a combination of tact, firmness, and pre-sige to influence them to act in what we understand to be their best interest.

Of course, patients may select a second opinion, but they are the opinions of other physicians, again vehemently expressed. Perhaps the day will come when physicians will be dispassionate dispensers of information about therapy choices, but today is not that day.

However, history teaches us repeatedly that a physician’s belief in a therapy does not make that therapy right. Making our belief vehement only makes us vehemently wrong. Physicians must therefore remain ever vigilant about patient harm: the more strongly we believe in the benefit of a therapy, the more we must protect our patients, their families, and our communities from the harm our actions may inadvertently cause. Strong vigilance must accompany strong belief. This is the research role of the two-sided test: to shine bright, directed light on our darkest unspoken fears — that we as physicians and healthcare workers, despite our best efforts, might do harm in research efforts.

8.4 Belief Systems and Research Design

The force behind vehement physician opinion can be magnified by the additional energy required to initiate and nurture an innovative and controversial research program. Relentless enthusiasm sometimes appears necessary to sustain a joint effort. The proponents of the intervention must persuade their colleagues that the experiment is worthy of their time and labor. The investigators must convince sponsors (private or public) that the experiment is worth doing, and their argument often incorporates a forcefully delivered thesis on the prospects for the trial’s success. This is necessary, since sponsors, who often must choose among a collection of proposed experiments, are understandably more willing to underwrite trials with a greater chance of demonstrating benefit. It is difficult to lobby for commitments of