October 2002: Be wary of surrogates. Accept substitutes warily. (Rule 4.9)

Rules of the month are numbered in accordance with the numbering in the book. Thus, Rule 1.1 refers to the first rule in Chapter 1. And so on. These comments do not repeat the material in the book but highlight and amplify it. A rule is stated—as found in the book—and then discussed.

Statement of Rule 4.9

"Be wary of surrogates. Accept substitutes warily."

Further discussion

Recall that a surrogate endpoint is considered a proxy for a desirable clinical endpoint. For example, a decrease in cholesterol level is thought to be a "good thing." The point is that a decrease in cholesterol level is of itself clinically neutral but is so far as it can be causally linked to the risk of heart disease its reduction is a desirable goal. As indicated in the discussion of Rule 4.1 in the text, surrogates have the potential seductive appeal of cost effectiveness, immediacy, face-validity, ease of measurement. But for the user of surrogates the warning still is *caveat emptor* (let the buyer beware).

The reason for this discussion is a notice in the Federal Register (2002) announcing a meeting of an advisory committee of the US Food and Drug Administration (FDA) on November 18, 2002 which will consider:

"the role of brain imaging as an outcome measure in phase 3 trials of putative therapeutic drugs for Alzheimer's disease; the discussion will not focus on specific drugs or on specific applications to the agency. The agency is considering whether brain imaging modalities can be utilized as surrogate markers; that is, as primary outcomes in definitive clinical trials to measure drug effect in lieu of clinical outcomes. The committee will specifically discuss the following issues in reference to each imaging modality:

1. How is the imaging modality best validated?
2. If one uses an imaging modality to support a disease-modifying effect claim, how does one establish that such an effect occurs?
3. Has any surrogate imaging modality been validated at the present time?
4. Even if no surrogate imaging modality has currently been validated, is it appropriate to use one or more such modalities as primary or ancillary outcome measures of efficacy in phase 3 clinical trials?"

This long quotation indicates that the issue of surrogates won't go away. One reason for the interest in surrogates in Alzheimer's disease is that disease progression currently is based on cognitive tests and activities of daily living. These measures are quite variable, may depend on caregiver

information, and take substantial time to measure. In addition when the disease is advanced these assessments become less and less informative.

A good reference, beside the papers mentioned in the text, is the paper by Fleming and Demets (1996). They list several of the points made in the text and conclude that surrogate endpoints are permissible for phase 2 trials but that "in definitive phase 3 trials, except for rare circumstances in which the validity of the surrogate endpoint has already been rigorously established, the primary endpoint should be the true clinical outcome."

What do you think? What are your answers to the four FDA questions?

Here are four more questions:
1. How would you distinguish between a surrogate endpoint and a clinical endpoint? Are surrogate endpoints always non-clinical?
2. Should the link between a surrogate endpoint and clinical endpoint be stronger in phase 3 trials than in phase 2 trials?
3. If your answer to Question 2 is "yes," how would you demonstrate that the link between surrogate #1 and clinical outcome is stronger than the link between surrogate #2 and the endpoint? What are some appropriate statistical procedures?
4. Beside the contrast of phase 2 and phase 3 trials, are there other contrasts where a surrogate may or may not be useful?

The meeting is open to the public with opportunity for comments. It will be held at the Holiday Inn in Gaithersburg, MD. See the *Federal Register* for additional information.

References

Food and Drug Administration (2002). Notice of meeting of the Peripheral and Central Nervous System Drugs Advisory Committee. *Federal Register*, **67:** Number 202, Friday, October 18, 2002.
Fleming, T.R. and Demets, D.L. (1996). Surrogate endpoints in clinical trials: Are we being misled? *Annals of Internal Medicine*, **125:** 605-613.

Responses

This section is intended to contain reader comments and perhaps responses from me. It provides a forum for discussion and further reflection.