Appendix C

Cohort-Varying Information Insert for Form for Consent to Participate in a Phase I Study

[Here we quote an article in which Benjamin Freedman suggested a template to be used for a more straightforward description of the purpose and design, risks and benefits of a Phase I study.—eds.]

COHORT-VARYING INFORMATION INSERT FOR CONSENT FORM TO PARTICIPATE IN PHASE I STUDY

Insert in section on Purpose and Design of Study

In testing new drugs and combinations of drugs for cancer treatment, the first study is designed to establish the highest dose that may safely be given. This is such a study. Underlying this trial is our understanding that, most commonly, drugs to treat cancer are most effective when given at the highest safe dose. The highest safe dose is the dose just smaller than that which produces unacceptable reactions.

A group of subjects is enrolled and given a very small dose. Their progress is followed, and if those patients do not develop unacceptable reactions to that dose, a new group of patients is enrolled at a higher dose. This process continues until a dose is reached that commonly produces an unacceptable reaction. [For cohort at highest dose substitute for last sentence: This process continues until a dose is reached that produces an unacceptable reaction in two subjects of the three enrolled at that level. If this unacceptable toxicity is repeated in one person from a further group of three subjects, [...] At that point the study is complete: It has shown us what the maximum tolerated dose of the drug or combination is.

In this trial, up to nine groups of subjects will be enrolled, at gradually increasing doses of [(drug) A] [(drug) A and (drug) B]. The earliest group of subjects (Group 1) will be [was] given the lowest dose, at a level that should not produce unacceptable toxicity but may also not be sufficiently potent against the cancer. The later the group into which a subject is enrolled, the higher the dose given. It is often, but not always, true that the higher the dose, the more powerful are the effects against cancer, but also the more likely to produce unacceptable side effects.

If I agree to participate in this trial, I will be in the [Nth] group of 9 planned groups.

Insert in section on Risks and Benefits

The likelihood and severity of side effects depends in part on the dose given, although even then these are not completely predictable. Some side effects may occur in patients given a low dose of drug (that is, patients enrolled in an early group), but are more likely to occur and to be more serious when [the drug is] given in higher doses. These side effects are [insert toxicities that continuously vary at the dosages given cohorts]. Other side effects are unlikely to appear at low dosages, but may appear at higher ones. These side effects are [insert toxicities with an expected threshold for appearance]. These side effects are more likely to occur in subjects of groups [N] through nine. Again, though, we cannot predict well an individual person's reaction to a dose, so it is quite possible that [a] subject in a late group may experience less harmful drug effects than a subject in an earlier group. [. . .]