of DFS is calculated from the date of randomization, the result appears to present a contradiction. In short, when subjects are enrolled, they are typically not disease-free. If they were disease-free at the time of enrollment, they would not meet the inclusion criteria for the trial. They can only be considered "disease-free" after, for example, surgery that is performed at the beginning of the study. According to Dr Sally Stenning, "[s]trictly disease-free survival can only apply to patients who are free from disease at your time origin, so for example it would be an appropriate outcome measure for patients in adjuvant therapy trials who are free from disease after surgery" (12). In any trial where patients are macroscopically free of disease at entry, for example, adjuvant therapy trials in breast or colorectal cancer, DFS dated from randomization is accurate and appropriate as an endpoint (13).

This slight contradiction might not make much difference if the interval between enrollment and surgery is short and where also the time from enrollment to the first endpoint is long.

At any rate, to avoid any contradiction, investigators should use a start date that resides after surgery, when calculating DFS. This is exactly what was done by Allum et al. (14), in designing a clinical trial of esophageal cancer. The actual motivation for using a start date set at 6 months after surgery was not really to avoid this contradiction, but instead to allow for a difference in timing of the surgery between the arms of the clinical trial. The following quotation reveals that overall survival was calculated by the conventional start date (randomization) but that DFS was calculated from a later date.

Allum et al. (15), wrote, "[o]verall survival was calculated from the date of random assignment to date of death from any cause and surviving patients were censored at the date they were last known to be alive. Disease-free survival was calculated from a landmark time of 6 months from random assignment to allow for the difference in timing of surgery between the two groups."

Consistently, Rothmann et al. (16), wrote, "[f]or resected disease, a frequently used approval endpoint is disease-free survival (DFS). For unresected disease an important endpoint that has been used for accelerated or regular approval is progression-free survival (PFS)."

IV. DISEASE-FREE SURVIVAL PROVIDES EARLIER RESULTS ON EFFICACY THAN OVERALL SURVIVAL—THE ADD-ON BREAST CANCER STUDY OF ROMOND

In a study of breast cancer, Romond et al. (17) treated women with surgery, and assayed tumor samples for expression of the biomarker, HER2. Only women with overexpressed HER2

[12]Stenning S. E-mail of March 30, 2011.

[13]Stenning S. E-mail of March 31, 2011.

[14]Allum WH, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J. Clin. Oncol. 2009;27:5062–7.

[15]Allum WH, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J. Clin. Oncol. 2009;27:5062–7.

[16]Rothmann MD, Koti K, Lee KY, Lu HL, Shen YL. Missing data in biologic oncology products. J. Biopharm. Stat. 2009;19:1074–84.

[17]Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. New Engl. J. Med. 2005;353:1673–84.