

Richard Sylvester  
EORTC DATA CENTER  
Avenue E. Mounier 83, Bte 11  
B - 1200 BRUSSELS (Belgium)  
Tel: +32 2 7741613  
Fax: +32 2 7723545  
E-mail: richard.sylvester@eortc.be

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852  
USA

13315 MAY 31 11:42

Brussels, 27 May 2005

Dear Sir,

Please find enclosed the comments of the EORTC Data Center on the draft guidance Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, docket number 2005D-0112 of the FDA.

Sincerely yours,



Richard Sylvester, ScD  
Assistant Director, Biostatistics  
EORTC Data Center

2005D-0112

C1

**FDA Document: “Guidance for Industry Clinical Trial Endpoints  
for the Approval of Cancer Drugs and Biologics”**

Summary of EORTC Data Center Comments

Lines 243 – 245 and lines 384 - 386

The idea of assigning a “theoretical” visit date as the date of progression for patients who progressed between scheduled follow visits [pages 7 (last paragraph), and 11 (top paragraph)] seems dangerous. It discards information (date progression was actually assessed) and leaves the door open to “data manipulation”. This approach implies that we would need to define for each theoretical visit time point an “acceptable window”, outside of which the visit would be considered either as belonging to a different theoretical visit or even as an extra-visit falling outside of all windows. For example, if progression is to be assessed every 4 weeks, what if PD is discovered at a visit 1 week before scheduled visit? Where do we put the limit?

It seems more important to spend time to ensure a similar frequency of follow up visits in each arm when designing the study and to make sure that the timing of the follow up visits is respected at the time of conducting the study in order to avoid the bias that would result from a different schedule of visits in each arm. Compliance to the visit schedule could then be descriptively investigated at the time of the analysis. If there is indeed a major discrepancy in the follow up visit schedule between the treatment arms, then no statistical techniques can completely solve this problem.

At several places (especially in Appendix 3) the documents mentions the idea of performing “sensitivity” analyses, and assigning “theoretical” visit dates to the date of progression, and/or censoring (or not) certain categories of “events”. This appendix encourages multiple analyses and “data dredging”, poor statistical methodology leading to problems of multiplicity. Problems of bias due to different follow up visit schedules and/or different patterns of follow up should be minimized by proper design and study conduct and should not be a rationale for performing numerous sensitivity analyses that can be easily abused and misinterpreted.

Lines 247 – 262 and lines 304 - 314

On pages 8 (top paragraph), page 9 (paragraph a), as an alternative to censoring, the authors should refer to methods that allow for competing risk analyses, for instance of competing causes of death for PFS or DFS endpoints. In addition, the document should also consider settings (such as elderly populations) where the causality of death may be difficult to assess and thus, when censoring non disease related deaths, may lead to incorrect conclusions.

Line 396

The title of paragraph e. on page 11 may be misleading as the methodology upon which the example is based is not new and is actually less advanced than time to event methodology. The discussion is correct, however the methodology should probably not be emphasized in a guidance document since it has not been used so far and its disadvantages outweigh its advantages.

Lines 460 – 506

The text has gone into a lot of detail describing potential problems in the analysis of progression free survival. While there is some discussion of the problems related to the analysis of symptom data, the analysis of the time to progression of cancer symptoms also suffers from many of the same problems as the analysis of progression free survival. However the text doesn't go into nearly as much detail concerning problems in

the analysis of symptom data as it does for the analysis of progression free survival so the reader may have the impression that the problems are less.

Lines 571 - 573

When considering non-inferiority studies, the document should not overemphasize the example of 50% retention of effect (page 15 – end of first paragraph of chapter B) but should be more general and speak of a proportion of the effect. This proportion should be such that the retained effect remains clinically relevant. Thus in most cases the margin is not set at the control drug's full effect but at some fraction of it (typically  $\geq 50\%$ ) such that the retained effect remains clinically relevant over no treatment/placebo/best previous treatment. This will avoid that trialists set the proportion retained at 50% without regards to the clinical relevance of the retained treatment benefit, or to other considerations such as decreased toxicity or the possibility for salvage after failure (delayed intervention) that may justify a fraction  $< 50\%$  in some circumstances.

General Remark

As a general remark, this document does not mention endpoints which are often used in hematological oncology studies, i.e. Event-Free Survival (EFS): time from evaluation of CR until relapse or death in CR; patients who did not reach CR after the induction course are considered as events at time 0. Such an endpoint is quite close to progression-free survival, where “progression” means relapse after occurrence of CR or lack of CR after 1 or 2 induction courses. Patients who do not reach CR after induction treatment go off-study and are then treated with a salvage therapy at the discretion of the local investigator. Thus EFS may be considered as an endpoint which measures the efficacy and morbidity of the induction treatment, for example, in non-pretreated leukemia patients. It combines the short term (CR rate) and long-term efficacy and morbidity in CR (DFS) of the initial treatment. The whole document should be reviewed by an expert in hematology. The authors have emphasized the “radiological” evaluation of the disease, whereas in hematology, a cytological evaluation is performed.



Richard Sylvester, ScD  
Assistant Director, Biostatistics  
EORTC Data Center