



Dockets Management  
U.S. Food and Drug Administration (FDA)  
5630 Fishers Lane, Rm 1061  
Rockville, MD 20852

**Re: Approaches to Assessment of Overall Survival in Oncology Clinical Trials Guidance for Industry (FDA-2024-D-5850)**

To Whom it May Concern:

Friends of Cancer Research (*Friends*) powers advances in science and policy that speed life-saving treatments to patients. *Friends* is committed to accelerating cutting-edge cancer care that extends and improves quality of life for patients. To accomplish this, we leverage groundbreaking collaborations, generate scientific evidence, and integrate patient input to shape public policy.

*Friends* commends the Agency for releasing guidance that supports its efforts to clarify the design and interpretation of overall survival (OS) data, particularly how interim OS analyses, are considered as an element of ongoing safety and benefit–risk evaluation. This guidance represents an important step toward harmonizing expectations for when and how OS results—particularly immature or interim analyses—should inform regulatory and clinical decision-making.

*Friends* is leading a multi-stakeholder Interim Overall Survival Project focused on improving the design and interpretation of interim OS analyses in oncology trials.<sup>1</sup> This ongoing effort includes simulation-based modeling to support best practices recommendations and to help contextualize early OS results within overall benefit–risk assessments. The initiative builds on *Friends*' recent white paper, *Enhancing Study Designs and Interpretation of Interim Overall Survival Data in Oncology Trials*,<sup>2</sup> which outlines methodological and policy considerations that complement the principles described in the draft guidance.

We offer the following targeted comments to support continued refinement of the guidance.

**Interpreting OS and Harm Within a Broader Clinical and Benefit–Risk Context**

- The guidance appropriately positions OS as a critical clinical endpoint, but FDA could further clarify that OS, particularly interim analyses, should be interpreted as one

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<sup>11</sup> <https://friendsofcancerresearch.org/interim-os/>

<sup>2</sup> <https://friendsofcancerresearch.org/wp-content/uploads/Enhancing-Study-Designs-and-Interpretation-of-Interim-Overall-Survival-Data-in-Oncology-Trials-1-1.pdf>

component of a broader benefit–risk framework that includes safety, tolerability, and patient experience.

- FDA refers to evaluating OS for potential harm but could strengthen the guidance by providing concrete examples or case illustrations that highlight key considerations for interpretation and how these may inform trial design decisions.
- Because OS reflects the ultimate outcome but may lag behind other indicators of harm, relying on survival status alone can provide an incomplete or delayed understanding of safety. Integrating additional data collected within the trial (such as serious adverse events, dose modifications, treatment discontinuations, or quality of life trends) allows earlier and more interpretable insights while avoiding undue emphasis on immature OS data.
- We encourage FDA to emphasize a multidimensional approach to interpreting OS and harm: one that considers statistical, clinical, and patient-reported information together to inform a balanced and clinically relevant assessment of benefit and risk.

### **Recognizing Design Trade-offs Between Interpretability and Patient-Centeredness**

- The guidance appropriately highlights challenges related to crossover and unequal randomization can complicate OS interpretation. However, these design features are often intentionally incorporated to enhance trial feasibility, patient acceptability, and ethical integrity.
- We recommend FDA acknowledge that while crossover and unequal randomization can affect interpretability, they also reflect efforts to ensure patient-centered design and ethical trial conduct. Overemphasizing “clean” OS interpretability could inadvertently discourage these designs.
- While these patient-centered design features can reduce statistical clarity, they often reflect important ethical and patient-focused considerations. FDA could acknowledge that optimizing interpretability and patient access are not competing priorities but components of a balanced trial design framework. Clearer guidance on how sponsors can preplan and analytically account for these design choices would promote both scientific rigor and patient- focused development.

### **Approaches for Defining and Interpreting Thresholds**

- The guidance highlights that interim OS analyses should be interpreted cautiously and acknowledges the potential role of modeling in exploring assumptions related to survival and treatment effects. However, it does not describe how modeling outputs might be operationalized to inform decision thresholds for interpreting interim OS data.

- In practice, simulation-based evaluations of operating characteristics, such as false-positive and false-negative rates, can help sponsors understand the reliability of interim OS conclusions under different scenarios (e.g., varying event rates, effect sizes, or crossover assumptions).
- Currently, the guidance only references use of upper confidence interval limits, noting both 90% and 95% confidence intervals as potential options. Greater harmonization and clarity around acceptable approaches would help establish a consistent standard across trials. For example, one could reasonably argue for use of a 90% confidence interval at interim analyses, with the upper bound compared against a prespecified threshold (e.g., HR = 1.3–1.8) to rule out potential harm.
- We suggest FDA consider expanding its discussion of modeling to illustrate how these methods can support the prospective planning and interpretation of interim OS analyses. Providing examples or referencing case studies could help clarify how modeling-based approaches may inform the definition and communication of thresholds for potential harm or benefit.

*Friends* appreciates FDA's leadership in advancing methodological clarity for interpreting OS in oncology trials. We look forward to continued collaboration to develop practical tools and frameworks that operationalize the principles outlined in this guidance and ensure OS data are leveraged appropriately to inform patient-centered, evidence-based decisions.

On behalf of Friends of Cancer Research,

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