

# The Challenges of Analyzing Drug Safety Data with Competing Risk Events and Some Thoughts

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**Abstract:** Drug sponsors are often requested to do an investigation of serious safety events, such as cardiovascular events, in clinical trials. However, such an analysis is often hampered by the presence of competing risk events, e.g., non-event related death, that preclude the observation of the event types of interest. The competing risk events are especially of concern when the event rates are not balanced between active and control arms. We were recently requested by a health authority to address such a concern, with the suggested subdistribution proportional hazard model. However, this model only considers patients experiencing competing risk events to remain in the risk set, without investigating how likely these patients could have experienced the events of interest if they had not had the competing risk events. The yielded results being liberal for the arm with more competing risk events, often do not address health authority's concerns. In this presentation, two alternative approaches are proposed. First, the tipping point analysis, which can help find out until which point along the increase in the number of events among patients who experienced competing risk events in both arms, the conclusion of no treatment difference is altered. This approach can be extended to include also patients who dropped out. Second, a mixture model, by considering patients with an event of interest prior to study completion or not in two separate distributions. A gamma distribution is assumed for patients with an event of interest before study completion, and a logistic regression model is fitted to indicate whether patients had an event of interest or not. The estimation is later on used to impute the data for patients who had a competing risk event and who dropped out. The final estimation is then based on the multiply imputed data from the mixture model, which accounts for the uncertainty of whether an event of interest could have occurred for those who dropped out early (due to competing risk events or not).