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Responses to discussants of ‘Joint modeling of survival and longitudinal non-survival data: current methods and issues. report of the DIA Bayesian joint modeling working group’

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We thank Professors Farcomeni, Pareek, and Ghosh (FPK), and Rizopoulos and Drs. Price and Wang for their kind comments and for their contributions to the discussion of joint models. We sought to provide a starting point for the application of joint models and, in so doing, encourage discussion of how they could be used effectively. Their citations to recent literature regarding further methodology development, the suggestions for how joint modeling can be used in more settings, and the insights as to the limitations and specific areas of application of joint modeling are the most welcome responses to that objective.

Professors FPK point out that joint modeling methods can be used to obtain dynamic predictions of survival probabilities because the estimates can be updated after each longitudinal assessment, leading to current prognoses. Professor Rizopoulos makes a similar point, and provides a number of citations of recent work on the derivation of dynamically updated individualized predictions. There is an undeniable appeal to this application, but much work needs to be performed to address issues such as identification of an appropriate association structure, extension of the ideas to multiple longitudinal measurements and multiple clinical endpoints, and reliability of the extrapolated predictions, especially to

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arbitrary points in time. We agree that this is an exciting area for exploration that can be useful for real-time prognosis and guidance for individual therapy. If there are tools that make the calculations practical in the usual clinical setting, then physicians can be educated in the appropriate use of the tools, and methods can be developed for presenting the analysis results in a way that patients and their families can understand and use effectively.

FPK point out that although much of the theoretical development is based on Gaussian longitudinal outcomes, more general models incorporating semi-continuous and categorical outcomes have been studied, including the use of frequentist and Bayesian methods with generalized linear models. More general event-time outcomes than simple survival models such as recurrent events, competing risks, and informative observation times have been addressed in the literature. We touched on some of these in passing, and appreciate the additional references that FPK provide. The availability of robust, reliable software that can be used in practice to carry out the calculations that these advances require is crucial if the benefits are to be more than theoretical.

Drs. Price and Wang point out the need to be clear about the inferential goals when considering the use of joint models for assessing data from clinical trials. The avoidance of bias due to model misspecification and the necessity for specifying the model for carrying out the calculations to confirm the clinical benefits of a product are key issues in the context of regulatory evaluation of medical products. This is especially true when evaluating longitudinal outcomes where event occurrences can result in discontinuation of longitudinal data collection, as can happen when patient-reported (PR) outcomes cease with disease progression. In such cases, the time of events may constitute informative censoring that is non-ignorable missingness, which must be accounted for properly to obtain valid inferences.

One of the key challenges that Drs. Price and Wang identify is the strong assumptions about the longitudinal and time-to-event processes that many (but not all) joint modeling approaches require. The in-depth knowledge of underlying biological processes that should drive these assumptions may or may not be available at the design stage of a registration trial, or at least before unblinding the data. If it is not available, then there is a risk of potentially serious bias due to misspecification of the model. The use of joint modeling methods for a primary analysis therefore will require justification of the assumptions and description of the effect of potential biases due to model misspecification. That said, however, joint models may be useful for sensitivity analyses, exploratory analyses, or informative secondary analyses. The potential value of the insights that joint models can provide should encourage appropriately designed and powered studies to capture both longitudinal and event-time data.

We conclude with some additional comments about a particular application of joint modeling methods. The standard approach to implementing PR outcomes within oncology clinical trials is to begin data collection at randomization, conducting one or more baseline assessments, followed by periodic assessment until disease progression or censoring (e.g., withdrawal of patient consent or the occurrence of a treatment-limiting adverse event). This approach results in a considerable amount of administrative/informative missing data because patients who do not provide data are likely to differ systematically from those who

do provide data (i.e., data not missing at random (NMAR)). For example, patients who do not experience an adverse event (and thus stay in the trial) are likely to have materially different quality of life scores from patients who exit the trial (causing missing data) when an adverse event occurs. Failure to properly recognize this phenomenon results in improper analyses that do not accurately account for the patient outcomes and conclusions regarding the effect of treatments.

The evaluation of PR outcomes together with the risk of disease progression or death that addresses the NMAR issue can be accomplished with the use of joint latent class models. The use of a discrete latent classification variable leads to calculations that do not involve numerical integration on the shared parameters [1], in contrast to shared parameter random effects models. A component of these joint models involves the use of pattern mixture modes (PMMs) to allow for the possibility that the missing data mechanism is NMAR. With PMMs, individuals are divided into groups based on the pattern of their missing data so that the effect of the missing data pattern on the outcome of interest can be assessed.

Evidence supporting the use of latent class analyses in this setting is being developed from PMMs applied to clinical trials. The PMM approach can be thought of as a more constrained version of latent class modeling. The results have shown two distinct classes based on probabilities of early or late censoring, each showing a distinct PR outcome trajectory by treatment arm. The PMM classification scheme showed significant benefit of the test treatment relative to the comparator with respect to PR outcomes that could not be demonstrated by routine mixed model approaches. Although the use of PMM was performed without jointly modeling the PR and survival outcomes, we believe that the application of joint latent class models will result in improved interpretability of these clinical trial endpoints and the correct handling of NMAR data [2].

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