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When to schedule the interim analysis in the presence of missing data?

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Single presentation or poster submission

Suppose an adaptive Phase III trial has an interim analysis scheduled at a given information fraction, e.g., 50%. The key question is: When will we reach 50% information? In a non-longitudinal setting, the information level for a continuous endpoint can be approximated by the fraction of patients with endpoint data at the interim analysis relative to the final analysis. However, longitudinal trials with repeated measures and missing data require more nuanced methods to estimate the information level accurately. The question then becomes: When will there be 50% information in the presence of missing data? Is it when half of the patients reach the final visit, or could it be earlier?

We propose an approach for projecting the information fraction in continuous longitudinal trials analysed using MMRM. We establish a relationship between information time and calendar time, providing practical guidance. At the design stage, prediction for the timing of interim analysis is based on assumptions about enrolment rate, total sample size, dropout rate, visit timing, and the correlation matrix. Once some data is available, this prediction is refined using the observed enrolment rates, dropout patterns, and updated correlation estimates, yielding a more accurate estimate of the current information level and an updated timeline for the interim analysis.

Through a practical example, we demonstrate how to project information timelines at the design stage and refine them as data accrues. We discuss how to navigate different missing data patterns, assess the current information level, and set a reliable timeline for the interim analysis.