# Estimand Strategies for Handling Deaths in Early-Stage Neurological Disorder Studies

*2024 EFSPI regulatory statistics workshop*

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**Study**: recruiting ~500 patients in the early stages of a neurological disorder

Expected **mortality rate**: 1%

Our proposed **estimand** (assuming death is the only intercurrent event):

- Treatment A vs Treatment B
- **Endpoint**:
  - Primary: Time to a progression event
  - Key Secondary: Continuous (same scale as in time to event)
- Strategies for handling the intercurrent event of **death**:
  - Time to event: **Composite** - death is counted as a progression event.
  - Continuous: **Hypothetical** - the statistical model will estimate what would have happened if the patient had not died

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## Feedback from the FDA:

- Time to event: composite strategy would not be appropriate for handling deaths unrelated to disease progression or study treatment
- Continuous: a hypothetical strategy is inappropriate for addressing the intercurrent event of death, because it is clinically implausible and does not reflect real-life situations

## Questions to the Regulators:

1. In a time to event context, what is the importance of differentiating unrelated disease progression deaths (frequency < 1%) when the composite strategy is conservative and penalises all deaths as events?
2. For a continuous endpoint any estimand strategy will be implausible for estimating the treatment effect of a person who died. Which estimand strategy do you suggest for handling deaths in this context?