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The Curse of Data Maturity in Observational Studies: Practical Advice from Protocol Development to Interpretation of Results

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CONTEXT & OBJECTIVES

Real-world settings considerations

- The use of **time-to-event distributions** for OS and PFS is common for **assessing treatment efficacy** and **comparing** it to **clinical trial** outcomes.
- **Anticipating** relevant endpoints, **estimating** relevant quantities, and **predicting** differences from clinical trials due to patient population and care variations are often **challenging**.
- This **uncertainty** makes **planning interim analyses** in advance difficult and assessing result **reliability** and **stability** uncertain until data is collected.
- **Assessing the stability of interim results** is key to determine their utility in **decision-making**, considering whether they are **likely to change** as the study progresses.

Study objectives

1. To **specify** the different concepts which are essential notions around **data maturity**
2. To **apply** data maturity assessment on a **mock observational study**
3. To **draw** pratical **recommendations** from protocol development to interpretation

STATE OF ART – KEY NOTIONS AROUND DATA MATURITY

I Defining maturity, stability, validity, quality of the estimate of the survival function

Maturity This is related to the precision of the estimate itself. How well are we able to estimate the true underlying survival function for a given study design?

Stability How much might the estimate of the survival function change under additional follow-up?

Validity What is the time domain over which the estimate of the survival function is valid/trustworthy/good? At some point in time, there may be very few patients remaining at-risk, leading to high variance in the estimate.

Quality Long follow-up is an indicator of a well-designed and executed study.

II Associated quantities

Maturity Use of the precision of the estimate (Gebsky 2018)

Stability Defined as the potential for change in the estimate (Betensky 2015)

Validity Suggested as the time domain over which the estimate of the survival function is interpretable without much concern about issues of stochasticity

MOCK OBSERVATIONAL STUDY – WHAT HAPPENS AFTER INTERIM CUTOFF?

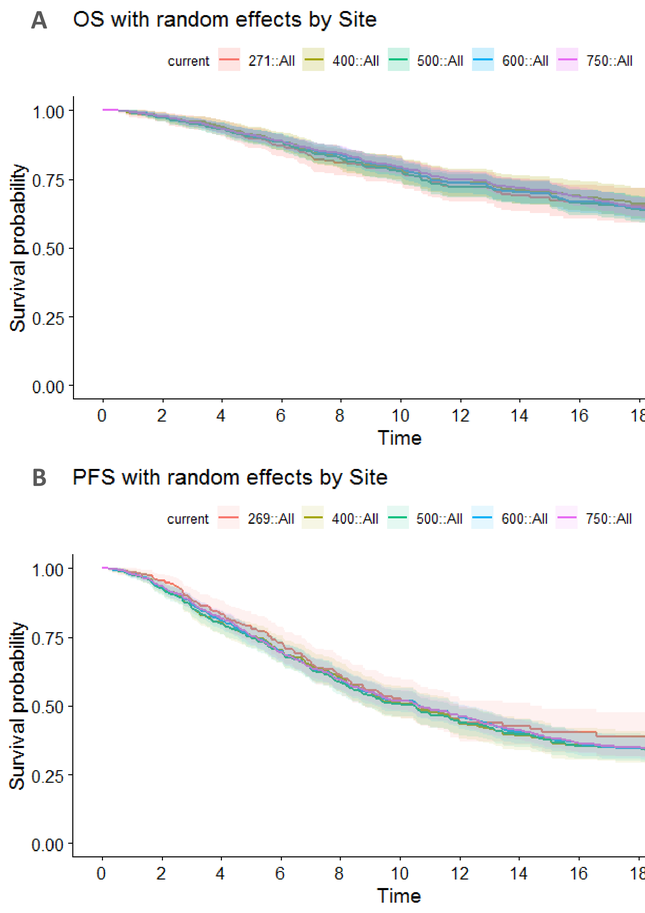

*Figure 1. KM estimates of the survival curves for OS (**A**) and PFS (**B**) for a single simulation*

Maturity Variations may be inter-individual or inter-centric. Standard error is $se(\hat{p}) = \sqrt{\frac{p(1-p)}{n} + \frac{\sigma_\alpha^2}{j}}$ and can be used to compute margin of error and implied confidence level, to be compared to initial protocol settings.

Stability Upper and lower limits of the KM curves for PFS and OS are calculated to show the range of possible estimates that could result from additional follow-up.

Simulation study

After interim cutoff, the statistical simulations proceed as follows:

1. Forecast the enrolment timing of patients that will be recruited into the study.
2. Sample event and censoring times (due to loss to follow-up) for future patients using the existing study sample. Because this will necessarily require extrapolation of the survival distribution beyond observed times, a parametric survival model is required.
3. Repeat step 2 for patients who are currently enrolled and have not had an event or been censored due to loss to follow-up.

Simulation example (Figure 1)

In this single simulation, there is some change in the curves with additional patients and additional follow-up. Moreover, the increased precision which is expected to occur with additional patients is evident.

Full simulation results (200 repeats) (Figure 2)

If the statistical simulation is an accurate description of reality, then the margin of error for the estimates of both OS and PFS at 12 months are anticipated to surpass the study design target.

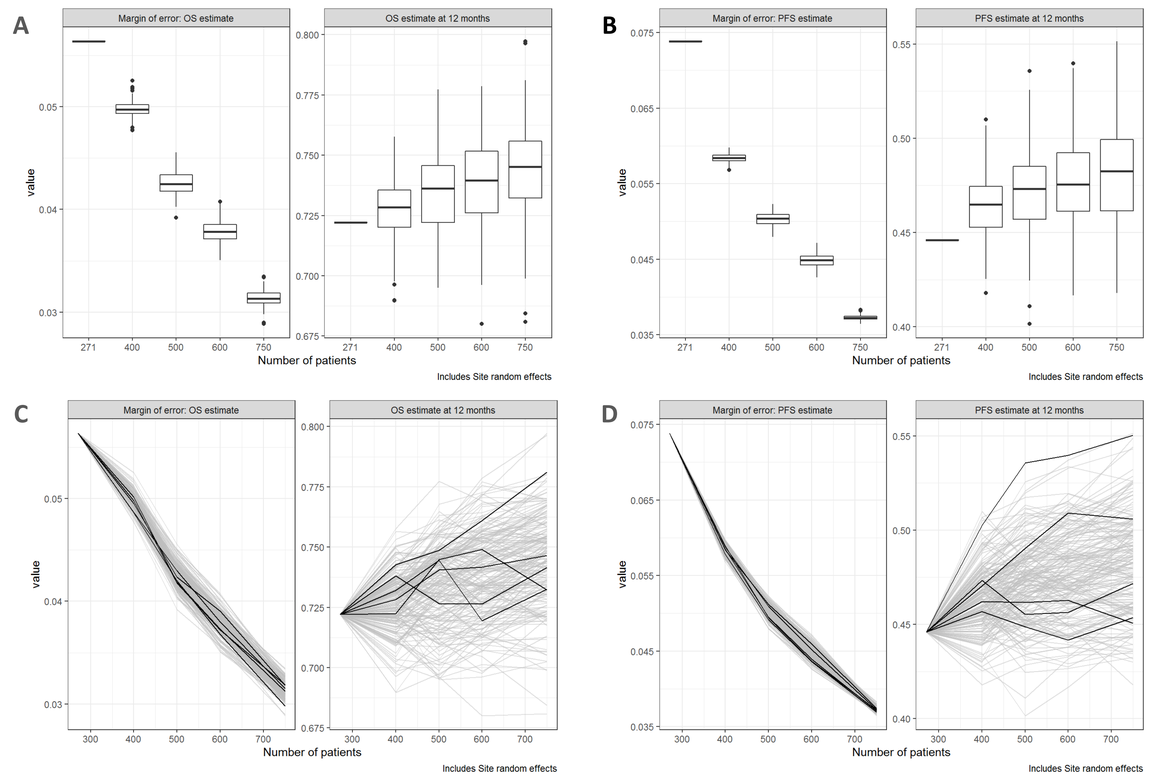

*Figure 2. Trajectories of the 12-month OS (**A**) and PFS (**B**) estimates and their estimated margin of error (**C** and **D** respectively)*

RECOMMENDATIONS

Study protocol	**Clearly** define precision targets and timelines for analyses with rationale Anticipate the **potential** range of future endpoint values
SAP	Establish **robust** analysis framework Incorporate **sensitivity analysis** to assess impact of assumptions
Interim analysis	**Exercise caution!** Sample size, number of events, etc. are well-known sources of variance and bias Monitor precision targets and **continuously assess** study maturity
Final analysis	Evaluate final endpoint **stability** Report **sensitivity analysis**

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