Weighted variogram analyses for estimating within-patient variance components using routine data from biomarker monitoring programmes

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Background
Measurement error in biomarkers is best estimated in Biological Variability Studies (BVS) where individuals have repeated measures both at the same and at different time points. However, BVS are not always feasible. We investigate whether measurement error can be estimated using routine data from biomarker monitoring programmes by application of a method known as the variogram.

Aims
To demonstrate the potential of the variogram using open-source monitoring programme data of serum albumin measurements on stage 2-4 primary biliary cirrhosis patients.

Methods
Variation in measurements from patients over time includes three components: true differences at baseline between-patients; true changes from baseline within-patients ('signal'); and measurement error ('noise'). The variogram considers differences within-patients computed between baseline and each follow-up point; the variances of these differences increase at a rate dependent on the magnitude of the within-patient variability. We grouped measurements by year, and assigned weights according to the closeness of the actual time to the midpoint using a Gaussian kernel approach. Weighted variances of differences in serum albumin were calculated per time. The variogram is a plot of weighted variance of differences (y-axis) against time (x-axis), with a fitted line estimated by linear regression, weighted according to sample size. Extrapolation of the fitted line to intersect the y-axis was used to estimate the measurement error ('noise').

Results
The measurement error ('noise') estimate was 0.10 $(gm/dL)^2$. 'Signal' first surpassed 'noise' at five years; the variance of differences at one year was estimated almost entirely 'noise'. Such results from weighted variogram analyses could be used to help define optimal measurement timings for monitoring programmes.

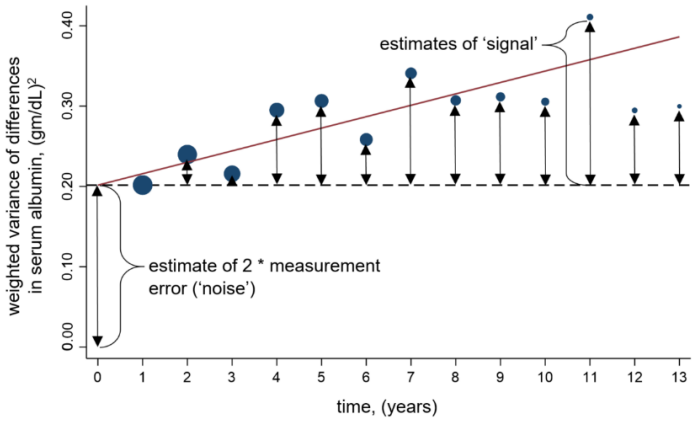

Figure 1: weighted variogram analysis

Conclusions
Weighted variogram analyses have potential for application where health status changes are unlikely; care should be exercised in implementation, particularly related to bias from dropout.

Keywords
Variogram, variability, monitoring, measurement error