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Feasability of interpreting blinded pharmacodynamic data: investigating normal variations in healthy subjects

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Citation
Hassing, G. J. M. (2024, April 23). *Feasability of interpreting blinded pharmacodynamic data: investigating normal variations in healthy subjects*. Retrieved from https://hdl.handle.net/1887/3747980

Version:	Publisher's Version
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Note: To cite this publication please use the final published version (if applicable).

FEASIBILITY OF INTERPRETING BLINDED PHARMACODYNAMIC DATA – INVESTIGATING NORMAL VARIATIONS IN HEALTHY SUBJECTS

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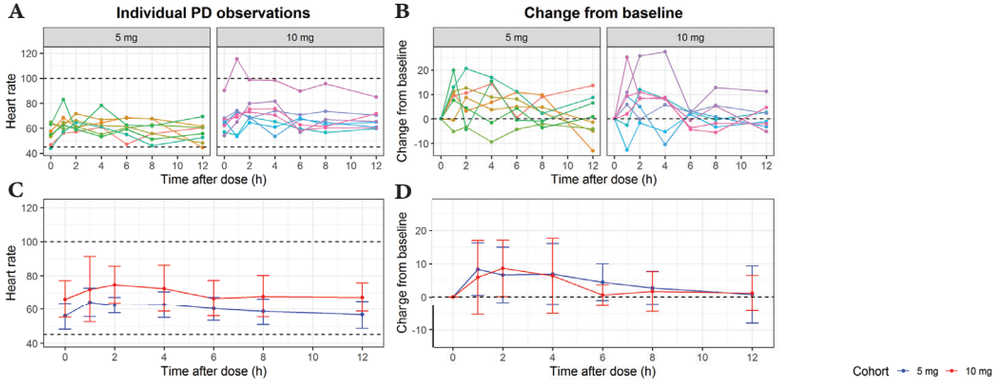
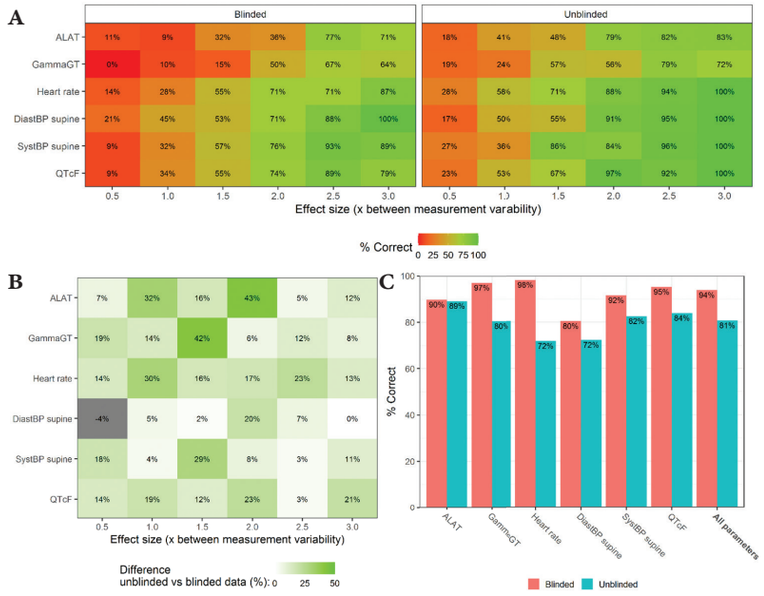
PAGE 29 ➢ CHAPTER 2 FIGURE 1 **Stochastic simulation of blinded response data for two cohorts with 6 active and 2 placebo subjects, presented as individual measurements (A), change from baseline (B), and summarized as mean ± standard deviation (C, D) over time.** Slope of 2 × between measurement variability of the heart rate parameter was simulated in this scenario. Dashed horizontal lines in figure A and C present normal range based on literature. Dashed horizontal lines in figure B and D depict reference line for no change from baseline.



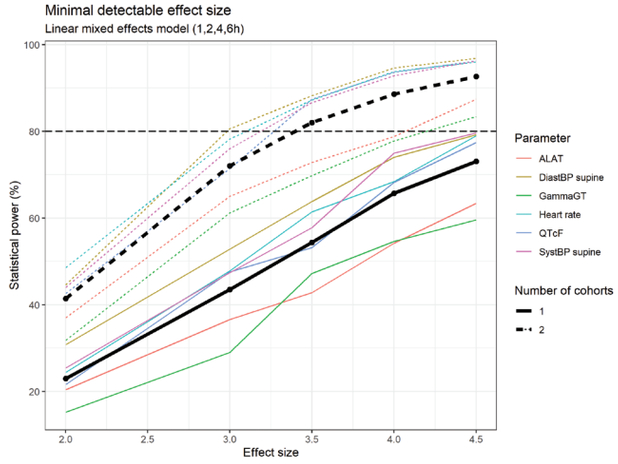
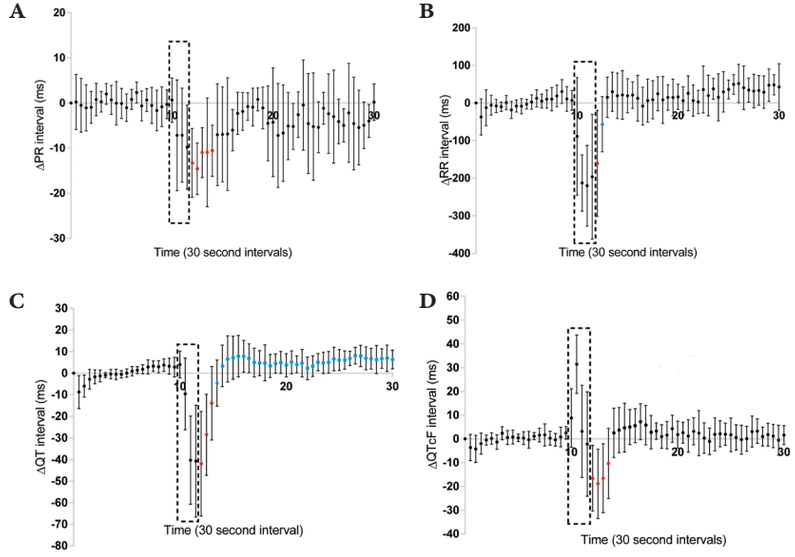
h = hours

PAGE 30 ➢ CHAPTER 2 FIGURE 4 **Heatmap with % correct decision of each parameter over effect size, based on blinded or unblinded data (A), the calculated delta (B), and all data combined (C).** Data is presented of two individuals who were shown both blinded or unblinded data. The % correct when no effect was simulated is presented in C. Parameters are sorted on the level of between measurement variability (high to low).



ALAT = alanine aminotransferase; DiastBP supine = diastolic blood pressure in supine position; SystBP supine = systolic blood pressure in supine position; QTcF = Fridericia corrected QT interval.

PAGE 33 ➢ CHAPTER 2 FIGURE 5 **Statistical power for each parameter with an effect size between 2.0 and 4.5 standard deviation effects as calculated with a linear mixed effect model for both single or double drug cohort simulations.** Dotted horizontal line highlights the statistical power to detect a minimal detectable effect size with 80% certainty.



PAGE 49 ➢ CHAPTER 3 FIGURE 3 **Electrocardiographic parameters (PR interval in A, RR interval in B, QT interval in C and QTcF interval in D) as measured in the male exercise bout group where each timepoint indicates the change from baseline (first 10 minutes) means with standard deviation over intervals of 30 seconds.** Dotted square indicates the exercise period. A. PR interval significantly (p<0.05) shorter for up to 120 seconds but never crossed the threshold of 25% change from baseline. B) RR interval significantly (p<0.05) shorter for up to 30 seconds and change from baseline larger than 20 ms for up to 60 seconds. C) QT interval significantly (p<0.05) shorter for up to 90 seconds and stabilized after 120 seconds but remained prolonged compared to baseline. D) QTcF interval significantly (p<0.05) shorter for up to 120 seconds and remained stable afterwards within baseline values.