

ECG Assay Sensitivity without Moxifloxacin

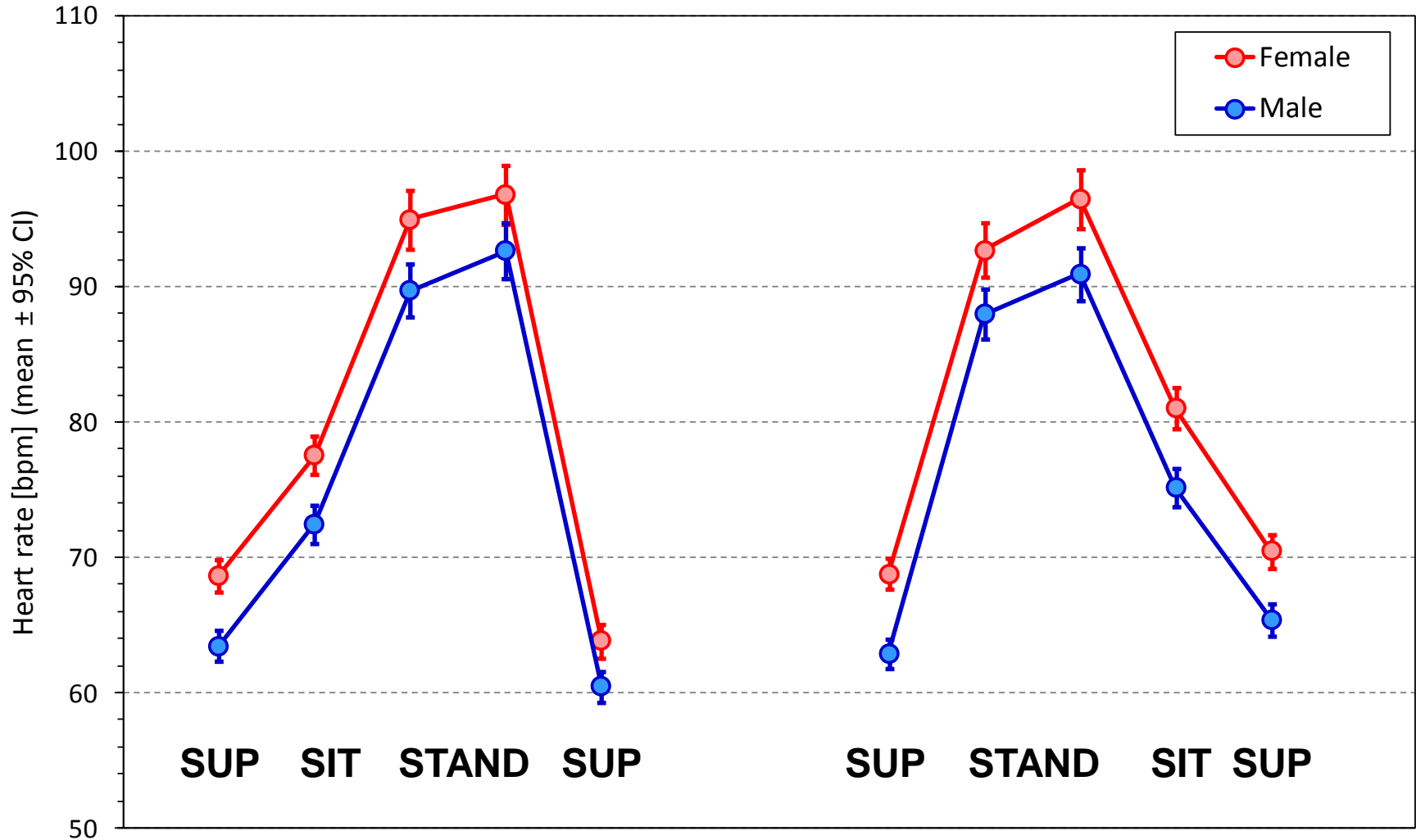
Moxifloxacin test

- It adds study costs (particularly in cross-over studies)
- It is not necessarily good enough

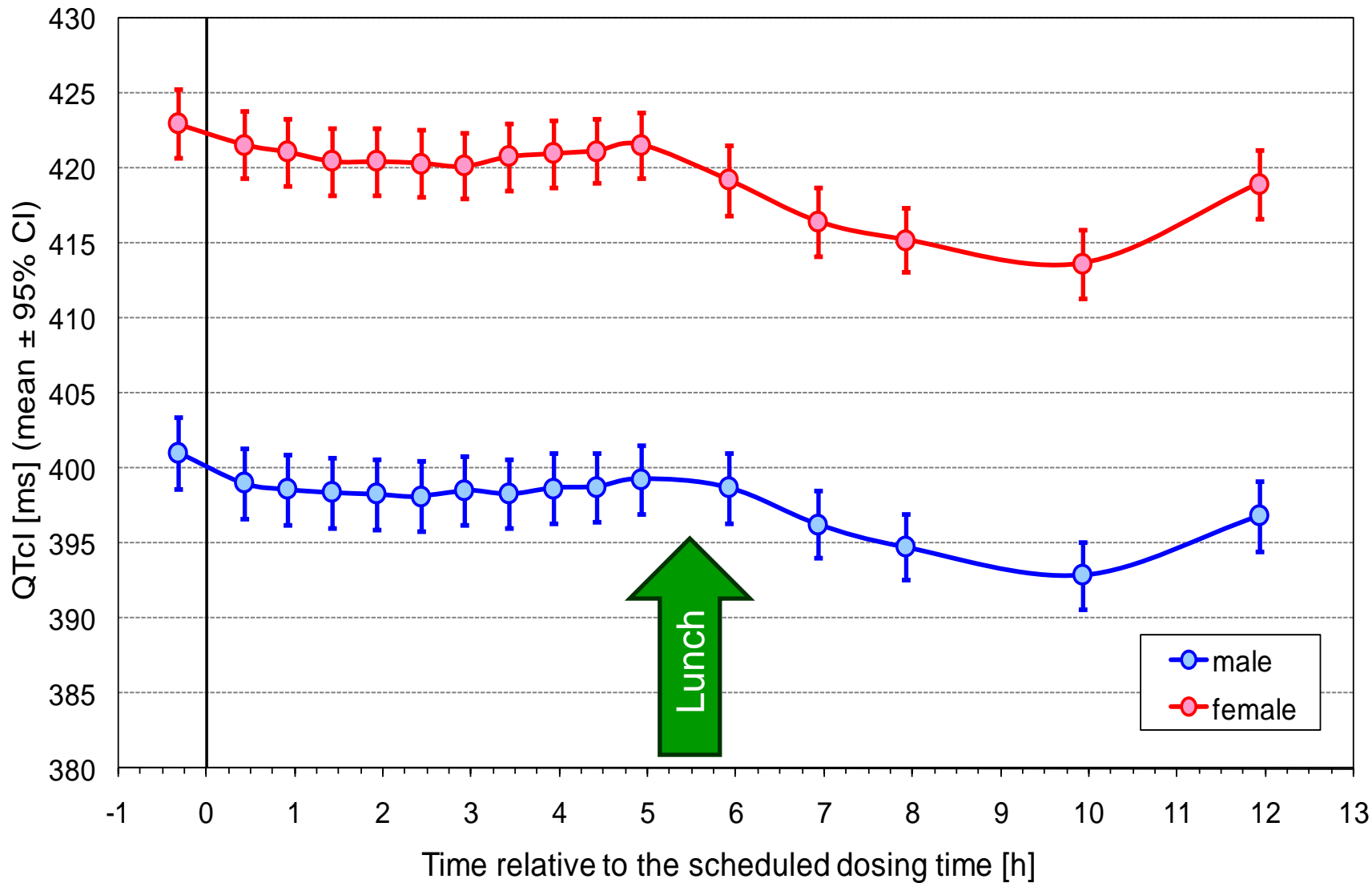
“Intelligent” assay sensitivity

- To find small QTc differences or small QTc changes reproducibly
- To span over a time period similar to the duration of the study
 - The “test window” can be longer but *not really much shorter*
- To simplify the study compared to the moxifloxacin test
- To be robust against possible abuse

Example of a potential problem



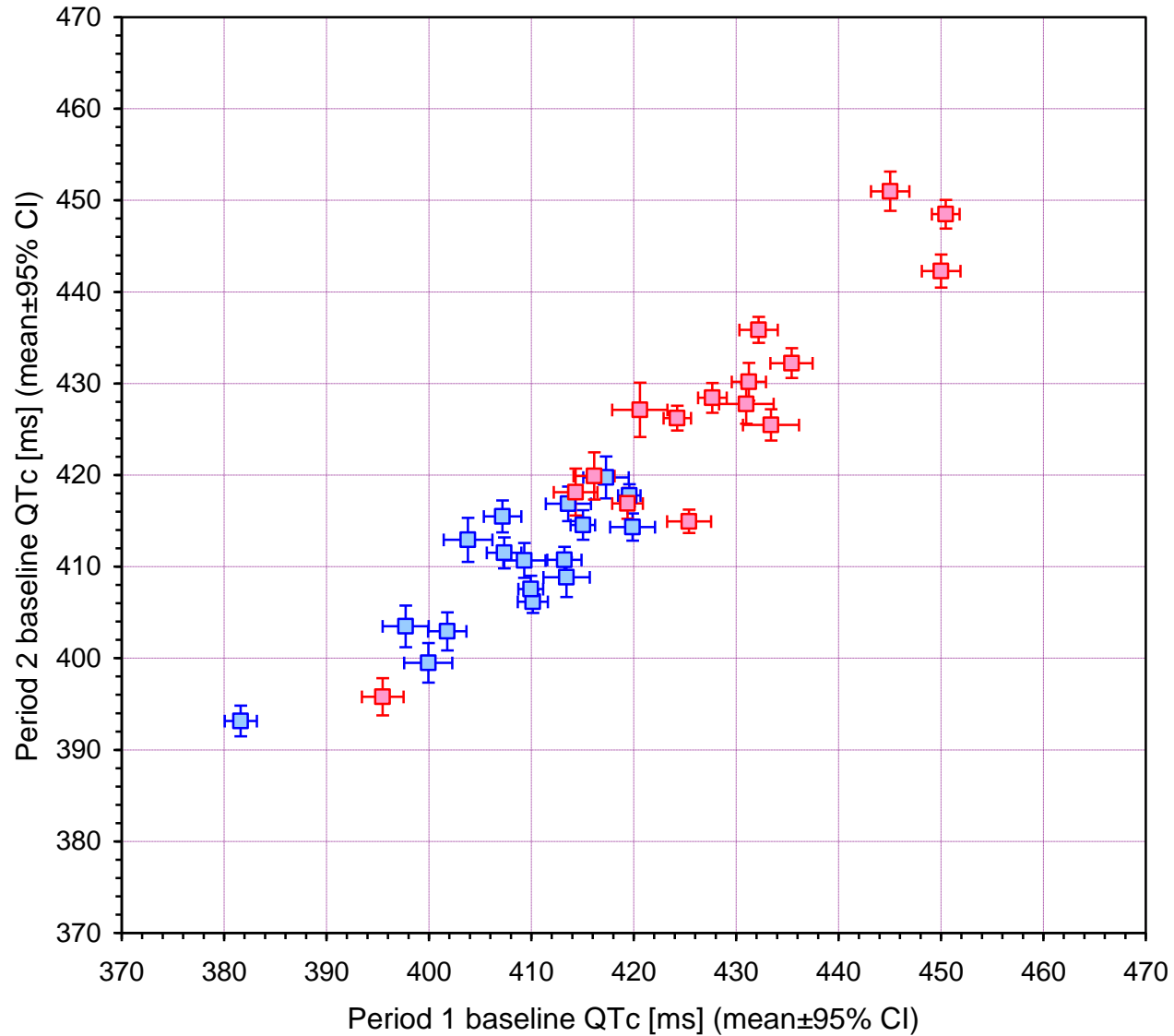
Example of a possible problem



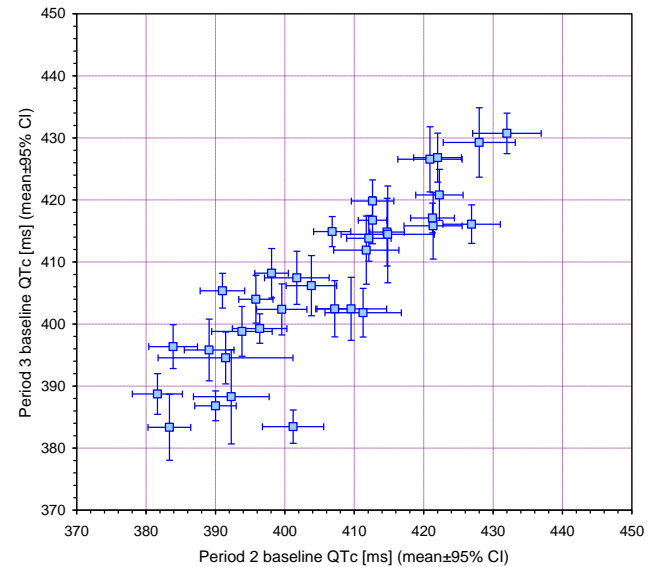
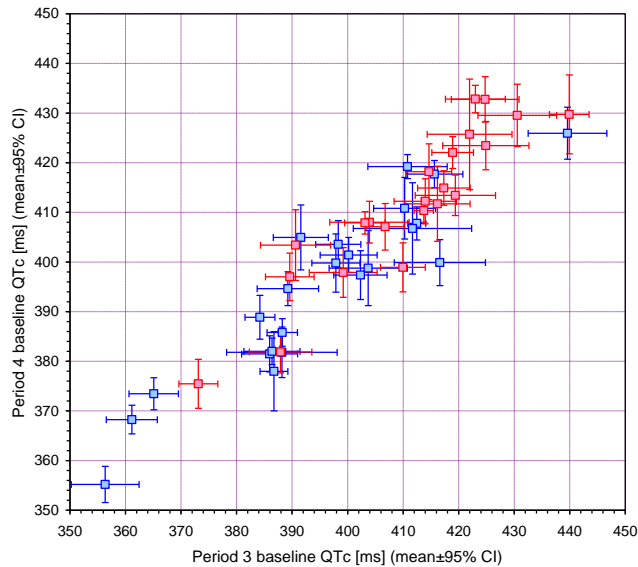
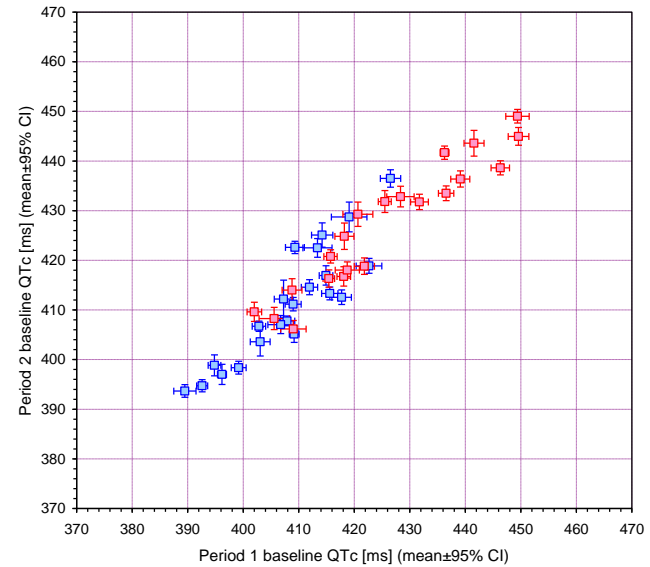
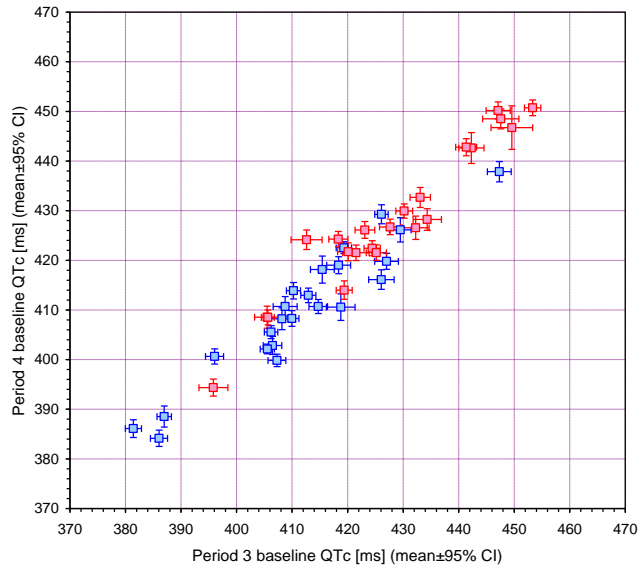
Small QTc differences

- Small QTc differences exist between subjects
- Possible assay sensitivity requires to show:
 - That there are differences between different study subjects at baselines
 - That different baselines reproduce each other

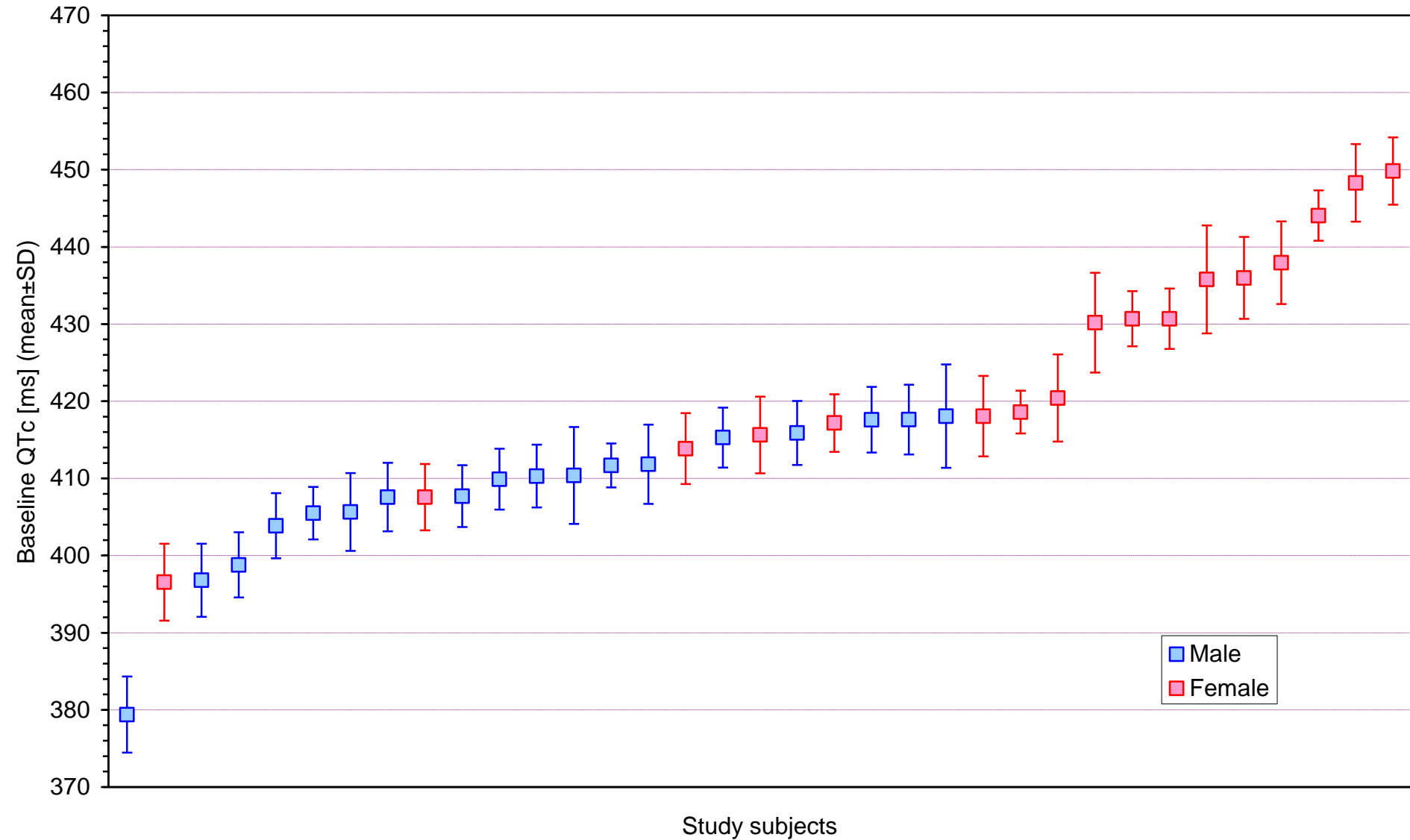
Small differences between subjects



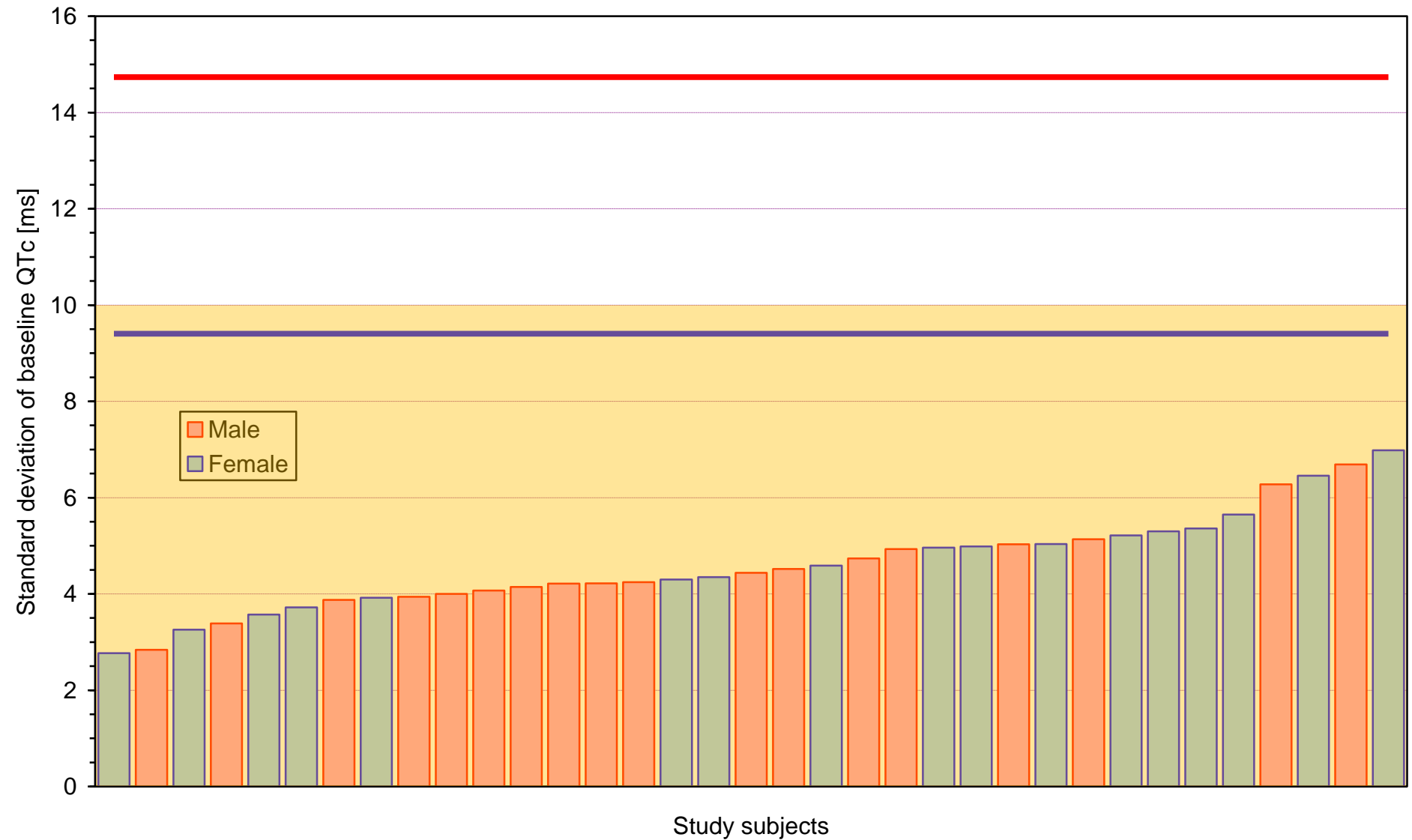
Small differences between subjects



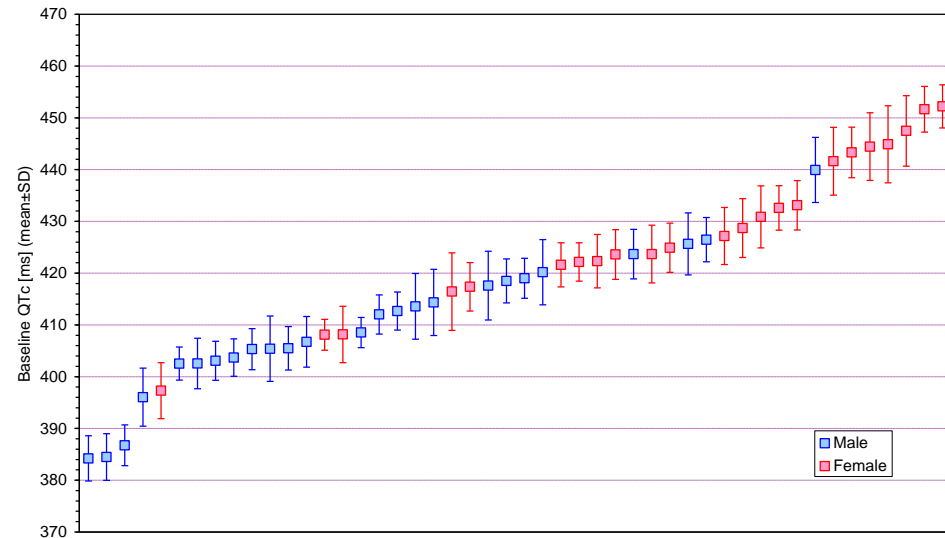
TEST1: Intra-subject variability



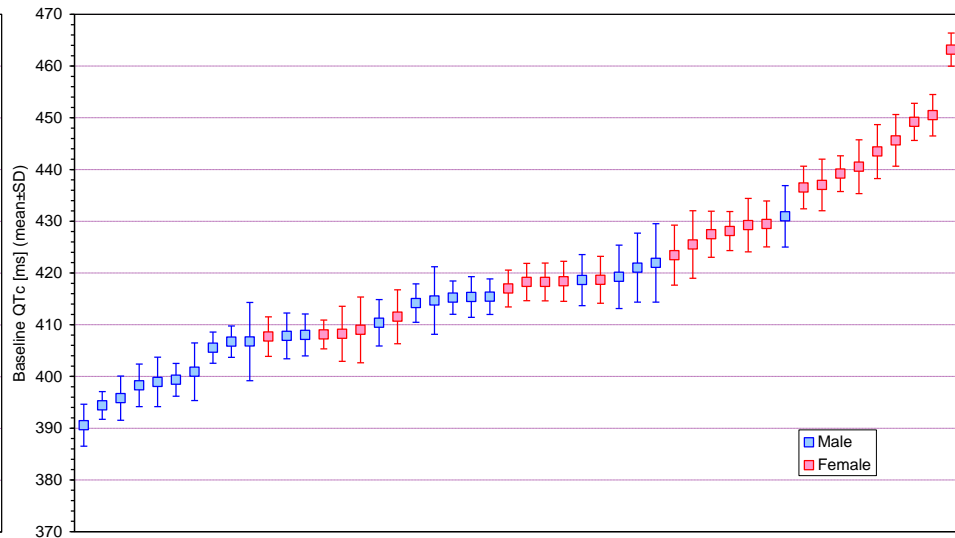
TEST1: Intra-subject variability



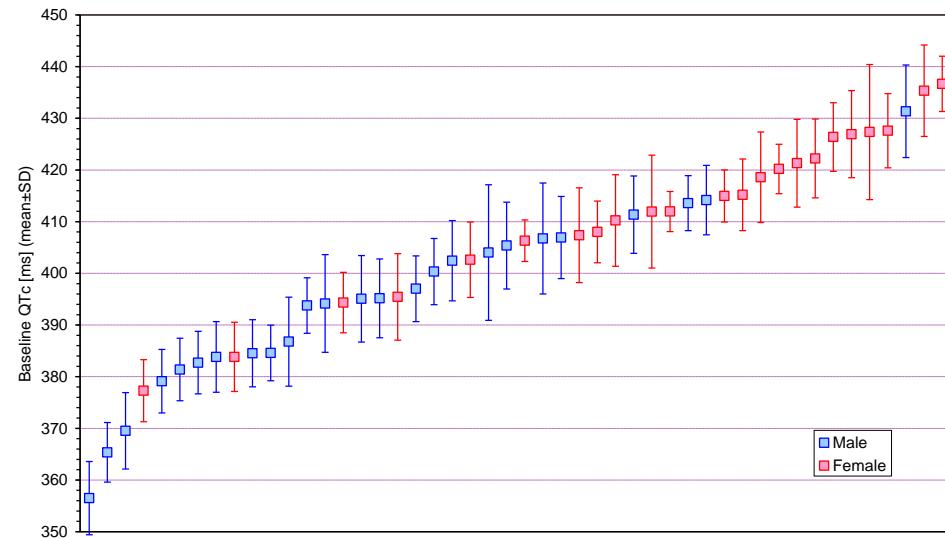
TEST1: Intra-subject variability



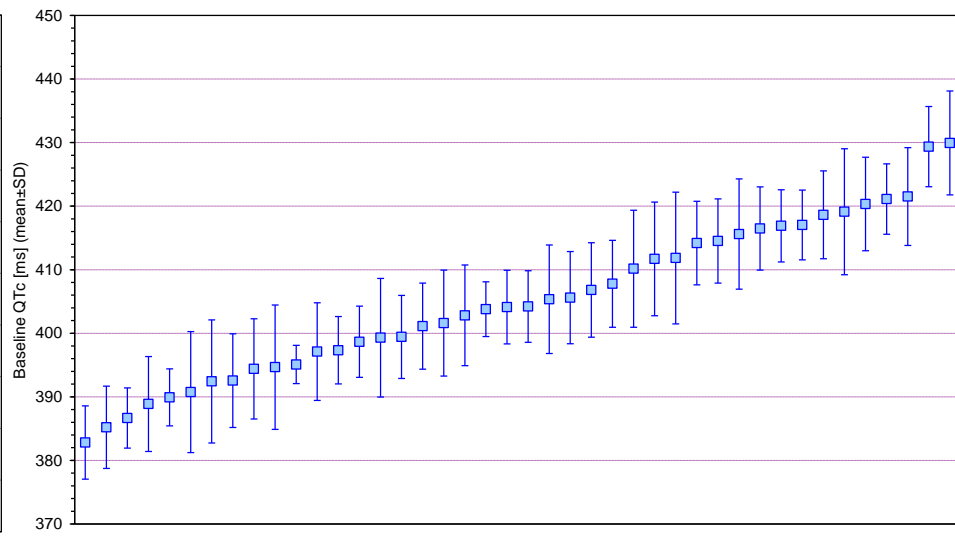
Study subjects



Study subjects

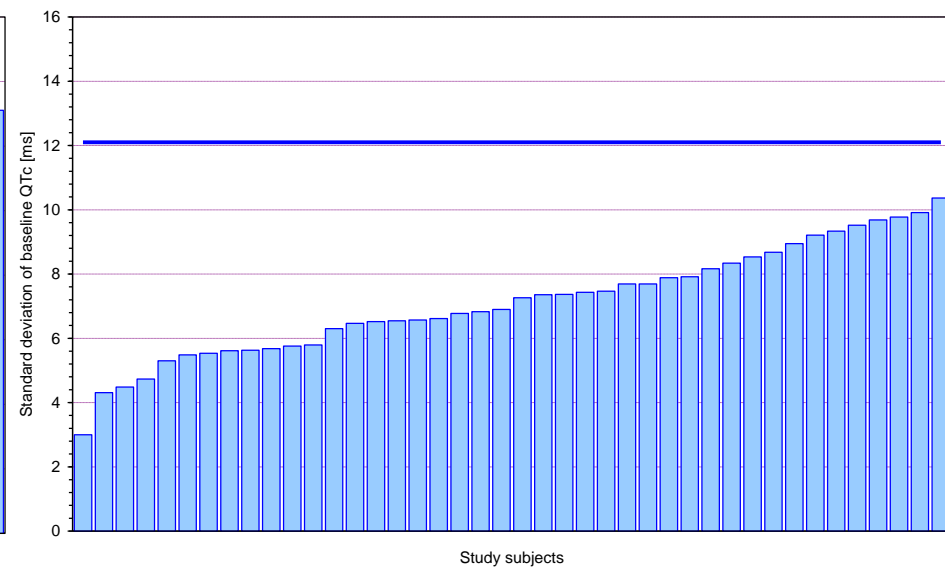
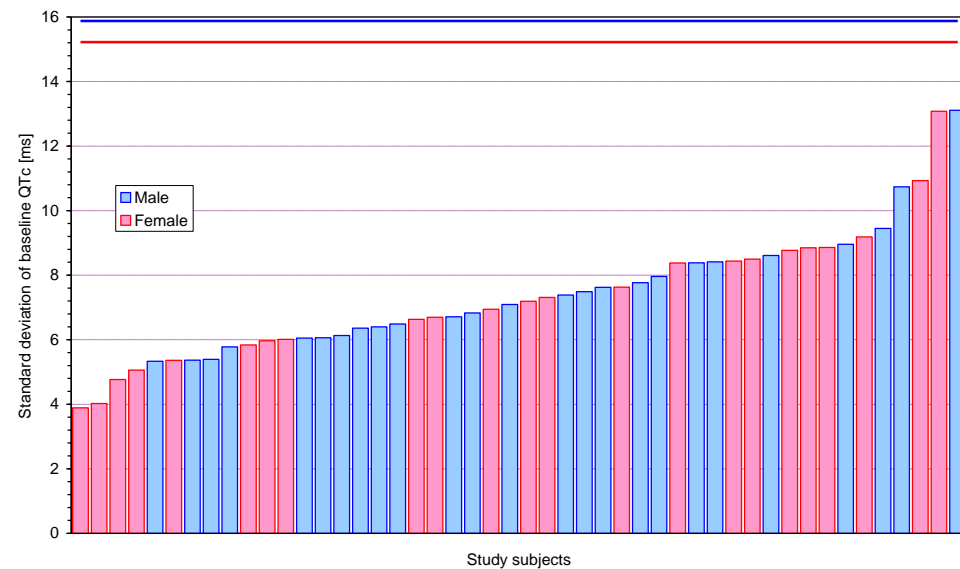
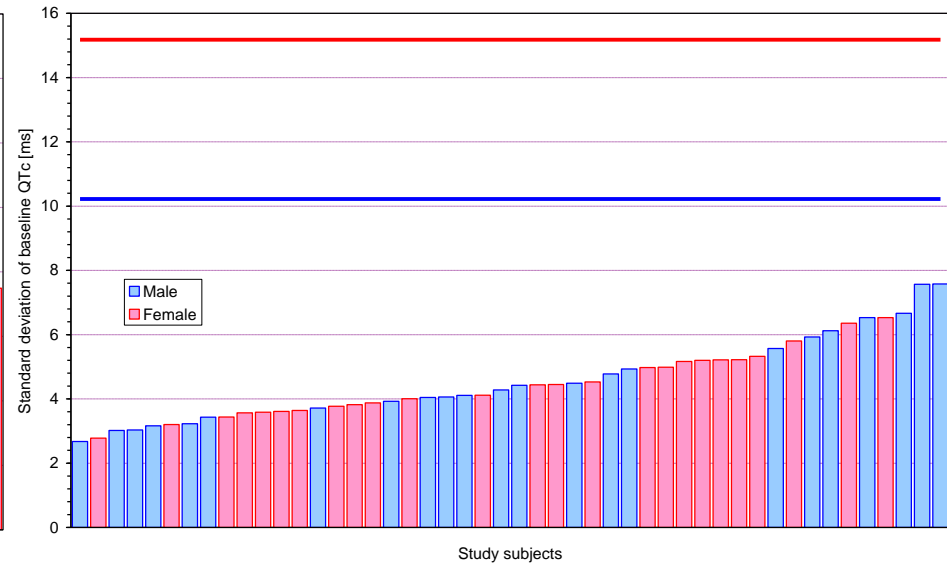
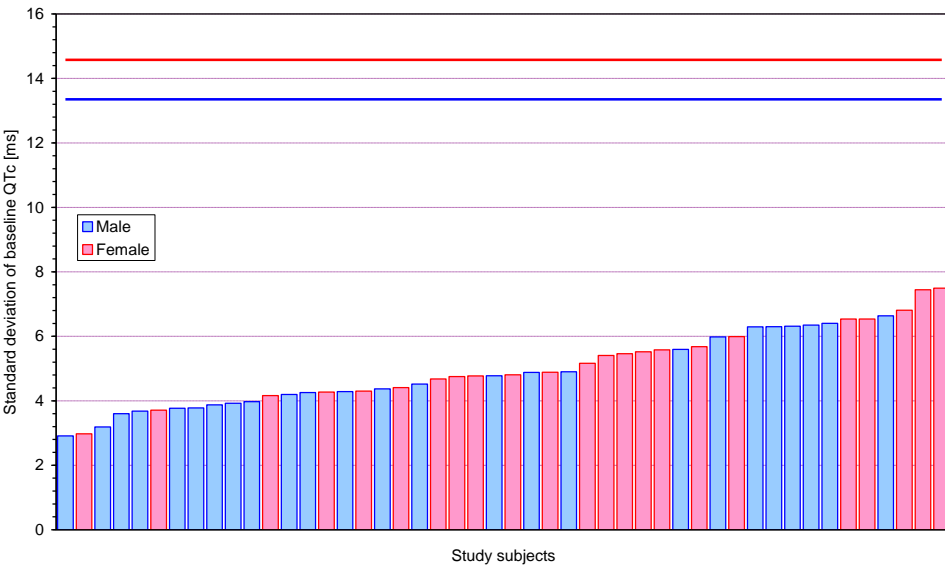


Study subjects

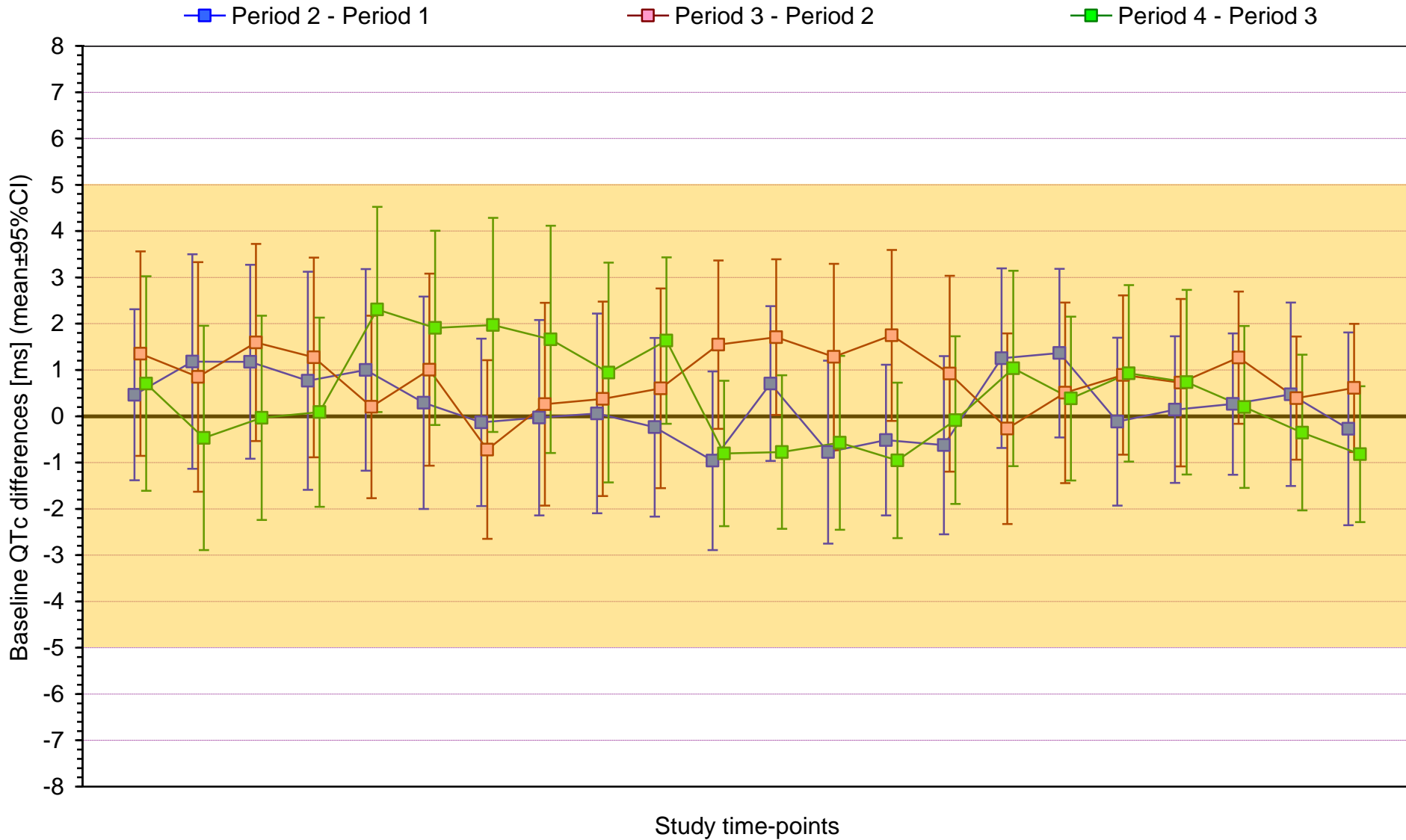


Study subjects

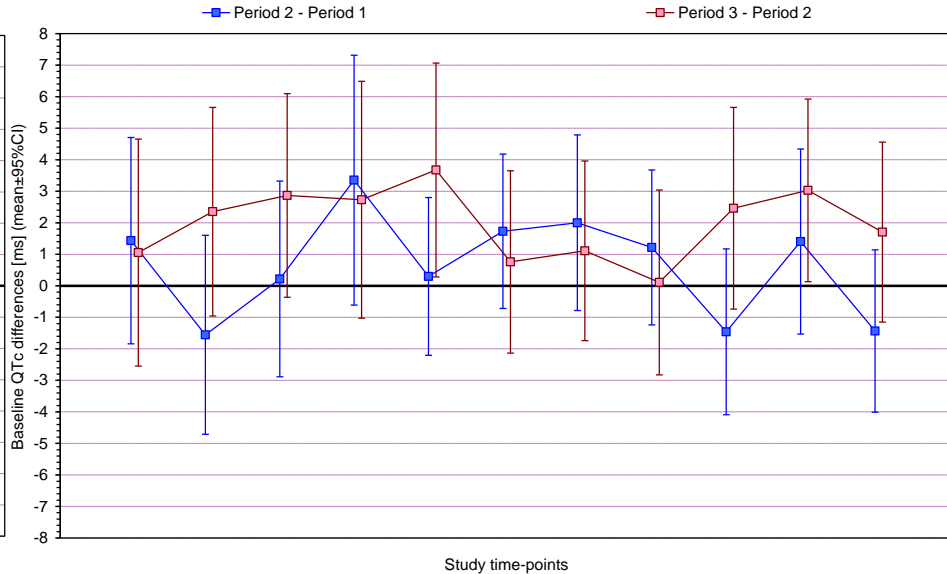
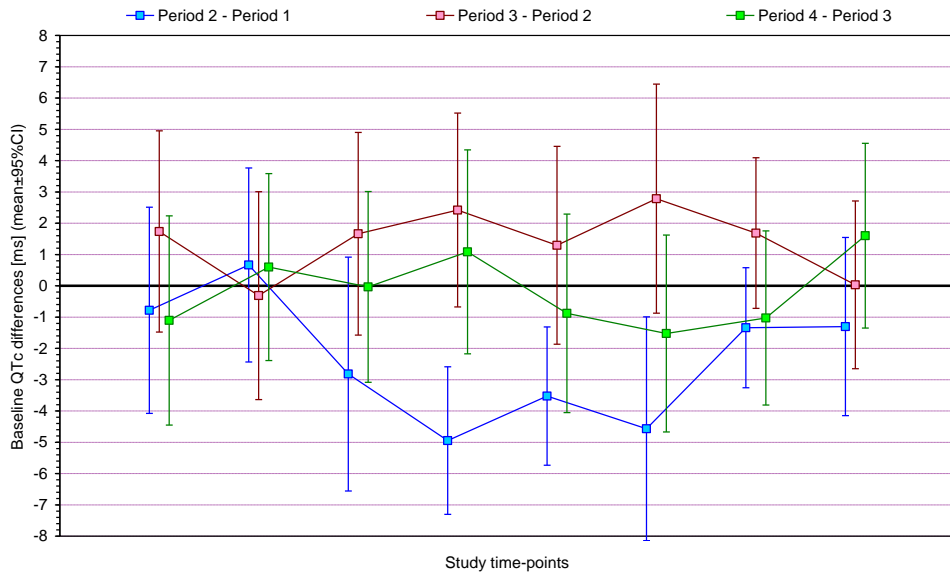
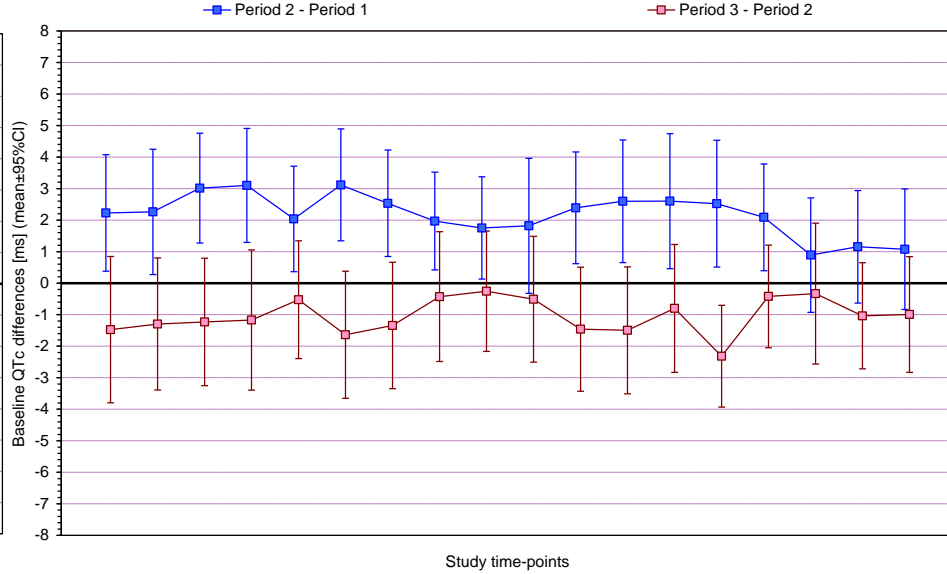
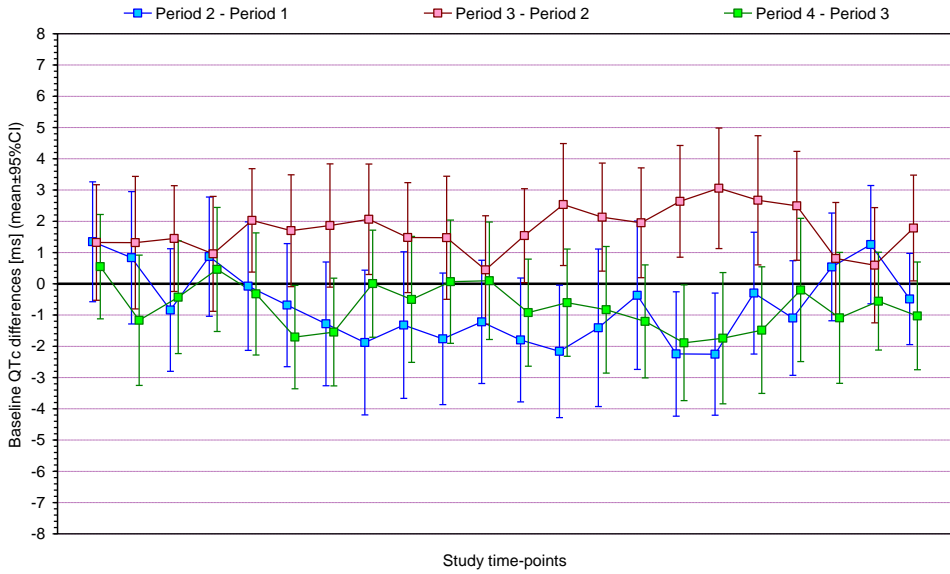
TEST1: Intra-subject variability



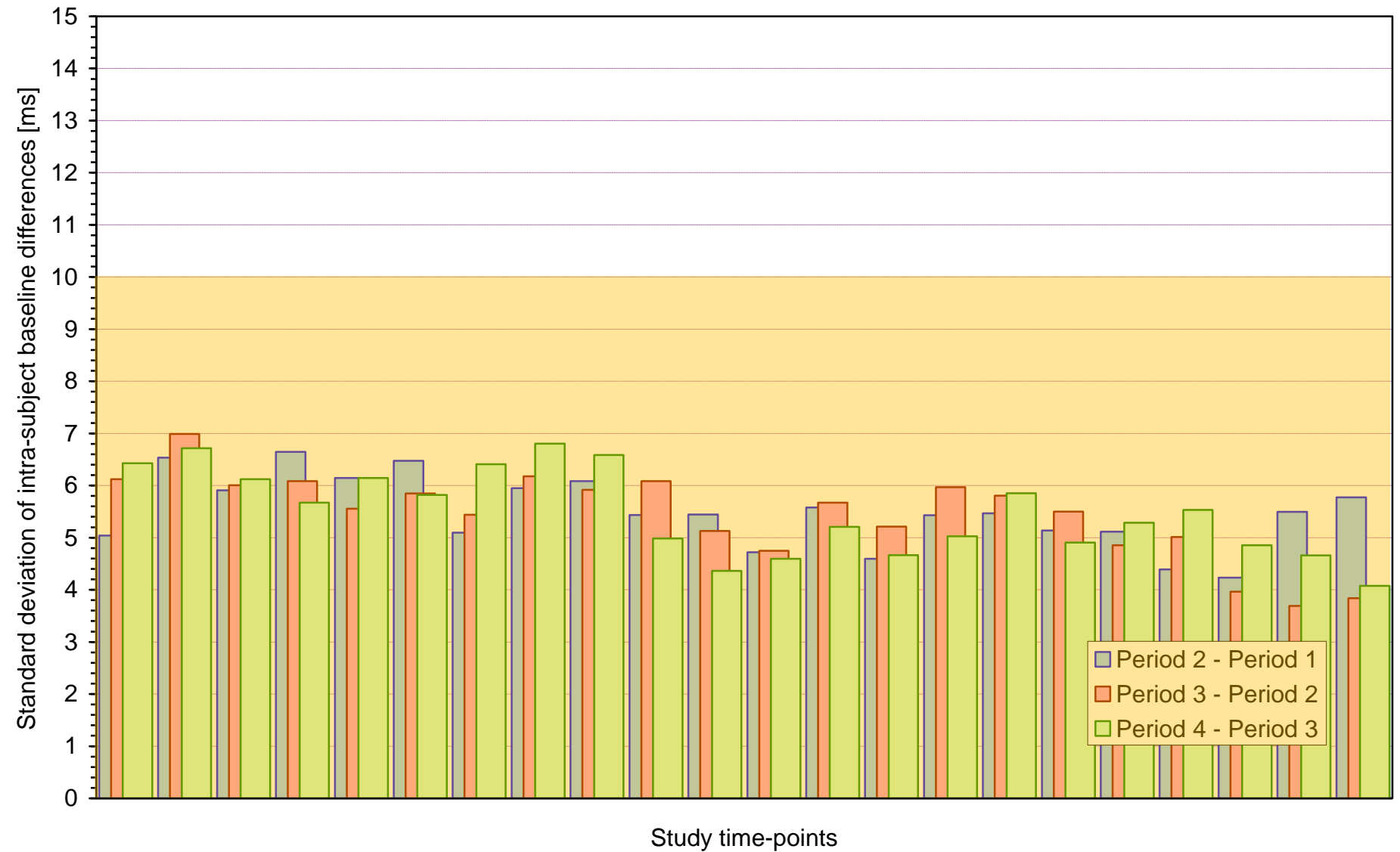
TEST2: Inter-baseline stability



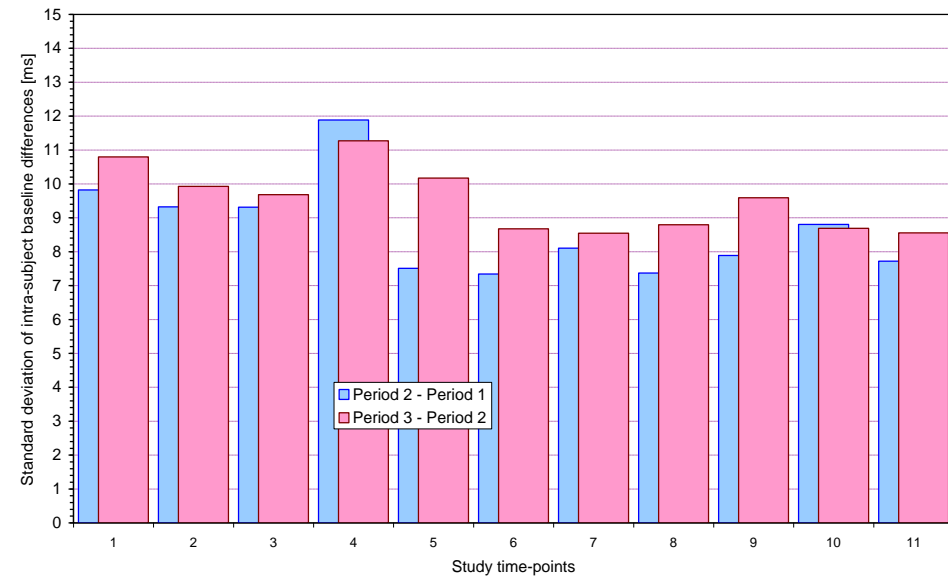
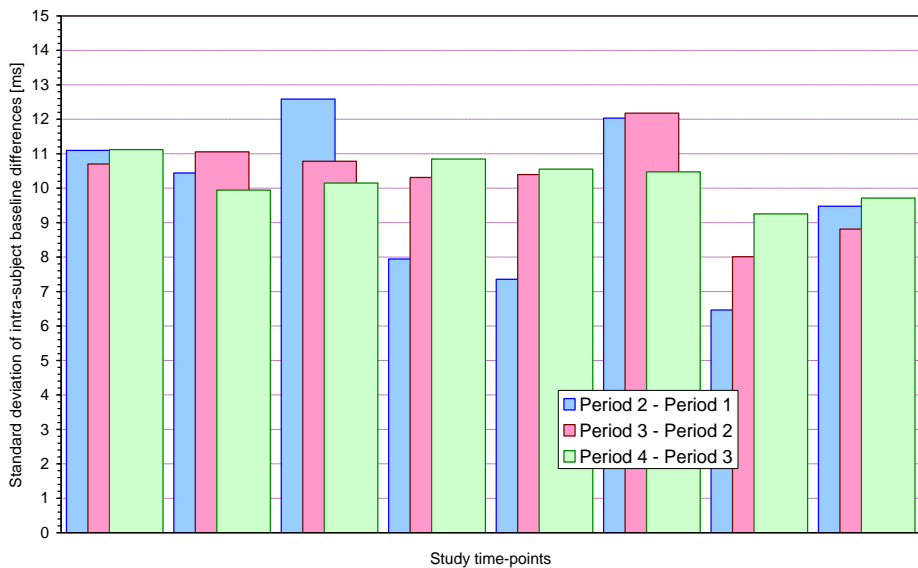
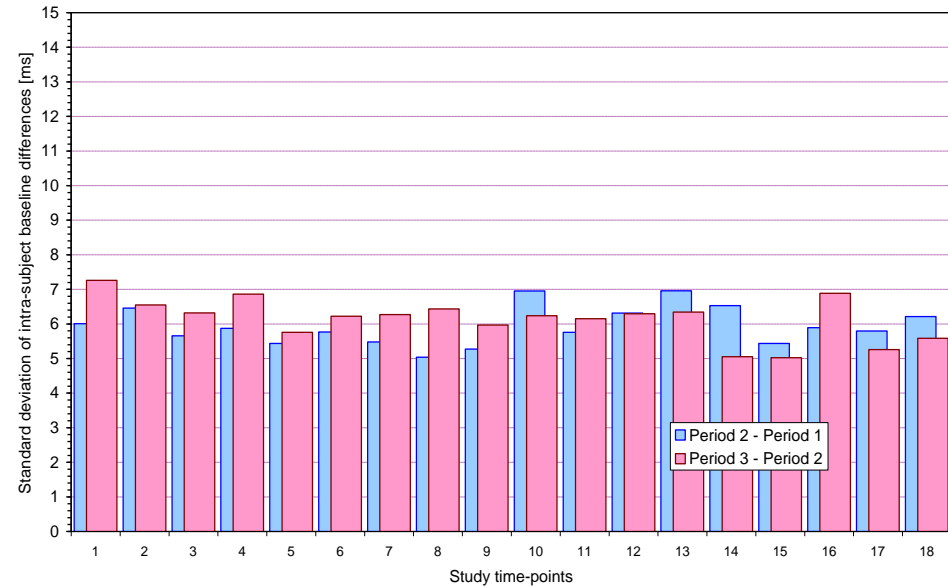
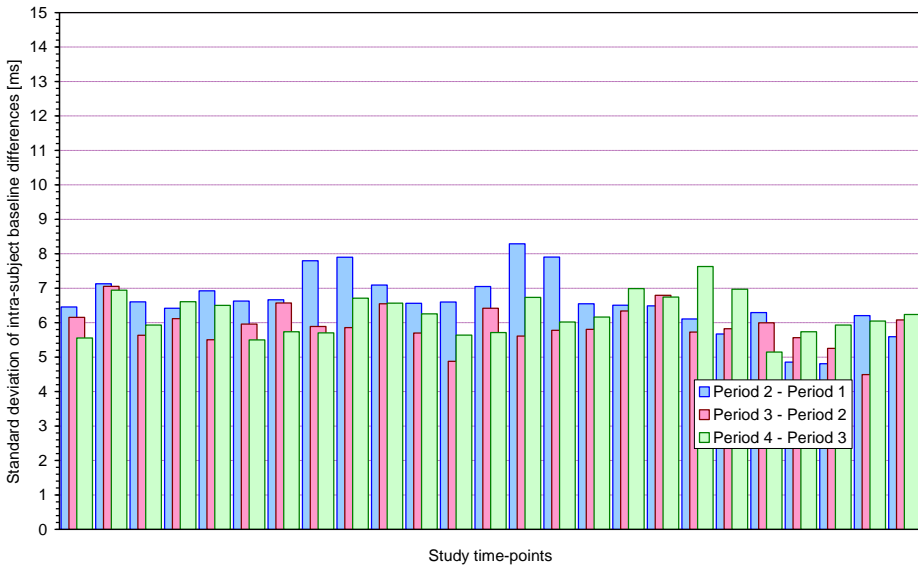
TEST2: Inter-baseline stability



TEST2: Inter-baseline stability



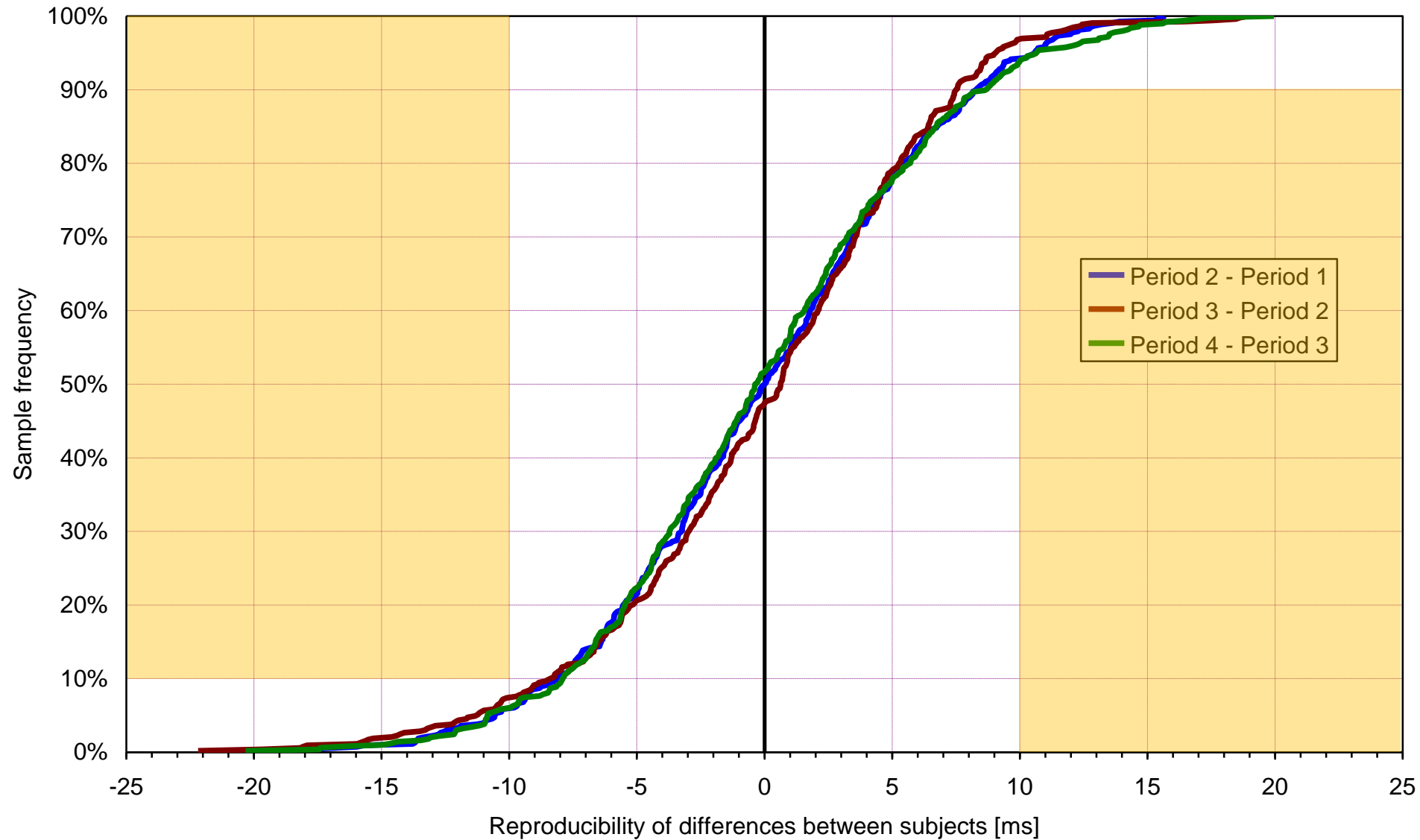
TEST2: Inter-baseline stability



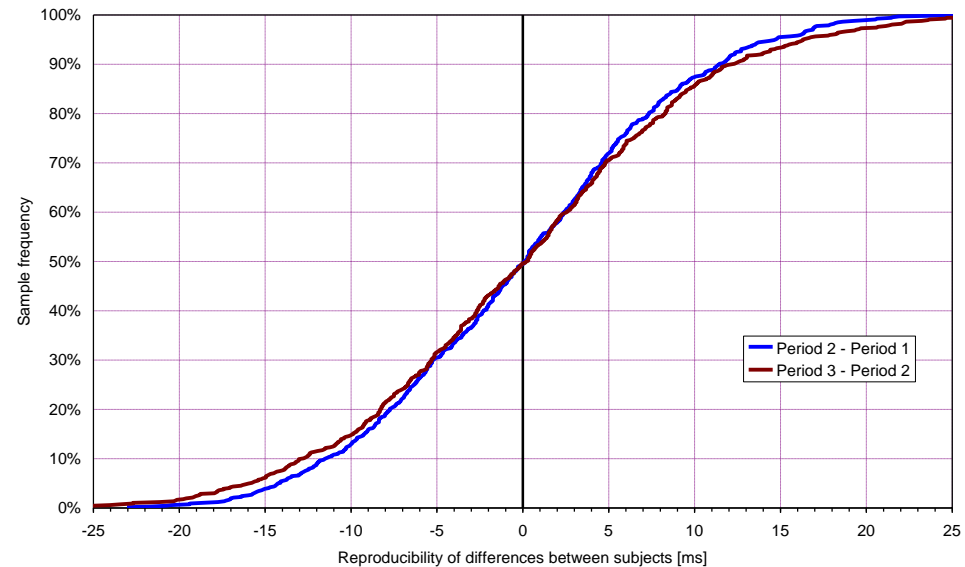
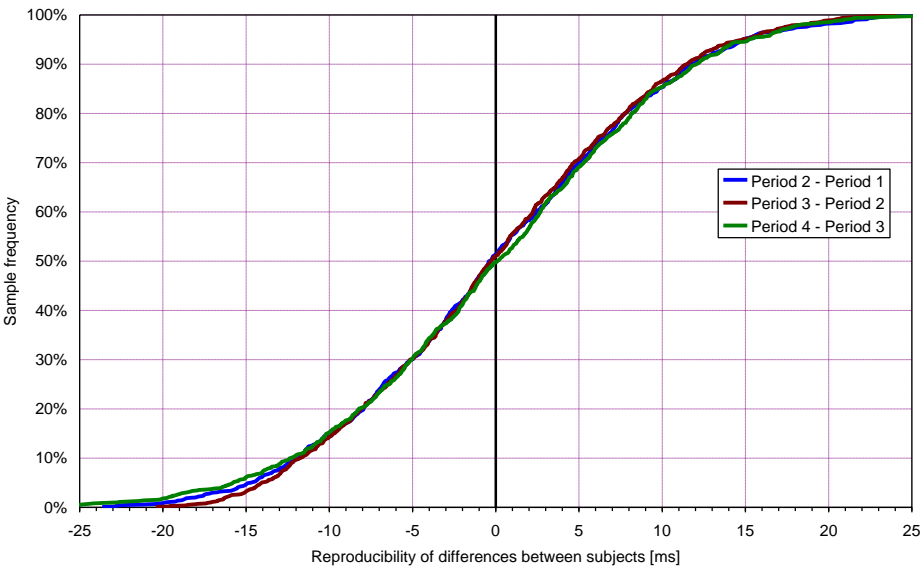
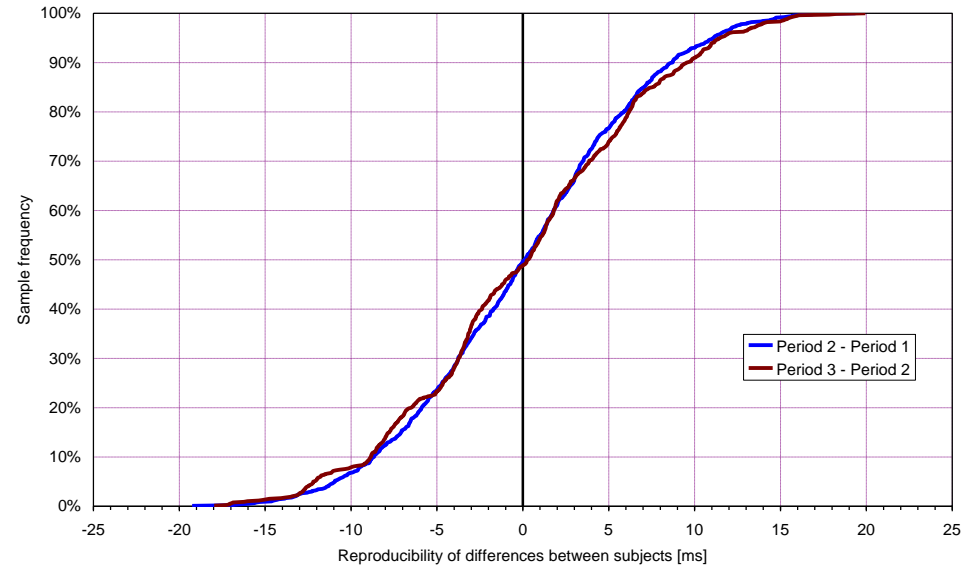
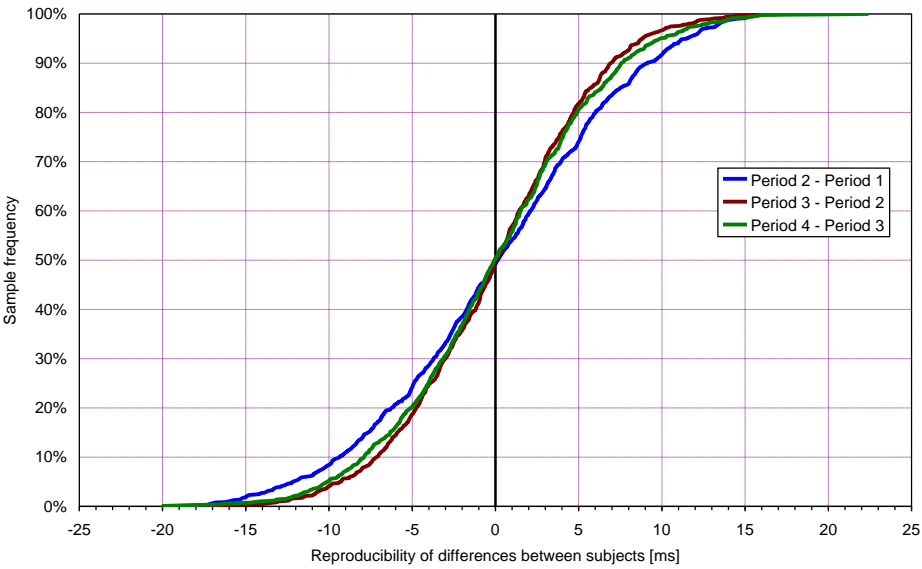
TEST 3: Reproducibility of IS differences

- Is the difference between subjects A and B at baseline X the same as at baseline X+1:
 - For all pairs A and B
 - For all subsequent baseline pairs

TEST 3: Reproducibility of IS differences



TEST 3: Reproducibility of IS differences



Possible Assay Sensitivity Tests

- (1) That intra-subject SD of QTc is smaller than inter-subject SD of mean QTc.
- (2) That 95% CI of baseline differences is small (e.g. between -5 and +5 ms)
- (3) That intra-subject SD of all QTc across all baselines is small (e.g. < 10 ms)
- (4) That inter-subject differences in one baseline are reproduced in other baseline (e.g. single-sided 90% tail < 10 ms)

Outlook

- To test this in the collection of previously submitted TQT studies for which multiple baselines exist (presently ongoing)
- To validate the tests in forthcoming TQT studies with multiple baselines
- To modify the technology to involve on-placebo recordings and parts of recordings
 - Possible use in SAD and MAD FIM studies

Thank You