



DATA ANALYSIS AND REPORTING

# Biostatistical Challenges in R&D

Conflicting regulators, upbeat  
developers and big data:  
How to bring them together?

Gonnie van Osta  
Author! et al. BV

# Introduction

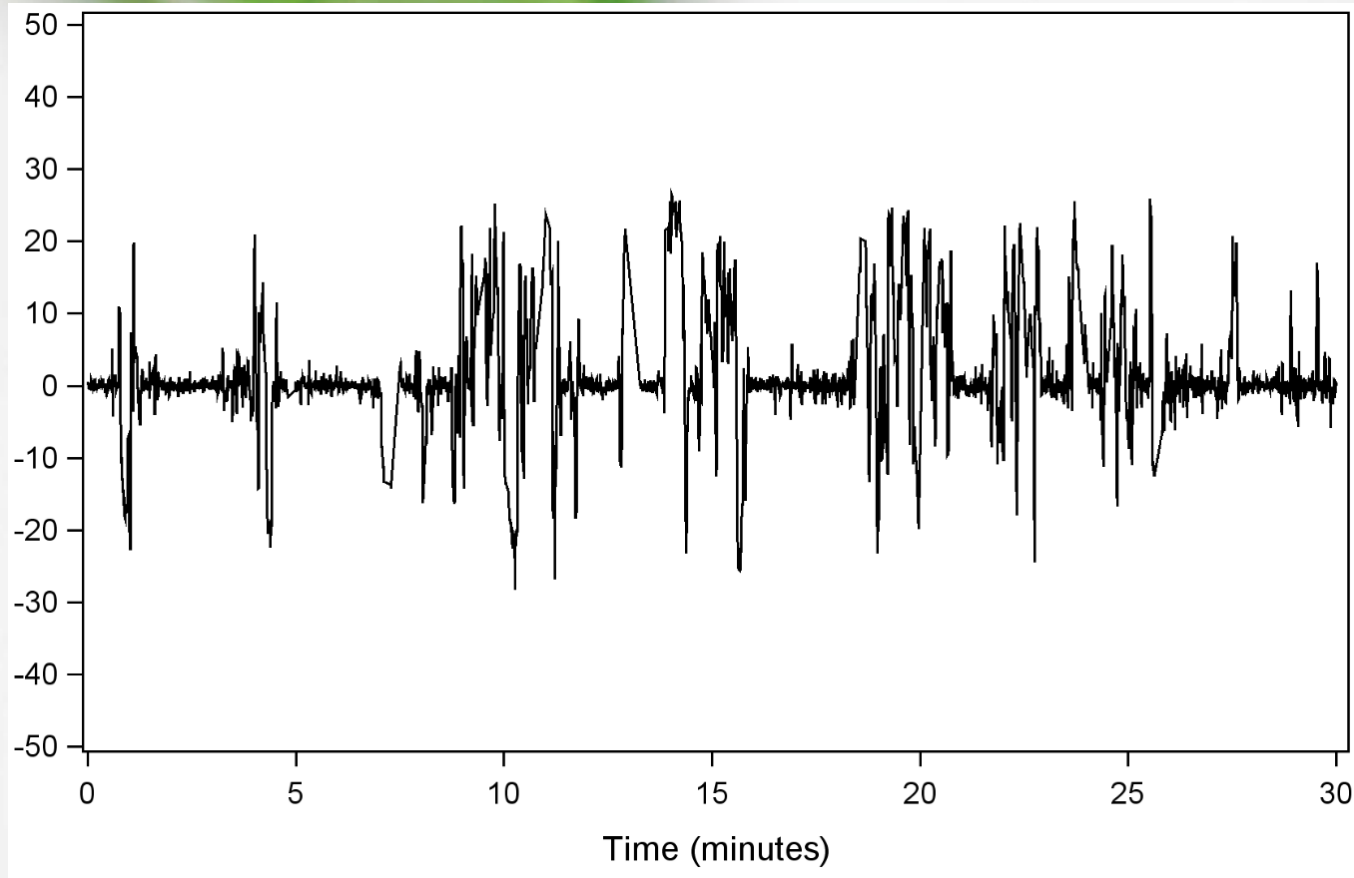
- ! Gonnie van Osta (Goes, 1962)
- ! First year, Human Movement Studies VU, 80s
- ! MSc in Mathematical Statistics UvA, 80s
- ! 3 years, statistical consultant DLO Wageningen
- ! 22 years in development (biometrics, quality, clinical, regulatory, pharmaceutical) Organon etc, Oss
- ! Registered biostatistician, 2000
- ! Scientific meeting organisator PSDM/EFSPI, 2002-2006
- ! Lean six sigma black belt, 2012
- ! Currently: statistical consultant at AUTHOR!

# Example: Diagnostic Medical Device

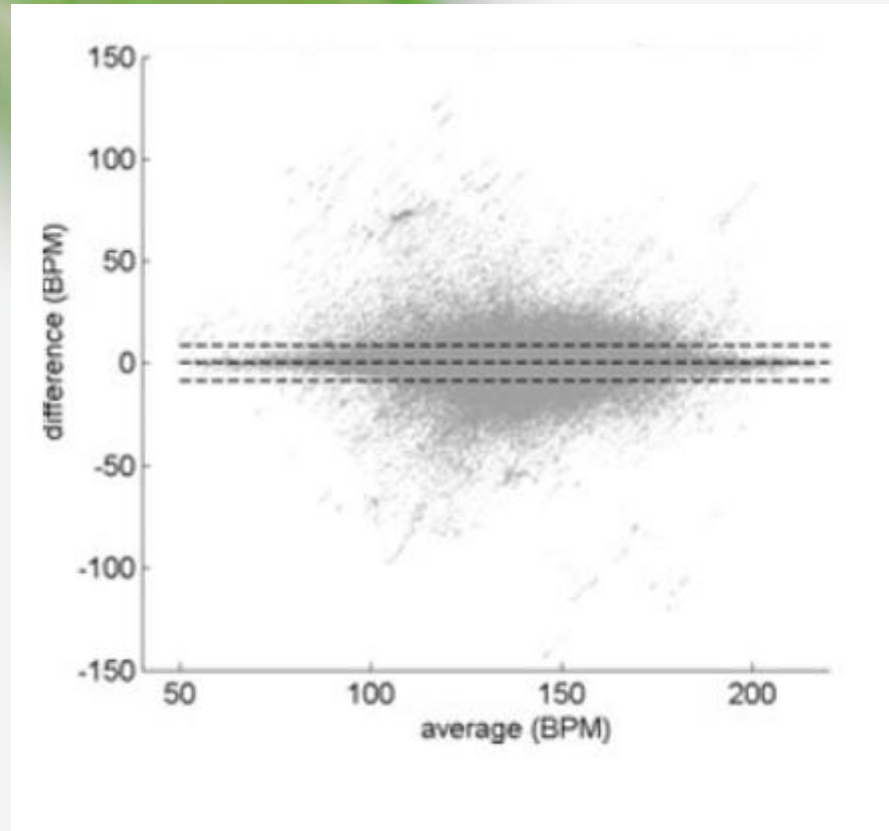
- ! New device to measure heartbeat, less invasive
- ! Aim: to replace the existing device with the new device
- ! Request: Study design/power calculations to show that the new device is as good as the golden standard
- ! What is measured?
  - 2 Devices in parallel (paired)
  - Heartbeat (periferal), in various stages of physical effort
  - Periods: several hours
  - 4 observations per second

→ Lots and lots of data

# The data, one patient, $\pm 7000$ points



# Indication literature



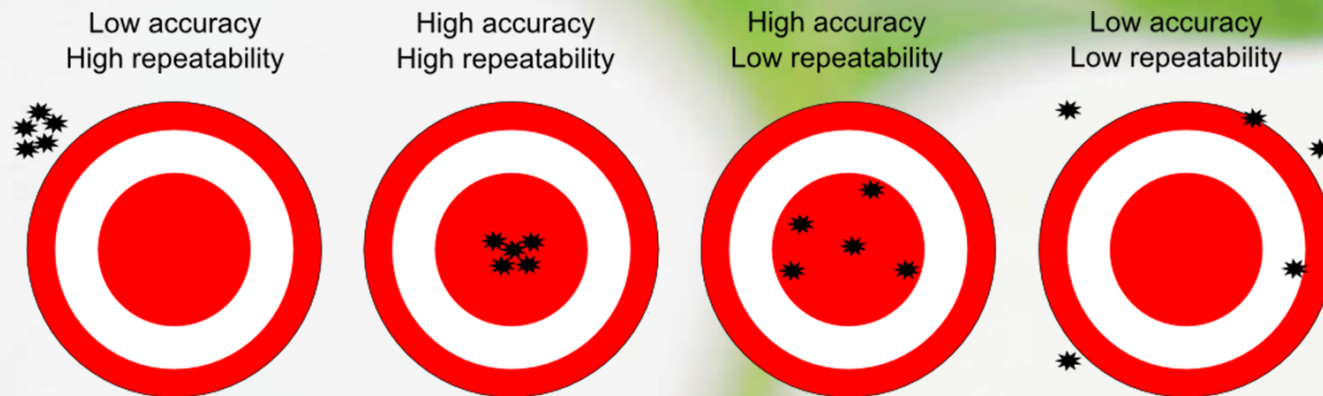
# Challenge

- ❗ Input: sponsor, indication literature, hospital EC, regulators
- ❗ Sponsor/Literature:
  - Literature, 3 arm study showing superiority of one new devices over another existing device.
  - Reliability=Percentage Positive Agreement=Percentage Time Heart Beat of 2 systems is within 10 beats
  - Accuracy: root MSE of differences (or against the regression of Bland-Altman plot?)
  - 3-arm study not feasible: non-inferiority 2-arm



# Aim for a reliability and accurate method

- Reliability=Percentage Positive Agreement=Percentage Time Heart Beat of 2 systems is within 10 beats
- Accuracy: SD estimation of paired differences
- Literature: Greenwood 1950: Sample Size Required For Estimating The Standard Deviation as a Percent of Its True Value, used for military (seemed appropriate), N=80



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# Challenge



- ❗ Regulators, show reliability and accuracy against golden standard:
  1. Reliability and Accuracy:  $N=80$  seems low, use Bland/Altman 1983 to determine sample size for limits of agreement and bias estimation
  2. Reliability: Proposed definition of reliability is loss of information and repeated measures, use Deming regression ( $\beta_0=0$ ,  $\beta_1=1$ ).
  3. Accuracy: there are correlated repeated measures, use bootstrapping methods when constructing CIs for bias, Bland-Altman (2007) analysis including plots.

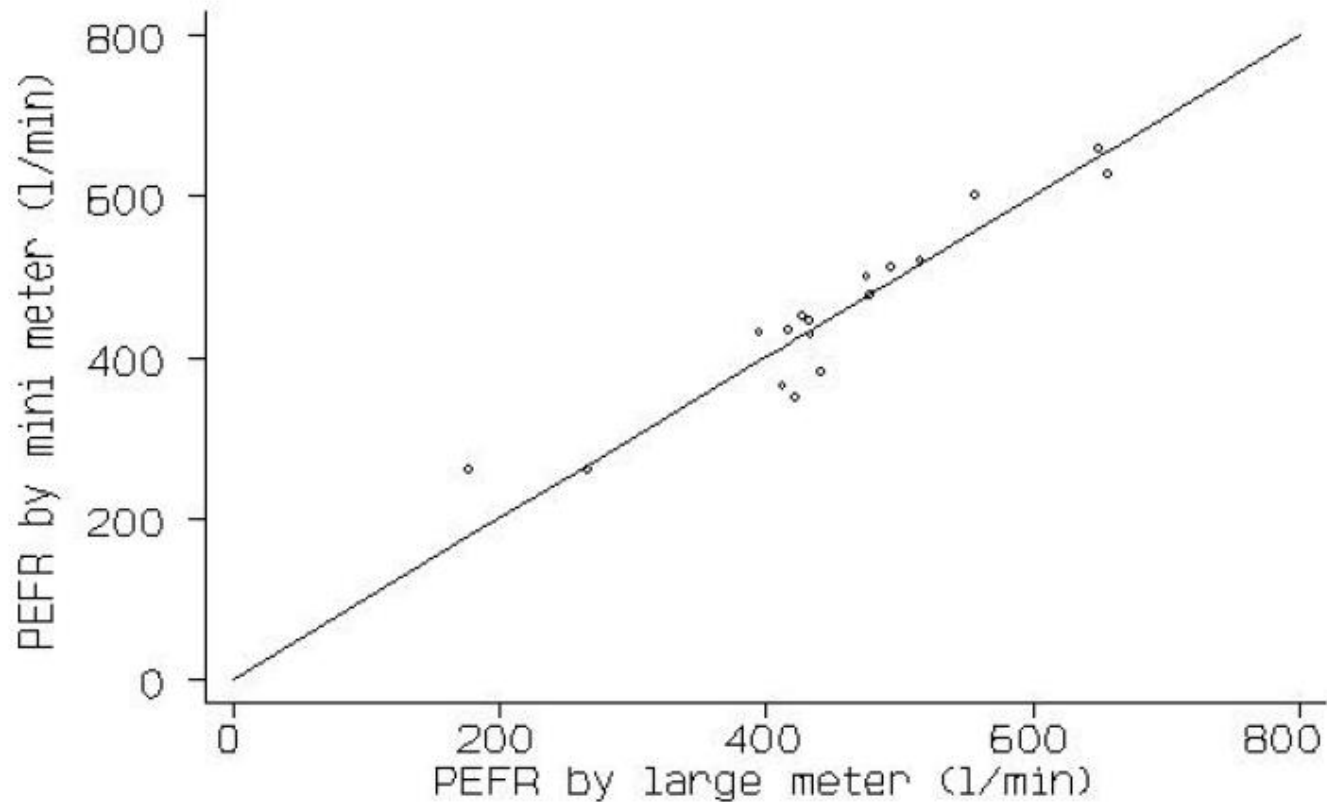
Limits of agreement is the new definition of reliability.

What is this new definition?

*Bland & Altman, Agreement between methods of measurement with multiple observations per individual. Journal of Biopharmaceutical Statistics, 17: 571–582, 2007*



# Bland-Altman (1983) side-step

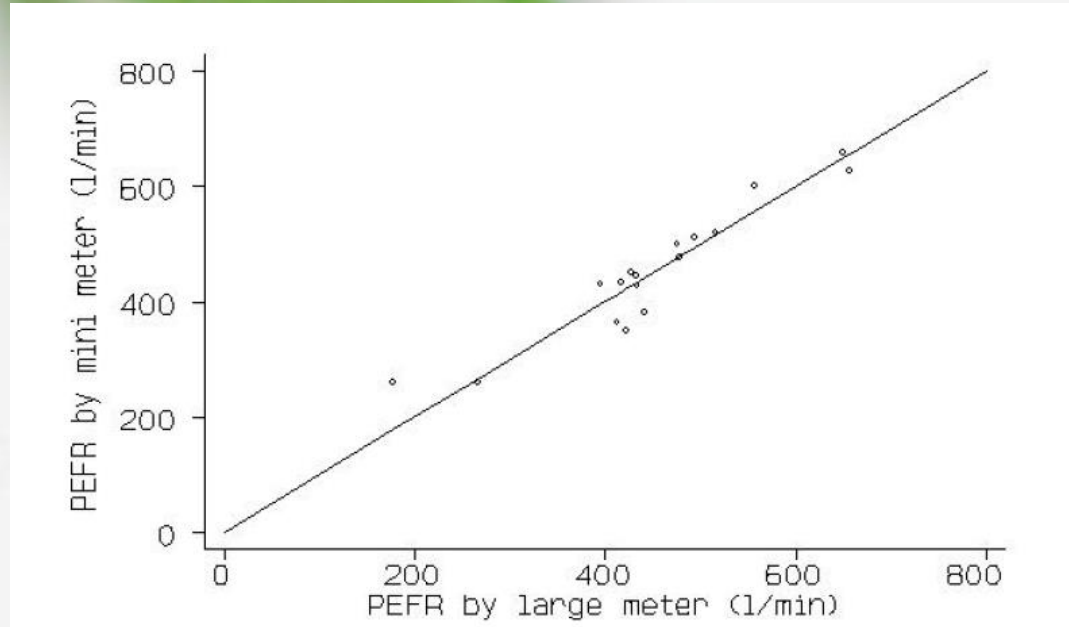


Altman DG, Bland JM. *Measurement in medicine: the analysis of method comparison studies.*  
*Statistician* 1983;32:307–17

23 November 2018

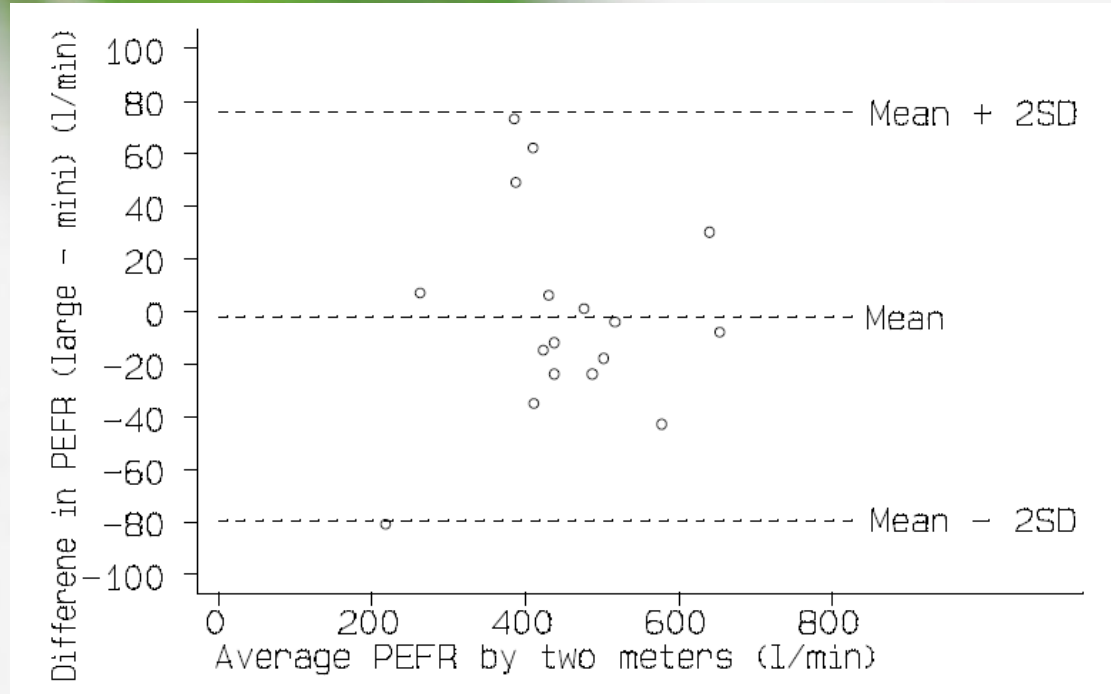
Gonnie van Osta

# Bland-Altman (1983) side-step



- Data will cluster around a regression line
  - The greater the range of measurements the greater the agreement will appear to be.
- regression is not the way

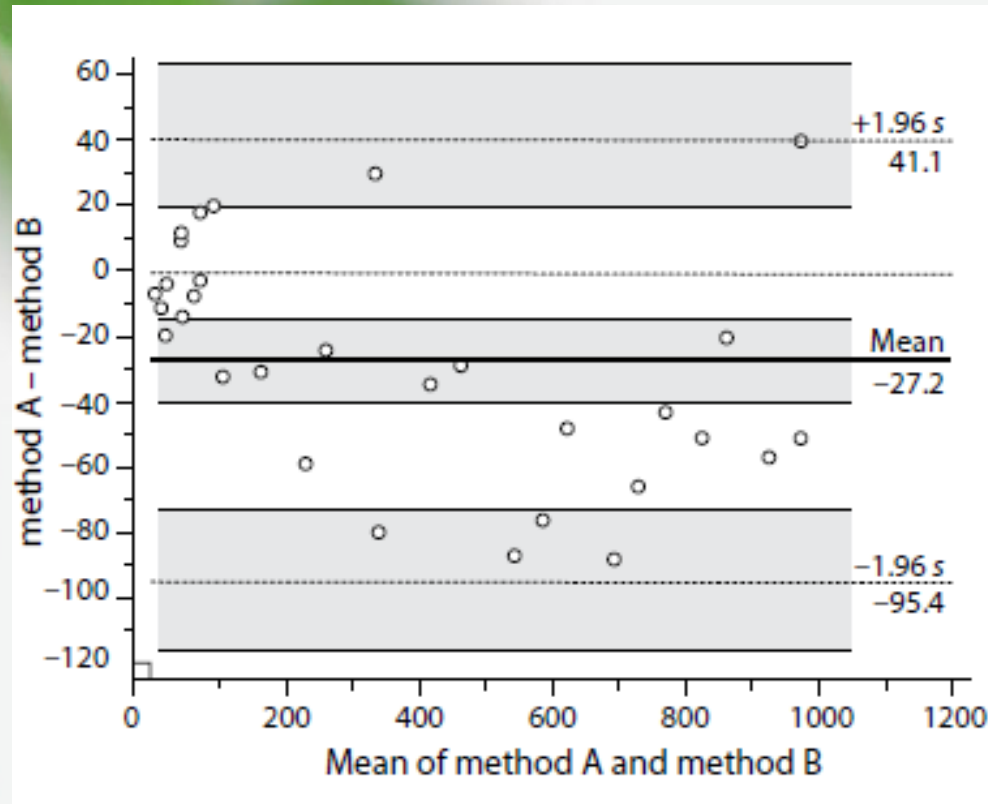
# Bland-Altman (1983) side-step



Bland-Altman plot:

- Difference against average
- Error and bias are much easier to assess
- Bias -2.1, mean  $\pm$  2\*SD ranges from -80 to +76, this lack of agreement not clear from regression figure

# Bland-Altman: Limits of agreement



Bland-Altman plot (continued):

- Estimation of precision of SD/limits of agreement depends on sample size, SE of limits is  $\sqrt{3S^2/n}$

Giavarina (2015), Lessons in Biostatistics: Understanding Bland Altman analysis

# Bland-Altman side-step

## Conclusions:

- ❗ Correlation does not measure agreement
- ❗ Least square regression does not measure comparability
- ❗ This is not calibration. Since calibration is the situation where the true value is known

## Summary/Assumptions:

- ❗ Paired (single readings)
- ❗ Uncorrelated
- ❗ Repeatability/plots: Investigate the between method differences and relation with the size of the measurements

# Example: Diagnostic Medical Device

So far, straightforward, use Bland-Altman.

❗ But which one? 1983 or 2007?

In the mean time:

❗ Trouble managing the large amounts of data

❗ Lots of (test) data

- Not keen on bootstrapping
- Plotting to check B&A assumptions is a challenge
- Deming regression ( $\beta_0=0$ ,  $\beta_1=1$ ) or Bland-Altman (dif vs average regression)?
- Accounting for correlated repeated data



# Bland-Altman side-step

Our example

- ! Paired observations ✓
- ! Independent observations X
- ! No relation between difference(bias) and mean ?

# Example: Diagnostic Medical Device

Our test data:

- ❗ Independent: **X**
- ❗ Relation Bias and mean ?
- ❗ Bland&Altman 1999/2007:
  - Number of obs per patient varies (2-5)
  - True value varies
  - One way analysis, estimate residual mean square (1 summary per patient).

But: observations within a patient are assumed independent

# Example: Diagnostic Medical Device

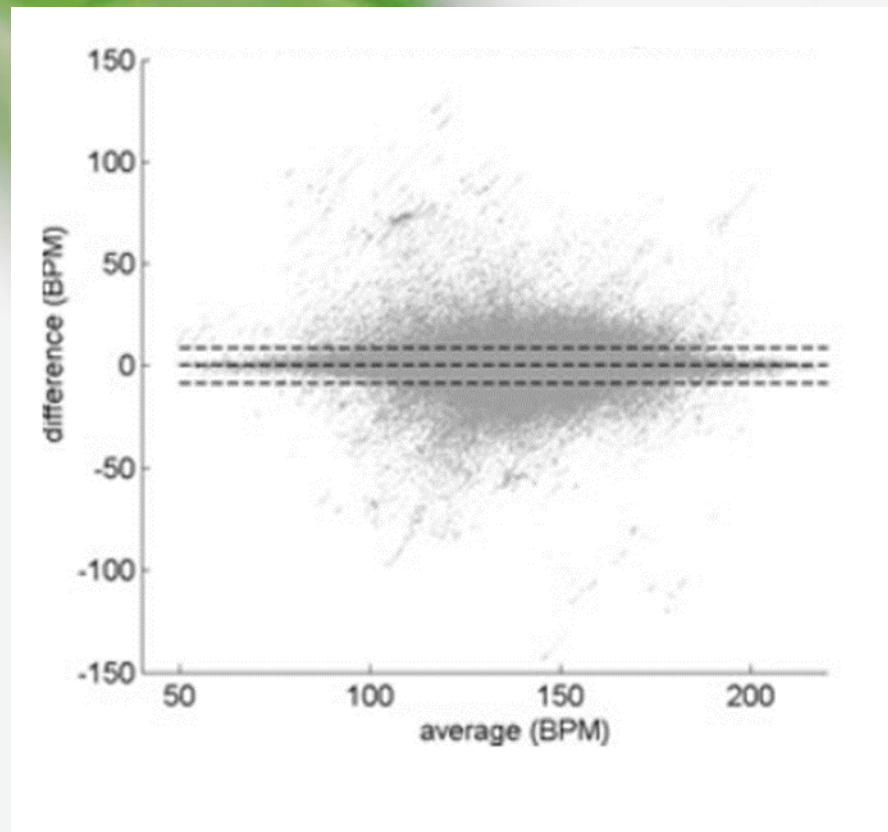
Our test data:

- ! Independent: **X**
- ! Relation Bias and mean ?
- ! Dependency
  - Estimate correlation or use only one data-point?

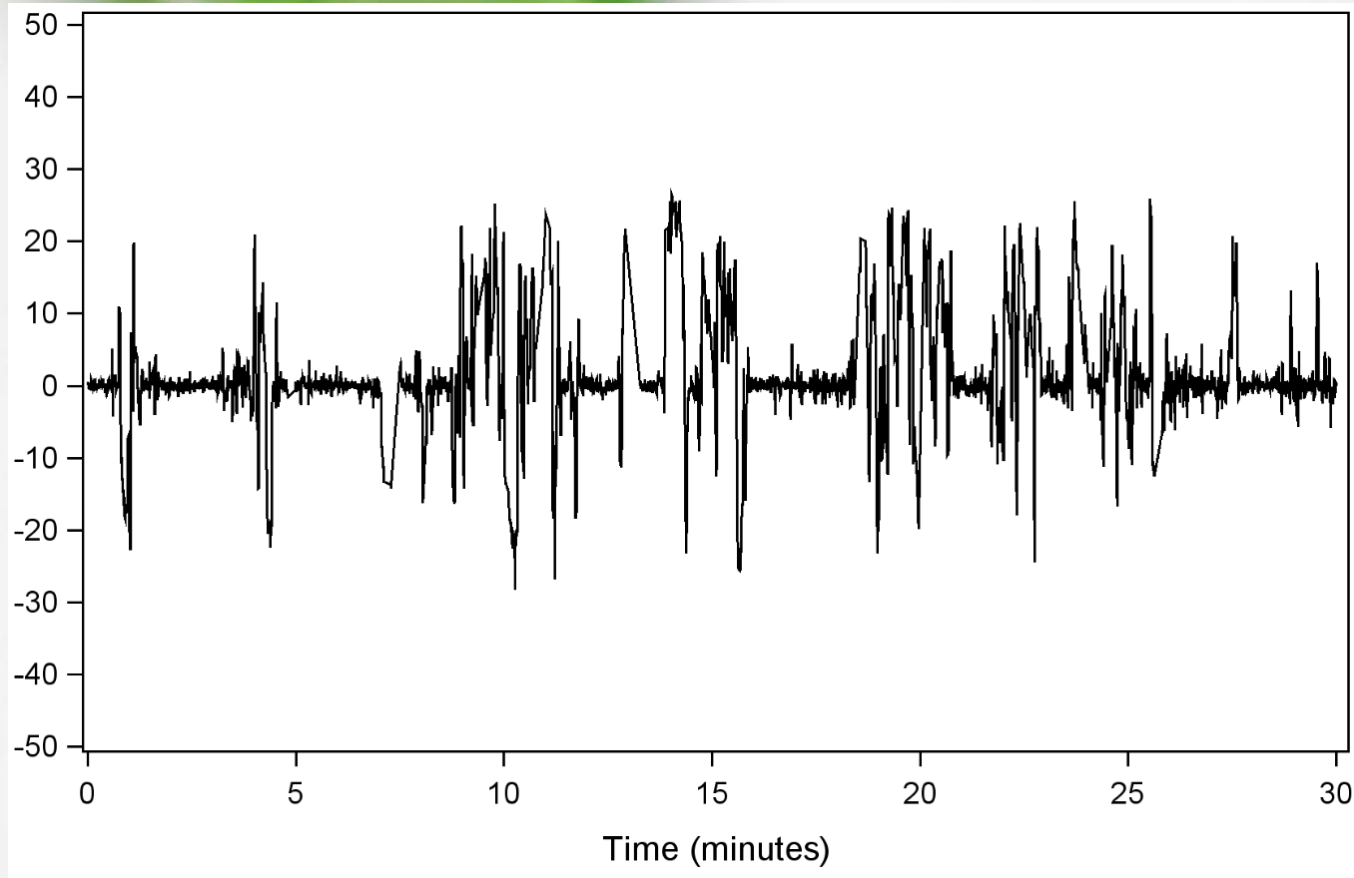
Hours\*minutes\*seconds\*4 >100.000 paired observations per patient

- Hard to estimate/model correlation
- Hard to explore graphically (B&A plot or Regression plot)

# Literature: Bland-Altman plots



# The data, one patient, $\pm 7000$ points



# Example: Diagnostic Medical Device

- ! Our final data (average ~55.000 paired points per patient)

How can it be that I am longing for fewer data-points?





# So, what did we do?

For regulators that were not concerned with repeated measures:

- ❗ Bland & Altman 1983, bias and limits of agreement testing based on summaries per patient
- ❗ Percentage time < 10 bpm

# So, what did we do?

- ❗ For regulators that were concerned with repeated measures:
- ❗ Same as for 1)
- ❗ Plus: Bootstrapping, one observation per patient, estimate the Mean accuracy and Limits of Agreement and associated Bootstrap confidence limits
- ❗ Bland-Altman plots investigating bias vs mean
- ❗ Added value of Deming regression not really understood

# Result

- ! First regulatory review resulted in certification
- ! Awaiting the second regulatory review