PhUSE SDE

Beerse, June 10, 2013

Identifying Atypical Sites with Central Statistical Monitoring

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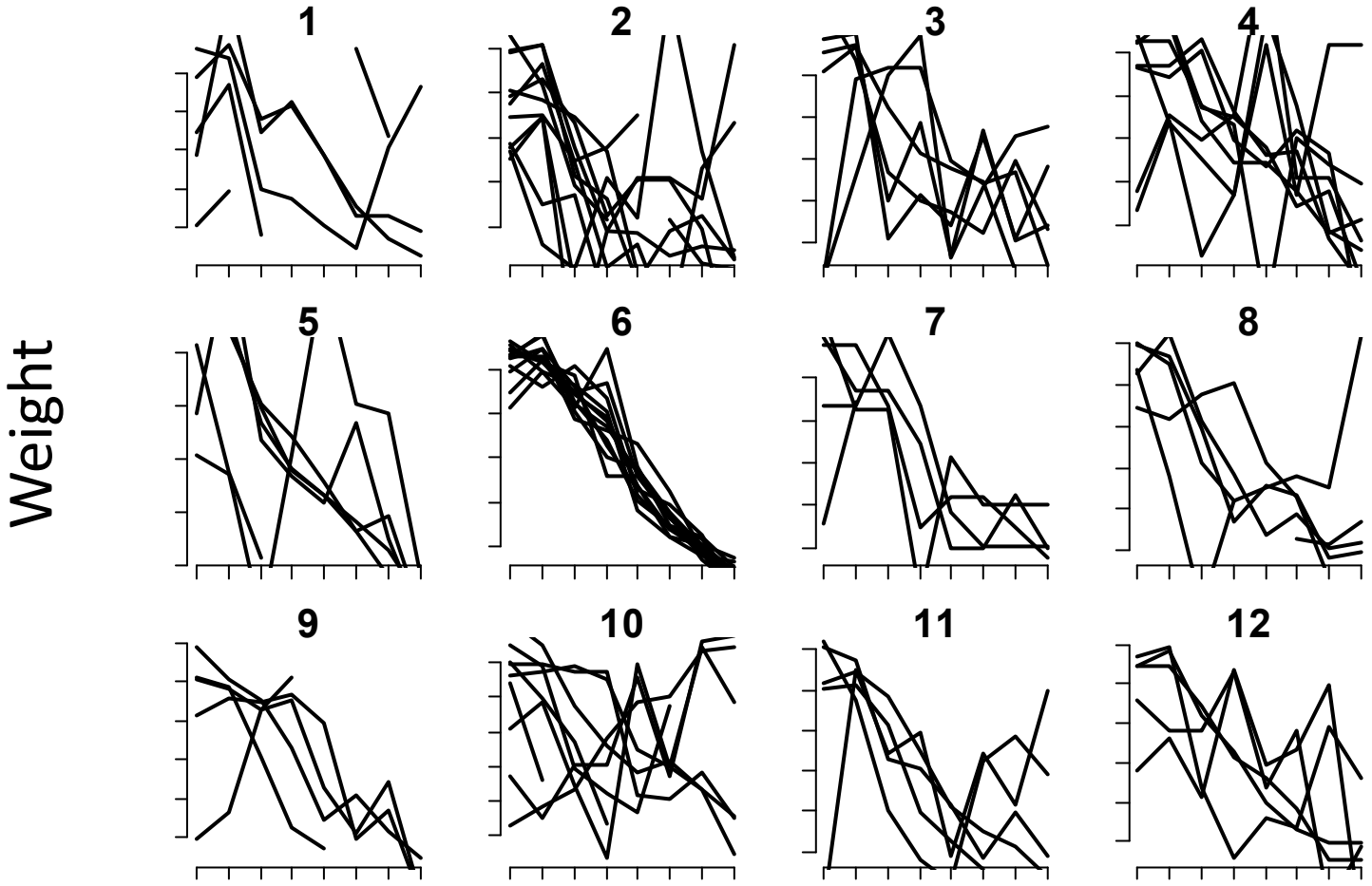
Weight loss pattern…Where is the outlier ?



Introduction
Central statistical monitoring

- Central $\rightarrow$ using the whole database
- Statistical $\rightarrow$ applying statistical methods
- Monitoring $\rightarrow$ “checking the quality or content of”

Ref: Venet et al, Clinical Trials 2012

Introduction
Why central?

- Evaluation of the entire trial
- Investigation of within-patient differences
  - more efficient than by on-site monitoring
- Investigation of between-patient differences
  - not in on-site monitoring (CRFs rarely compared across patients)
  - detection of differences between labs, centers, investigators, etc.

Introduction
Why statistical?

- Summary measures needed
- Significance of differences may need to be assessed
- Humans are poor random number generators
  - Fraud may be detected statistically

Introduction
Why monitoring?

- Can be applied at many different stages of the conduct of the trial
  - May encounter limitations early in the trial

- Can be used to guide on-site monitoring or the study conduct

Introduction
The goal of CSM

- Identification of groups of patients with “atypical” data patterns
  - Without pre-specifying neither the data items nor the type of patterns

- Usually, patients are grouped by center
  - Other grouping, e.g., by investigator, could be considered as well

Methods
Statistical principles

- Exploit the structure of data
- Use every variable
- Compare each center against all other centers
- Do many tests, then summarize them (using a score or a rank)

Methods

Statistical tests

A wide range of statistical tests is used:

- proportions of outliers
- means
- global variances, within patient variances
- event counts
- distributions of categorical variables
- proportion of week-days
- proportion of missing values
- correlation between several variables

Methods
Statistical tests

- The tests compare each center against all other centers
- One P-value is generated per center per test (p_{ij})
- P-values are structured as a matrix with as many rows as centers and as many columns as tests

Methods

Each center is assigned a score

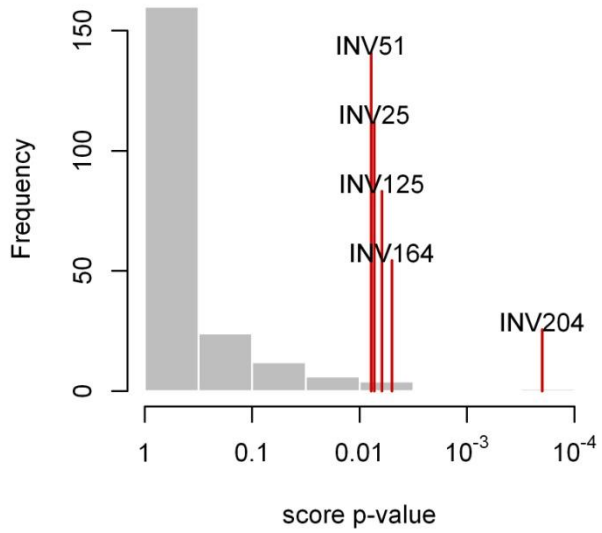
$$\begin{Bmatrix} p_{11} & \cdots & p_{1j} \\ \cdots & \cdots & \cdots \\ p_{i1} & \cdots & p_{ij} \end{Bmatrix} \Rightarrow score_i = \exp\left(\frac{1}{N}\sum_{j=1}^{N}\log p_{ij}\right)$$

P-values matrix

Score of each center calculated from vector of *P*-values p_{ij}

Case study 1
A trial in infectious disease

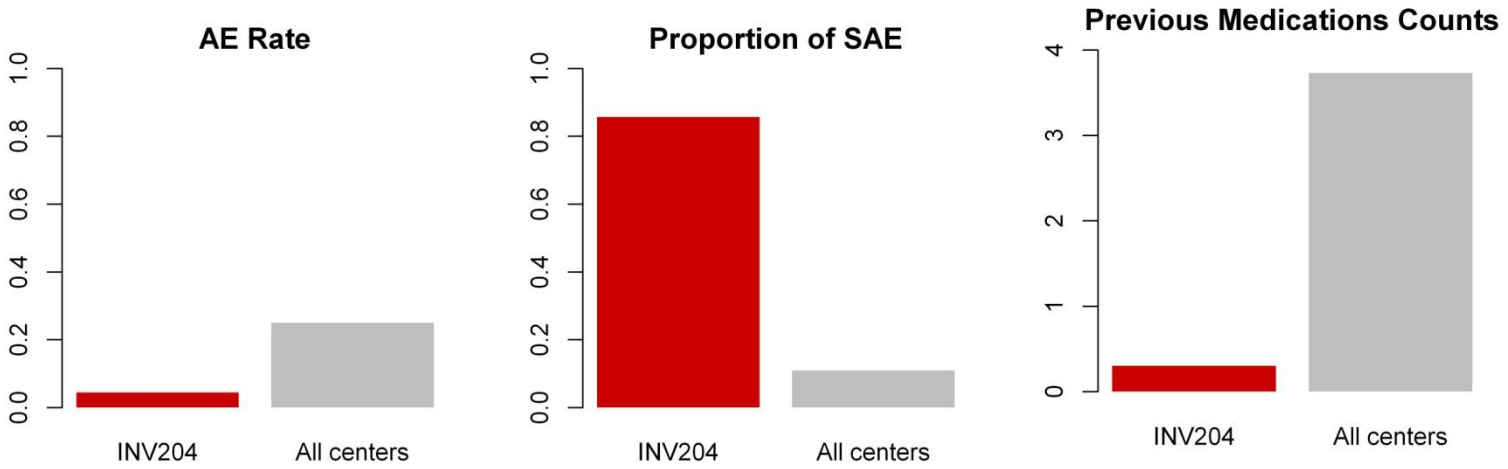
- Over 11000 statistical tests perfomed
- Score flagged INV204 as outlier



Center	Rank	P-value
INV204	1	0.0002
INV164	2	0.005
INV125	3	0.0062
INV25	4	0.0073
INV51	5	0.0078

Case study 1
A trial in infectious disease

- INV204 flagged for tests on event counts and missing values
- Interpretation: underreporting of non serious AE, medication



Case study 2
Vaccination trials

- Two vaccination trials (similar protocol, different target populations)

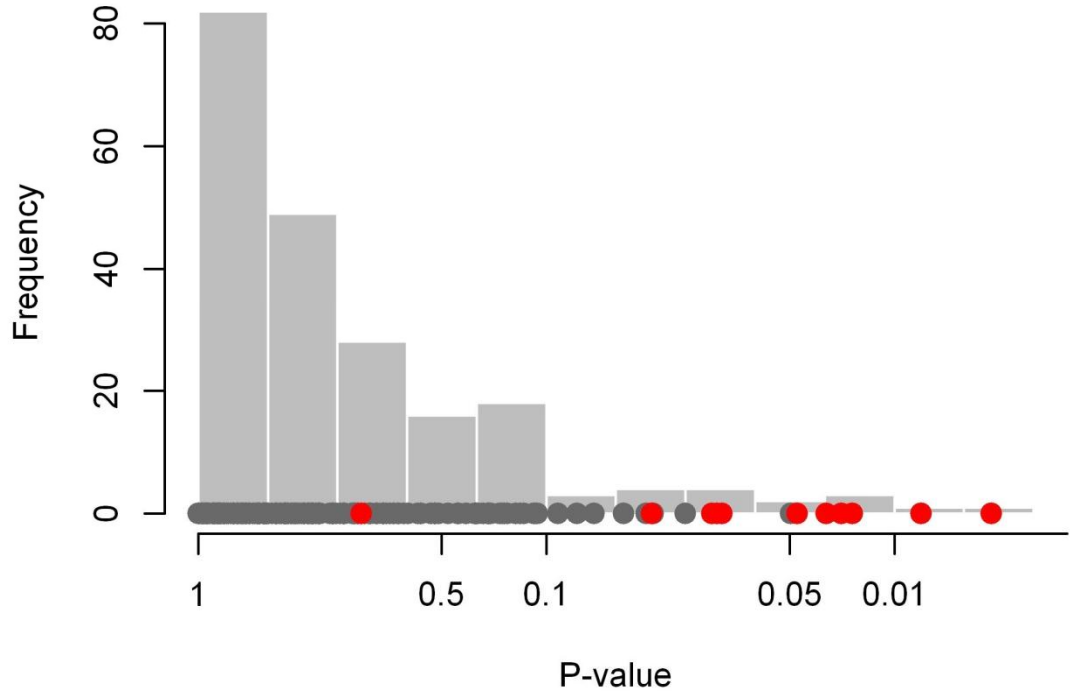
- Over 16 000 patients in each trial

- Early stage of the trials

Case study 2
Vaccination trials

- Test on mean temperature: many centers in country X (red dots) differed significantly

- Explanation: miscalibrated equipment (same lot)



Case study 3
Ophthalmology Trial

- Patients received intra-ocular therapy
- 900 patients
- 60 centers
- Completed pivotal trial

Case study 3
Ophthalmology Trial

Too little variability in the measurement of blood pressure and respiratory rate for almost all patients in one site

Visit	SBP (mm Hg)	DBP (mm Hg)	Respiratory rate
Baseline	130	80	16
Visit 1	130	80	16
Visit 2	130	80	16
Visit 3	130	80	16
Visit 4	130	80	16
…	…	…	…

Conclusion

- Central statistical monitoring provides help to identify problems ranging from quality issues to fraud

- Limitations are related to the availability of data (as with any statistical approach)