AR-04

Finding anomalies and outliers in clinical trial time series data

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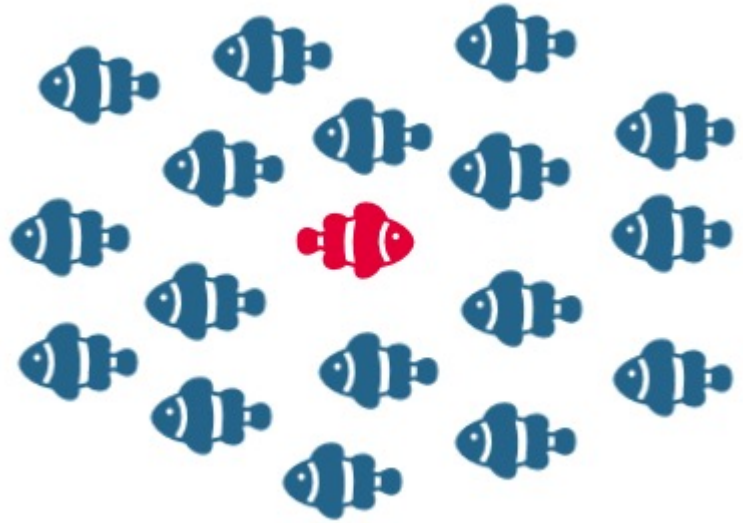


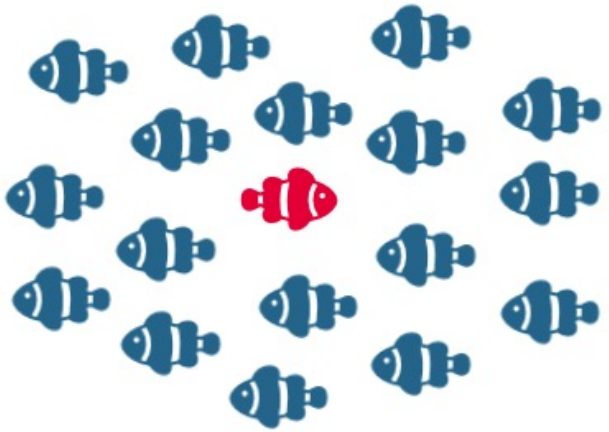
Ensuring the high quality of clinical trials

Motivation

- Trial sponsor is responsible for ensuring the high quality of the data collected
- Examples of sponsor activities
  - On-site visits: e.g. source data verification, review of documents, investigator interviews
  - Central monitoring: e.g. protocol compliance review. Have the visits been taken at correct intervals? Were inclusion and exclusion criteria met?
  - Central *statistical* monitoring: analysis of results collected at the site to identify anomalies and outliers.

- Data is reviewed regularly as the study is on-going.
  - Certain errors can be corrected by site, e.g. data entry errors.
  - If a systematic bias at a site is identified early enough, the site can be offered additional training to ensure compliance.
  - Fraud performed by site can lead it to be excluded from the study.

- In this talk, I will present an internally developed tool for flagging sites and subjects with anomalous time series.

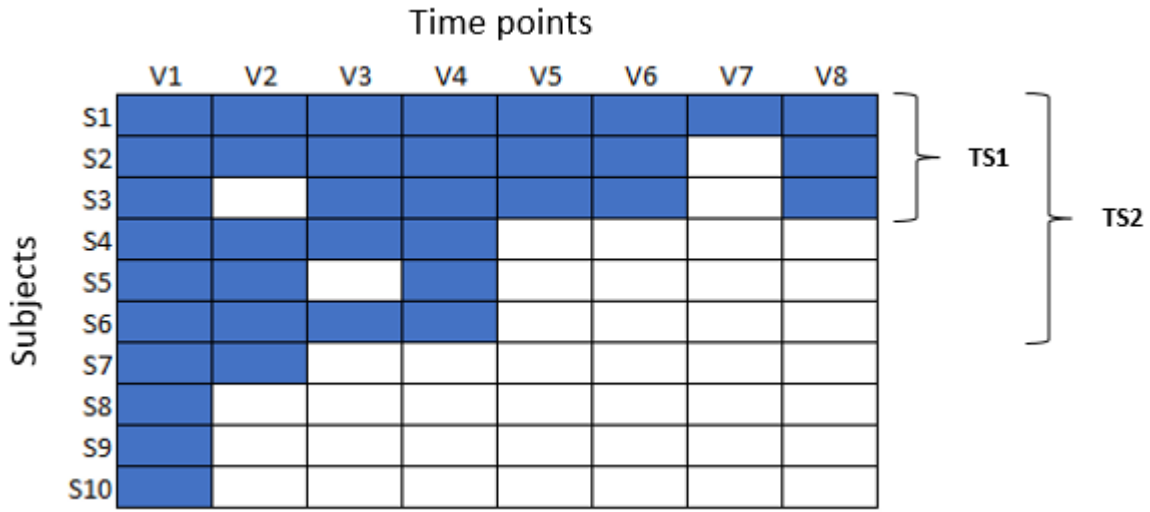


Talk agenda

- **Time series**
  - Definition
  - Time series features
- Flagging sites
- Identifying individual subjects with anomalies
- Implementation
- Ideas for further development

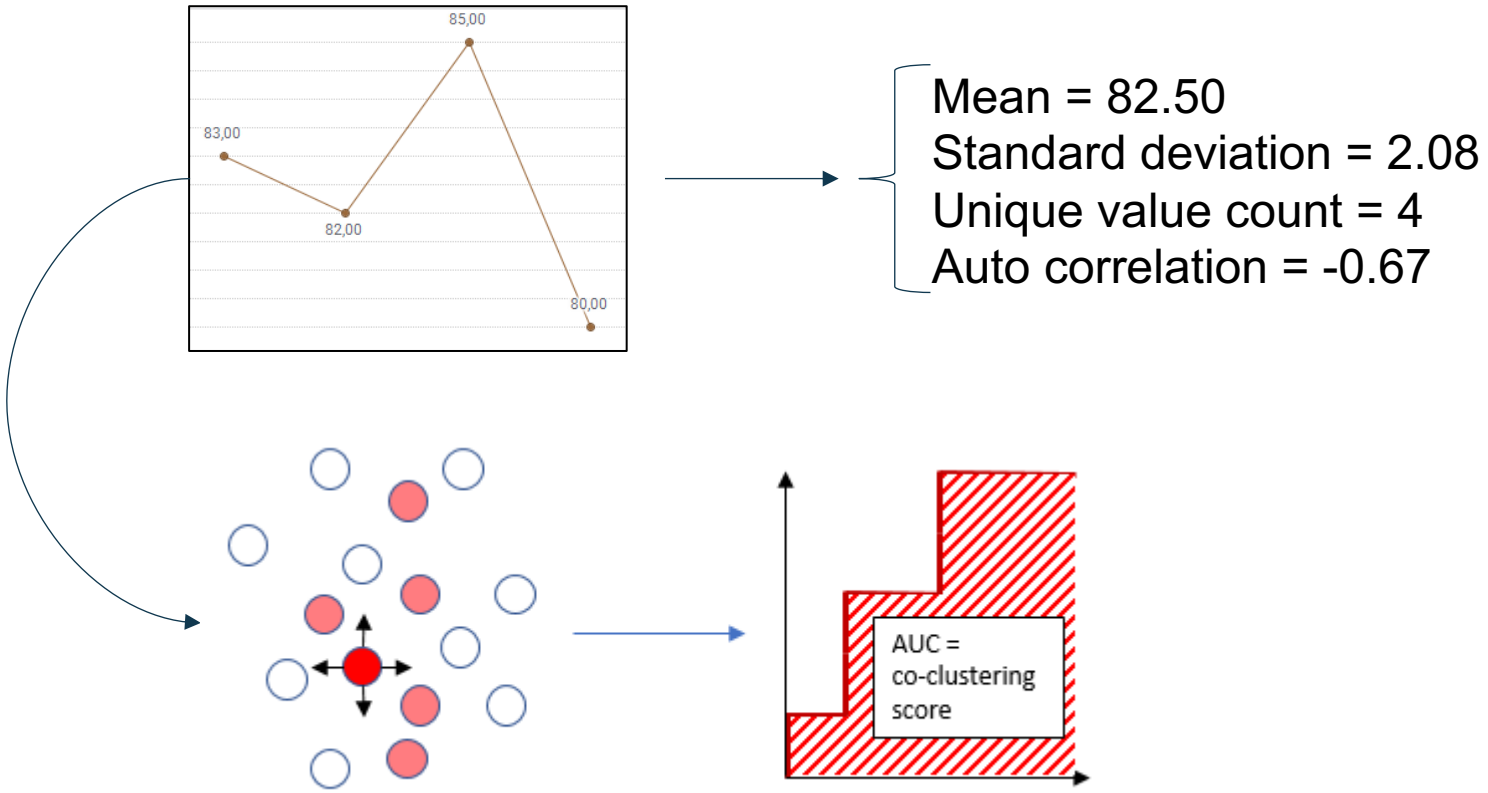
Defining a time series

- Time series is a sequence of time points where a parameter of interest has been measured.
  - At least three time points.
  - Subjects with at most 30% missing are included in the time series.
  - Time series must be non-redundant and have at least 30 eligible subjects.
- More than one time series might be defined per parameter.



Time series features

For each time series, a set of features is calculated.



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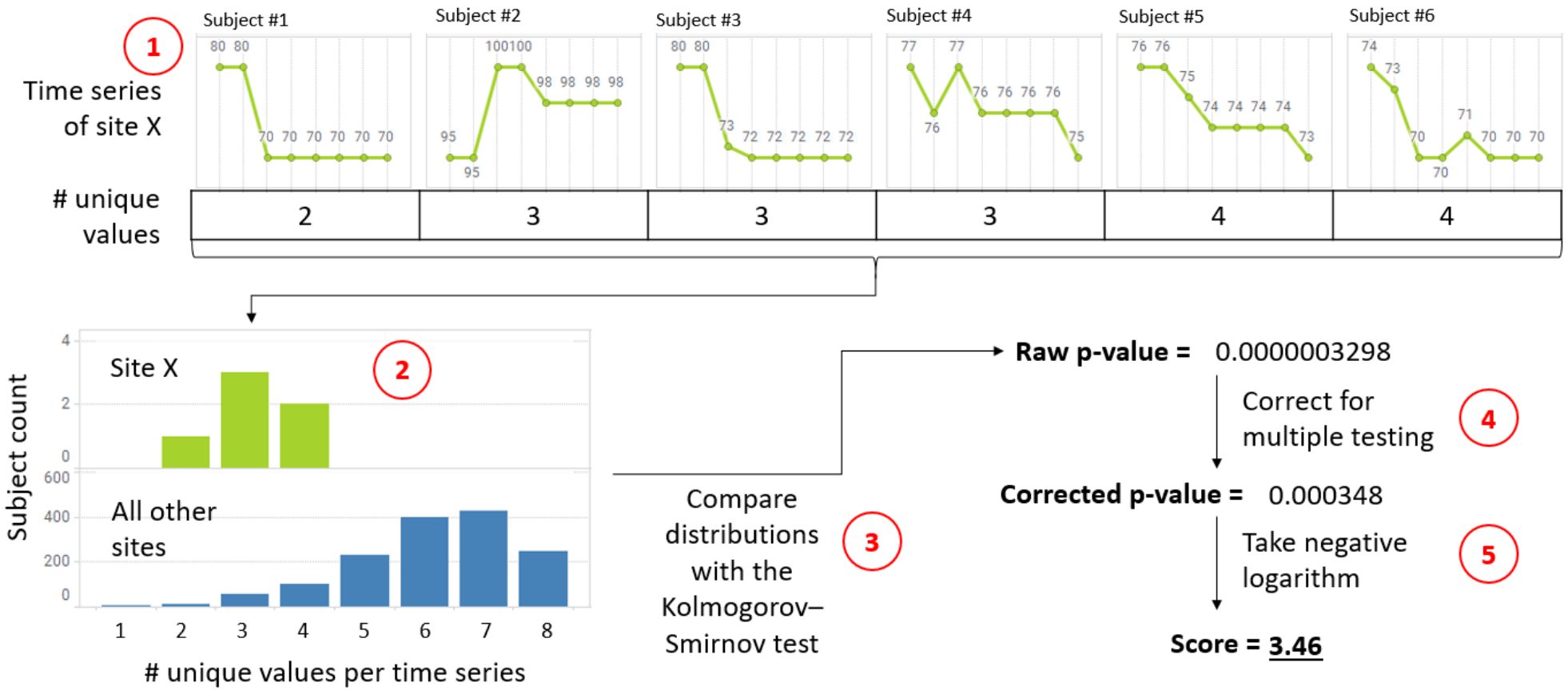
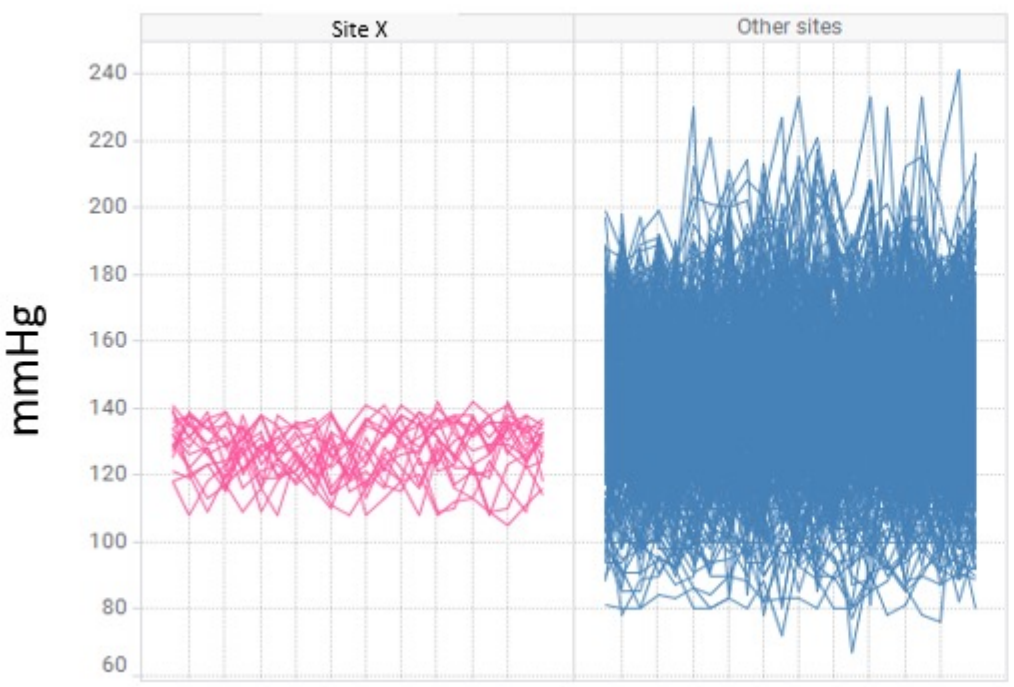
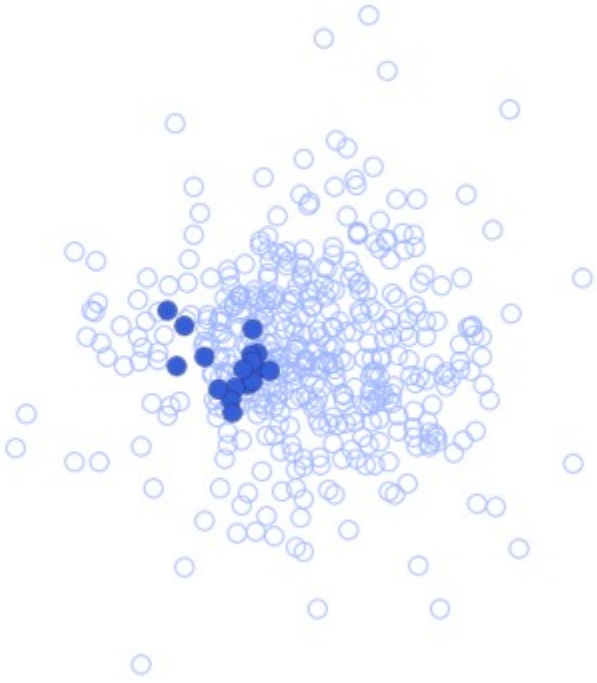
Flagging sites



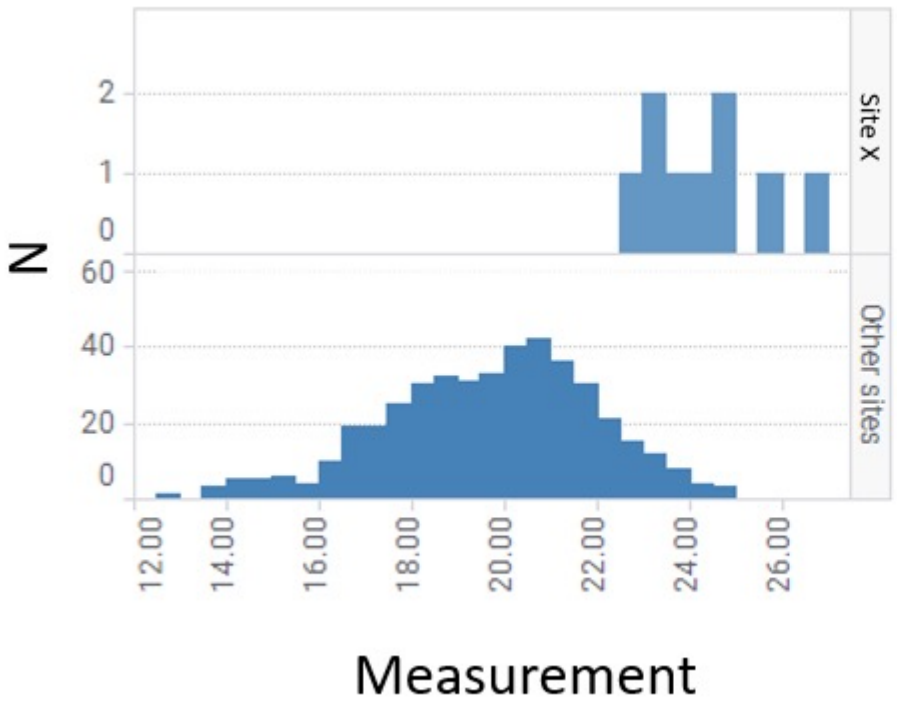
Site with co-clustered blood pressure profiles





Potential reasons: result fabrication, “sample” splitting, bias in subject selection

Site with high time series averages



Potential reasons: bias in subject selection, in-correct assay calibration (local labs), errors in sample handling (central labs)

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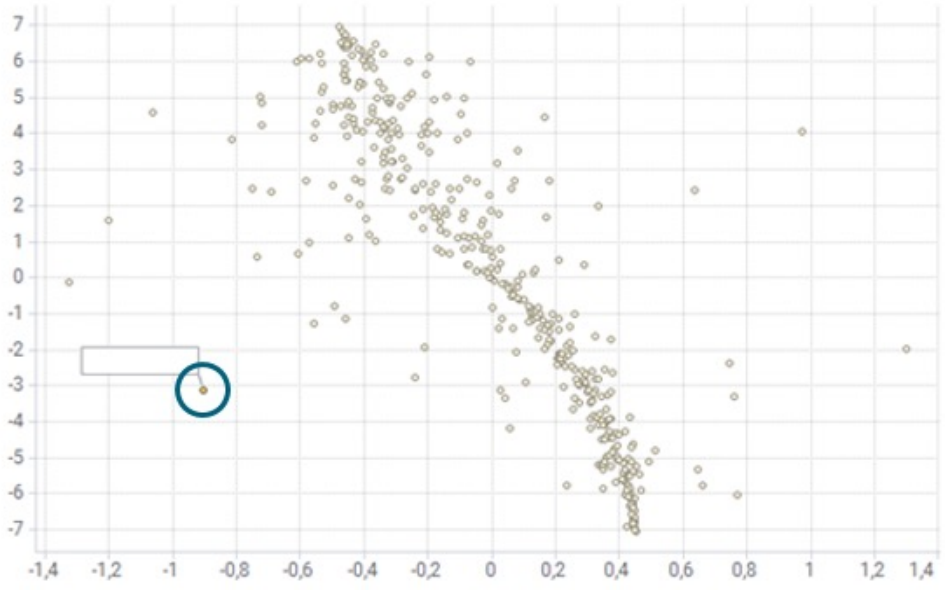
Identifying individual outliers

Also individual time series might be outliers although the site as a whole does not raise alarms.

Example: an “interesting” weight profile.

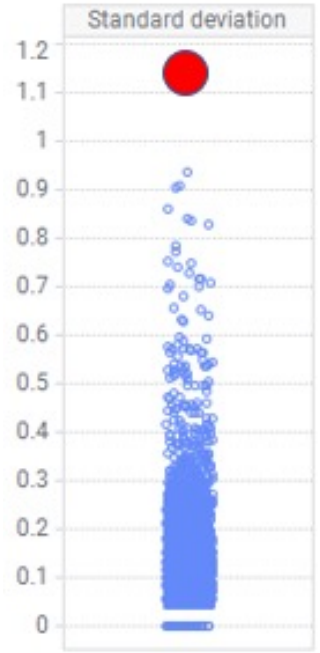
The outlier time series below is due to a data entry error.



Identifying individual outliers

Extreme time series feature values can indicate anomalies.

Large deviation seen below might not be due to misconduct at site but this could be interesting due to a potential safety issue.



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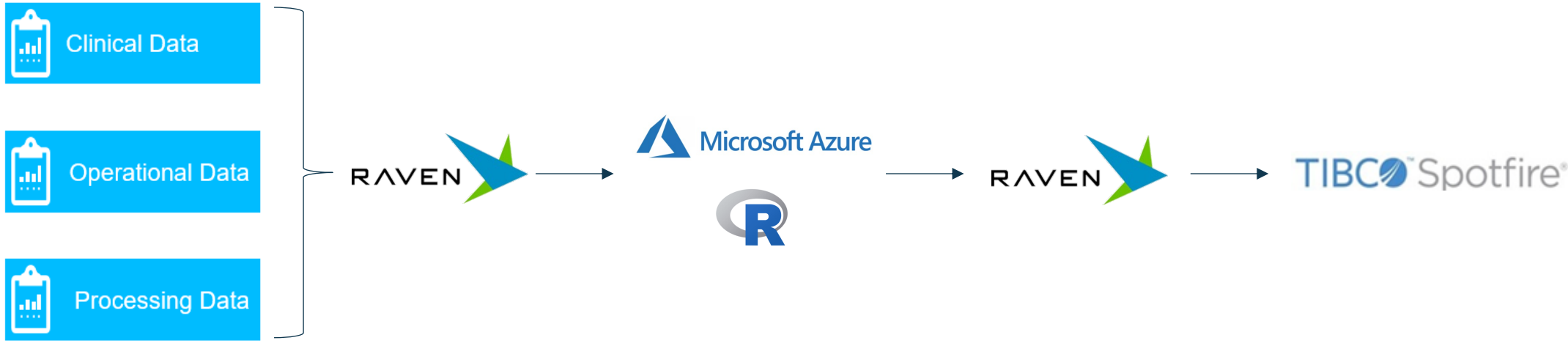
- **Implementation**
- Plans for further development

Implementation

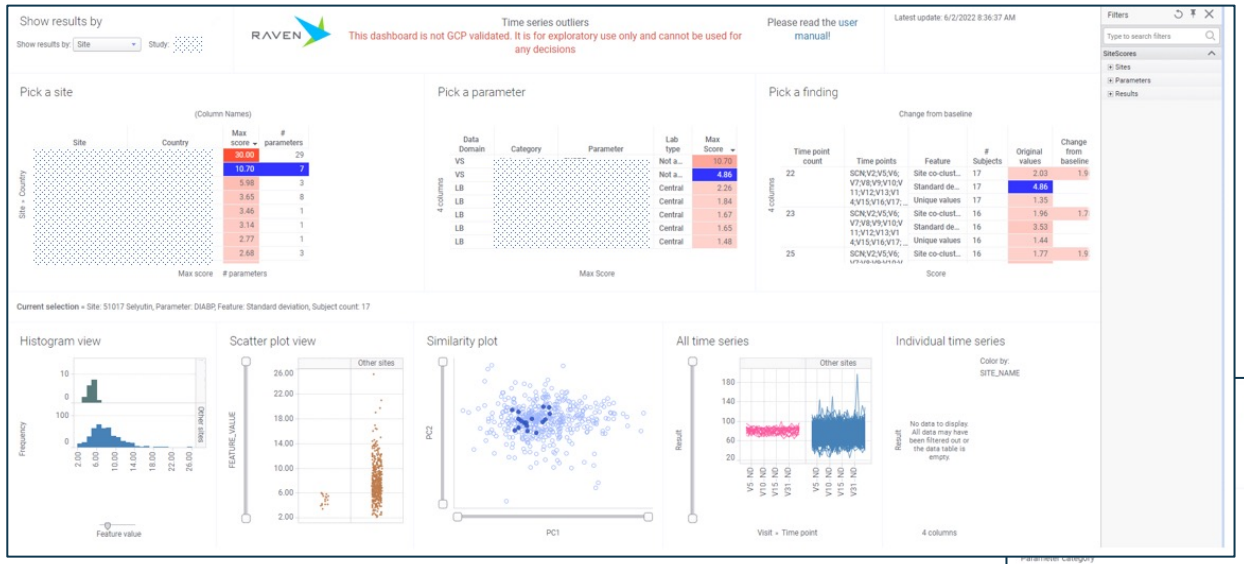
Calculation backend

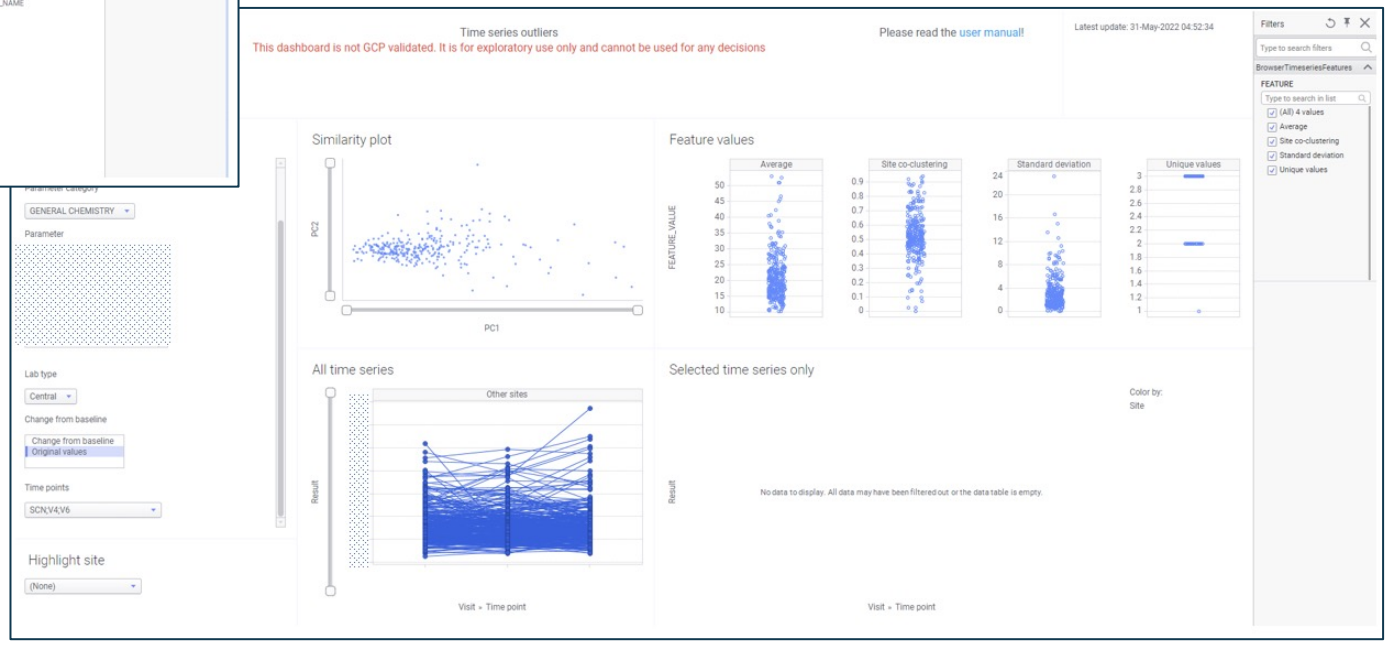


RAVEN = internally developed data warehouse for clinical trial data

Implementation

Dashboard



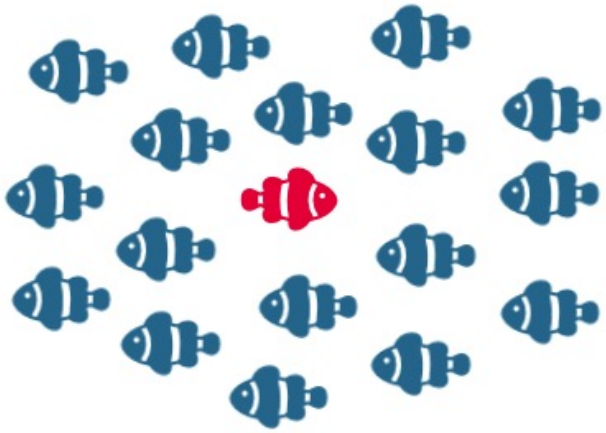


Implementation

Where is it used?

- The dashboard is available for all our on-going studies and is accessible by the study teams.

- So far, it has been used to…
  - support site inspections
  - perform regular data review
  - support planning for new studies



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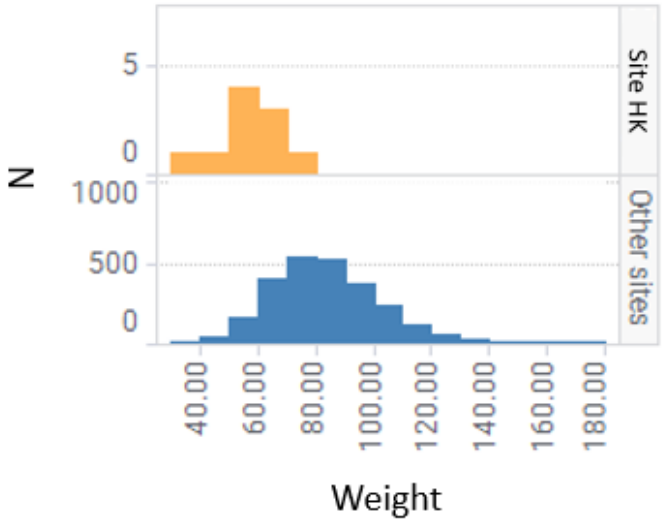
Plans for further development

Controlling for local population characteristics

- In global studies, the general local population characteristics can lead to a site getting flagged.
  - In the current version, a site is compared to all sites globally. In some cases, sites from the same part of the world might be a better context.

Site in Hong Kong flagged due to a bias in subject average weights. However, the site average is close to the general adult weight in Asia.



Region	Adult population (millions)	Average weight
Asia	2,815	57.7 kg (127.2 lb)
Africa	535	60.7 kg (133.8 lb)
World	4,630	62.0 kg (136.7 lb)
Latin America and the Caribbean	386	67.9 kg (149.7 lb)
Europe	606	70.8 kg (156.1 lb)
Oceania	24	74.1 kg (163.4 lb)
North America	263	80.7 kg (177.9 lb)

Plans for further development

- Improve the sensitivity for identifying anomalies in small sites.
- Add additional data domains such as questionnaires/PROs.
- E-mail alerts when a site gets flagged.
- Potentially, we will co-develop the tool further within the IMPALA consortium.

Acknowledgements

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