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# Detecting counterfeit data in clinical trials

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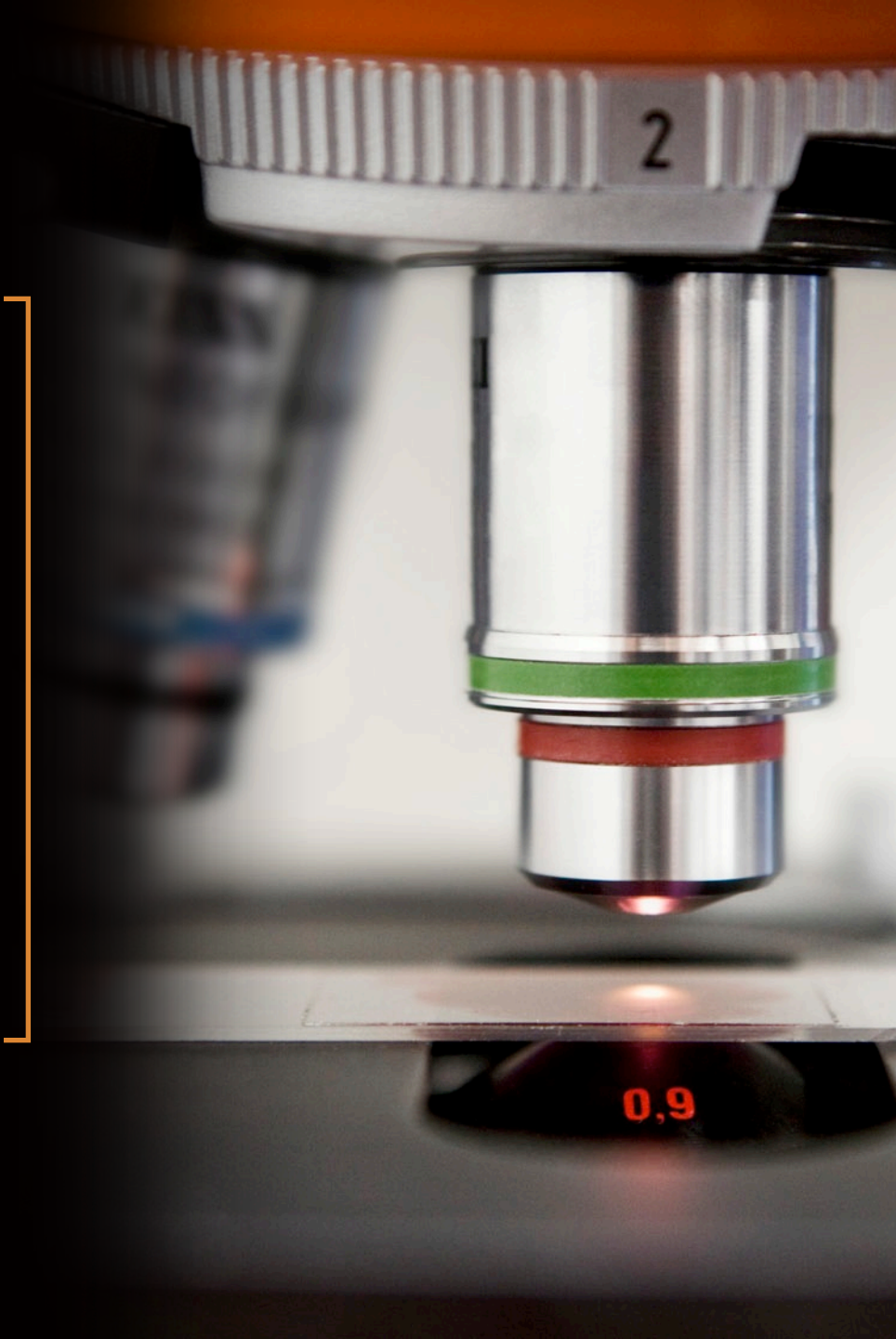


# Disclosures

Support of this presentation was provided by AbbVie. AbbVie participated in the review and approval of the content.

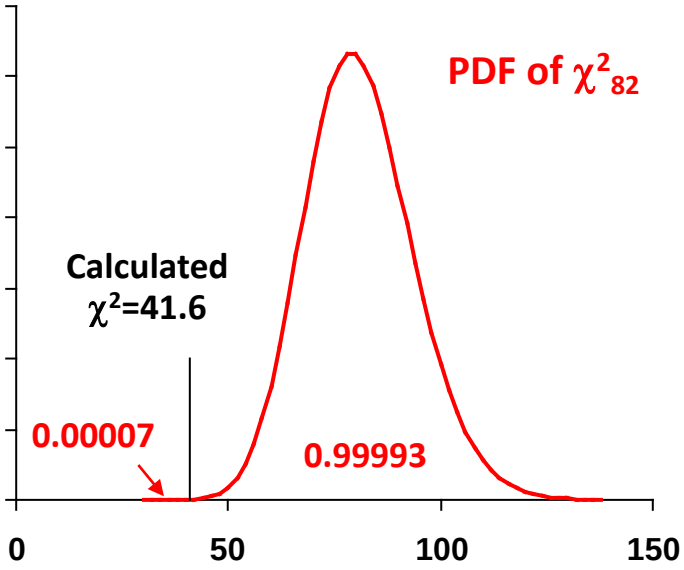
Martin King is an employee of AbbVie, Inc.

# The long history of falsified data

Ptolemy, Galileo, Newton all accused of scientific misconduct

R.A. Fisher (1936) re-analysis of Mendel's data

- Observed frequencies agreed too closely with expected
- "Assistant who knew too well what was expected" ?
- "Fictitious data can seldom survive a careful scrutiny, and, since most men underestimate the frequency of large deviations arising by chance, such data may be expected generally to agree more closely with expectation than genuine data would."



# Outline

Fraud in clinical research

- Deliberate falsification/fabrication of data
- Rare but potentially serious problem

Investigating suspicious data

- Role of the statistician
  - Case studies 1 and 2: Investigating data in multi-center clinical trials
  - Case study 3: Fallout from disclosure of fraud in a multi-center clinical trial

- Some statistical tools

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# CASE STUDY 1

# Case study 1

International, multi-center study

Quality assurance contacts Biostatistics department with open-ended request to look into data at Site Y

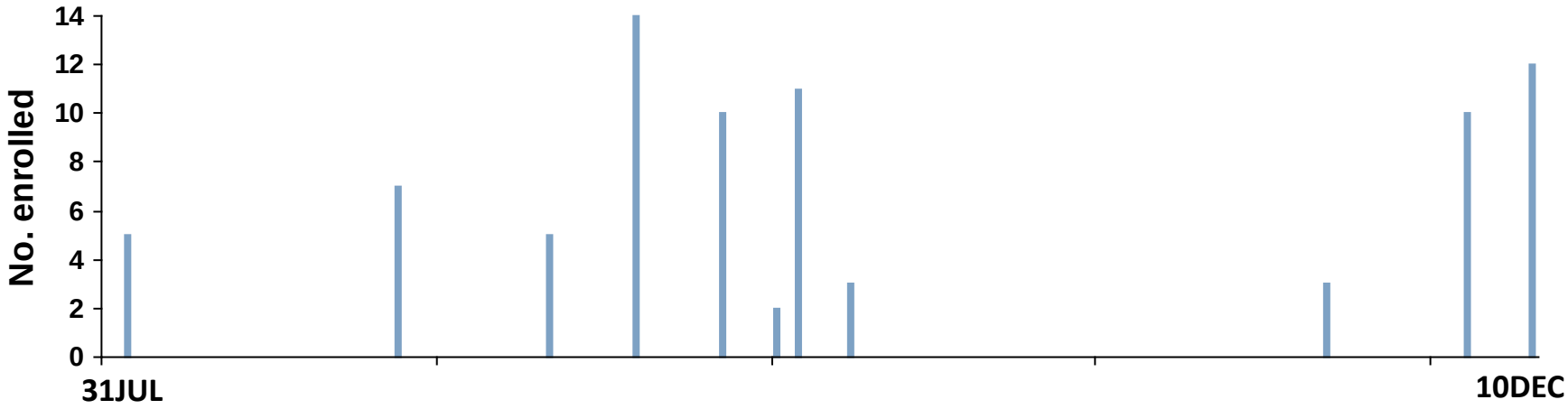
- What next?

# Case study 1 – subject enrollment

Site Y noted to be one of the highest enrolling sites

Always enrolled multiple subjects

- Not necessarily unusual, but allows possibility of creating fictitious data




Dropouts:

- No dropouts during lead-in (vs. 10% d/c at other sites)
- No dropouts over 6-10 months on study (vs. 13% annualized d/c rate at other sites)

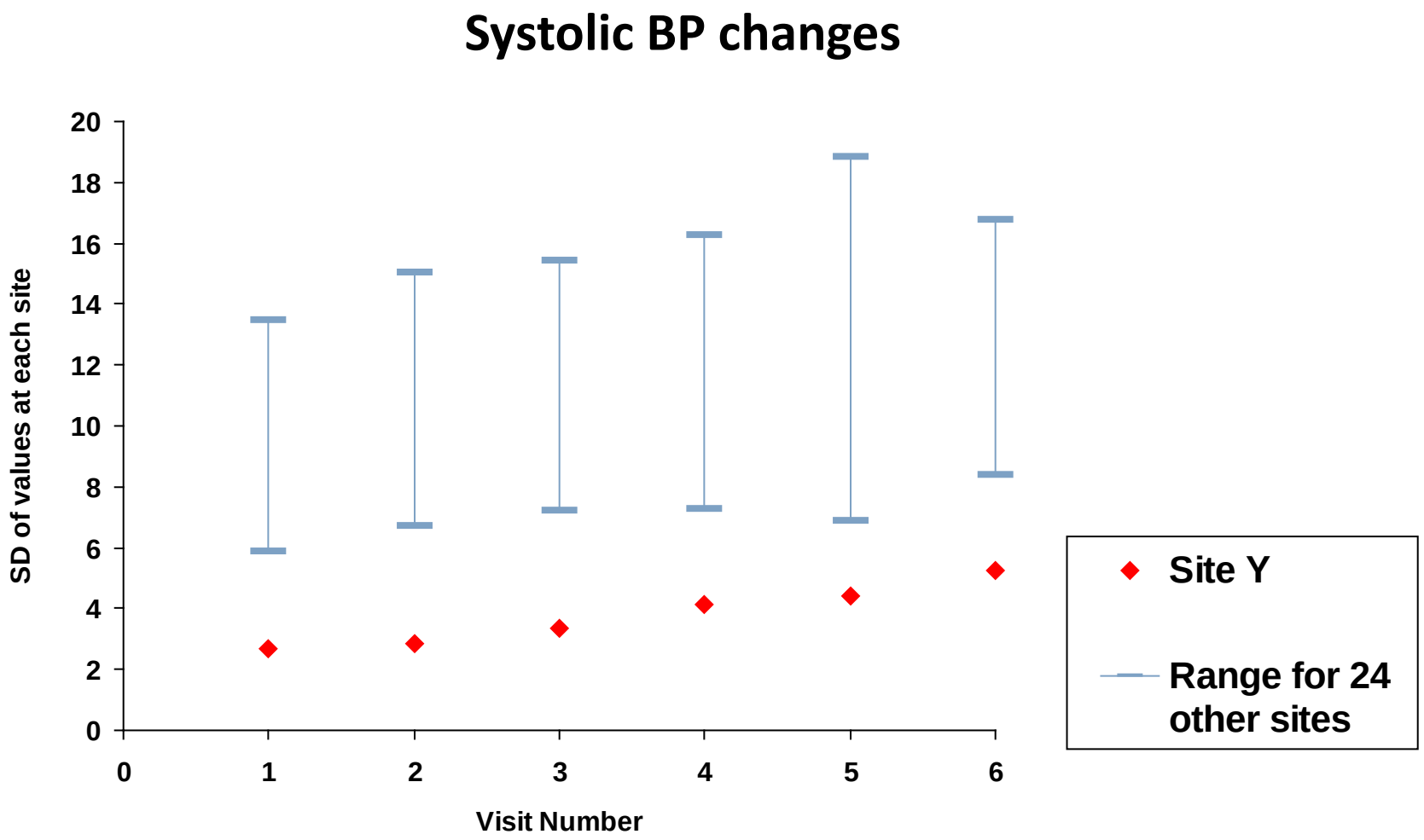
# Case study 1 – variability of site-measured data

Site-measured data (e.g., vital signs) theoretically easiest to fake

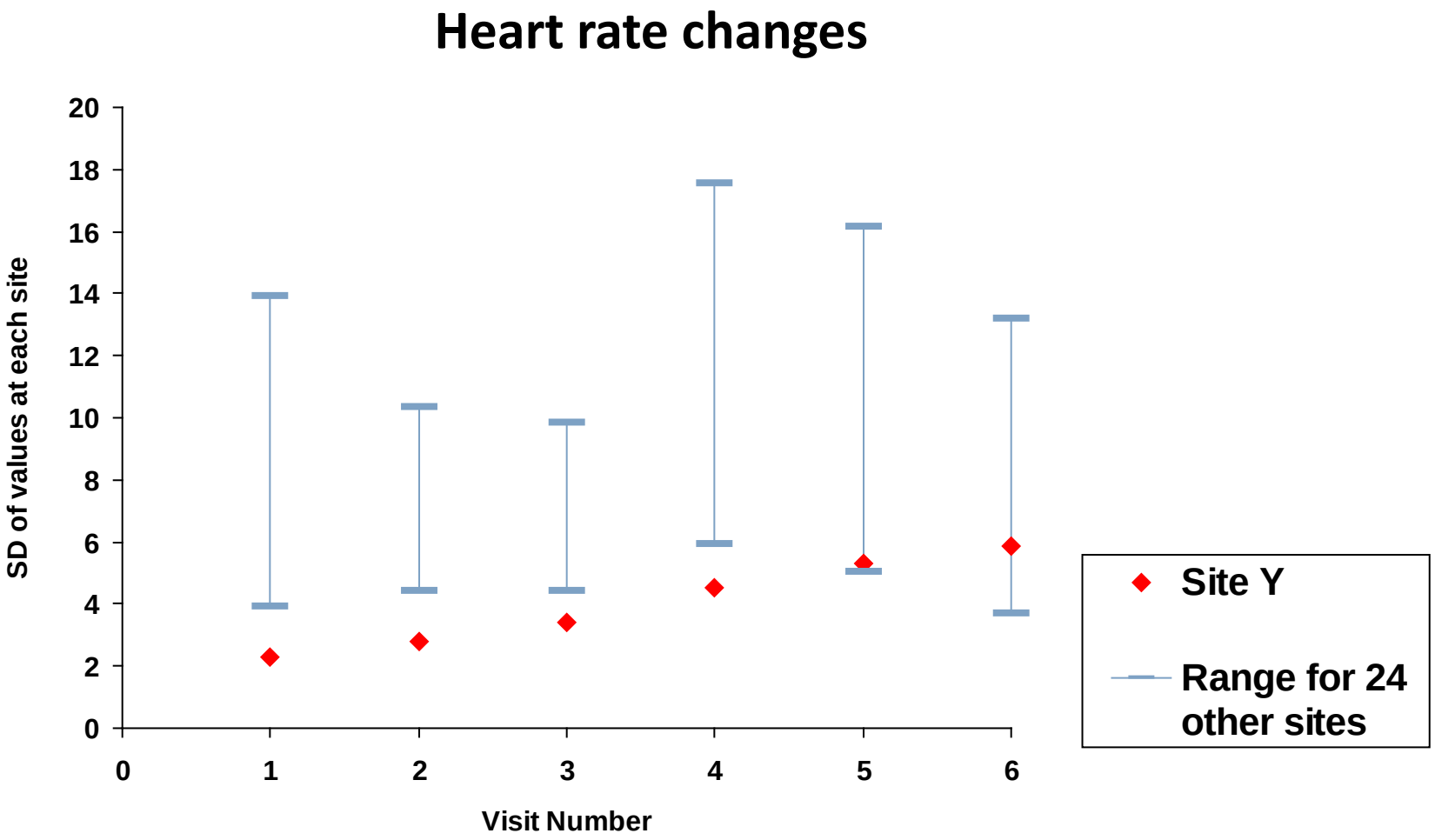
Variability in change from baseline data at Site Y assessed and compared vs. that of 24 other sites

- Systolic BP
- Heart rate
- Weight

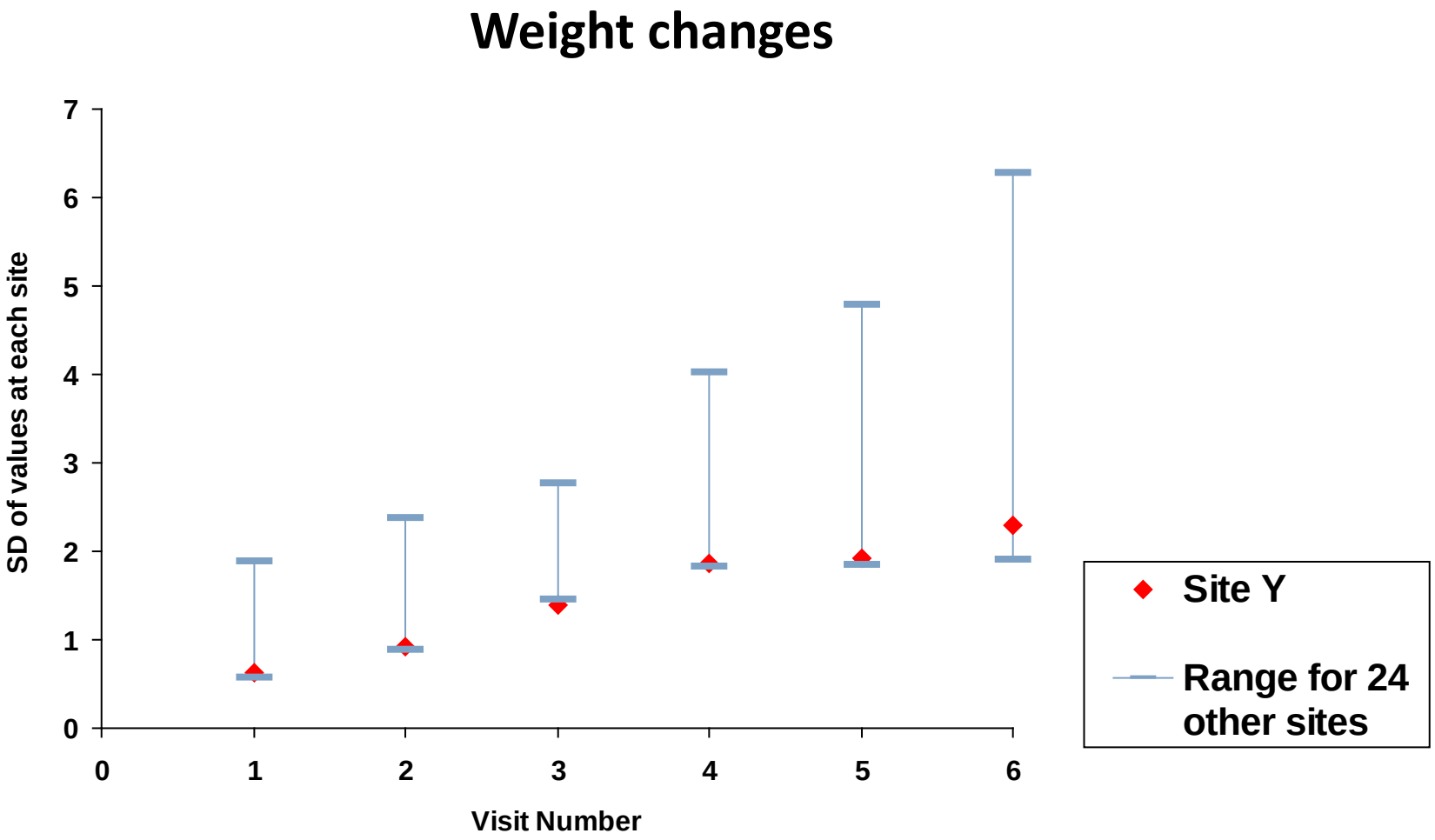
# Case study 1 – variability of site-measured data



# Case study 1 – variability of site-measured data



# Case study 1 – variability of site-measured data

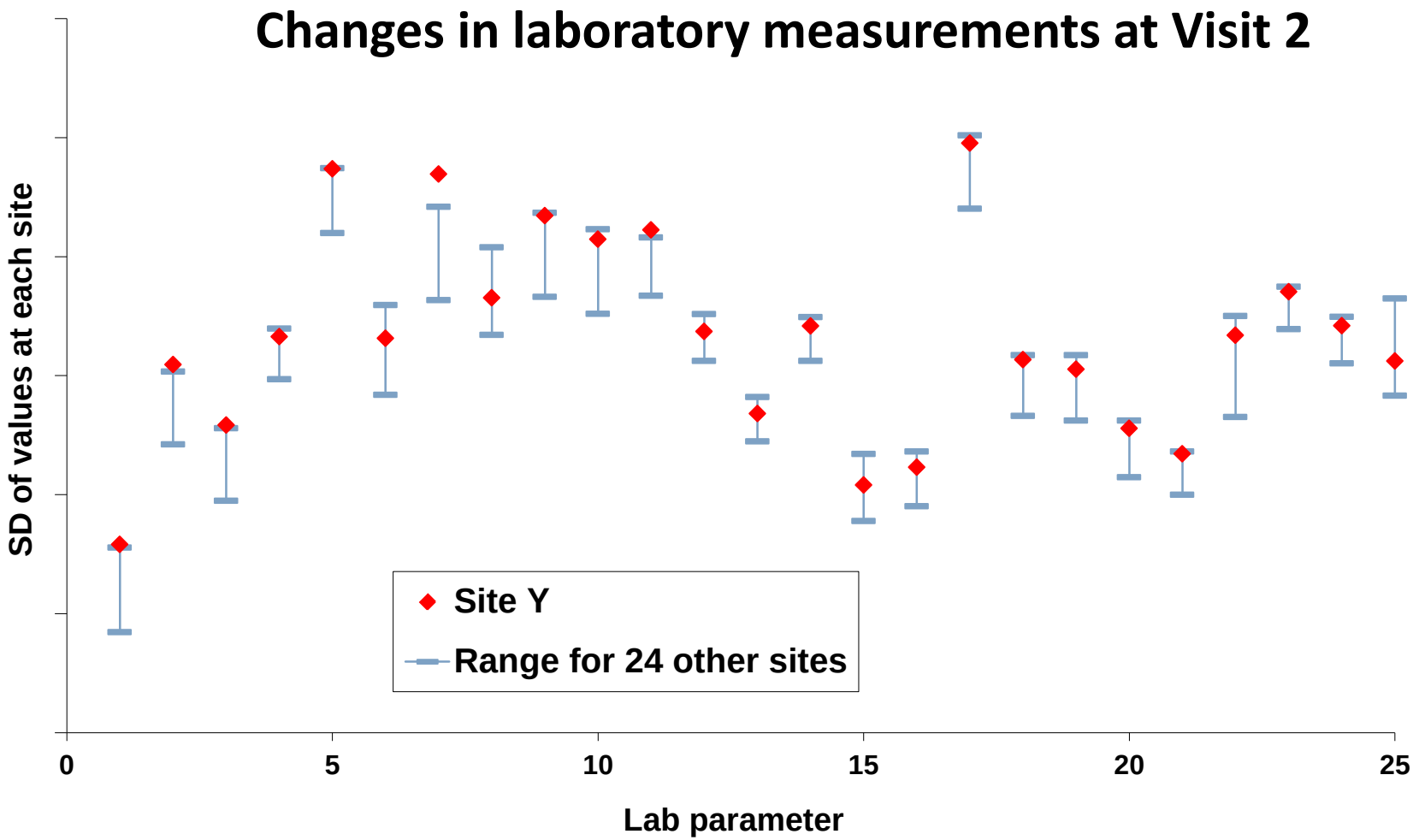


# Case study 1 – variability of lab-measured data

Laboratory values presumably more difficult to falsify directly (measured by central lab)

- For a single visit, variability of lab changes from baseline assessed and compared vs. other sites
- For each sampling date, lab data searched for (nearly) identical values

# Case study 1 – variability of lab-measured data



# Case study 1 – summary

## Repeatedly lower variability of site-measured data

- Consistent with concept that it is difficult for made-up data to have sufficiently large variability

## Repeatedly higher variability of laboratory value changes

- Speculation: assuming within-subject lab values are correlated, poor matching of baseline and visit data samples by the site could result in larger-than-expected variability

## On several dates, lab results from different subjects nearly identical

## Result

- Re-audit of site inconclusive; site request to enroll more subjects denied
- Sensitivity analyses excluding data from Site Y performed

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# CASE STUDY 2

# Case study 2

International study, 33 sites

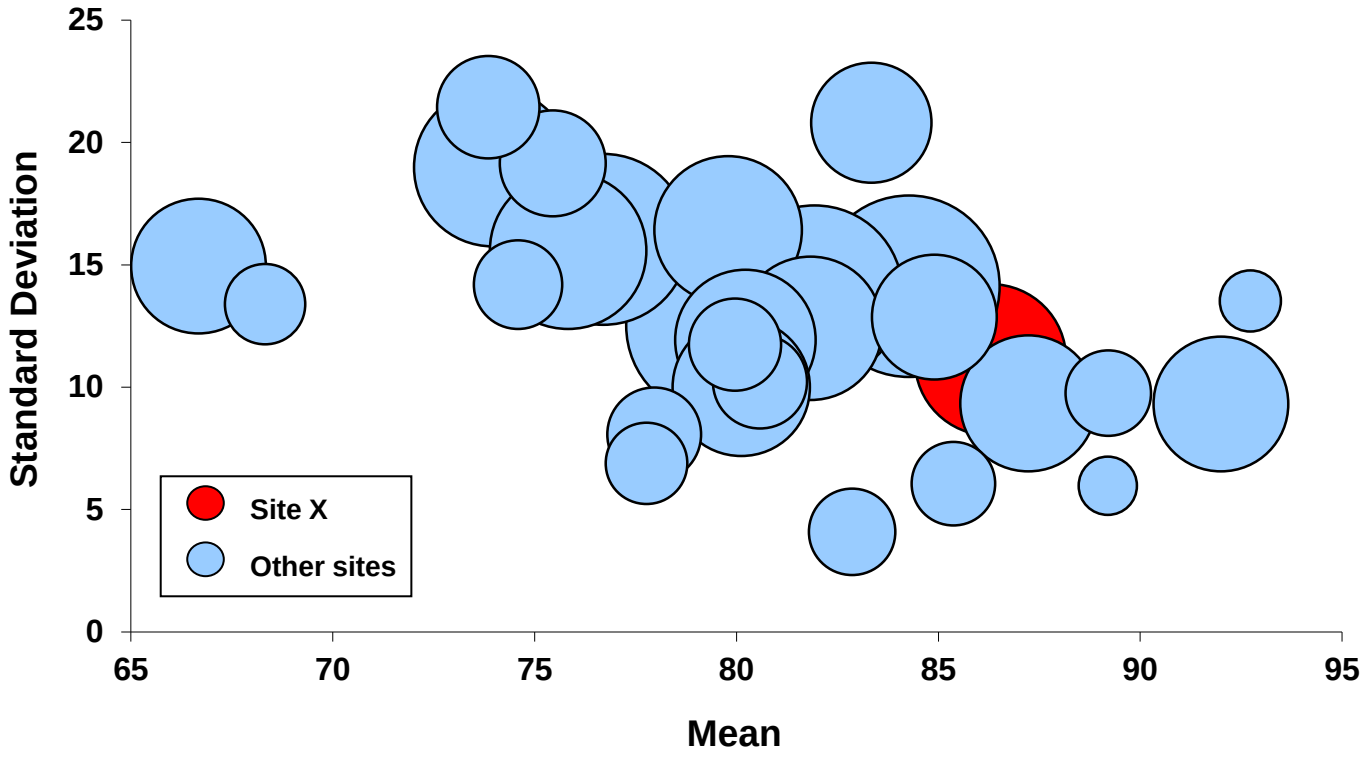
Quality assurance department contacts project statistician with request to assess data from the site

- Concerns about data from a subject-completed questionnaire
  - Key question: “How would you rate your current state of health from ‘0’ to ‘100’?”

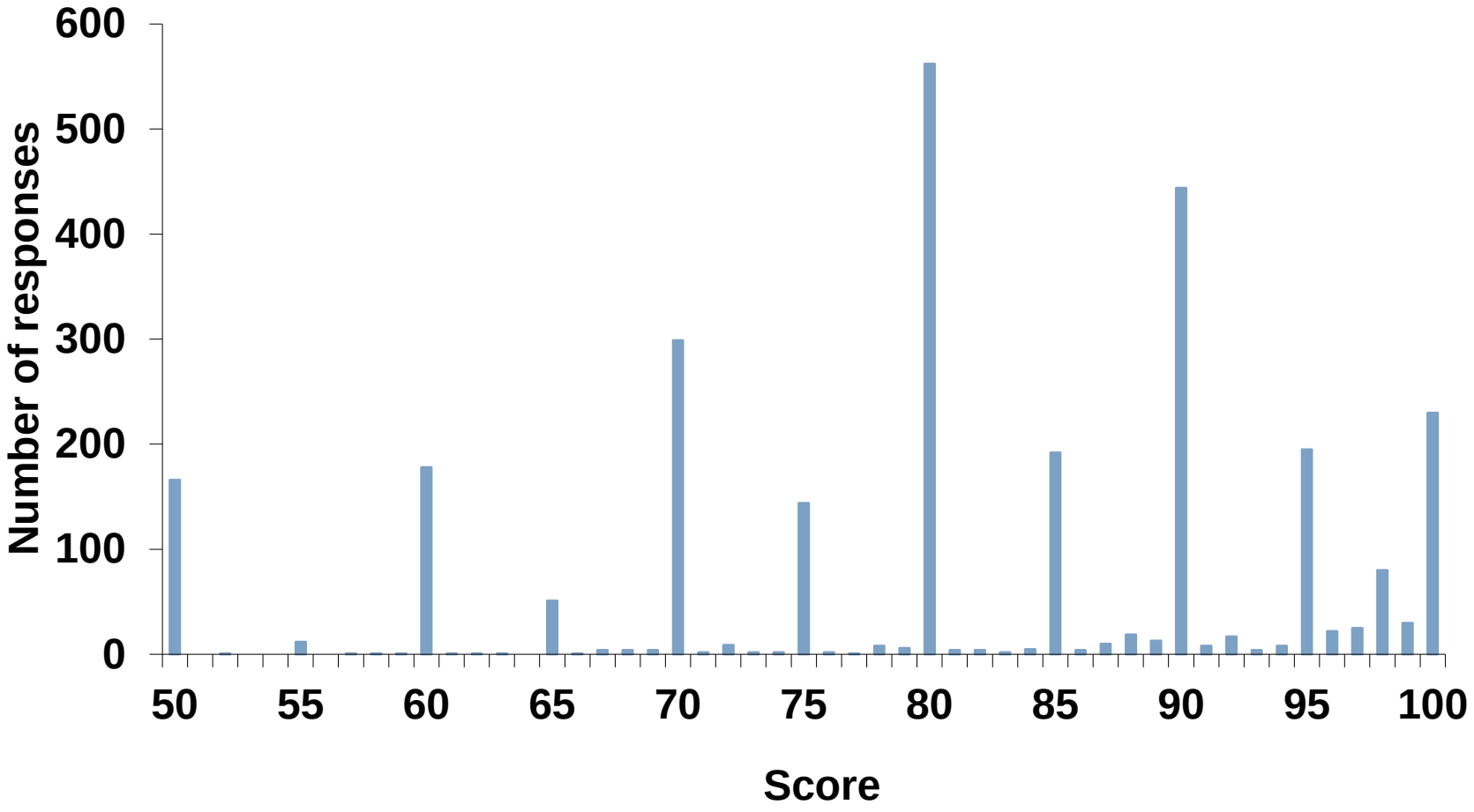
- What next?

# Case study 2 – global health state question

Site X had somewhat higher values than most sites, but neither mean nor standard deviation appear to be outliers

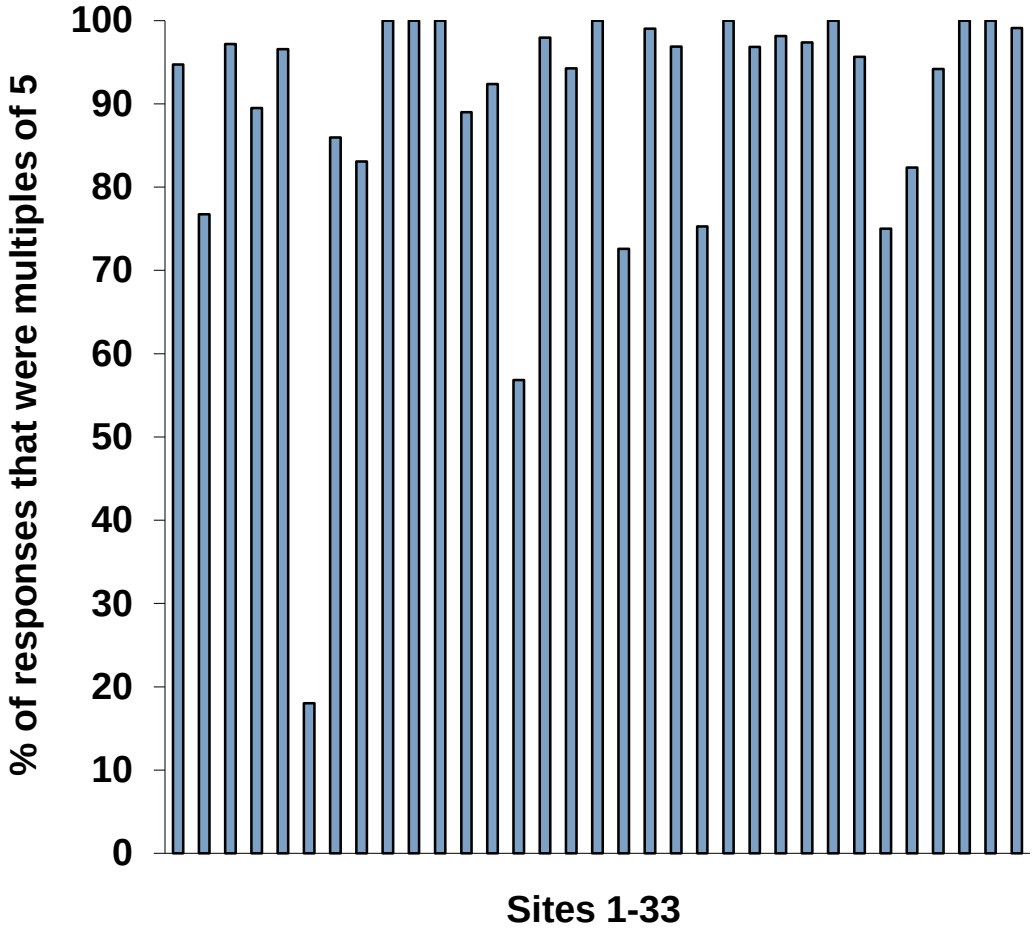


# Case study 2 – How would you rate your current state of health from 0 to 100?



# Case study 2 – What % of responses were multiples of 5?

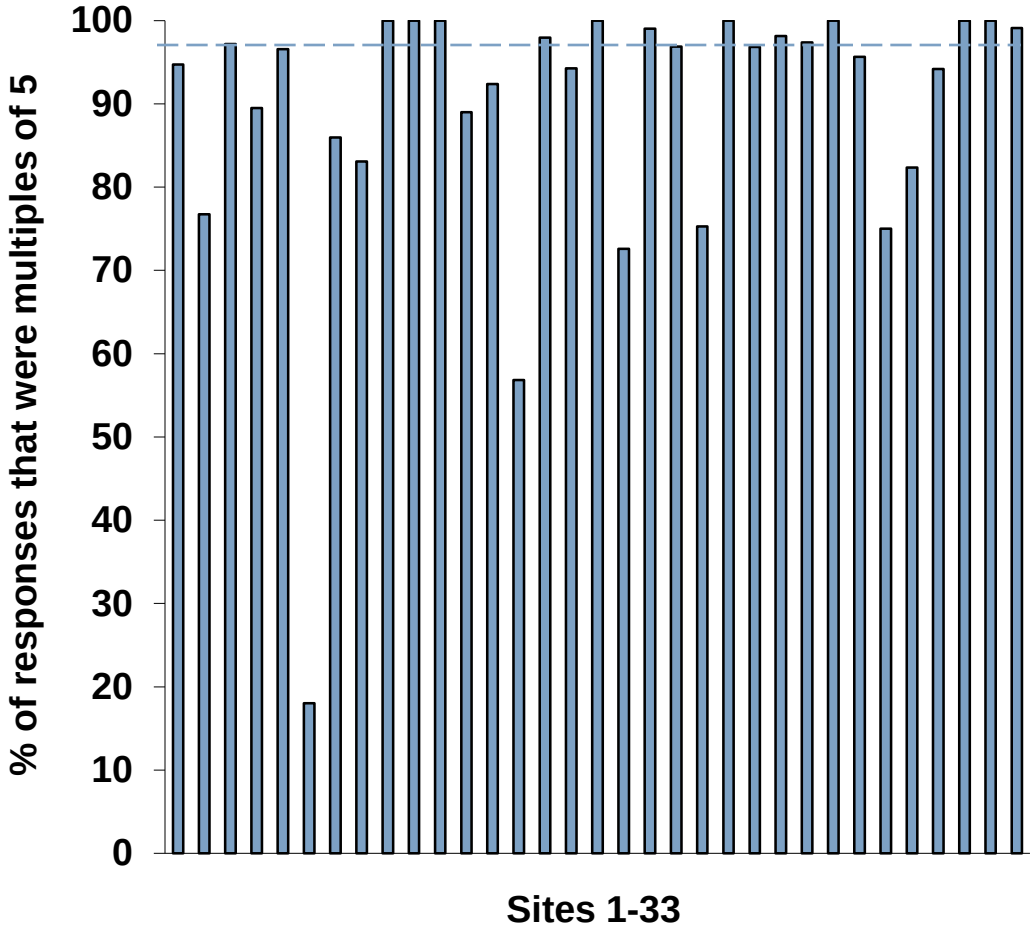
Overall, 89% of responses were multiples of 5



# Case study 2 – What % of responses were multiples of 5?

Overall, 89% of responses were multiples of 5

Among the 33 sites, median % of responses that were multiples of 5: 97%

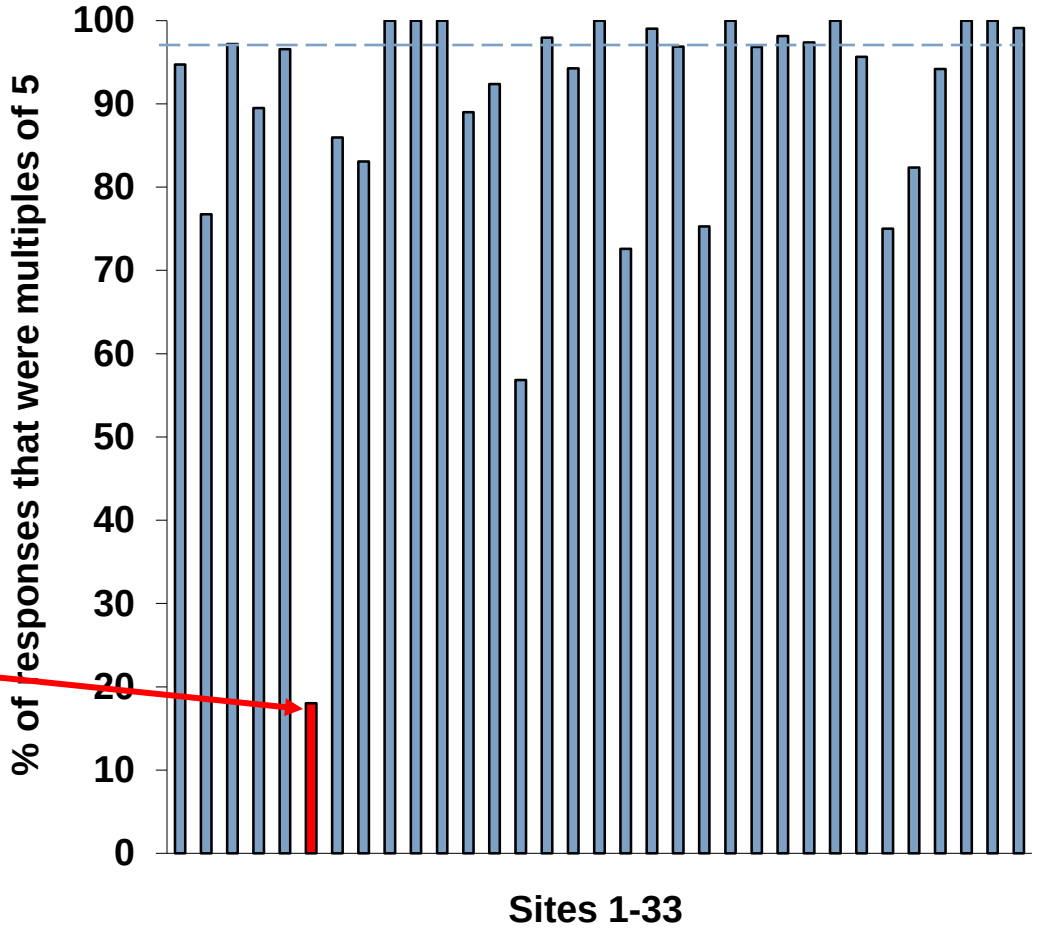


# Case study 2 – What % of responses were multiples of 5?

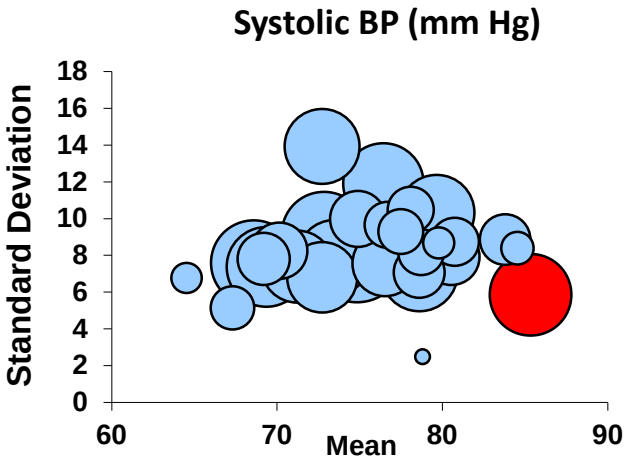
Overall, 89% of responses were multiples of 5

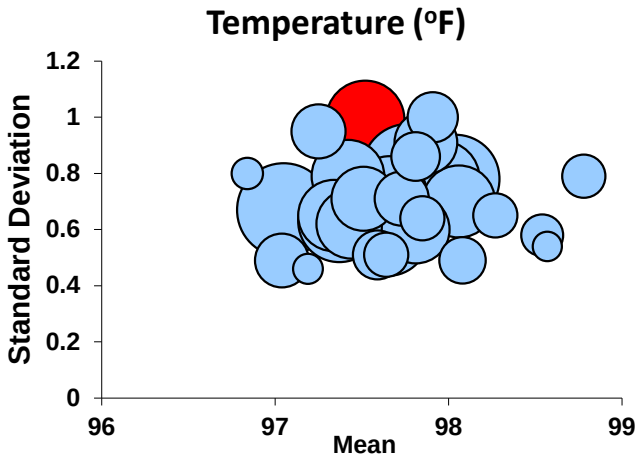
Among the 33 sites, median % of responses that were multiples of 5: 97%

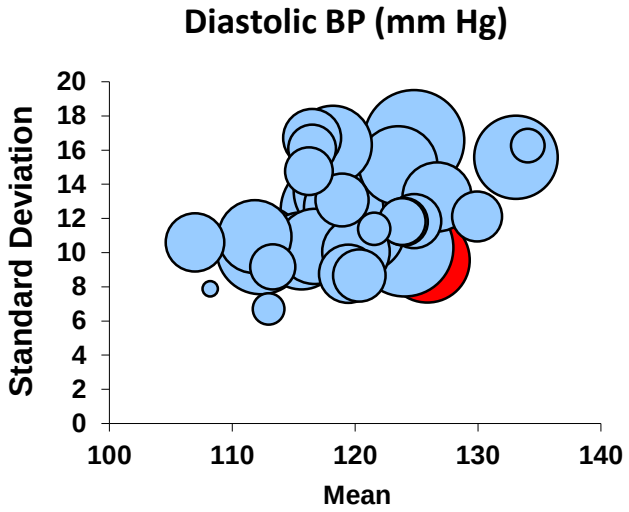
At Site X, 16% of responses were multiples of 5

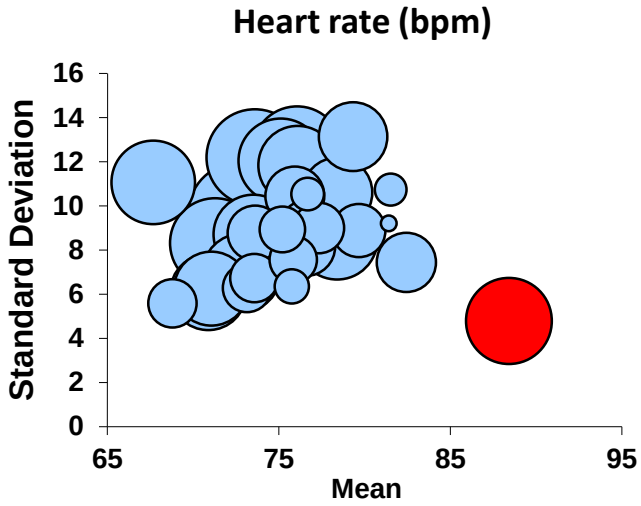


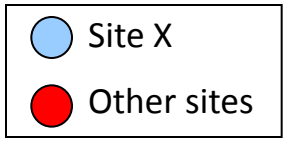
# Case study 2 – site-measured data



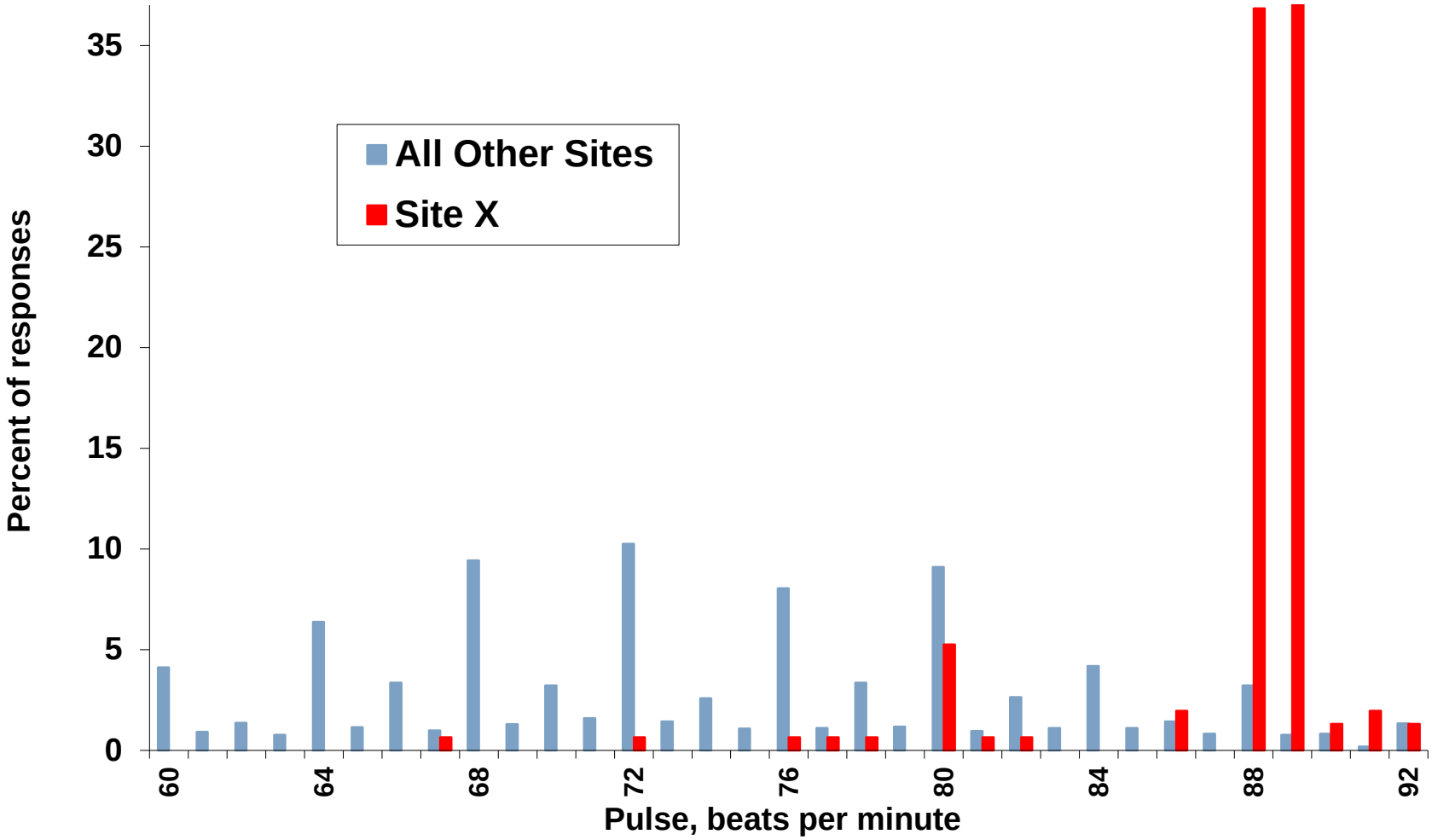



# Case study 2 – distribution of heart rate data



# Case study 2 - summary

Obvious separation between Site X and other sites on global health state question

Unusual site-measured data, particularly heart rate

Result

- Site X shut down subsequent to QA audit
- CSR included sensitivity analyses excluding data from Site X

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# CASE STUDY 3

# Case study 3 – Why worry?

Safety study of Ketek (n=24,000)

- Jan 2002: Sponsor “uncomfortable” with highest-enrolling site (Site Z, n=407), requires “additional monitoring”

- Feb 2002: CRO noted to sponsor:
  - Lack of “proper diagnosis for an appropriate medical condition”
  - “Very limited” medical charts
  - Lab results “suspiciously similar” for multiple patients
  - Subjects enrolling during lunch when office closed

- Mar 2002: Sponsor statistician internal report:
  - Lab results for Site Z “consistent” with other top enrollers, “systematic pattern [of fraud] is unlikely”

# Case study 3 – Why worry?

- July 2002: Sponsor submits study to FDA without mention of any problems with Site Z
- Fall 2002: FDA conducts site audits of highest enrollers. At Site Z:
  - Some patients reported never receiving medication
  - Some patients treated for weight loss, not respiratory infections
  - Some patients family and friends of investigator
- Early 2003: AIDAC convenes, concerns about study not mentioned by sponsor or FDA
  - Committee votes for approval
- March 2004: Investigator Z pleads guilty to fraud, 4+ years in prison

# Case study 3 – Fallout

1 May 2006

- WSJ: “Fraud, errors taint key study of widely used Sanofi drug”

- Press Release from Sen. Grassley (R-Iowa): “Grassley slams FDA for citing fraudulent safety study”
  - http://grassley.senate.gov/news/Article.cfm?customel_dataPageID_1502=9696

14 June 2006

- ABC World News Tonight: “Unsafe drug makes it to market?”


**"…many of the test results were faked. And now, there have been some deaths."**


**"'It's a situation where I smell a cover-up.'"**


**"'There's too chummy of a relationship between companies and the FDA. I can say, without a doubt, it should have been withdrawn.'"**

"Unsafe drug makes it to market?" ABC World News Tonight

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# SOME STATISTICAL TOOLS

# Statistical tools for detecting counterfeit data

## Digit preference

- Unnatural affinity for round numbers
- Site X: unnatural aversion to round numbers
- Benford's law: for variables with large enough dynamic range, the probability that the first significant digit is D is $P(D) \sim \log_{10}(D+1) - \log_{10}(D)$

## Date checking

- Visits usually don't occur on weekends! (WEEKDATE function in SAS)
- Memorial Day/Labor Day/Thanksgiving; UK bank holidays

## Mahalanobis distance

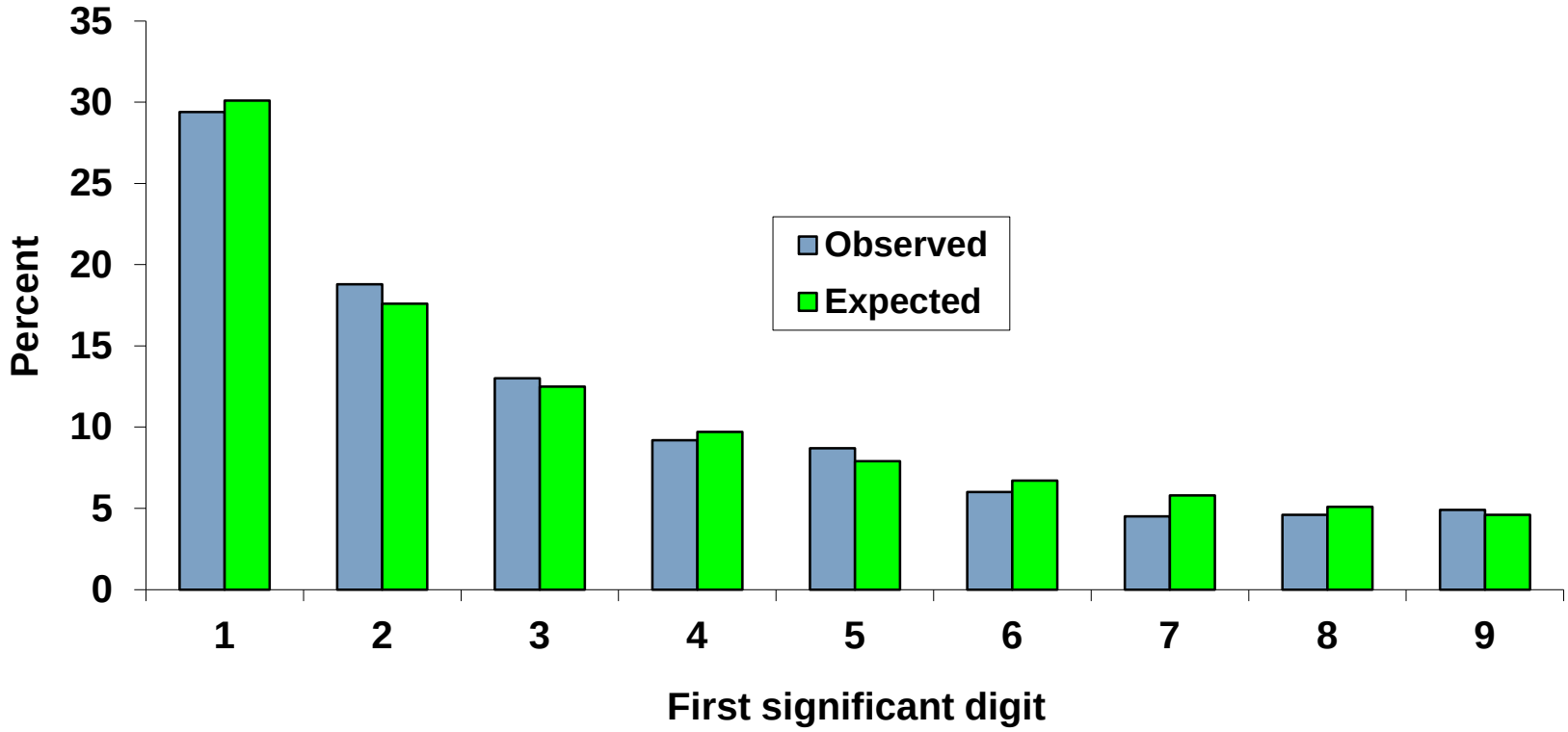
- Detecting multivariate inliers and outliers

## Correlation heat maps for questionnaire data

# Digit preference – Benford's law in action

Baseline viral load (copies/mL) in an HIV study

- (n~600, data range 1000 to ~6,000,000)



# Mahalanobis distance

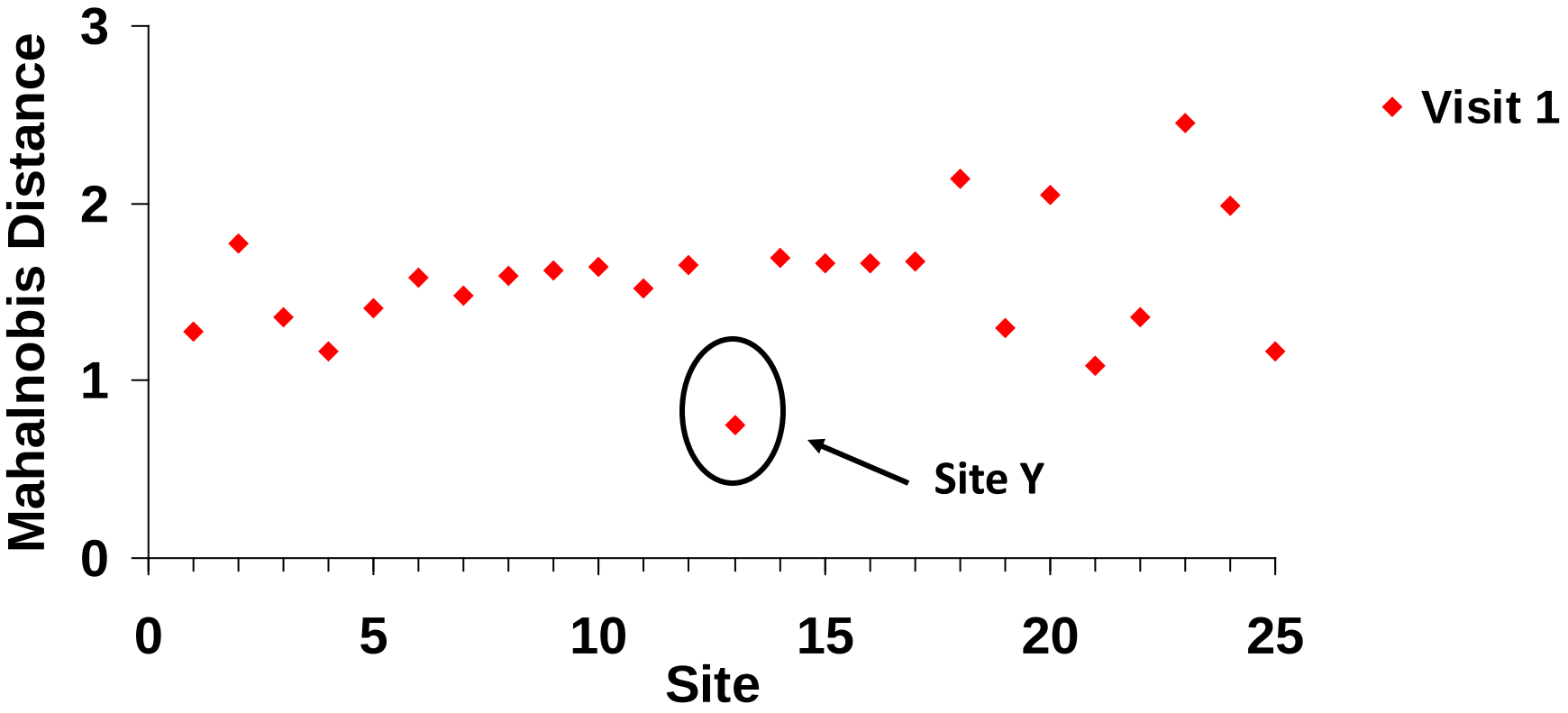
Measures distance between 2 data vectors (or a data vector and a mean vector), accounting for covariance structure

$$M = \sqrt{(x-\mu)'\Sigma^{-1}(x-\mu)}$$

# Mahalanobis distance example

Average Mahalanobis distance calculated for Case Study 1 by site

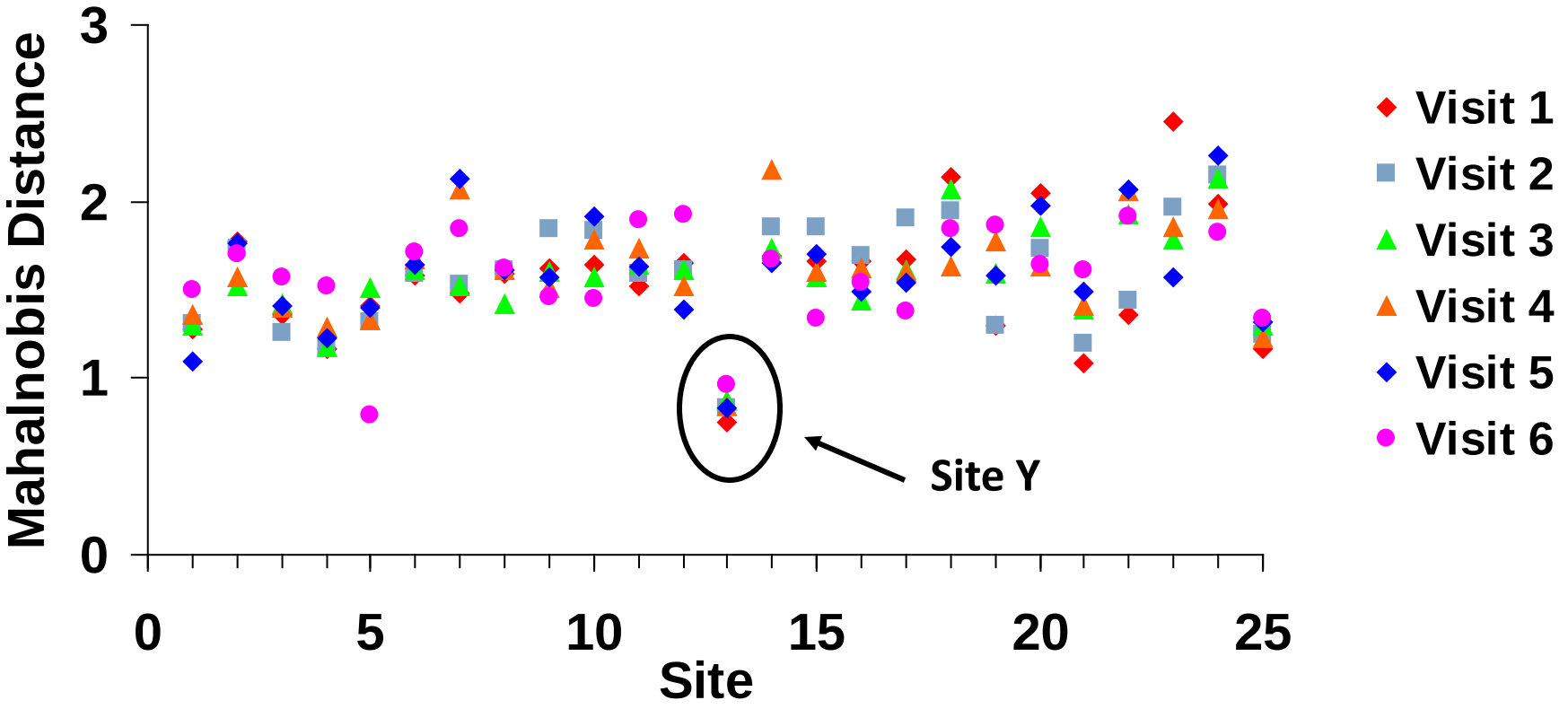
- Change from baseline to each visit for Systolic BP, heart rate, weight



# Mahalanobis distance example

Average Mahalanobis distance calculated for Case Study 1 by site

- Change from baseline to each visit for Systolic BP, heart rate, weight



# Summary

Counterfeit data in clinical trials

- Rare
- Serious
- Can be reduced
  - Simplify eligibility criteria and minimize required data
- Can be detected
  - Plausible data are difficult to invent

When counterfeit data are detected

- Impact should be quantified
  - Analyses with/without site in question?
- In multicenter trials, impact may be negligible

# Selected references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# Runway for RBM

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Director, Data Sciences – Operations Analytics


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# Disclosure

This presentation was sponsored by AbbVie. AbbVie contributed to writing, reviewing, and approving the publication.

Nareen Katta is an employee of AbbVie, Inc.

# Runway to RBM

Technology considerations before you take-off

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"We're all very excited. Most of the other consultants do everything in a slide show presentation."

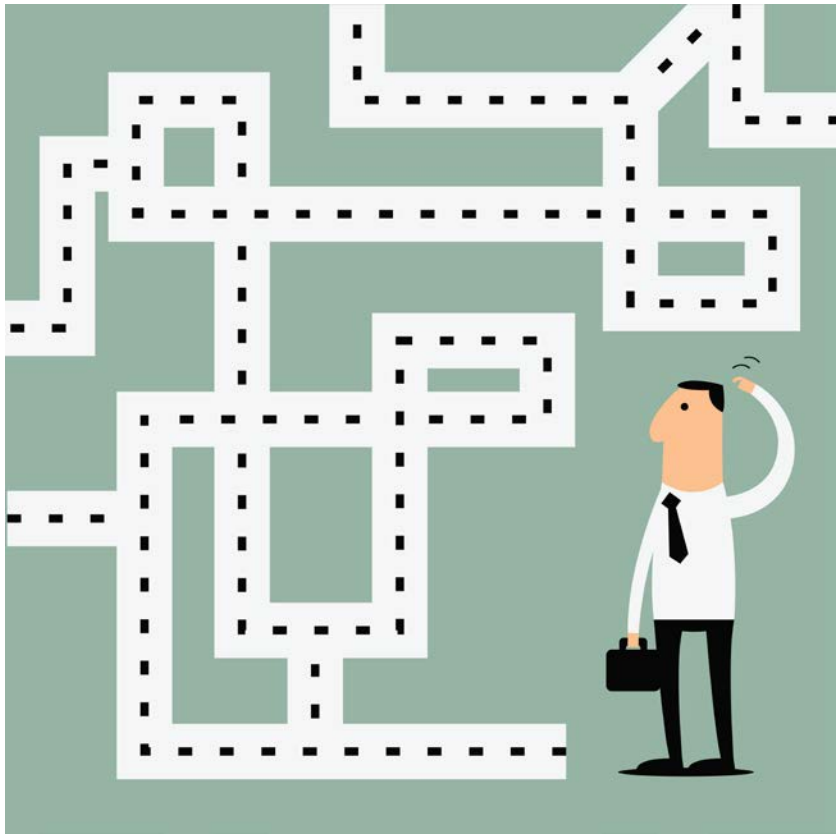
# Objectives

1. Understand the complex technology and industry landscape
2. Determine where to start: study level vs. enterprise level
3. Change management considerations
4. AbbVie's Journey

# Recipe

Transcelerate published the Risk Based Monitoring position paper in June 2013

- Comprehensive framework
- RACT and other tools



# Complexity

We are playing in the R&D space

Operations are unique at different companies

Same task is performed by different roles at different companies

Variable technology maturity levels (e.g. Issue tracking)

Different technology solutions for the same process (EDC)

CROs

Outsourcing

Global variability

Regulatory expectations (FDA vs. EMA)

M&A

# Where to Start

Find your data

Establish seamless access to data

Adjust SLAs to enable data access

Find people who are data savvy

Build the process

# Buy vs. Build

Start with a prototype

Understand your current state

Identify key gaps and address them

Assess potential vendors

Invest in a long term solution

# Validation

Validate data

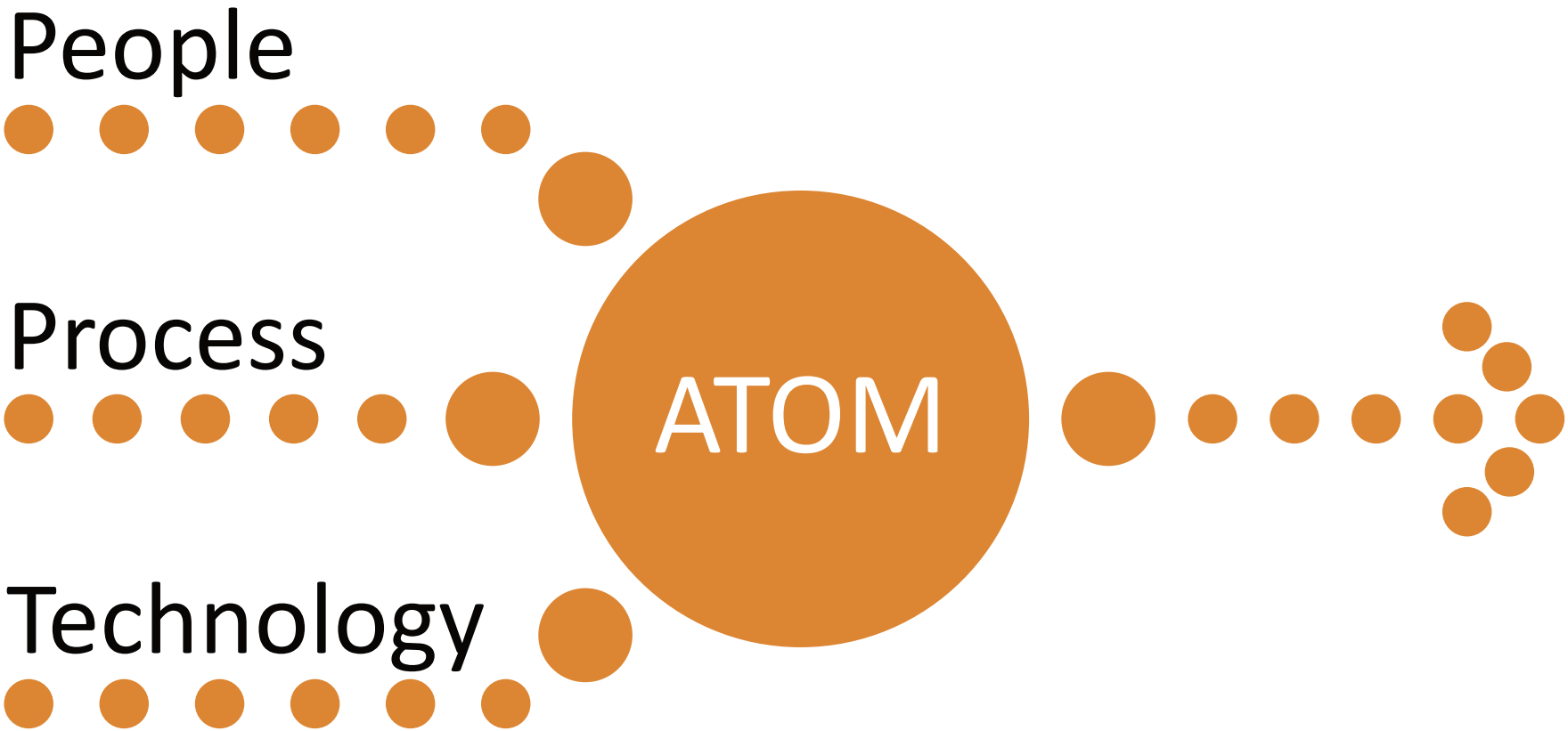
Validate process

Validate people’s knowledge

Validate system

# AbbVie's Journey

# AbbVie's Journey




ATOM – AbbVie Trial Oversight Methodology

# AbbVie's Journey 1/2

Process Workshops

Translate methodology into AbbVie's context

Recognize the limitations and possibilities

Pick the right study

# AbbVie's Journey 2/2

Rapid prototyping methodology

Get toys in the hands of the users

Don't try to get it perfect

Enhance experience (e.g. Snapshots)

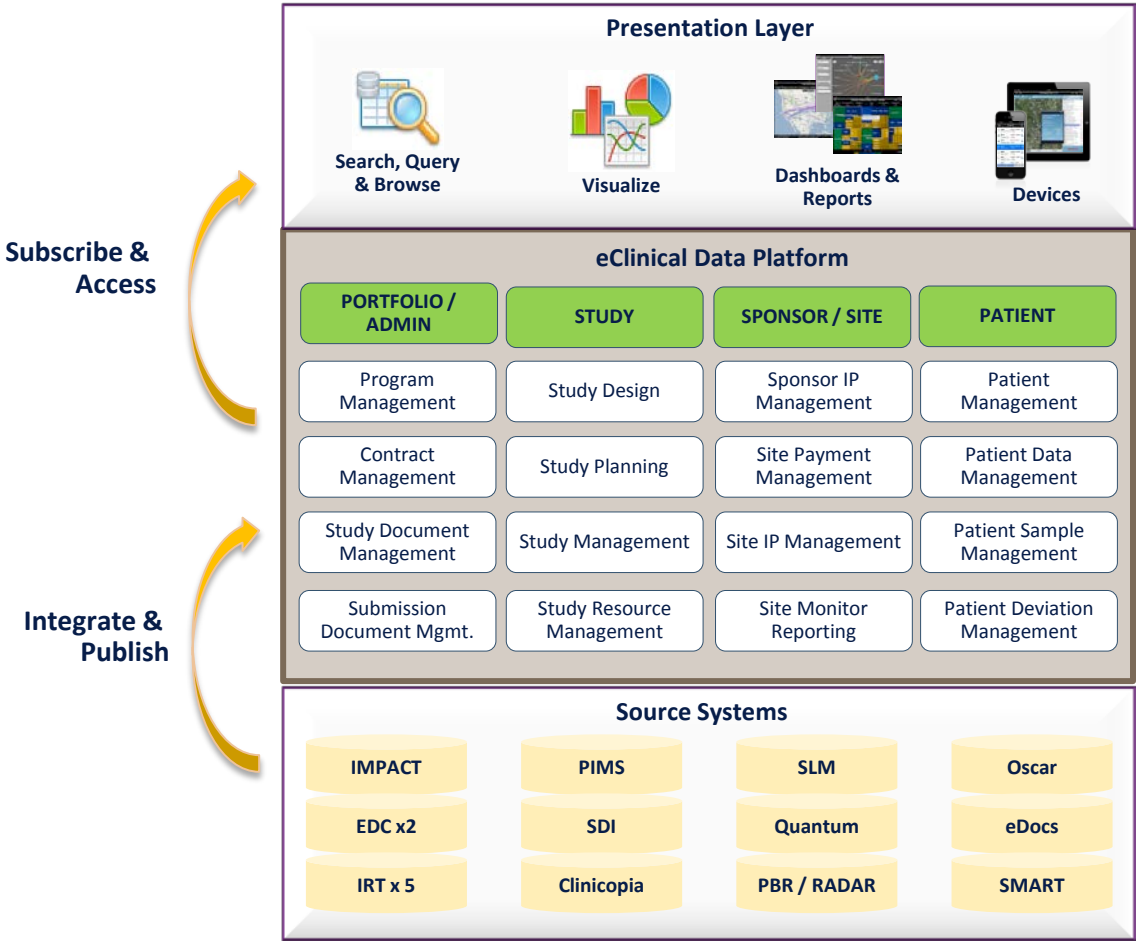
Understand the appetite

Manage the wish-list

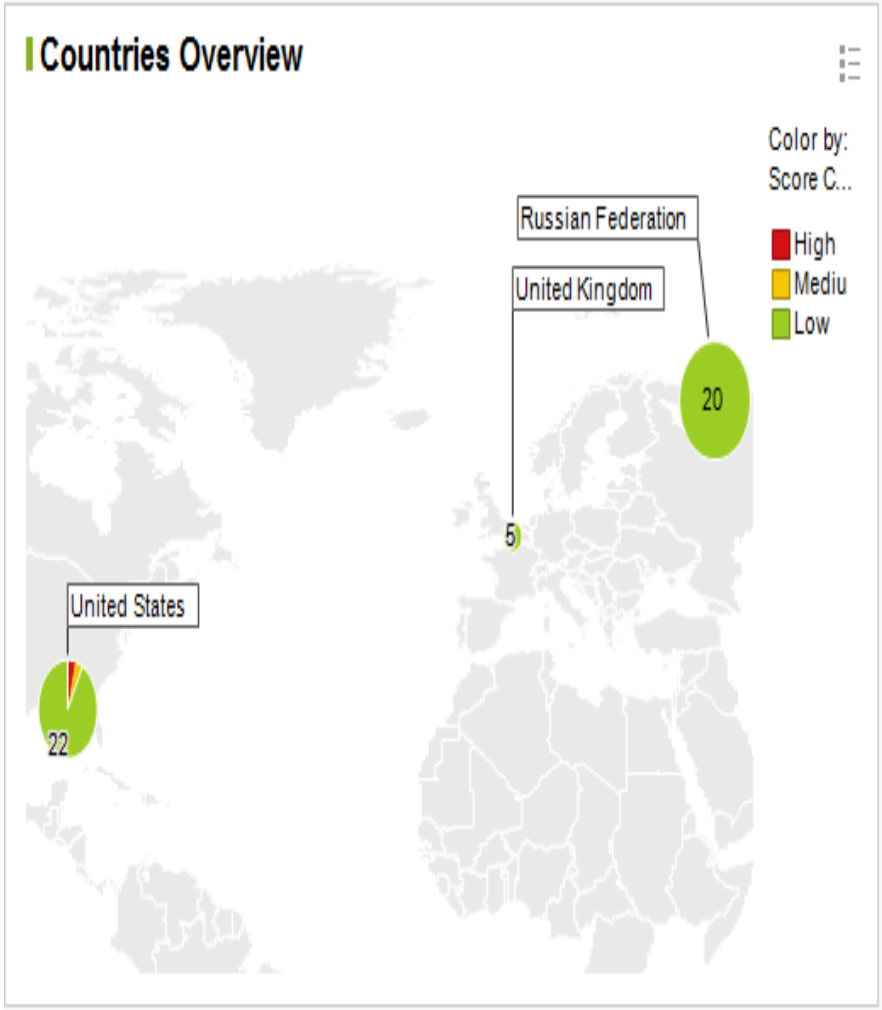
# eClinical Data Platform

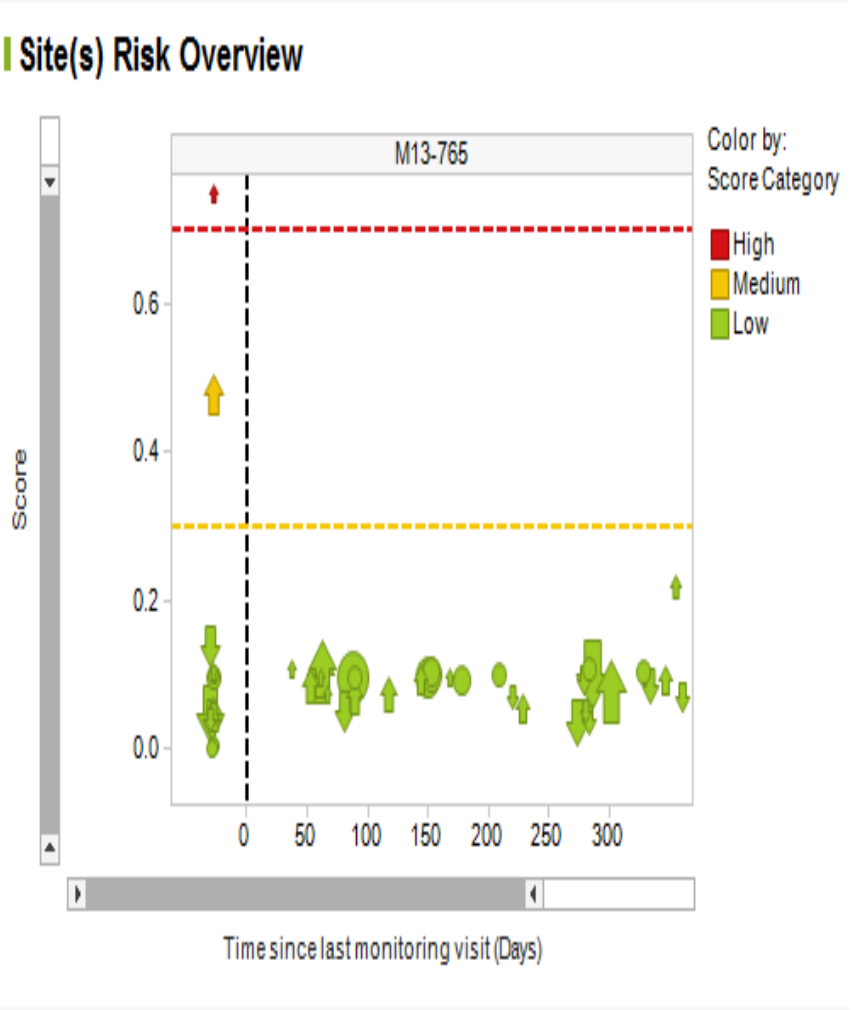
**A highly flexible solution that provides a tailored user experience, cross-functional capabilities, and harmonized data united from multiple applications into a single source of truth by joining formerly silo'd applications and data.**

- User Experience tailored to business needs and preferences
- Users access consolidated information across functional processes and business activities
- Delivers harmonized and remediated information shared from multiple sources
- A common platform infrastructure provides the foundational support for information management
- Flexibility to add data sources and destinations for information viewing and analysis



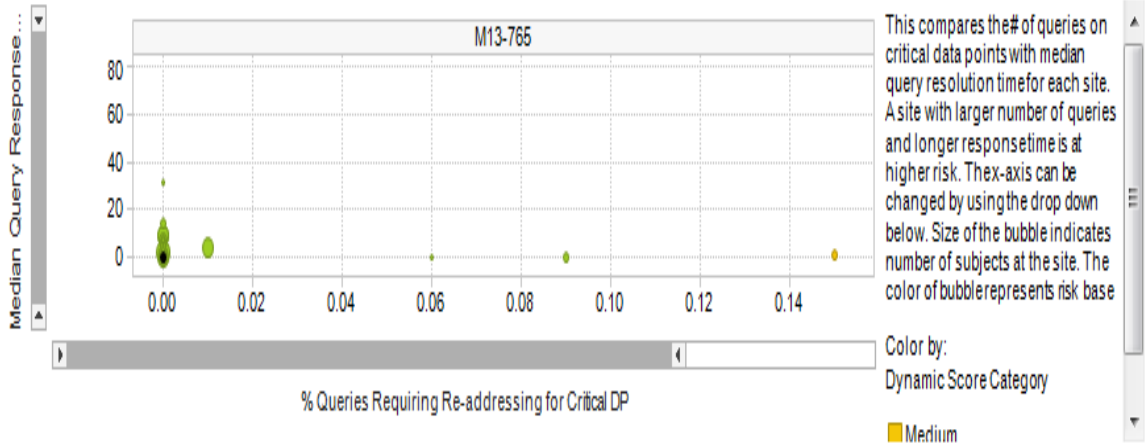
# ABACAS (AbbVie Agile Clinical Analytics Suite)



# ABACAS (AbbVie Agile Clinical Analytics Suite)

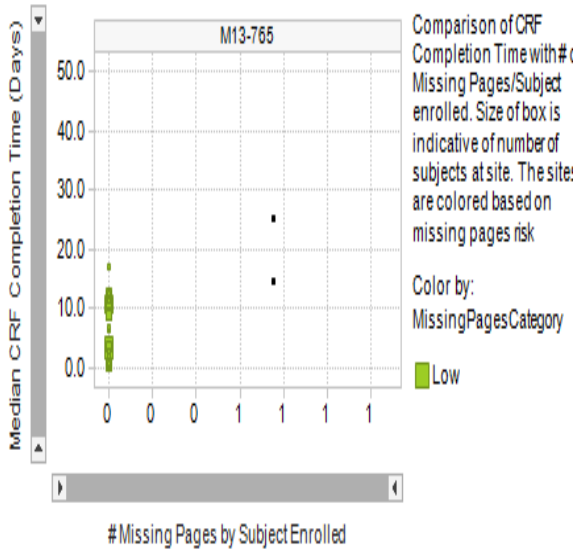
## Queries per Site (on Critical DP)




All Queries

Select risk indicator for X-axis: % Queries Requiring Re-addressing for Critical DP

## CRF Completion Time vs Missing Pages




## Site Data Quality Risk Indicators

| Median Query Response Time (in days; for Critical DP) | Query Response Time (in days; for Critical DP) | Median CRF Completion Time (days) | CRF Completion Time | Missing Pages/Subj... | Missing Pages/Subject | Missing Pages |
|---|---|---|---|---|---|---|
| 3 | | 25 | | 0.75 | 0.75 | |
| 0 | | 15 | | 0.75 | 0.75 | |

# AbbVie's Journey – Next Steps

Make organizational adjustments.

Formalize the approach

Enhance the infrastructure

Modernize the technology landscape (eTMF)

Keep learning and tuning

***We believe the Journey never ends***

# Final thoughts….

1. Control your data to control your RBM initiative
2. Find the right people
3. Don’t try to get it right the first time

# Don’t forget you need to land….maintain tight control