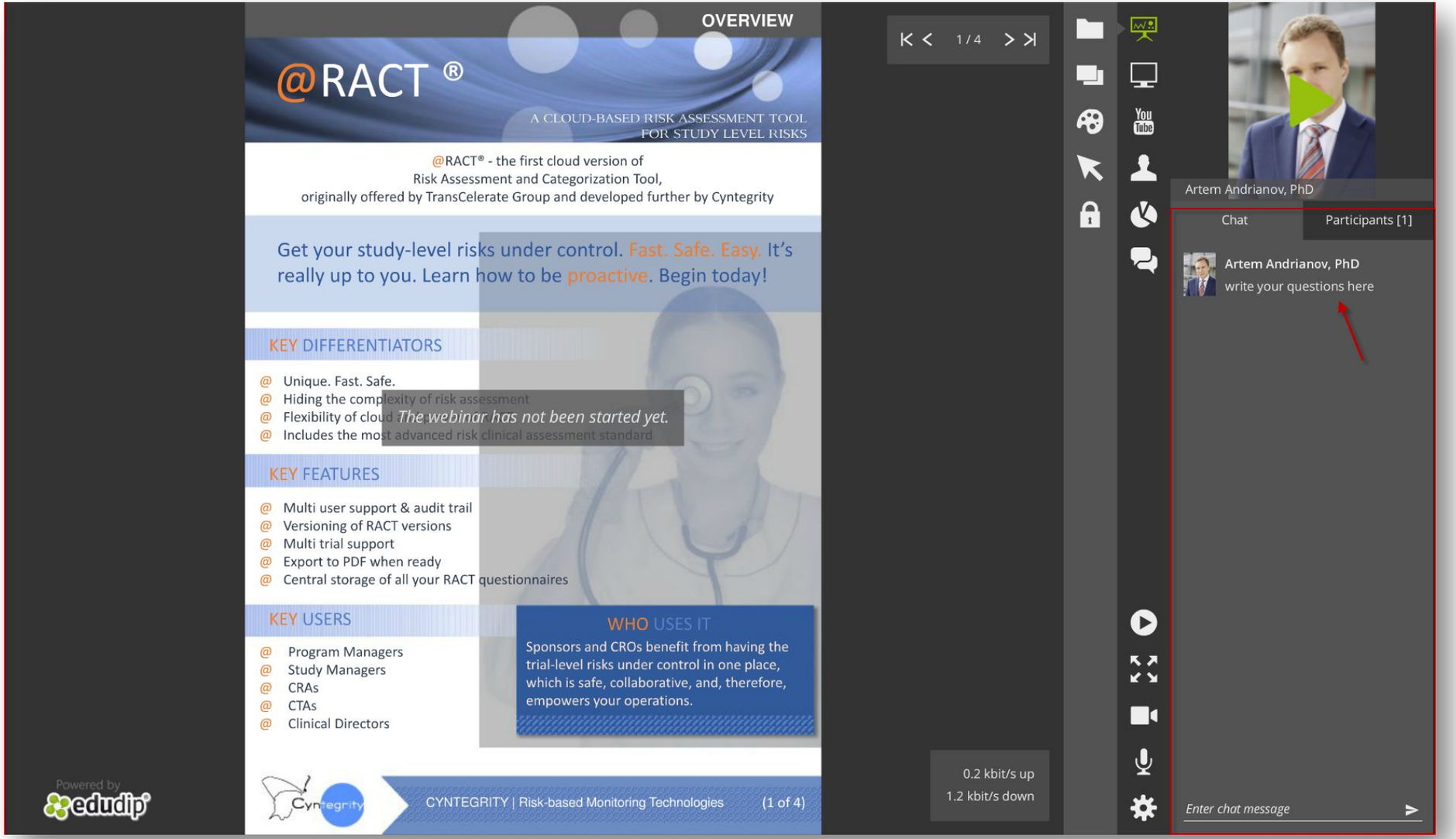
Trust in Data

Fraud and Sloppiness Detection in Clinical Trials

With Practical Examples

Webinar | Thursday, September 26, 2019

Ask your questions here >



The Company

Since:	**2014**
Founders:	RB(Q)M pioneers, **ERT**'s former Quality Data Systems Development Lead and team and co-founded by **Bayer**'s former Head of Global Data Management
Focus:	Full-service RB(Q)M solutions, exclusively **designed for clinical purpose**
Headquarters:	Olof-Palme-Str. 15, D-60439 Frankfurt am Main, **GERMANY**

Artem Andrianov, PhD

CHIEF EXECUTIVE OFFICER

Artem Andrianov has more than 15 years of experience in data quality projects (GlaxoSmithKline, Johnson & Johnson and ERT), RB(Q)M and data management for the Life Sciences and Medical Devices industries.

Artem is a much sought-after, charismatic speaker on topics related to RB(Q)M, Spirometry, ECG, Oncology, ePROs and Clinical Data Management at conferences such as DIA, PCT, DGGF and PharmaDay.

Artem holds a PhD in Mathematics and master's degrees in Business Administration, Financial Management and Corporate Strategy.

The Butterfly Effect: Why Small Acts Can Have Big Effects

Fraud and Sloppiness Detection in Clinical Trials

Definitions US Public Health Service:

- *"Research misconduct means **fabrication**, **falsification**, or **plagiarism** in proposing, performing, or reviewing research, or in reporting research results;*
- *Fabrication is **making up** data or results and recording or reporting them;*
- *Falsification is **manipulating** research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record;*
- *Plagiarism is the **appropriation** of another person's ideas, processes, results, or words without giving appropriate credit;*
- *Research misconduct **does not include honest error or differences of opinion**."*

Do you want to be the next 'scandal'?

- *More than **40% of researchers** are aware of misconduct but do not report it.*[1]
- *More than **2000 scientific articles** have been retracted over the last 40 years.*[2]
- *The number of retractions has **increased dramatically in recent years** and most of these retractions are due to **research misconduct**, especially **data fraud**.*[3]

What's your organization doing to protect against fraudulent activity? Have you taken the necessary measures to reduce **monetary loss**, keep **brand reputation** high while keeping organizational efficiencies on track?

1. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3700330/
2. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4340084/
3. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4340084/

Either intentionally or unintentionally, fraud and error in clinical research happen…

Why Fraud or Misconduct Happens?

Why Fraud and Misconduct Happens?

The reasons:

- Need to obtain a desired result, e.g. ‘statistical significance’
- Monetary gain, enhancement of prestige
- Compensate for laziness, sloppiness in data collection
- Include subjects who would otherwise be excluded
- Ignorance, naivety
- Carelessness, sloppiness
- Improper methods
- Statistical ‘fallacies’

Source: Habermann B, Broome M, Pryor ER, Ziner KW. Research coordinators’ experiences with scientific misconduct and research integrity. Nurs Res. 2010;59:51–7.

Why Fraud and Misconduct Happens?

The consequences:

- Damages corporate reputation - fraud cases can destroy a large research organization
- Financial costs connected with recalls
- Damage reputation of many innocent researchers and collaborators
- Negative impact to related on-going research

➔ Victims

Why Fraud and Misconduct Happens?

The different types:

SITES

- Manipulation with protocol
- Misuse of measurement tools
- Wrong calibration
- Inclusion criteria fraud
- Manipulation of parameters for trial inclusion

MEASUREMENTS

'**Professional patients**' – people who participate in many trials simultaneously.

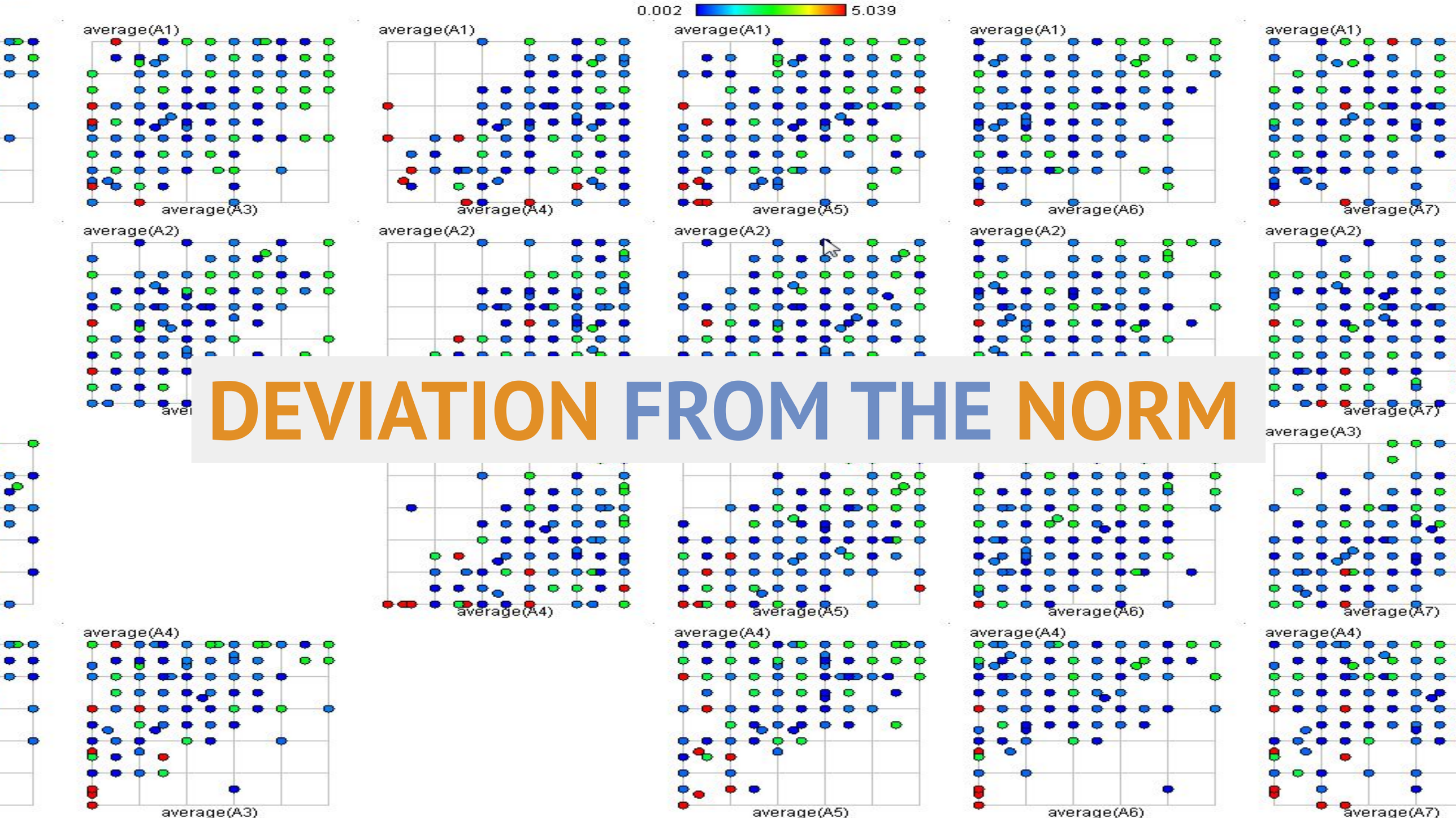
CROs

- Error-hiding
- Unintended technical defects
- Unnoticed data defects

DATA EXPORTS

- Error-hiding
- Inventing new data (**forging**)
- Reporting only selected observations (**cooking**)
- Deleting outliers (**trimming**)

How to Detect Fraud and Error?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MyRBQM® Analytics and Fraud Detection

MyRBQM® Analytics and Fraud Detection

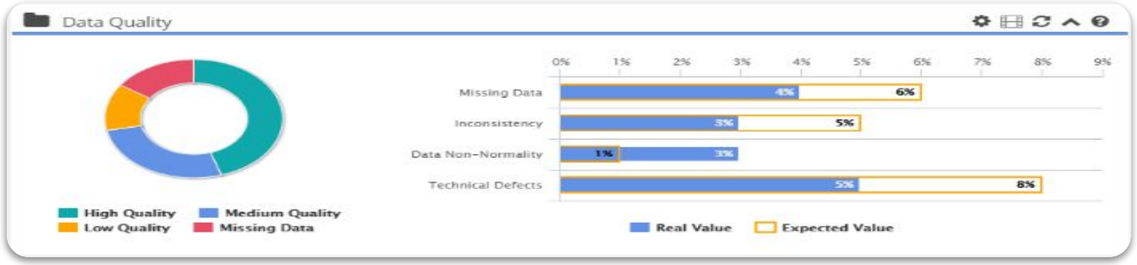
Technology essential features:

Clinical Risk Management

- Umbrella Principle – unification of CTMS, EDC, etc.
- Risk mitigation communication
- Concentration on systemic risk, not random artefacts

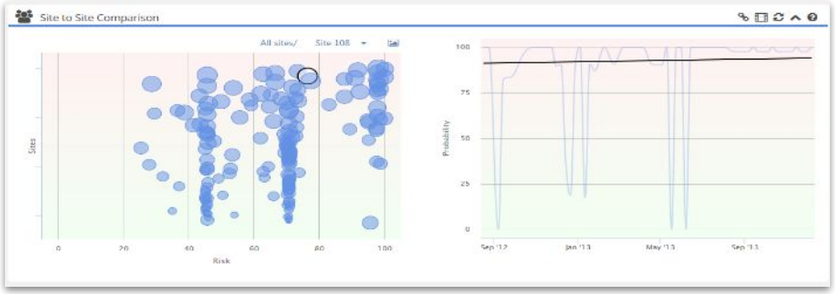
Data Quality Monitoring

- P-value control for essential variables
- Geographical quality spread
- Data quality dynamics and comparison values



Site Ranking

- Transparent communication and site involvement
- Historical Root-Cause feedback graph



MyRBQM® Analytics and Fraud Detection

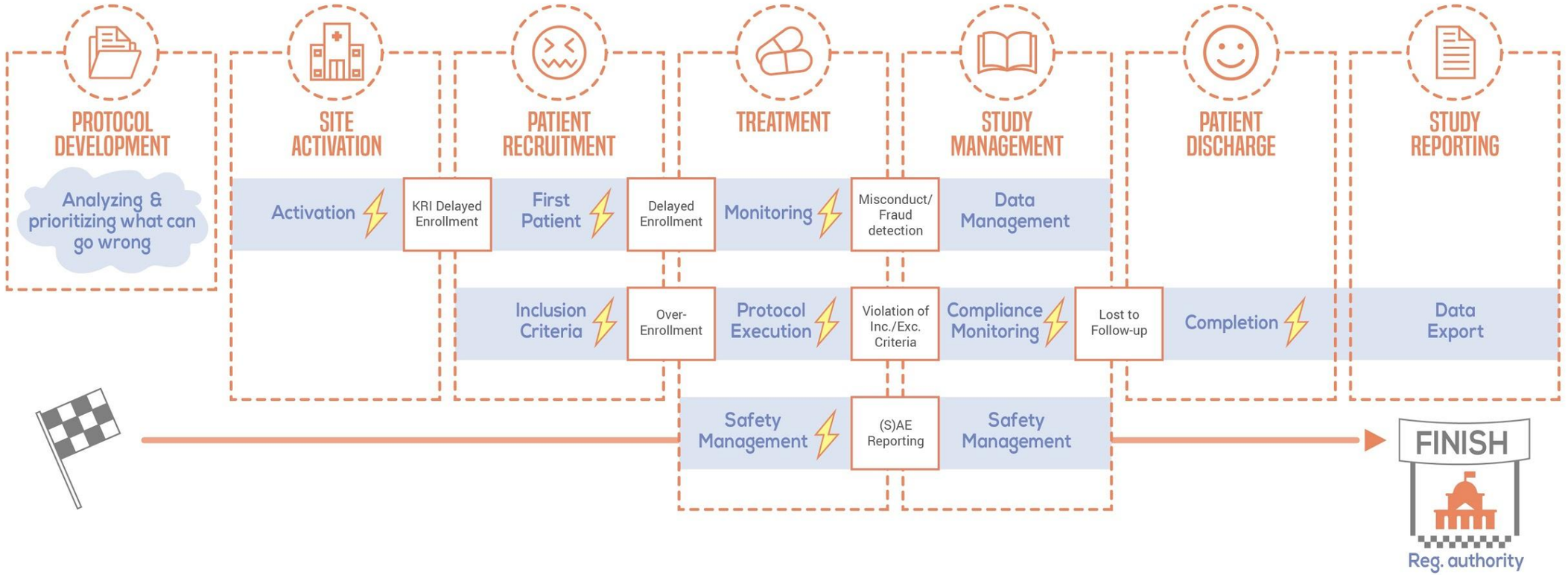
Preconditions:

Regulatory compliance - tools and technology designed for clinical purpose

MyRBQM® Analytics and Fraud Detection

Preconditions:

Holistic approach - all risks in scope from start to finish

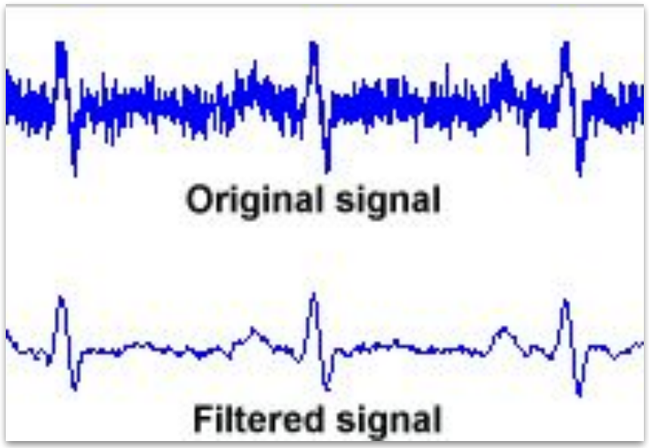


MyRBQM® Analytics and Fraud Detection

Key Risk Indicators (KRIs):

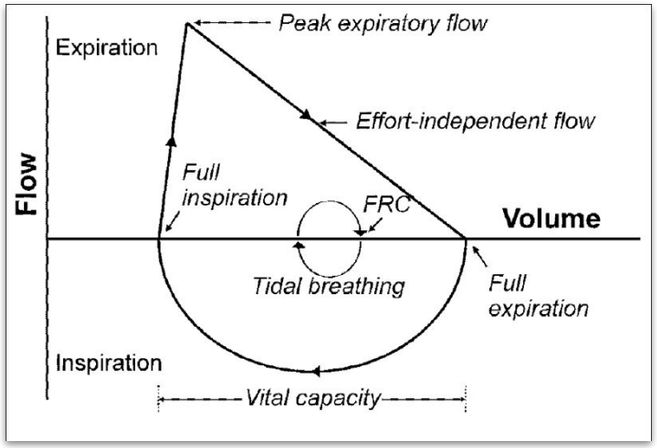
ECG KRIs

- ECG Noise Level
- Lead Misplacement
- Empty leads
- Low Contact Impedance
- Parameter Analysis for, e.g., QT check



Spirometry KRIs

- ATS Criteria Check
  - Repeatability
  - Recognizing correct and incorrect FVC maneuvers
- Efforts quality
- Parameter Integrity



How Can We Prevent Fraud and Misconduct?

How Can We Prevent Fraud and Misconduct?

The measures:

- Adopt **zero tolerance** - all suspected misconduct
- Using **statistical and data mining tools** in identification of inconsistent data
- Using **centralized statistical monitoring methods** (across study and sponsor)
- Continuous acceptability & sanity **data checks**
- **Rules Engine Check** (based on medical knowledge)
- **Data mining**: Gaining new information from data analysis and using it to tune the detection
- Development of **fraud classification** and a method of fraud **categorization**
- Calculating and assigning independent **Fraud Credibility Ranking** of Sites, CROs and organizations involved in clinical research (Low, Medium, High Risk Site)
- More discussion should be directed towards possibilities to decrease **incentives** connected with fraud, misconduct and sloppiness

MyRBQM® CSM Fraud Detection Algorithms

MyRBQM® Centralized Statistical Monitoring (CSM)

Fraud detection algorithms:

Digit Preference - within-study comparison

The algorithm is able to **compare leading or trailing digits** between user-defined groups in a clinical trial. For example, for sites or for randomization arms (for checking whether randomization is correct).

The algorithm:

- calculates a contingency table for frequency distribution of digit of interest
- performs Cochran-Mantel-Haenszel “Row Mean Square Differ” test, which effectively compares rows of contingency tables between each other
- Scores are calculated from the p-values and are highlighted in a report if a p-value is lower than a user-defined significance level, **which means that the data is suspicious and the case should be investigated**

MyRBQM® Centralized Statistical Monitoring (CSM)

Fraud detection algorithms:

Digit Preference - What is Benford's Law?

Benford's law, also called the Newcomb–Benford law, the law of anomalous numbers, or **the first-digit law**, is an observation about the frequency distribution of leading digits in many real-life sets of numerical data. The law states that in many naturally occurring collections of numbers, **the leading significant digit is likely to be small**.

For example, in sets that obey the law, the number 1 appears as the leading significant digit about 30% of the time, while 9 appears as the leading significant digit less than 5% of the time. If the digits were distributed uniformly, they would each occur about 11.1% of the time. Benford's law also makes predictions about the distribution of second digits, third digits, digit combinations, and so on.

https://en.wikipedia.org/wiki/Benford%27s_law

MyRBQM® Centralized Statistical Monitoring (CSM)

Fraud detection algorithms:

Digit Preference - Benford’s Law

The algorithm is able to detect fraud by **checking if the first significant digit (FSD) frequency distribution complies with Benford's Law**. The algorithm triggers a warning if some of the data compliance properties are not observed.

This algorithm:

- finds frequencies of values of one or two leading digits in data
- finds second-order frequencies of two leading digits
- compares these frequencies with the expectation of Benford’s Law
- Scores are calculated from p-values and are highlighted in a report if a p-value is lower than a user-defined significance level, which means that the **data is suspicious and the case should be investigated**

MyRBQM® Centralized Statistical Monitoring (CSM)

Fraud detection algorithms:

Digit Preference - uniformity check

The algorithm detects data collection errors and fraud by **checking if the trailing digits frequency distribution is uniform or not**.

This algorithm:

- finds frequencies of values of one or two trailing digits in data
- compares these frequencies with the expectation of uniform distribution
- p-values produced by statistical tests are adjusted for multiple comparisons by the Benjamini-Yekutieli method and compared with the significance level specified by a user
- Scores are calculated from p-values and are highlighted in a report if a p-value is lower than a user-defined significance level, which means that the **data is suspicious and the case should be investigated**

MyRBQM® Centralized Statistical Monitoring (CSM)

Fraud detection algorithms:

Interquartile Range - IQR

IQR is used in case of univariate **outliers detection** to identify the values of numerical variables which are **abnormally distant** from most of the observations to detect **data collection errors, sloppy data or fraud.**

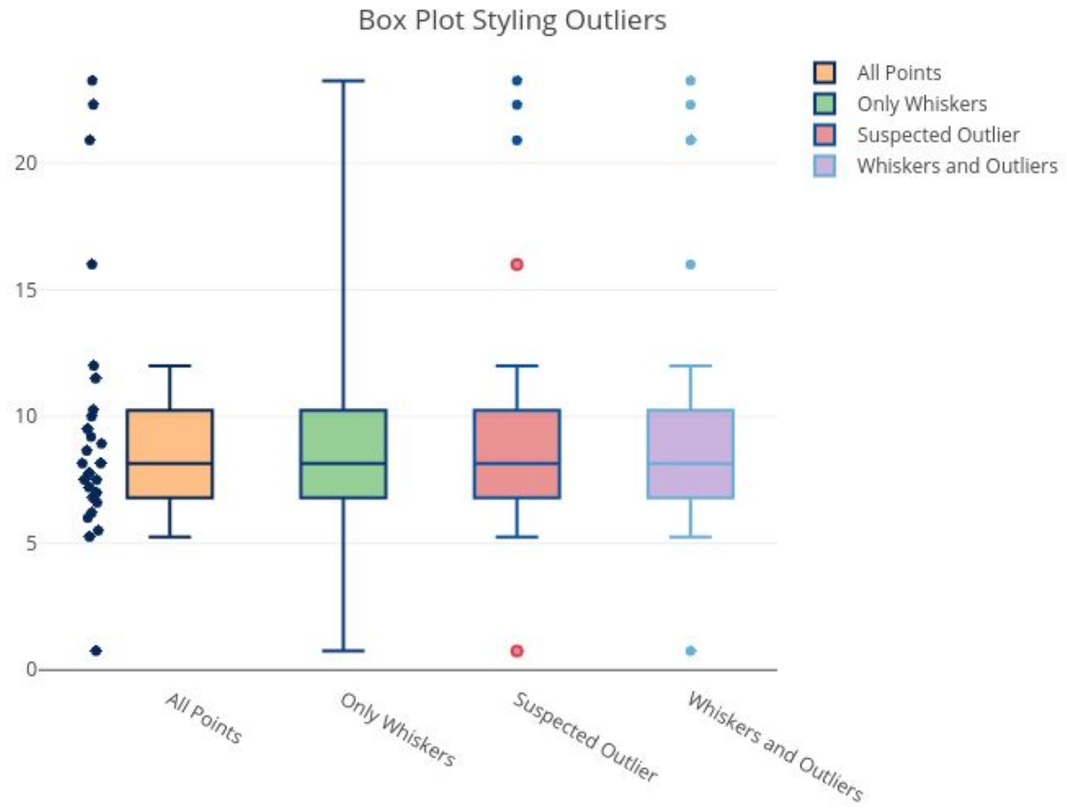


Image Source: https://plot.ly/r/box-plots/

MyRBQM® Centralized Statistical Monitoring (CSM)

Fraud detection algorithms:

Scatter Plot

A scatter plot is a two-dimensional data visualization that uses dots to represent the values obtained for two different variables — one plotted along the x-axis and the other plotted along the y-axis. The scatter diagram graphs pairs of numerical data, with one variable on each axis, to look for a relationship between them.

It helps to **detect fraud by observing correlations between variables and finding outliers**.

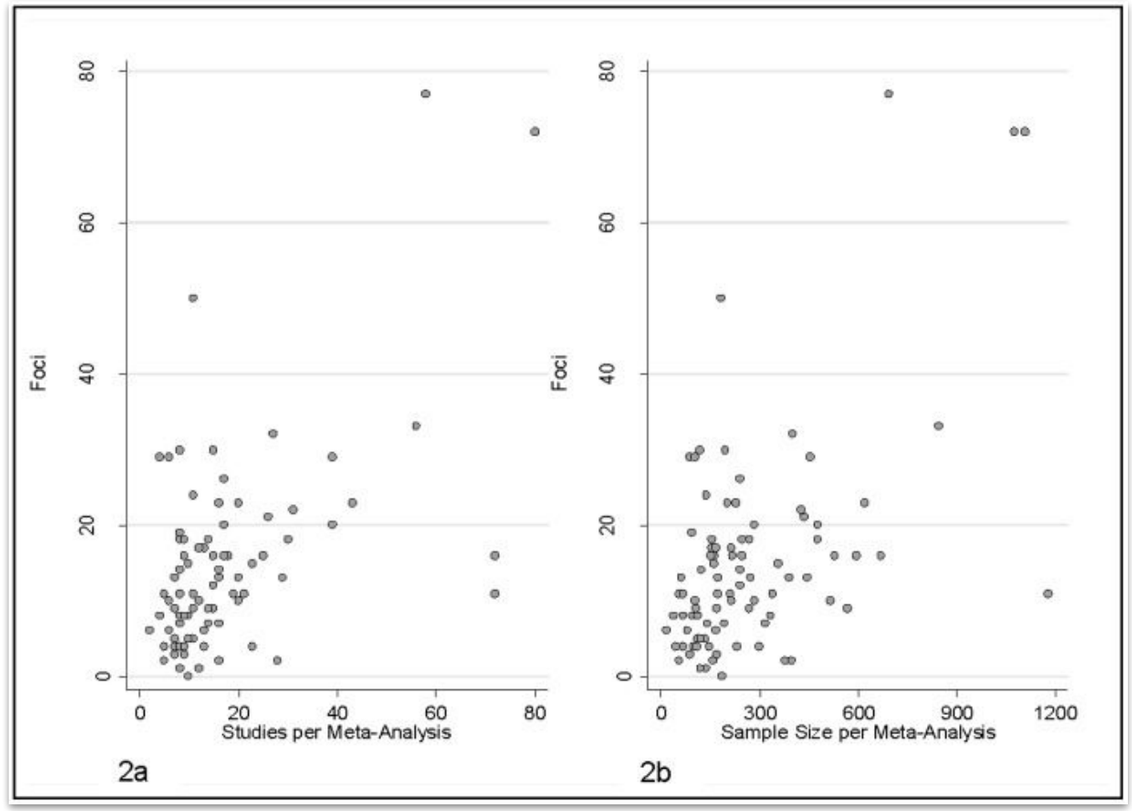


Image Source: David, Sean & Ware, Jennifer & Chu, Isabella & Loftus, Pooja & Fusar-Poli, Paolo & Radua, Joaquim & Munafò, Marcus & Ioannidis, John. (2013). Potential Reporting Bias in fMRI Studies of the Brain. PloS one. 8. e70104. 10.1371/journal.pone.0070104.

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Fraud detection algorithms:

Correlation Matrix

Correlation matrix aims for **statistical dependence or association** between two variables discovering interrelations of variables for the **detection of fraud and tampering with data.**

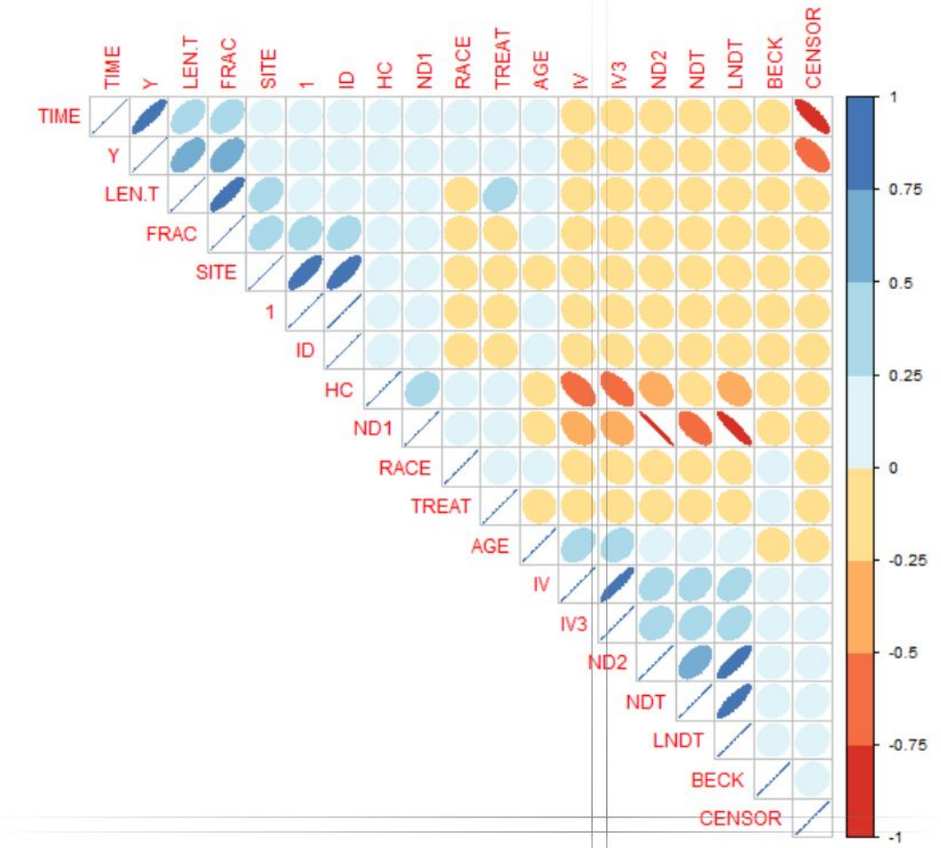


Image Source: MyRBQM® Portal

MyRBQM® Centralized Statistical Monitoring (CSM)

Fraud detection algorithms:

Histogram of all numeric values

A histogram is an accurate representation of the distribution of numerical data. It differs from a bar graph, in the sense that a bar graph relates two variables, but a histogram relates only one. It helps in **anomaly detection** in the process of **finding outliers in data sets**.

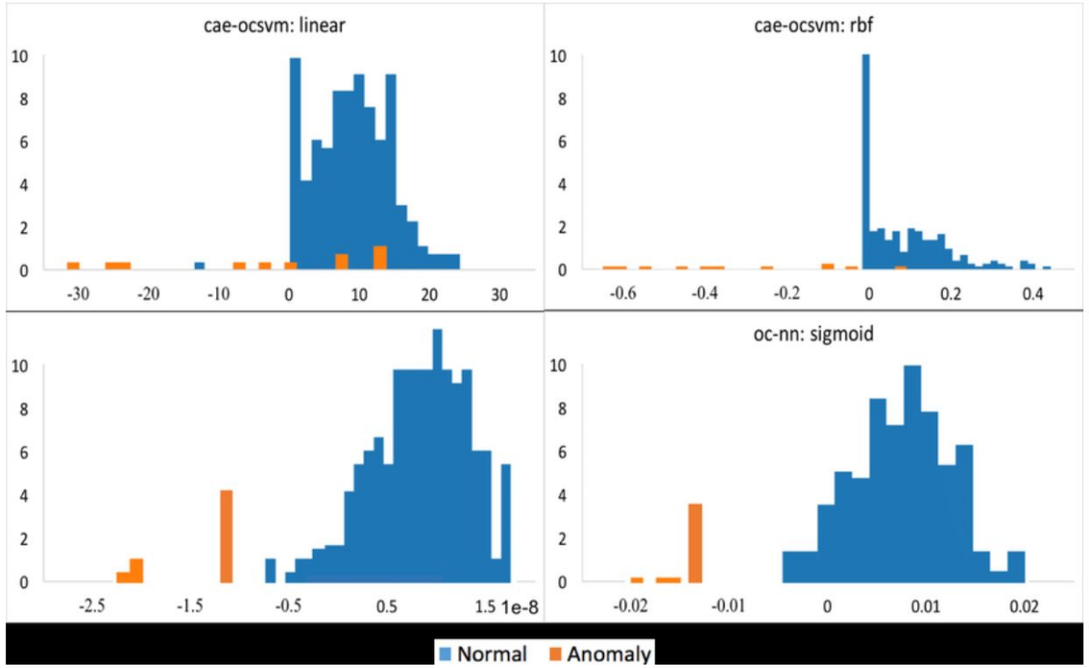
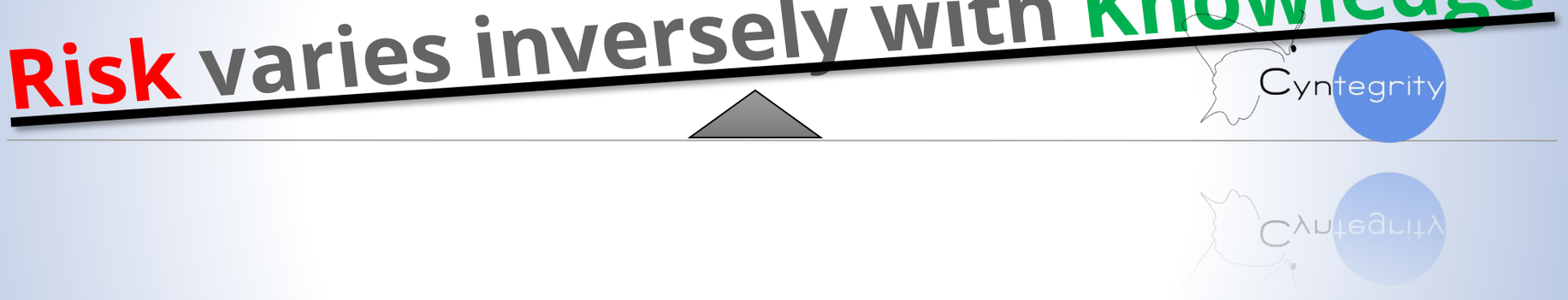


Image Source: Chalapathy et al. (2018) Anomaly Detection using One-Class Neural Network. arXiv:1802.06360v1

Risk varies inversely with Knowledge



Irving Fisher (1867-1947)

Q&A

Type in your questions using the chat box on the right side of your screen.

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Further Questions?

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