# Retractions: Observations of a Quality Assurance Professional

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# What is Quality Assurance?

- Required in regulated laboratory and field studies, clinical trials and manufacturing (GXP)
- Provides an independent assessment that research is being performed according to the standards, protocol and procedures identified for the study
- Reviews the raw data to ensure that it is complete, accurate and available
- Reviews the final reports to assure that it accurately reflects the study data
- Provides training and advice throughout the study life-cycle

# Study Life Cycle

# Quality Assurance

- Asks the question “How do you know?”
- Assists in defining the “Quality System”.
- Make a distinction between quality and integrity

Data Quality:  Extent to which data are fit for use, accurate and/or meet a predetermined standard

Data Integrity: Extent to which data quality is maintained throughout the life cycle

# Retraction Impacts

## Regulated Research vs Non-regulated Research

- Observational
- Regulated research seldom published, although heavily scrutinized
- Explore some pervasive attitudes, misunderstanding and challenges and the role quality assurance can play in developing quality practices and culture.
- Identify what might add value in a non-regulated research environment

# Regulated Study Planning: The Protocol

- On an individual study basis
- A critical phase of regulated research
- Each study protocol is written, with a beginning and an end and fully descriptive of the study
- Distributed to all involved
- Highly supportive of the integration of multiple investigators and facilities and documenting the study

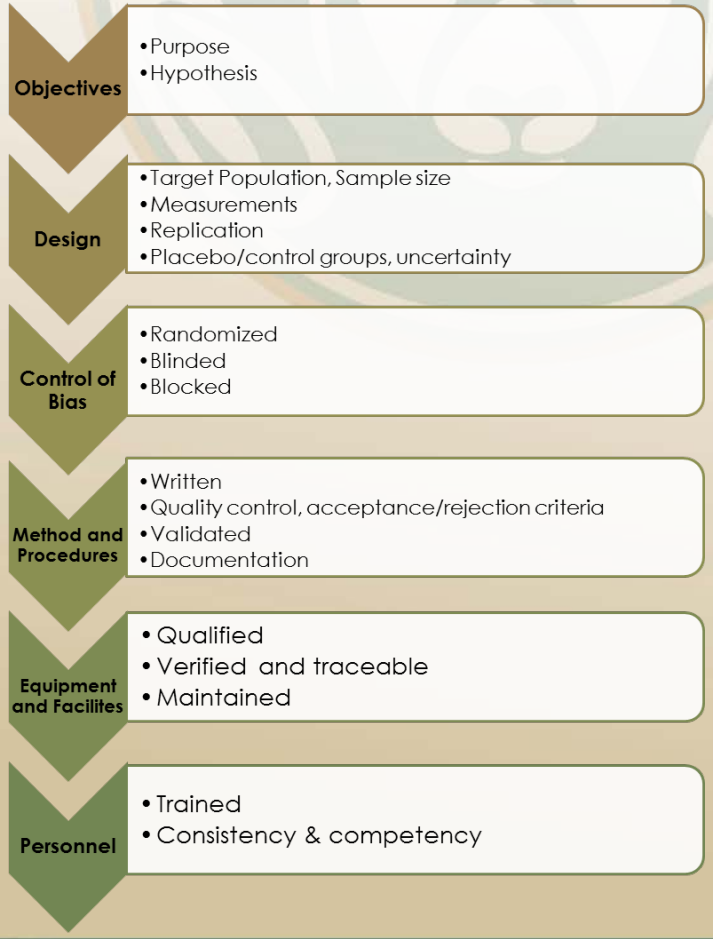
# Study Plans

- Current Trends
  - Published protocols
- Current Challenges
  - Lack of expectation and understanding the value
  - Lack of experience in writing
  - Lack of agile and flexible systems ( e.g., protocol development, in capturing amendments and deviations, changes in objectives or methods)
  - Individual study planning underfunded and undervalued

# Research Planning

- The Simple Research Protocol
  - Objectives
  - Study design
  - Control of bias
  - Procedures/Methods
  - Analysis plan
- Added value
  - Roles and responsibilities
  - Publication/authorship
  - Data Retention and control (electronic and hard copy)

❖ Better designed studies; higher quality data



# Regulated Study: Standards and Controls

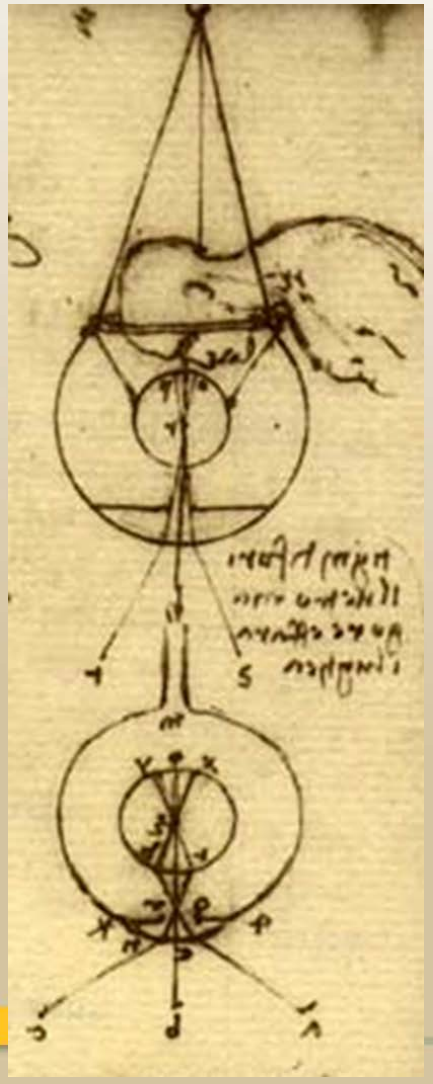
- Promote principles and practices of
  - Documentation
  - Traceability
  - Validation
  - Quality Control
  - Measurements of uncertainty

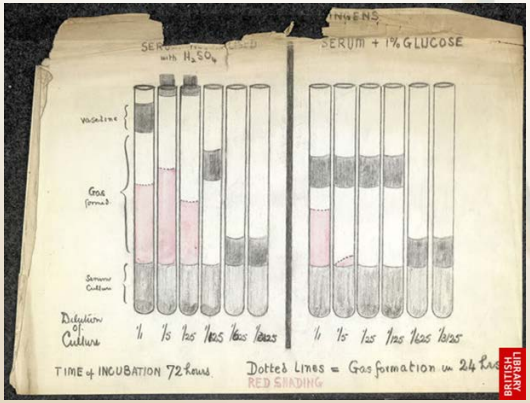
# Data Quality Principles: Collection, Curation, and Harmonization

- Data management planning and standards established
- Accessible throughout the study lifecycle
- Allow study reconstruction and reproducibility
- Data security
- Standards apply to hard copy and electronic data

**Documentation Principles**
A L C O A:
Attributable to the person generating the data
Legible and permanent
Contemporaneous
Original record (or 'true copy')
Accurate

*And….*
Available
Enduring
Complete
Consistent




SERUM + 1% GLUCOSE
Vaseline
Gas formed
Dilution of Culture
1/1 1/5 1/25 1/125 1/625 1/3125
TIME of INCUBATION 72 hours
Dotted Lines = Gas formation in 24 hrs
RED SHADING
BRITISH LIBRARY

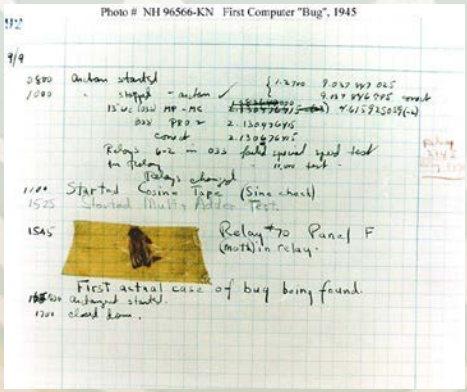
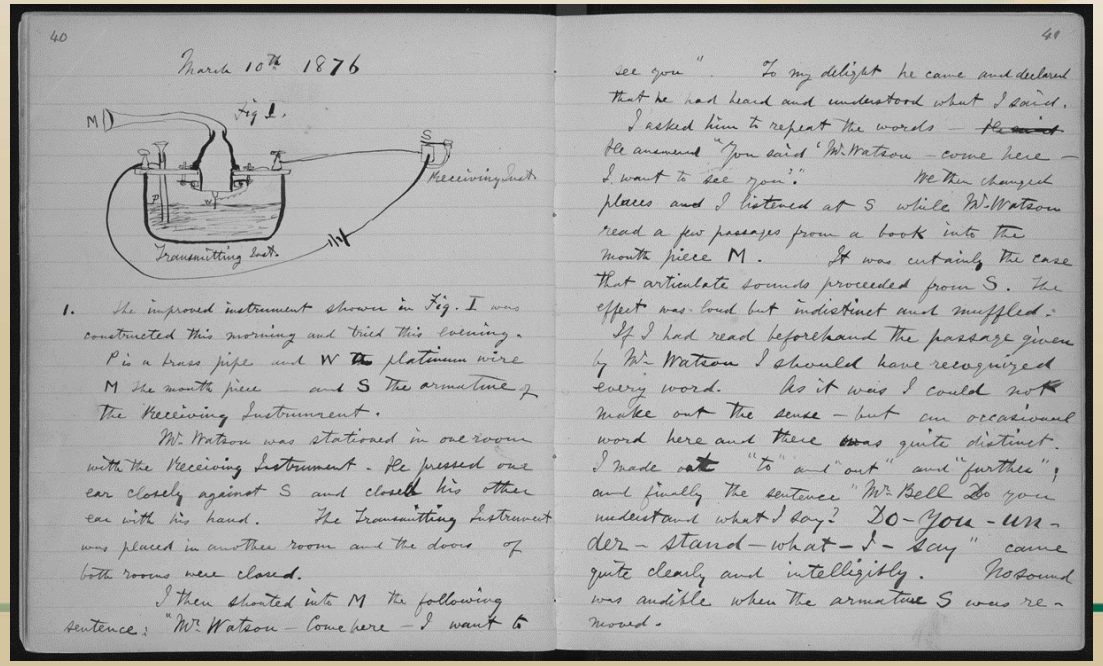


Photo # NH 96566-KN First Computer "Bug", 1945
1100 Started Cosine Tape (Sine check)
1545 Relay #70 Panel F
First actual case of bug being found.


March 10th 1876
Fig 1.
M
S
Receiving Instr.
Transmitting Instr.
1. The improved instrument shown in Fig. 1 was constructed this morning and tried this evening. P is a brass pipe and W the platinum wire M the mouth piece — and S the armature of the Receiving Instrument.
Mr. Watson was stationed in one room with the Receiving Instrument - He pressed one ear closely against S and closed his other ear with his hand. The Transmitting Instrument was placed in another room and the doors of both rooms were closed.
I then shouted into M the following sentence: "Mr. Watson — Come here — I want to see you". To my delight he came and declared that he had heard and understood what I said.
I asked him to repeat the words — He said he answered "You said 'Mr. Watson — come here — I want to see you'."
We then changed places and I listened at S while Mr. Watson read a few passages from a book into the mouth piece M. It was certainly the case that articulate sounds proceeded from S. The effect was loud but indistinct and muffled.
If I had read beforehand the passage given by Mr. Watson I should have recognized every word. As it was I could not make out the sense — but an occasional word here and there was quite distinct. I made out "to" and "out" and "further", and finally the sentence "Mr. Bell Do you understand what I say? DO-YOU-UN-DER-STAND-WHAT-I-SAY" came quite clearly and intelligibly. No sound was audible when the armature S was removed.

# Data Quality

- Current Trends
  - Increased emphasis on open data and transparency
  - FAIR Principles (Findable, Accessible, Interoperable, Reusable)
  - Increasing recognition of the challenges, especially of big data
  - Plethora of software and management tools
  - Harmonization within disciplines increasing with regard to terminology and units of measure, disciplinary controlled terminology

- Challenges
  - Not all data are equal, variable and unassessed quality
  - Format, version and access control problems (e-data)
  - Security and availability
  - Completeness and robustness
  - Lack of source data/original data review
  - Ownership and retention inconsistently addressed

# Traceability and Quality Standards

- Often to a national standard
- High level of validation and control required, especially when internally provided standards, controls, etc

- Current trend
  - Increased awareness of impact (e.g. cell line integrity and identification)

- Challenges
  - Often overlooked as critical to data quality

# Validation and Calibration

- Applies to methods, equipment and electronic systems
- Federal guidelines available

- Current trend
  - Variably addressed
  - Unvalidated use of coding tools

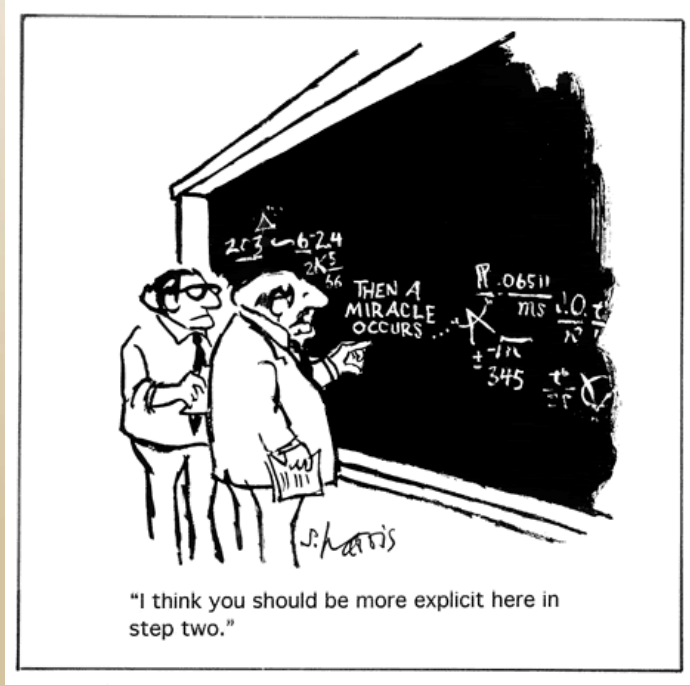
- Challenges
  - Often overlooked as critical to quality

# Standard Operating Procedures

- Reduce errors
- Assist in reducing inter-observer variation
- Act as a detailed historical documentation of procedures used
- Great training tool
- Assists in method validation

But…..

- Take time to manage
- No academic training in how to create and manage an effective SOP system



# Final Reports and Retention

- Inclusive of all study activities and data, single report per study
- Independently assessed by Quality Assurance personnel
  - Focused on the audit trail
  - Assesses the completeness and accuracy

- Current Trends
  - Peer-review publication retraction rate under active review and assessment

- Challenges
  - Quality Assurance review unusual in non-regulated research publications
  - Quality Assurance resource scarce and unfunded in most non-regulated environments
  - Long term data archives unfunded and unavailable
  - Publications don't allow for a full description of the study which limits repeatability and reproducibility

# The cost of Quality Systems?

| Quality Costs | Failure Costs |
|---|---|
| System planning, development and management | Rework, rectification, |
| Quality Assurance services | Loss of public trust in science |
| Training | Loss of scientific advancement |
| Standards, validation and calibration | Loss of funding, reputation |
| Equipment replacement/servicing | Equipment replacement/servicing |
| | Harm to patients |
| | Lack of trained work force of high integrity |

# Academic Attitude toward Regulatory Research

- Anti-regulatory science bias in academia
- Myth that regulated research inhibits innovation
- Under-valuing of the core components ‘quality system’ and the value of application
- Often there is confusion between the GXP ‘quality system’ and ‘Guideline Studies’
- Historical GXP applications have not been science-driven and have been over-applied

- Lack of understanding and training
- Lack of experience in developing efficient and effective quality systems

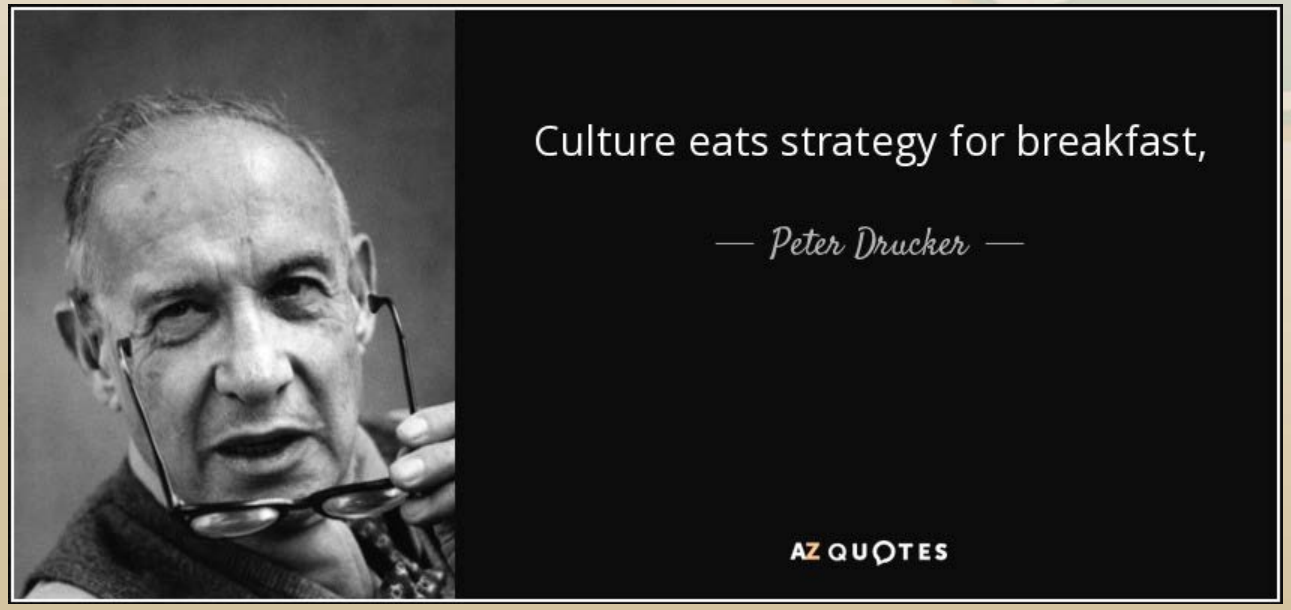
# Incentive, Motivation, and Reward

- Financial Support
- Scientific Community Expectations
- Public Expectations

❖ Not in alignment

# Quality Culture

~ Peter Drucker



# Culture > Strategy

- Culture determines and limits strategy
- Amount of time given to culture is disproportional to its importance compared to strategy
- Culture is an outgrowth of leadership
- Culture should not be passively accepted

# Professionalism and Integrity Program

Three causes played a part in most cases:

| *Proximate cause* | *Ultimate cause of researcher lapse* | *% of participants* |
|---|---|---|
| Lack of attention | Overextended, not detail-oriented or distracted by personal problems. | 72% |
| Unsure of rules | An increase in regulations since researcher began career, lack of mentoring or cultural differences. | 56% |
| Did not prioritze compliance | Failed to recognize seriousness of violations, biased thinking or cultural differences. | 56% |

DuBois, J. et al., Nature, Vol 534, 9June2016, p 173

Challenges

- Clearly articulate ‘quality’ expectations
- Promote quality planning and research management skills
- Fund, reward and incentivize quality systems

# Office of Research Integrity Findings on Lack of Data Integrity

1. Inadequate record keeping and lack of guidance from mentors and Institutions on how to record and retain research data
2. Failure of mentors to regularly review raw data; overreliance on derivative data (PowerPoint presentations) at lab meetings
3. Unquestioning acceptance of data that others consider “too good to be true”
4. Lack of transparency within the laboratory and among the staff
5. Labs so large that authority becomes diffuse
6. P.I.s are spread too thin, and do not provide adequate training and guidance to students

- *The bottom line – good mentorship and the consistent review of raw data can profoundly reduce the likelihood of research misconduct.*

# Instilling a Quality Culture

- Must be Visible and a Priority
- Create clearly articulated goals and expectations
- Create a common language
- Demonstrate value and expectations around those goals
- Acceptance and Ownership

# Instilling a Quality Culture

- Daily Activities
  - Identify and discuss quality issues and expectations
  - Ask for improvement ideas (continuous quality improvement)
  - Bring in QA Professionals or other guests to discuss quality issues
  - Observe
  - Look at raw data or original source data
- When things go wrong
  - Use root cause analysis tools (the 5 Whys)

# Culture of Quality and Collegiality

Importance of
- Personal Integrity
- Knowledge
- Expectations

Promote Policies/Procedures/Guidances
- Authorship
- Adopt Quality System core components and compliance (GRP)
- Address issues of Data Ownership, Security, Access
- Code of Scientific Conduct

# Quality Practices: What does that look like?

- What is your source data?
- What are the quality expectations of your source data?
- What system do you have to communicate and ensure data quality and integrity throughout the data cycle?
- How do you measure and trend your data integrity?  How do you know?

# Winding down….

# Current Quality Challenges

- No clearly defined ‘Quality System’ standard; no minimum quality standard for non-regulated research

Leading to…

- Core components, such as research planning and protocol development under-valued and poorly supported, understood, or experienced
  - Study can be poorly designed and procedures not communicated to team members leading to incomplete and inaccurate data
  - Statistical support critical but often not included
- Validation
  - Is often overlooked, undocumented and unfunded
- Quality Culture
  - Is not consistently valued
  - Quality expectations are not clearly articulated or prioritized

# Recent trends in publication

Recent survey published in PLoS Biology (2016):

- 441 biomedical journal articles published in 2000–2014 were surveyed
- Only one study provided a full protocol
- None made all raw data directly available
- Only 4 included replication studies
- Only 16 studies included data in a subsequent systematic review or meta-analysis.

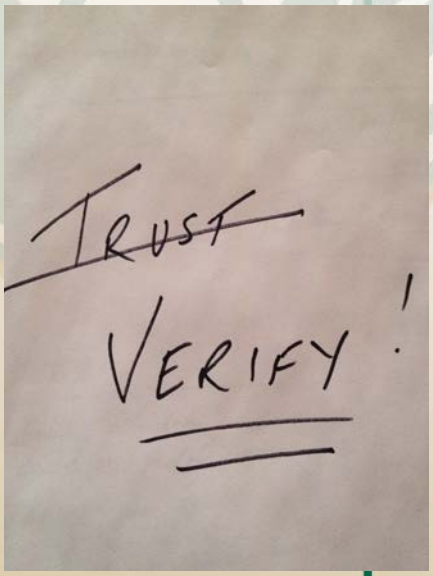
Iqbal SA, Wallach JD, Khoury MJ, Schully SD, Ioannidis JPA (2016) Reproducible Research Practices and Transparency across the Biomedical Literature. PLoS Biol 14(1): e1002333. doi:10.1371/journal.pbio.1002333

# To Do List

- Support development of innovative, agile and flexible quality system that supports the intended research
- Risk-based
- Rewarded and acknowledged
- Normalize the quality culture
- Develop minimum quality system standards
- Develop tools/training to make it easier to apply
- Increase acknowledgement and requirements (RFPs, publications, etc)

# To Do List

- Implement ‘Quality by Design’ approaches and best practices
- Understand the value, develop and promote the Quality Assurance Profession
  - Use a quality assurance professional to review critical publications prior to publication
- Understand the value, and develop and promote core components of the Regulatory Sciences

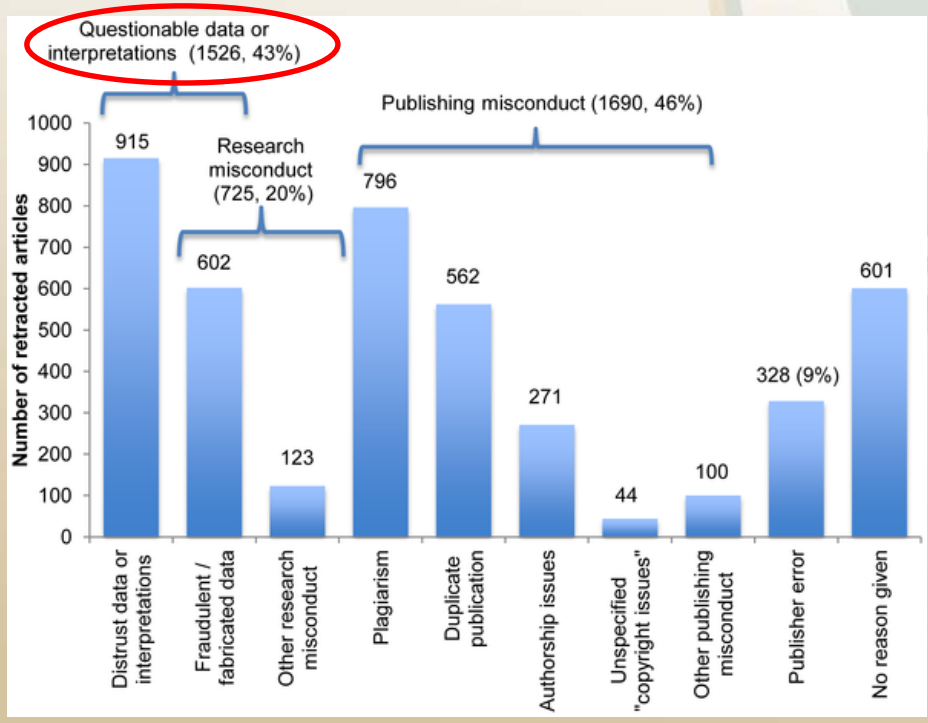


# Quality by Design Tools

## Model it! Prevent it!

| Model it! | Prevent it! |
|---|---|
| Data collection Procedures and Forms | Data collection Procedures and Forms |
| Training | Training |
| Mentoring | Independent Oversight Review |
| Incentives and Rewards | Loss of access and privileges |
| Quality Culture | Emphasize expectations and attitudes |
| Periodically Assess | |
| Communicate | |

# Recent trends due to poor Data Governance




Grieneisen ML, Zhang M (2012) A Comprehensive Survey of Retracted Articles from the Scholarly Literature. PLoS ONE 7(10): e44118. doi:10.1371/journal.pone.0044118
http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0044118

# CONCLUSION

## Quality Assurance Principles and Practices

- Value added components of good research practices, but seldom consistently implemented
- Historical attitudes and lack of understanding, training and access to QA resources can hinder application
- Can improve data quality and integrity
- Assist in establishing a quality culture

❖ Could assist in reducing retractions.

# Quality Assurance Professionals support study design, data quality, and reporting

- Focuses on “How do you know?”
  - Data that links information together in order to assure accuracy and completeness, and provide meaning and contexts to the data.
  - Allows for robust data review and verification
  - A part of the Quality System that assures data quality, fitness for use and data reporting accuracy, reconstruction and reproducibility.
- Independent
- Supports the data life cycle

❖ Applications to retraction prevention and publication pre-review

Society of Quality Assurance™
Promoting Quality in the Regulated Research Community

Colorado State University


- Contact Us
- Mission
- Training
- QA Services & GxP
- ClinicalTrials.gov
- IND/INAD/IDE Support
- Investigator's Brochure
- Use of Computers in Research
- FDA Guidance on Cell-Based Products