Data Integrity Workshop

Gulf Coast Consortia

Melissa Eitzen, MT(ASCP), MS, RQAP-GLP

13 June 2018

Schedule

10:00 – 10:05	Objectives & Agenda
10:05—10:25	Background: Quality Practices in Biomedical Research, Reproducibility & Reconstructability
10:25—10:55	Prescriptive Documents / Activity 1
10:55—11:40	Good Documentation Practices / Activities 2 & 3
11:40—12:00	**Break (pick up lunch)**
12:00—12:10	Change Control
12:10—12:30	Labeling, Materials and Reagents / Case Study 1
12:30—1:15	Raw (Source) Data, Research Records Laboratory Notebooks
1:15—1:30	Risks to Research / Case Study 2
1:30—1:55	Quality Management Systems / Activity 4
1:55—2:00	Culture of Quality & Closing Thoughts

Working Lunch

Resources are provided at the end of this presentation

Overview

Data Integrity Workshop

This workshop is designed to cover fundamental elements necessary to help assure the quality and integrity of data derived from research studies. The workshop will review best practices for documentation of research activities, data capture, data (and document) management, and introduce risk mitigation strategies to enhance study reproducibility. A combination of mini lectures, case studies, and group exercises will comprise the activities. Knowledge gained will allow attendees to implement lessons learned within their research environment as elements of a quality system or internal to an individual research project.

Target Audience: Research scientists, post-doctoral fellows, and graduate students

June 13, 2018

10:00 am – 2:00 pm, including a working lunch

Learning Objectives & Outcomes

LEARNING OBJECTIVES

- Apply the principles of ALCOA to research practices
- Identify gaps in research records
- List potential risks to research
- Describe the elements of a Quality Management System

LEARNING OUTCOMES

- Improve data quality and integrity from research studies
- Improve the reproducibility of research studies
- Reduce potential high risks to research
- Change the culture through execution of quality practices and effective research leadership

Data Integrity Workshop

Background

Quality Practices in Biomedical Research

Reproducibility & Reconstructability

Data Integrity

"I already wrote the paper. That's why it's so hard to get the right data."

Product Approval Pathway

Data

Data

Discovery / Research

Non-Clinical Proof of Concept

Non-Clinical Safety

Clinical Phases 1, 2, 3

Clinical Phase 4

No Regulatory, mandated Quality Practices

GLP

Regulatory Decision

Regulatory Decision

FDA Good Laboratory Practices

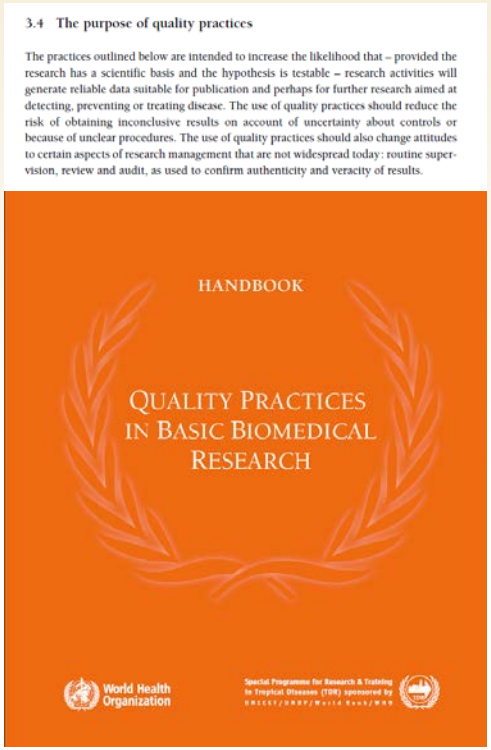
21 CFR Part 58 Subpart A—General Provisions

§58.1 Scope.

(a) This part describes good laboratory practices for conducting nonclinical laboratory studies that support or are intended to support applications for research or marketing permits for products regulated by the Food and Drug administration…compliance with this part is **intended to assure the quality and integrity of the** safety **data**…

Quality Practices

"(Quality) practices…are intended to increase the likelihood that—provided the research has a scientific basis and the hypothesis is testable—research activities will generate ***reliable data*** *suitable for publication and perhaps for further research aimed at detecting, preventing, or treating disease…"*



3.4 The purpose of quality practices

The practices outlined below are intended to increase the likelihood that – provided the research has a scientific basis and the hypothesis is testable – research activities will generate reliable data suitable for publication and perhaps for further research aimed at detecting, preventing or treating disease. The use of quality practices should reduce the risk of obtaining inconclusive results on account of uncertainty about controls or because of unclear procedures. The use of quality practices should also change attitudes to certain aspects of research management that are not widespread today: routine supervision, review and audit, as used to confirm authenticity and veracity of results.

HANDBOOK

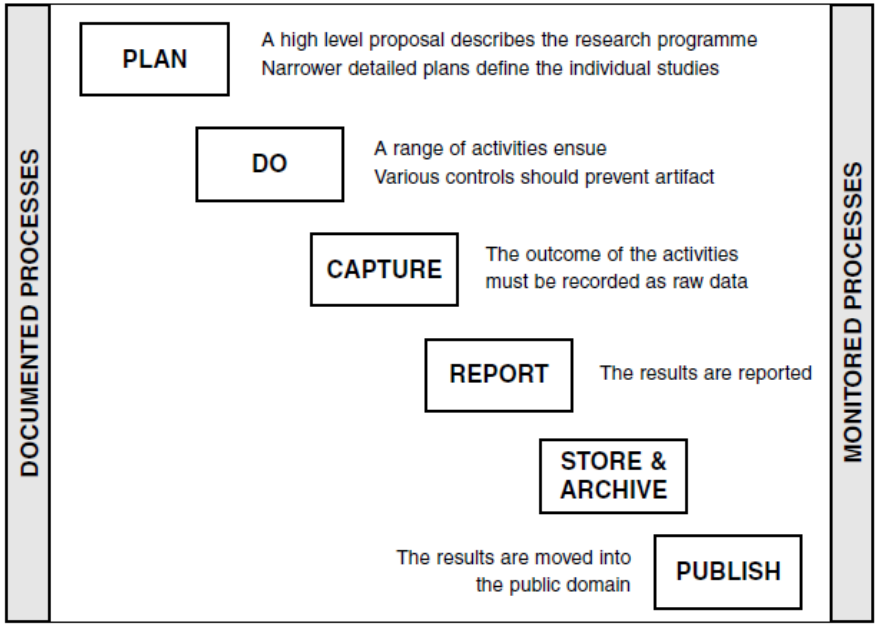
QUALITY PRACTICES IN BASIC BIOMEDICAL RESEARCH

World Health Organization

Research Activities

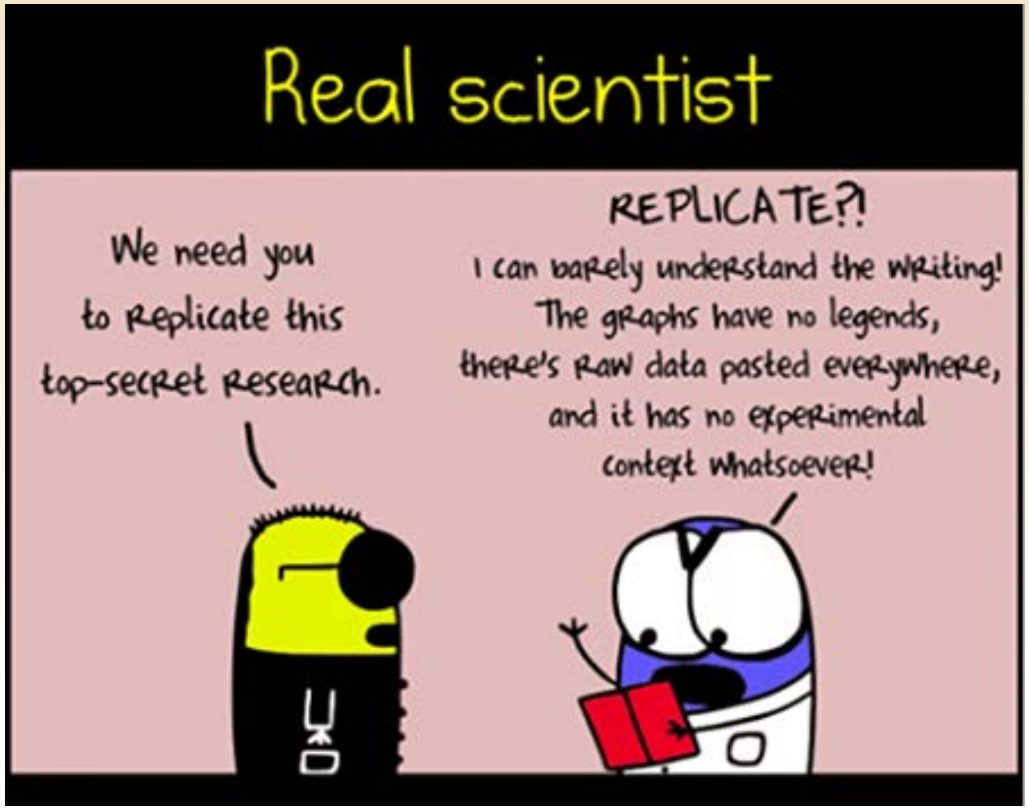
It must be stressed here that the quality practices for biomedical research described in this document do not address the scientific content of a research programme or proposal, but are concerned with the way the research work is organized and planned, performed, recorded, reported, archived, monitored and published. Figure 1 sketches the main steps in this process.

Figure 1. Flow of research activities



14

Reproducibility



Economics of Reproducibility

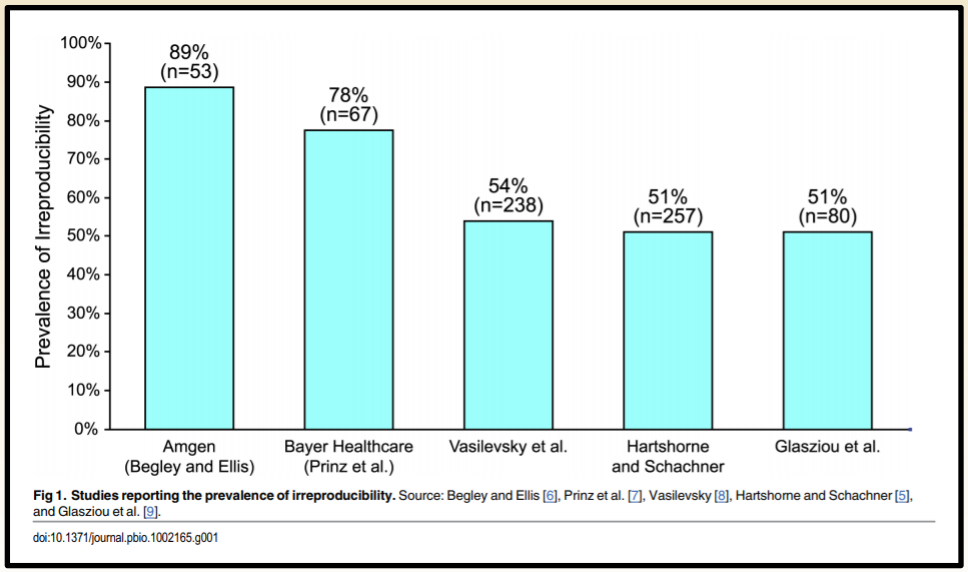


Fig 1. Studies reporting the prevalence of irreproducibility. Source: Begley and Ellis [6], Prinz et al. [7], Vasilevsky [8], Hartshorne and Schachner [5], and Glasziou et al. [9].

doi:10.1371/journal.pbio.1002165.g001

http://journals.plos.org/plosbiology/article/file?id=10.1371/journal.pbio.1002165&type=printable

PLOS | BIOLOGY

PERSPECTIVE

The Economics of Reproducibility in Preclinical Research

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Abstract

Low reproducibility rates within life science research undermine cumulative knowledge production and contribute to both delays and costs of therapeutic drug development. An analysis of past studies indicates that the cumulative (total) prevalence of irreproducible preclinical research exceeds 50%, resulting in approximately US$28,000,000,000 (US $28B)/year spent on preclinical research that is not reproducible—in the United States alone. We outline a framework for solutions and a plan for long-term improvements in reproducibility rates that will help to accelerate the discovery of life-saving therapies and cures.

OPEN ACCESS

Citation: Freedman LP, Cockburn IM, Simcoe TS (2015) The Economics of Reproducibility in Preclinical Research. PLoS Biol 13(6): e1002165. doi:10.1371/journal.pbio.1002165

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Competing Interests: Dr. Simcoe currently works as a Senior Economist for the Council of Economic Advisers (CEA). The CEA disclaims responsibility for any of the views expressed herein and these views do not necessarily represent the views of the CEA or the United States.

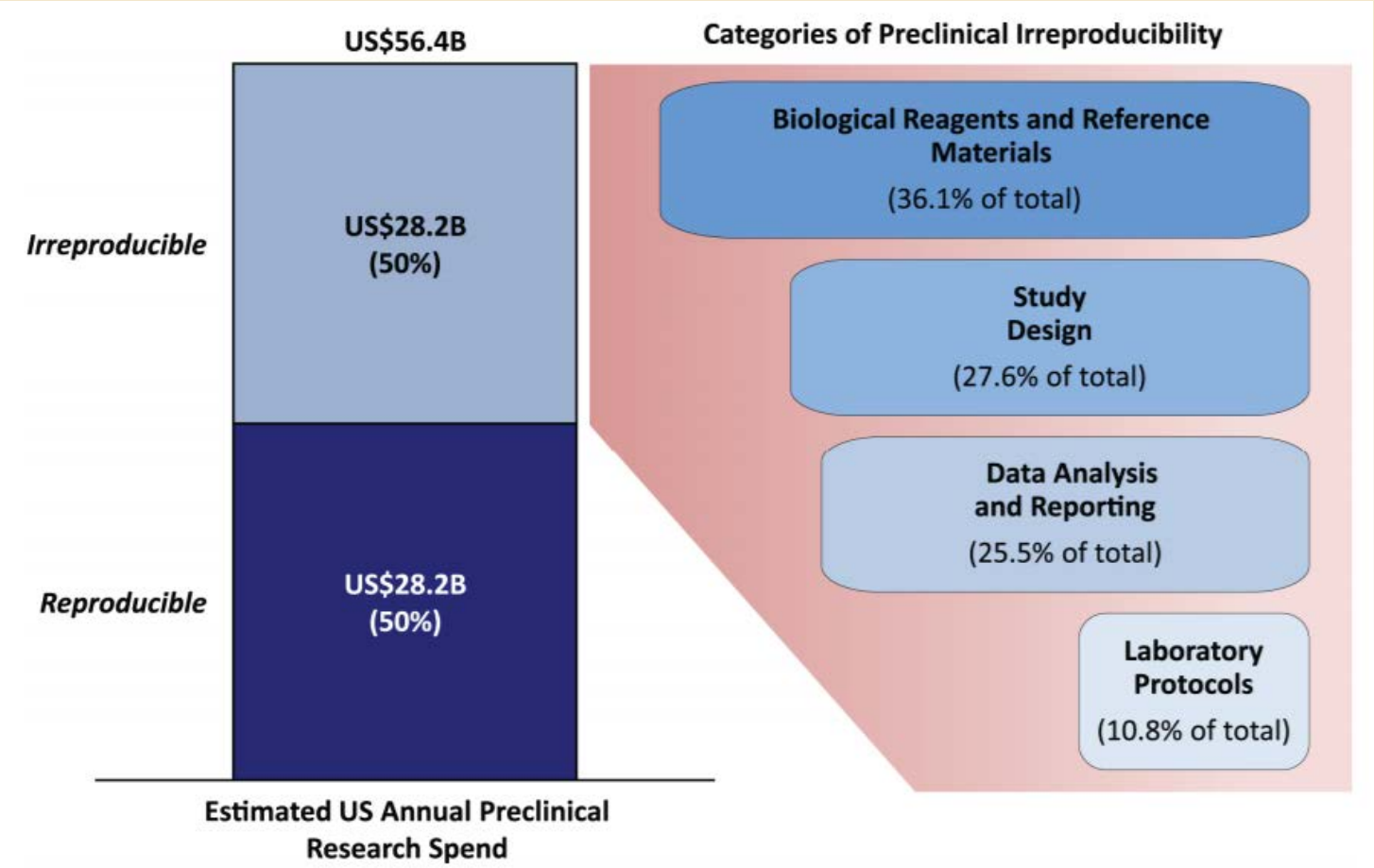
Abbreviations: AAAS, American Association for the Advancement of Science; FDA, US Food and Drug Association; GBSI, Global Biological Standards Institute; IETF, Internet Engineering Task Force; NIH, National Institutes of Health; PI, principal investigator; STR, short tandem repeat; W3C, World Wide Web Consortium.

Introduction

Much has been written about the alarming number of preclinical studies that were later found to be irreproducible [1,2]. Flawed preclinical studies create false hope for patients waiting for lifesaving cures; moreover, they point to systemic and costly inefficiencies in the way preclinical studies are designed, conducted, and reported. Because replication and cumulative knowledge production are cornerstones of the scientific process, these widespread accounts are scientifically troubling. Such concerns are further complicated by questions about the effectiveness of the peer review process itself [3], as well as the rapid growth of postpublication peer review (e.g., PubMed Commons, PubPeer), data sharing, and open access publishing that accelerate the identification of irreproducible studies [4]. Indeed, there are many different perspectives on the size of this problem, and published estimates of irreproducibility range from 51% [5] to 89% [6] (Fig 1). Our primary goal here is not to pinpoint the exact irreproducibility rate, but rather to identify root causes of the problem, estimate the direct costs of irreproducible research, and to develop a framework to address the highest priorities. Based on examples from within life sciences, application of economic theory, and reviewing lessons learned from other industries, we conclude that community-developed best practices and standards must play a central role in improving reproducibility going forward.

utmb Health

Economics of Reproducibility



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Economics of Reproducibility

- 53 landmark studies
- 6 confirmed (11%)
  - Controls
  - Reagents
  - Investigator bias
  - Described complete data set

COMMENT

AVIAN INFLUENZA Shift expertise to track mutations where they emerge p.534 | EARTH SYSTEMS Past climates give valuable clues to future warming p.537 | HISTORY OF SCIENCE Descartes' lost letter tracked using Google p.540 | OBITUARY Wylie Vale and an elusive stress hormone p.542

SCIENCE PHOTO LIBRARY

Many landmark findings in preclinical oncology research are not reproducible, in part because of inadequate cell lines and animal models.

Raise standards for preclinical cancer research

C. Glenn Begley and Lee M. Ellis propose how methods, publications and incentives must change if patients are to benefit.

Efforts over the past decade to characterize the genetic alterations in human cancers have led to a better understanding of molecular drivers of this complex set of diseases. Although we in the cancer field hoped that this would lead to more effective drugs, historically, our ability to translate cancer research to clinical success has been remarkably low[1]. Sadly, clinical trials in oncology have the highest failure rate compared with other therapeutic areas. Given the high unmet need in oncology, it is understandable that barriers to clinical development may be lower than for other disease areas, and a larger number of drugs with suboptimal preclinical validation will enter oncology trials. However, this low success rate is not sustainable or acceptable, and investigators must reassess their approach to translating discovery research into greater clinical success and impact.

Many factors are responsible for the high failure rate, notwithstanding the inherently difficult nature of this disease. Certainly, the limitations of preclinical tools such as inadequate cancer-cell-line and mouse models[2] make it difficult for even ▶

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Economics of Reproducibility

- Were studies blinded?
- Were basic studies repeated?
- Were all results presented?
- Were there positive and negative controls?
- Were valid ingredients used?
- Were appropriate statistics applied?

ILLUSTRATION BY DAVID PARKINS

of a policy that promotes rapid, open access to observing data, following the protocols developed in the International Polar Year[9]. Frameworks for helping to plan and coordinate long-term observing activities across the scientific community and other sectors need to be established.

The community-based observing networks from the International Polar Year, which focus on variables related to local environmental threats or benefits, are a good start. But to be accessible to others, these data should be entered into wider networks such as those of the WMO. Similar to the practice of joint resource management[10], the scientific community, stakeholders and decision-makers all need to be included in governance from the outset to help ensure relevance and efficiency.

Opportunities remain for the private sector to contribute to such collaborative networks. Offering up commercial vessels or infrastructure as platforms for scientific observations, sharing data and engaging the research community in the planning stages of industry observing programmes would go a long way towards establishing a 'network of networks'.

Last month, I was fortunate to be out in a small boat off Toksook Bay in Alaska with ice experts and hunters from the Yup'ik people. We were surrounded by jagged, fast-moving chunks of ice that, to me, seemed hostile. To my companions, it was all in a day's work. I recalled a sentiment I had heard from a marine-mammal expert in Barrow, more than 1,000 kilometres farther north, where the ice is now unstable. He stated that the key to adapting to increasingly dynamic ice is to learn from those to the south, such as in Toksook Bay. The charge to the scientific community is to help to create a foundation for such mutual learning to occur. ■

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COMMENT

Six red flags for suspect work

C. Glenn Begley explains how to recognize the preclinical papers in which the data won't stand up.

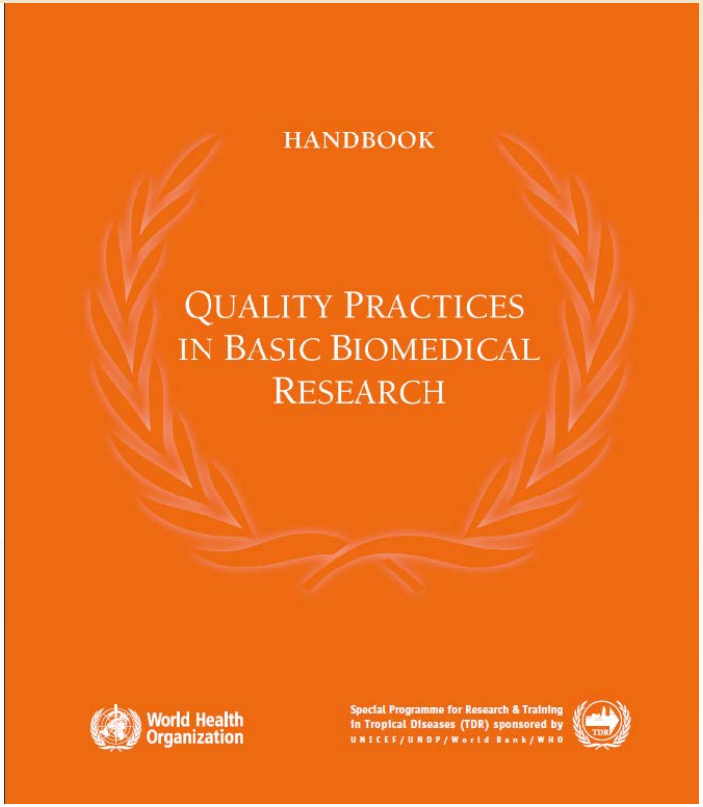
A few months ago, I received a desperate e-mail from a postdoctoral scientist. Researchers — including me and my colleagues — had just reported that the majority of preclinical cancer papers in top-tier journals could not be reproduced, even by the investigators themselves[1,2]. The postdoc pleaded with me to identify those papers, saying: "I could be wasting my time working on that project." This was true, but we had signed confidentiality agreements that prevented us from revealing the specific papers. Furthermore, identifying them would not address the broader, systemic issues in research and publishing that create a plethora of papers that don't stand up to scrutiny.

There were some glaring differences ▸

Reproducibility

3.3 Reproducibility

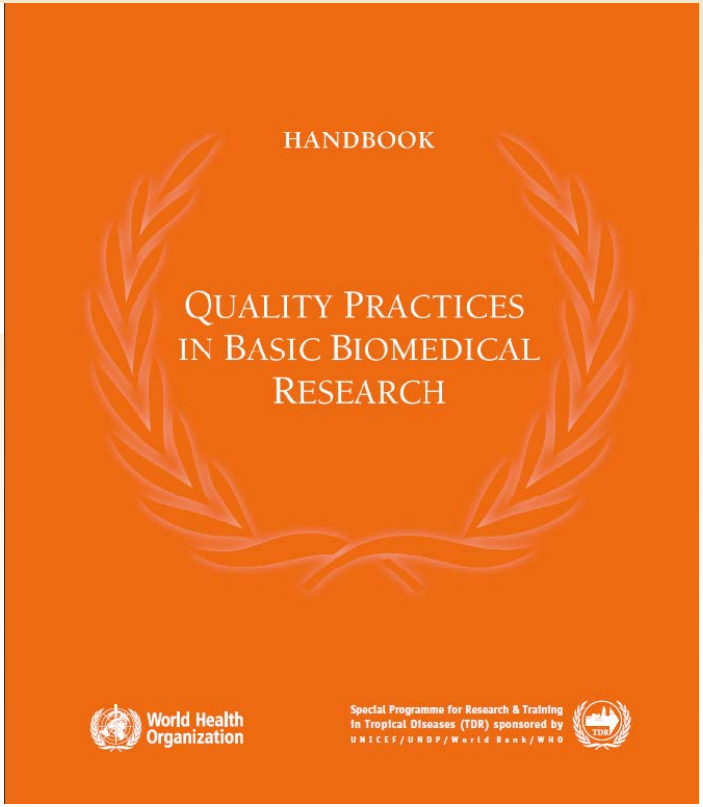
Reproducibility is one way of testing the reliability of data. This means that if the investigator or someone else were to repeat the experiment in the same set-up, equivalent data would result. Or if specimens were collected in the field, another visit to the same or a similar habitat at the same time of day/year would yield a similar collection. Since especially significant, valuable or controversial findings often require confirmation by repeating a study, all studies should be designed, managed, controlled, recorded and reported sufficiently to ensure reproducibility of the findings.



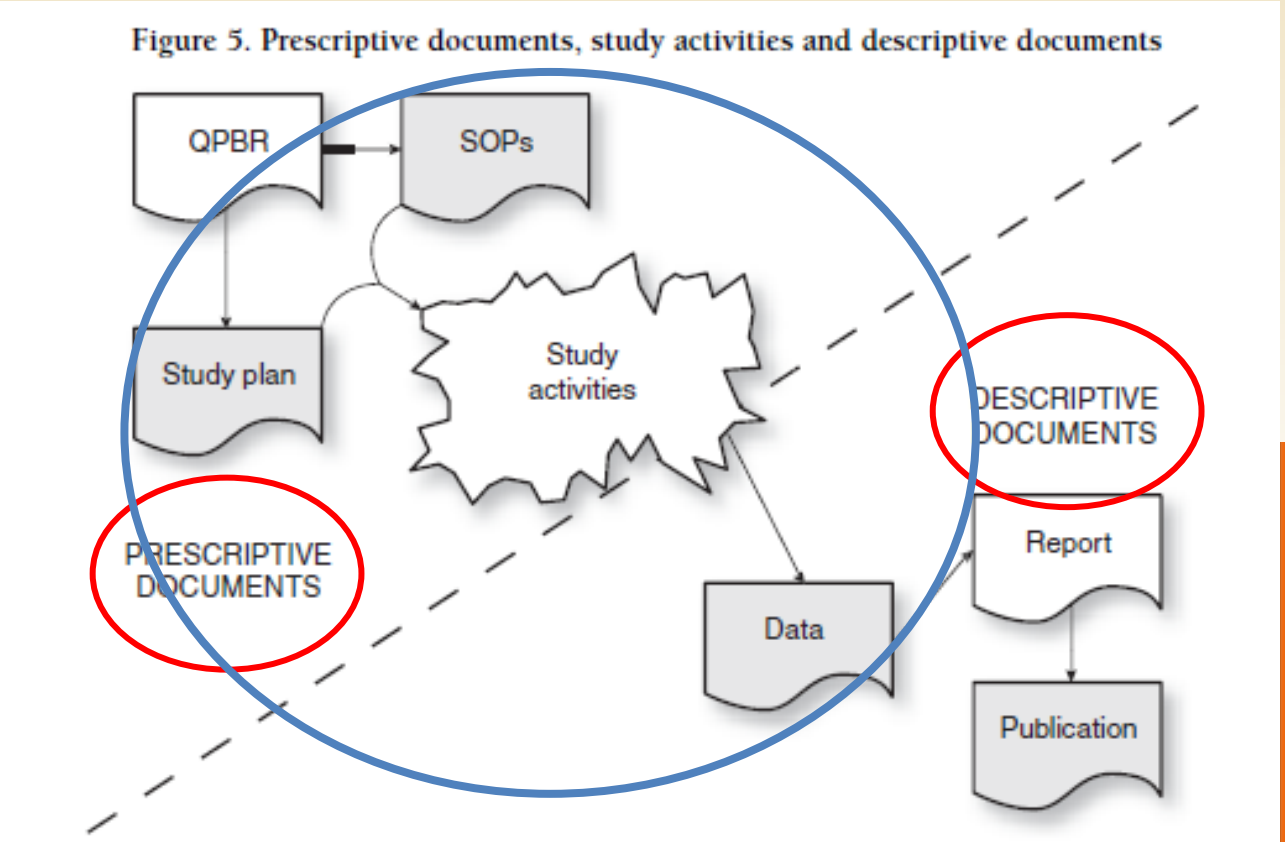
Reconstructability

4.3 Documentation

Making a full record of all information is essential not only to permit appropriate scientific interpretation of the results but also to enable complete reconstruction of the study, should this be necessary. Documentation is the only way of demonstrating what actually went on at the time of the experiment. *Without documentation the process is meaningless; essentially there has been no study.*



Reconstructability



Data Integrity Workshop

Prescriptive Documents:

Study Protocols (Plans) & Standardized Methods

Policies, Protocols, Procedures…

Document Hierarchy

Regulations / Rules / Policies

vs.

Customized Project Plans

Study Protocol (Plan)

EXAMPLE – Animal model

- Title
- Purpose / Summary
- Identification / Information of test and control articles
- Name of sponsor (grant number)
- Identification / Information of test system (number, body weight range, sex, source, species, strain, substrain, age, etc.)
- Diet (e.g., certified feed)
- Dosing information (mg/kg, frequency, method of, etc.)
- Analytical Testing (types and frequency, including necropsy)
- Contributing scientists
- Records to be maintained (including retention location and duration)
- Statistics
- Approval signatures

Study Protocol (Plan)

EXAMPLE—Laboratory Assay Qualification (Characterization)

- Title
- Purpose / summary
- Critical Reagents
- Methods
  - Precision
  - Accuracy
  - Robustness
  - Specificity
  - Sensitivity
- Statistics
- Approval

Preanalysis Plan

EXAMPLE—Social Science Research

- Statistical models
- Dependent variables
- Covariates
- Interaction terms
- Multiple testing corrections

Document Hierarchy

Regulations / Rules / Policies

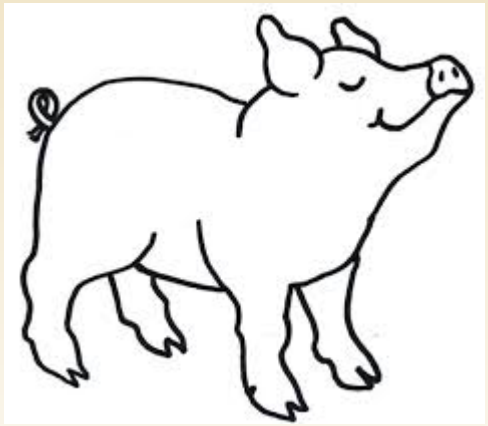
vs.

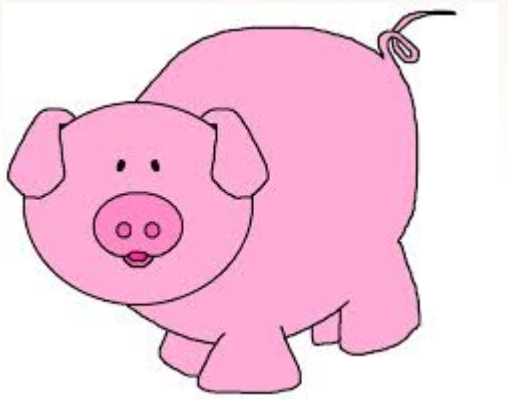
Customized Project Plans

vs.

Methods, Assays, Activities, etc. used across multiple studies/projects

Activity 1: How to Draw a Pig





Round 1: Draw a Pig

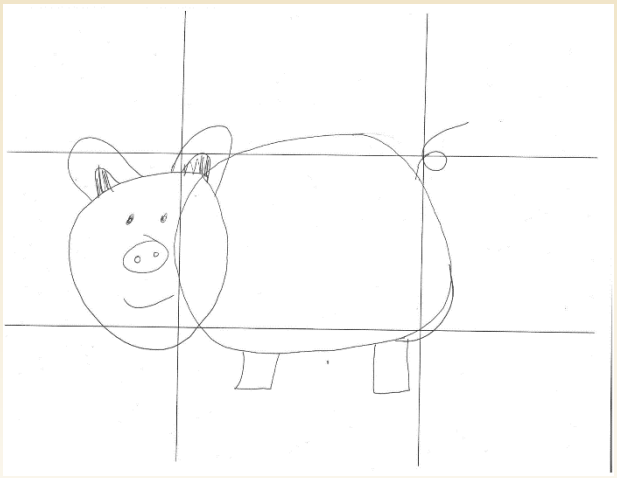
Instructions:

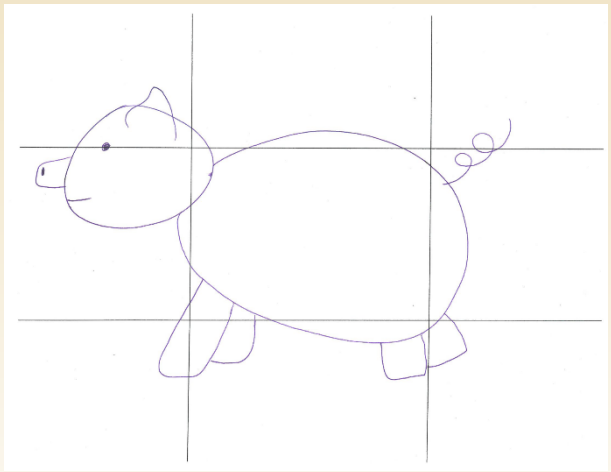
Draw a whole pig with entire body,

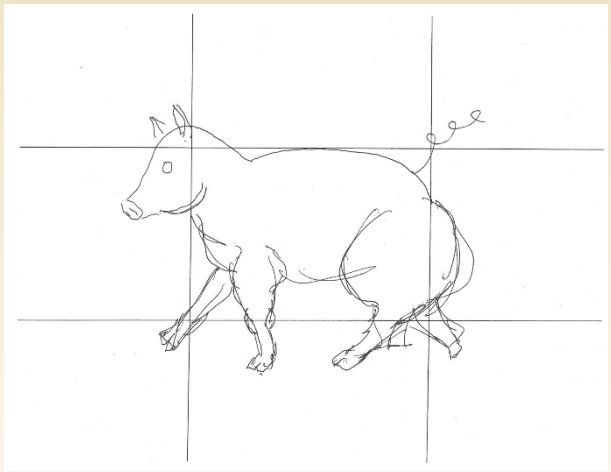
Facing the left side of the grid, and

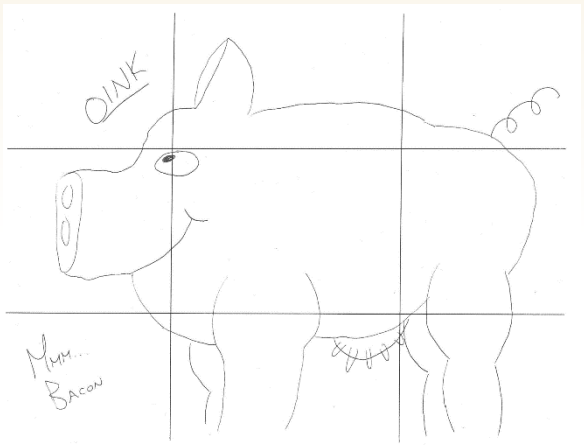
Covering most of the page (touching all grids)

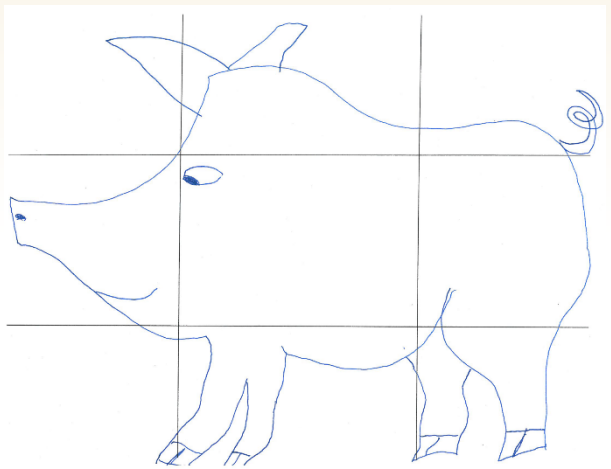
Round 1: Outcomes

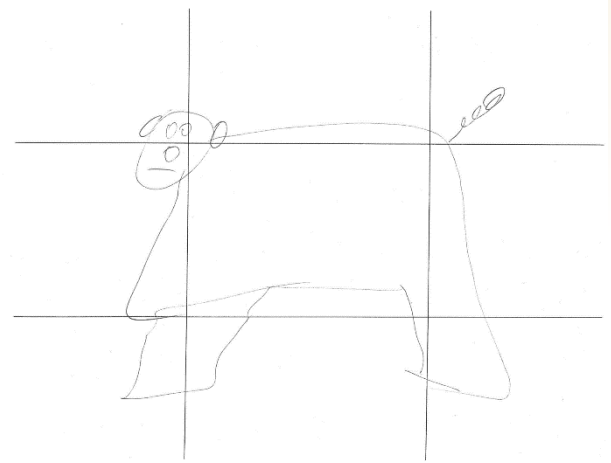










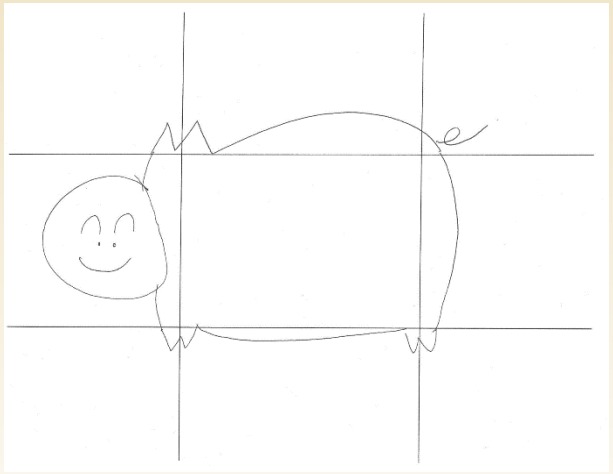
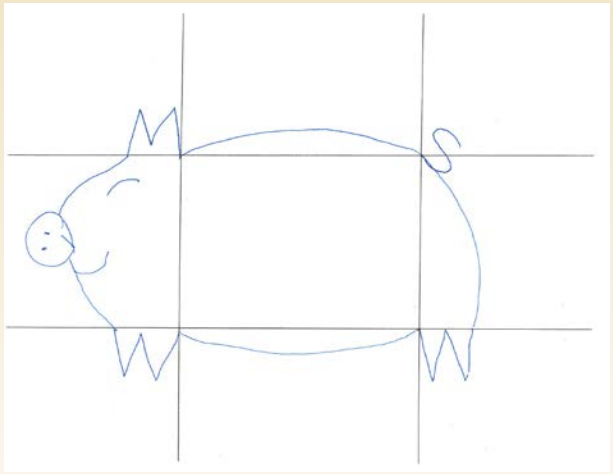
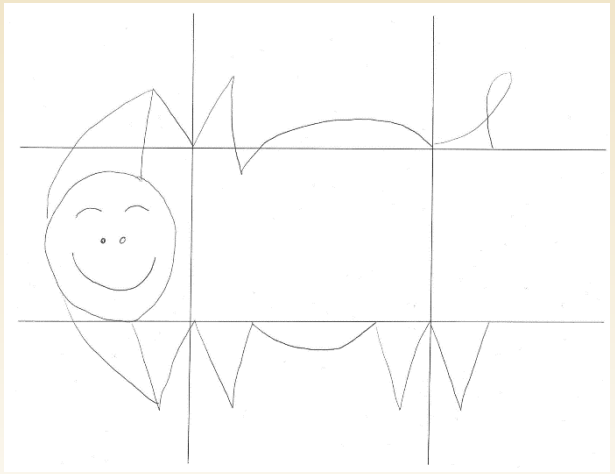
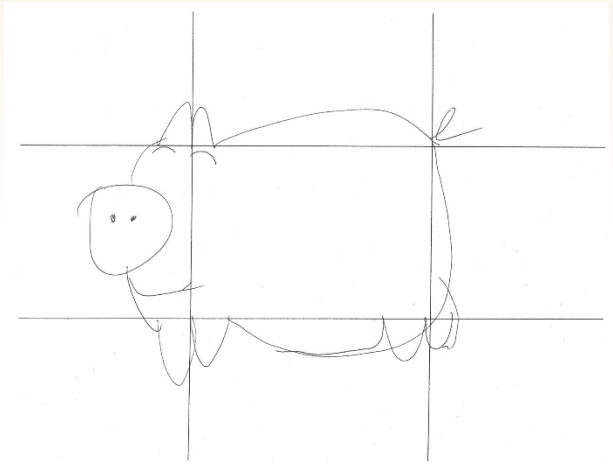
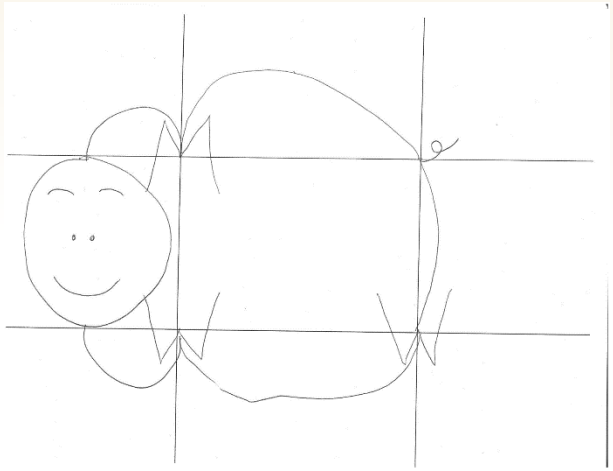
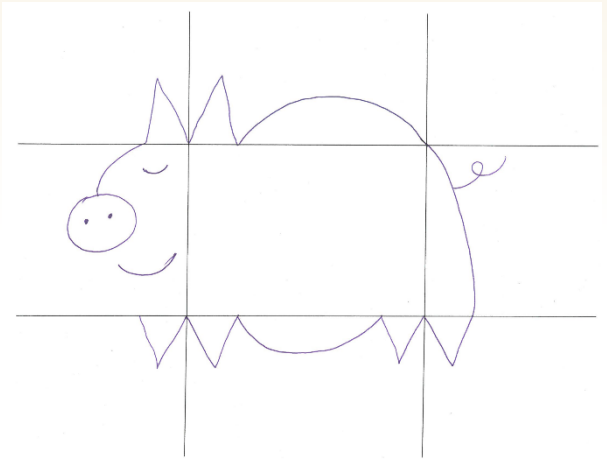


Round 2

Standard Operating Procedure Standardize Work Instruction	Status Final Revision 1 Rev. Date 02 Jan 2014
Procedure Number PIG-OOOl-A	Page 1 of 1

Task	Description	Sub-Task	Instructions
1	Draw a letter M at the top left intersection.	1.1	Bottom center of M touches intersection
2	Draw a letter W at bottom left intersection	2.1	Top center of W touches intersection
3	Draw letter W at bottom right intersection	3.1	Top center of W touches intersection
4	Draw arc from letter M to top right intersection		
5	Draw another arc from top right intersection to bottom right W		
6	Draw an arc between the two bottom Ws		
7	Draw the letter O in center left box		
8	Draw arc from letter M to top of the circle		
9	Draw arc from left W to bottom of the circle		
10	Draw an arc for the mouth	10.1	Halfway between the W and circle
		10.2	Must be a happy pig
11	Draw an arc for the eyes	11.1	Halfway between the M and circle
12	Draw cursive letter e near top of arc on right		
13	Draw two dots in middle of circle for pigs' nose.		

Round 2: Outcomes

Round 3

Standard Operating Procedure Standardize Work Instruction	Status Final Revision 2 Rev. Date 09 Jan 2014
Procedure Number PIG-OOOl-A	Page 1 of 1

Task	Description	Sub-Task	Instructions
1	Draw a letter M at the top left intersection.	1.1	Bottom center of M touches intersection
2	Draw letter W at bottom left intersection	2.1	Top center of W touches intersection
3	Draw letter W at bottom right intersection	3.1	Top center of W touches intersection
4	Draw arc from letter M to top right intersection		
5	Draw another arc from top right intersection to bottom right W		
6	Draw an arc between the two bottom Ws		
7	Draw the letter O in center left box		
8	Draw arc from letter M to top of the circle		
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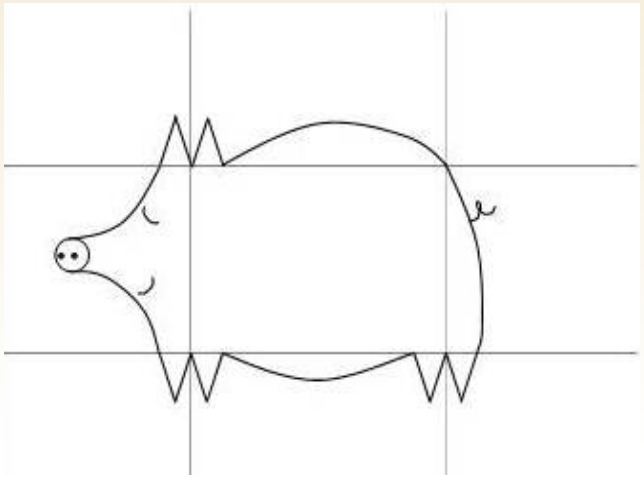
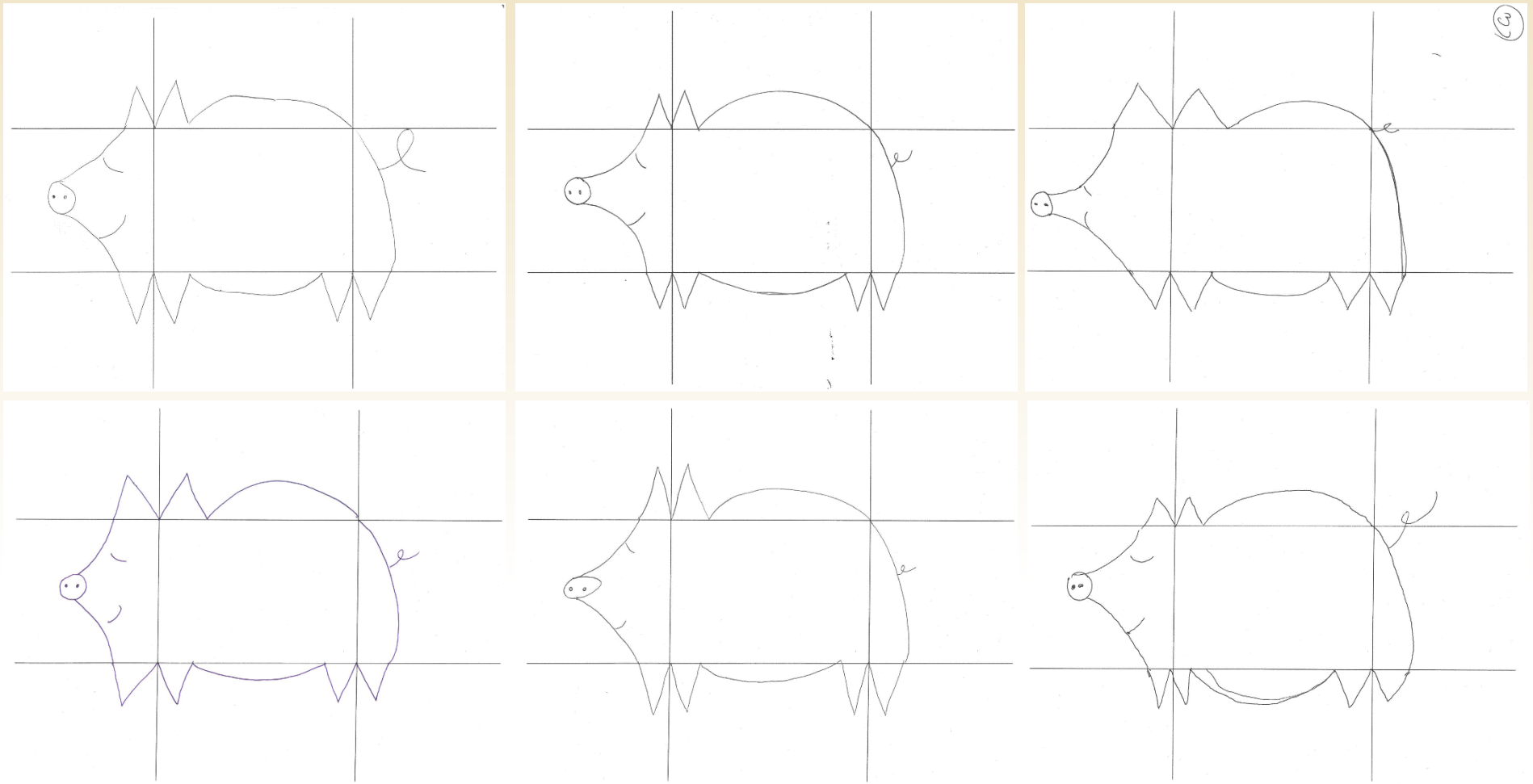
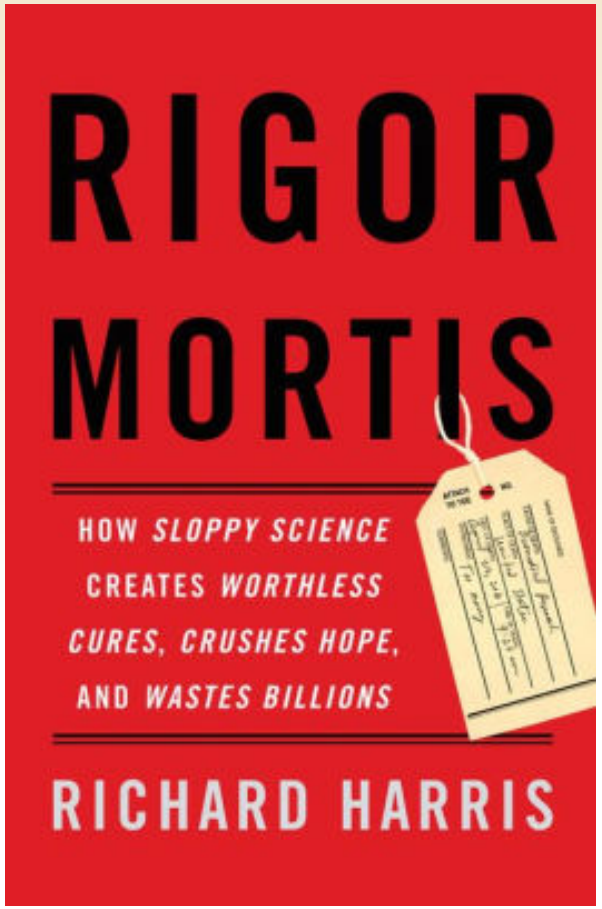


Round 3: Outcomes



Procedures

rial. Olaf Andersen at the Weill Cornell Medical College told me he nearly lost a friendship over differing results published by his lab and that of a close colleague. Finally, after some bitter words, they decided to sit down and try to resolve the discrepancy. Sorting through the possibilities took months, but apparently the difference boiled down to this: Andersen cleaned his glassware with acid, while his colleague used detergent.



Something to think about…

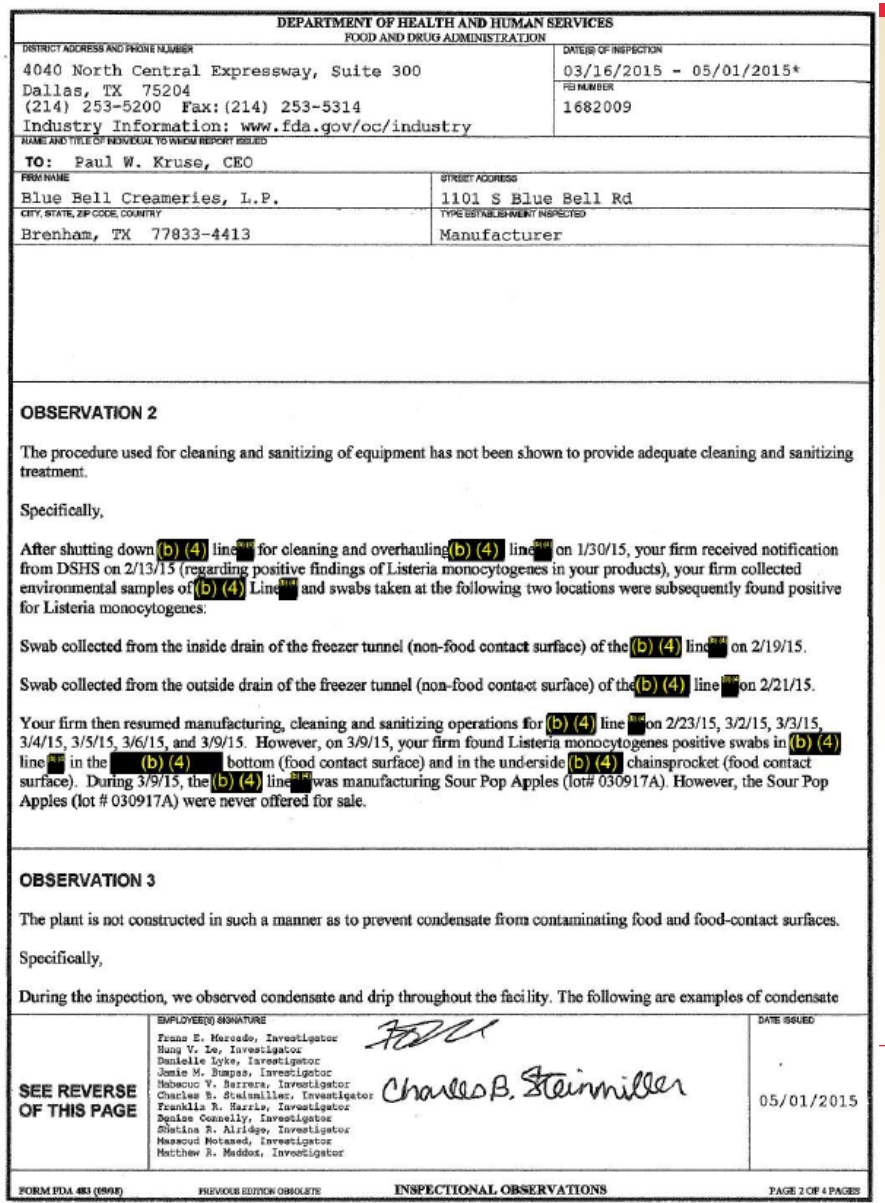
The Joint Commission Questions of the Week—Waived Testing:

What is a waived laboratory test?

As defined by Clinical Laboratory Improvement Amendments (CLIA) of 1988, a waived test is categorized as a simple laboratory test that has a relatively small risk of an erroneous result. Blood glucose and urine pregnancy tests are examples of waived tests. However, it is important to recognize that errors can occur anywhere in the testing process, particularly when the manufacturer's instructions are not followed. Competency must be assessed for waived testing.

Source: UTMB Weekly Relay communication

Something to think about…



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER
4040 North Central Expressway, Suite 300
Dallas, TX 75204
(214) 253-5200 Fax:(214) 253-5314
Industry Information: www.fda.gov/oc/industry

DATE(S) OF INSPECTION
03/16/2015 - 05/01/2015*

FEI NUMBER
1682009

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
TO: Paul W. Kruse, CEO

FIRM NAME
Blue Bell Creameries, L.P.

STREET ADDRESS
1101 S Blue Bell Rd

CITY, STATE, ZIP CODE, COUNTRY
Brenham, TX 77833-4413

TYPE ESTABLISHMENT INSPECTED
Manufacturer

OBSERVATION 2

The procedure used for cleaning and sanitizing of equipment has not been shown to provide adequate cleaning and sanitizing treatment.

Specifically,

After shutting down (b) (4) line [redacted] for cleaning and overhauling (b) (4) line [redacted] on 1/30/15, your firm received notification from DSHS on 2/13/15 (regarding positive findings of Listeria monocytogenes in your products), your firm collected environmental samples of (b) (4) Line [redacted] and swabs taken at the following two locations were subsequently found positive for Listeria monocytogenes:

Swab collected from the inside drain of the freezer tunnel (non-food contact surface) of the (b) (4) line [redacted] on 2/19/15.

Swab collected from the outside drain of the freezer tunnel (non-food contact surface) of the (b) (4) line [redacted] on 2/21/15.

Your firm then resumed manufacturing, cleaning and sanitizing operations for (b) (4) line [redacted] on 2/23/15, 3/2/15, 3/3/15, 3/4/15, 3/5/15, 3/6/15, and 3/9/15. However, on 3/9/15, your firm found Listeria monocytogenes positive swabs in (b) (4) line [redacted] in the (b) (4) bottom (food contact surface) and in the underside (b) (4) chainsprocket (food contact surface). During 3/9/15, the (b) (4) line [redacted] was manufacturing Sour Pop Apples (lot# 030917A). However, the Sour Pop Apples (lot # 030917A) were never offered for sale.

OBSERVATION 3

The plant is not constructed in such a manner as to prevent condensate from contaminating food and food-contact surfaces.

Specifically,

During the inspection, we observed condensate and drip throughout the facility. The following are examples of condensate

SEE REVERSE OF THIS PAGE

EMPLOYEE(S) SIGNATURE
Irene E. Mercado, Investigator
Hung V. Le, Investigator
Danielle Lyke, Investigator
Jamie M. Bumpas, Investigator
Rebecca V. Barrera, Investigator
Charles B. Steinmiller, Investigator
Franklin R. Harris, Investigator
Denise Connelly, Investigator
Shatina R. Alridge, Investigator
Masoud Motamed, Investigator
Matthew R. Maddox, Investigator

Charles B. Steinmiller

DATE ISSUED
05/01/2015

FORM FDA 483 (09/08) PREVIOUS EDITION OBSOLETE INSPECTIONAL OBSERVATIONS PAGE 2 OF 4 PAGES

Solutions…

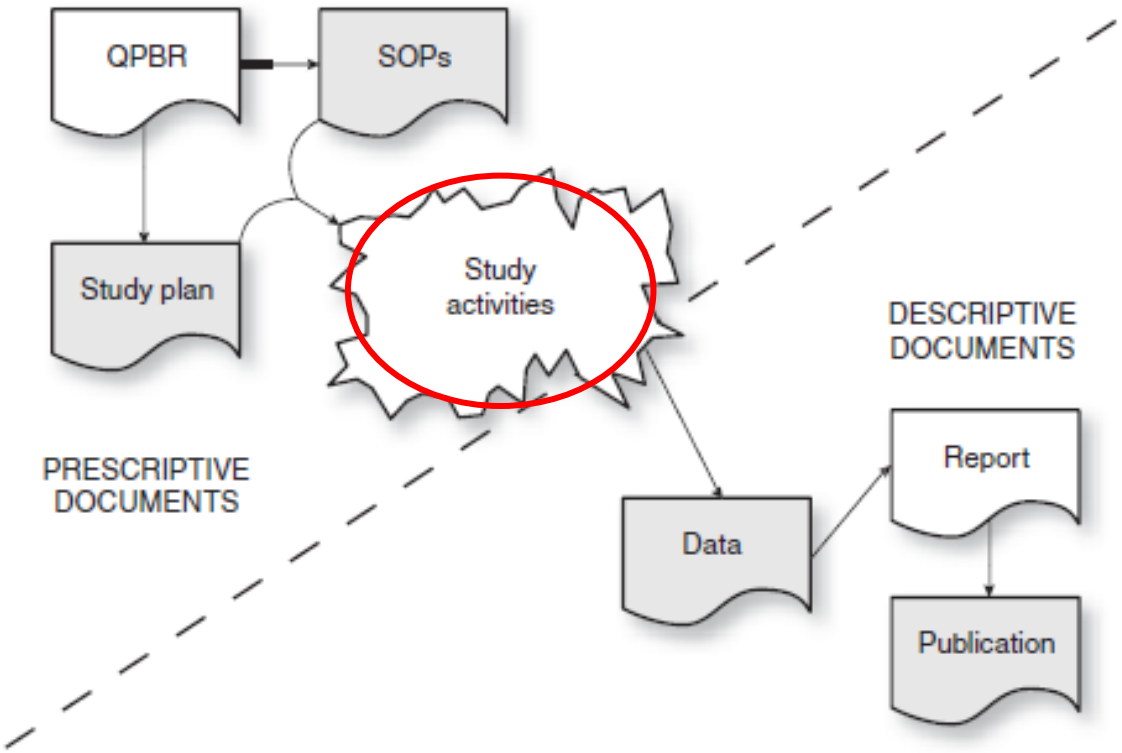
- Exercise: Have everyone write down how they perform the procedures and then compare
- Standardize procedures for routine methods
  - Think about how to document
  - Include an effective date!

Data Integrity Workshop

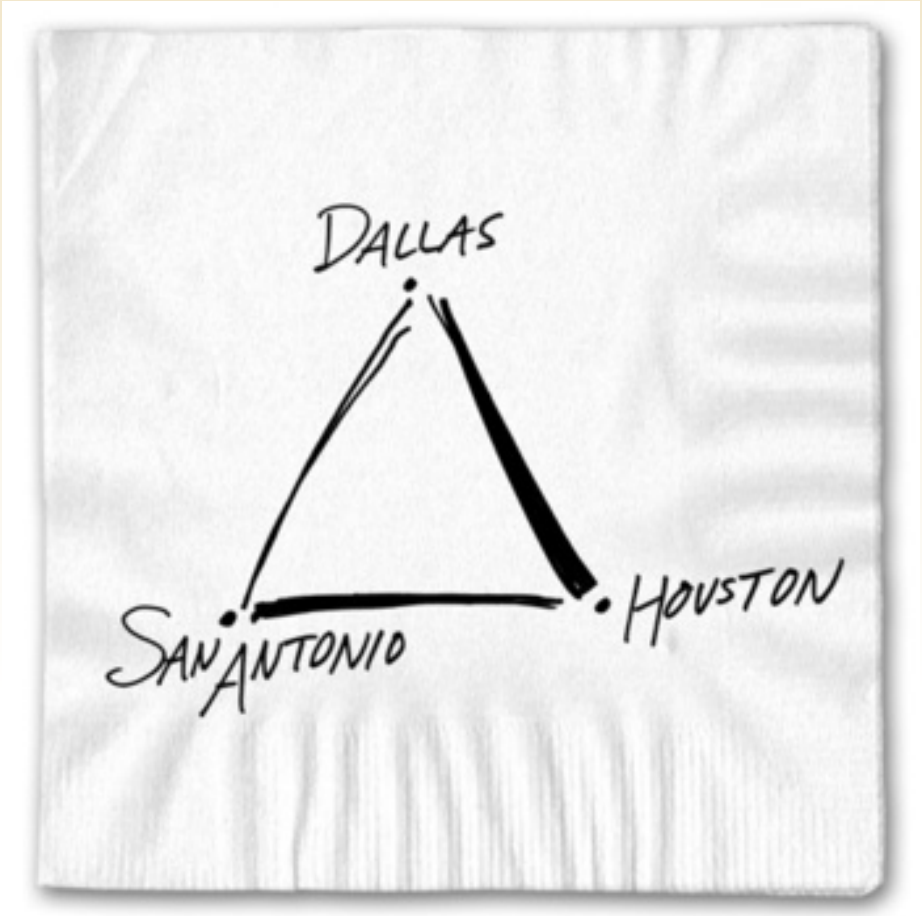
Good Documentation Practices

Documenting Study Activities

Figure 5. Prescriptive documents, study activities and descriptive documents



Documentation…



Data Quality and Integrity

Data Quality

- **A** ttributable
- **L** egible
- **C** ontemporaneous
- **O** riginal
- **A** ccurate

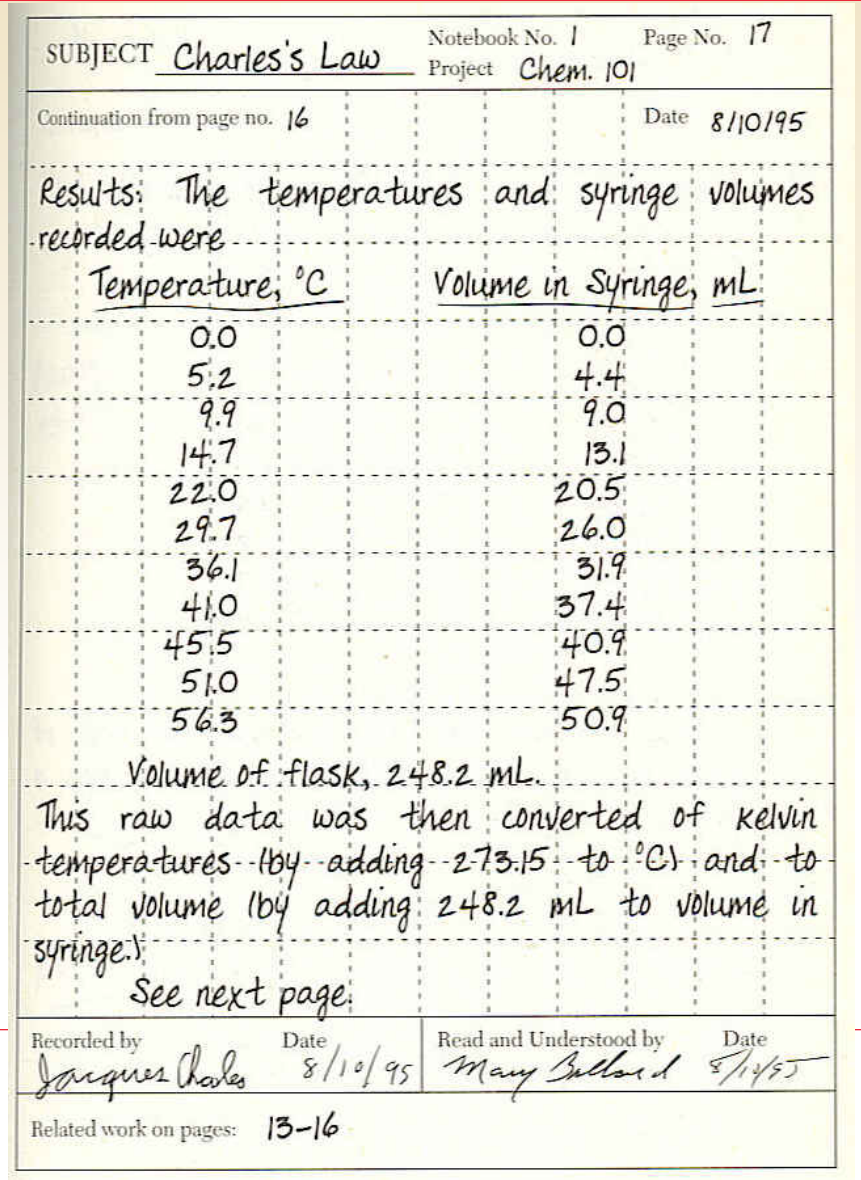
Data Integrity

Complete, Consistent,

Enduring, Readily Available

Documentation—Example

- ✓ Attributable
- ✓ Legible
- ✓ Contemporaneous
- ✓ Original
- ✓ Accurate



SUBJECT Charles's Law Notebook No. 1 Page No. 17
Project Chem. 101

Continuation from page no. 16 Date 8/10/95

Results: The temperatures and syringe volumes recorded were

Temperature, °C	Volume in Syringe, mL
0.0	0.0
5.2	4.4
9.9	9.0
14.7	13.1
22.0	20.5
29.7	26.0
36.1	31.9
41.0	37.4
45.5	40.9
51.0	47.5
56.3	50.9

Volume of flask, 248.2 mL.

This raw data was then converted of Kelvin temperatures (by adding 273.15 to °C) and to total volume (by adding 248.2 mL to volume in syringe.)

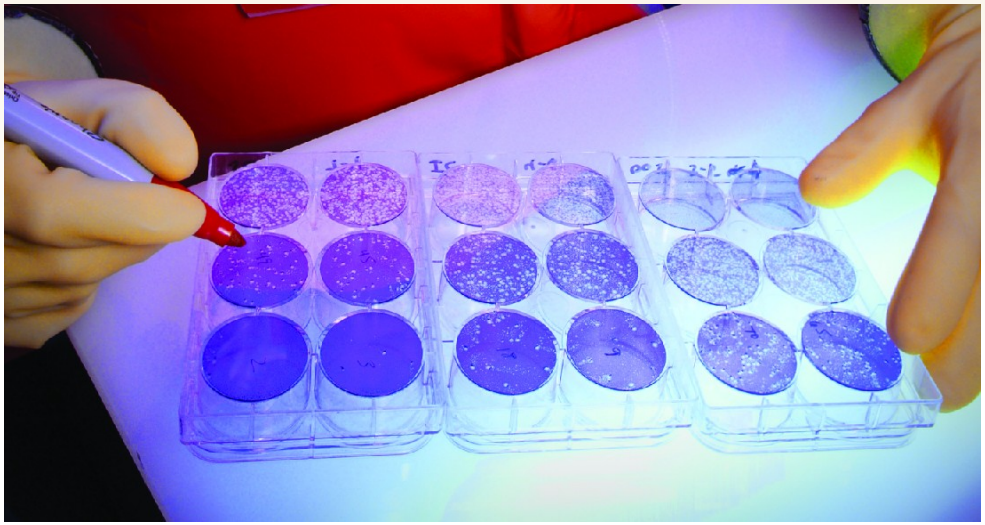
See next page.

Recorded by Jacques Charles Date 8/10/95 Read and Understood by Mary Gallard Date 8/14/95

Related work on pages: 13-16

Source: Google Images

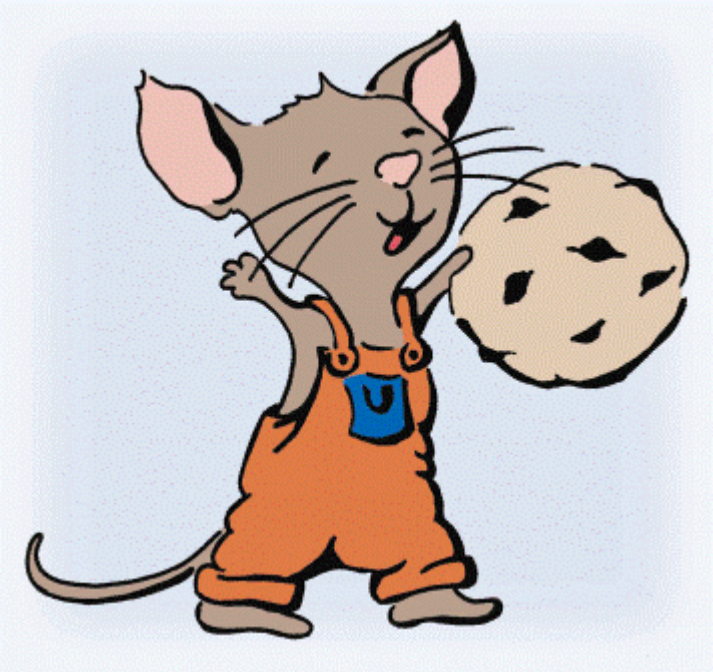
Documentation—The ALCOA Test!



This shows Hanczyc and Merkle by the cabinet where the work with hydrogen cyanide were conducted. Merkle is writing notes on the glass, while Hanczyc holds a sample of reacted hydrogen cyanide. Credit: Photo: *Birgitte Svennevig/SDU*

Activity 2: Documentation

- ✓ Attributable
- ✓ Legible
- ✓ Contemporaneous
- ✓ Original
- ✓ Accurate



Identification Number 45924

Documentation—Corrections

Making Corrections

- **S**ingle
- **L**ine
- **I**nitial
- **D**ate
- **E**ntry
- **R**eason

EXAMPLE

ID 45924:
Active, eating MME 29 May 2018

Documentation—Corrections

Making Corrections

- **S**ingle
- **L**ine
- **I**nitial
- **D**ate
- **E**ntry
- **R**eason

EXAMPLE

ID 45924:

~~Active, eating~~ MME 29 May 2018

Active, holding cookie

Documentation—Corrections

Making Corrections

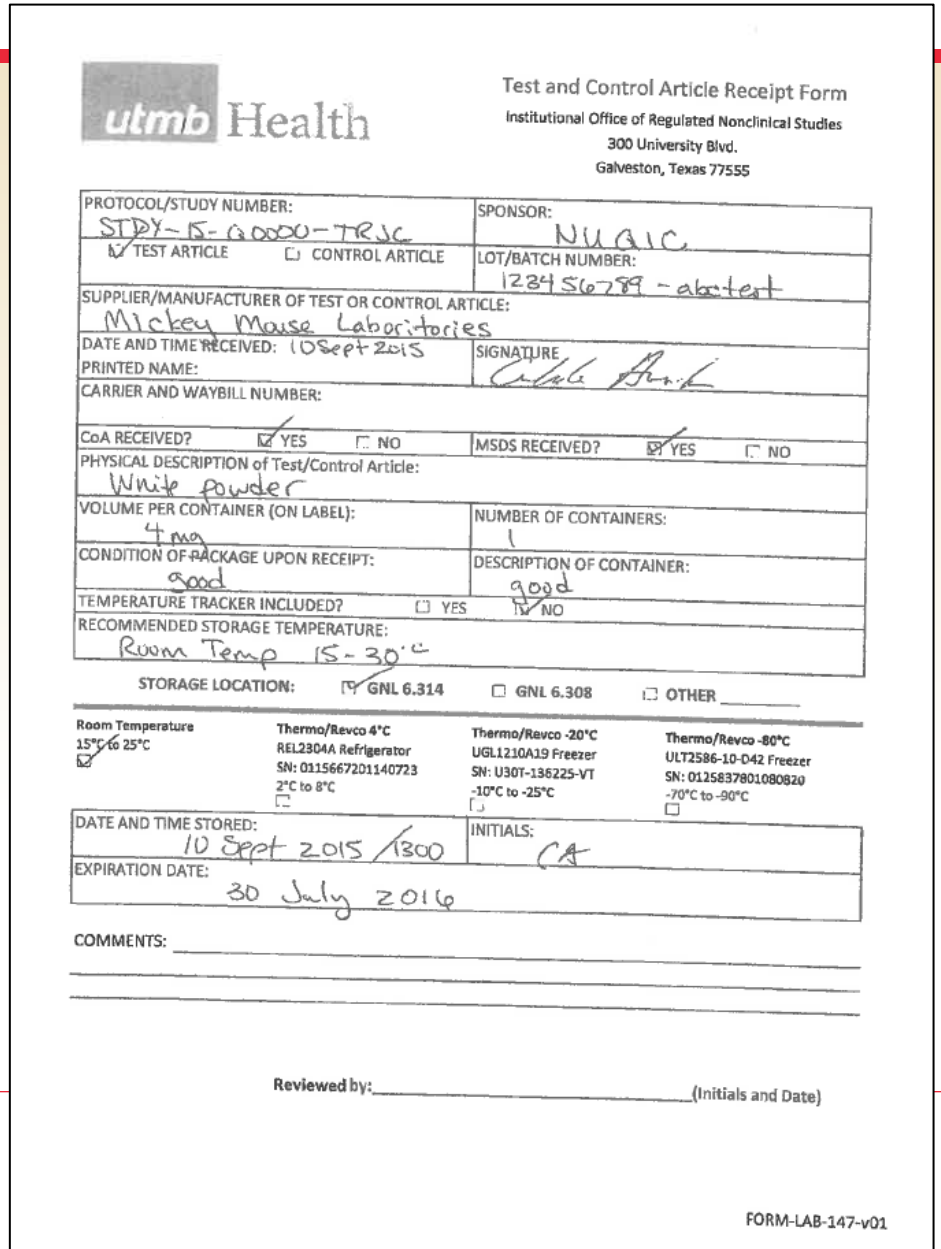
- **S**ingle
- **L**ine
- **I**nitial
- **D**ate
- **E**ntry
- **R**eason

EXAMPLE

ID 45924:
~~Active, eating~~ MME 29 May 2018
Active, holding cookie*

*Incorrectly wrote observation for 45923 in animal 45924 record. Error found during QC.
MME 31 May 2018

Documentation—Missing Information



utmb Health

Test and Control Article Receipt Form

Institutional Office of Regulated Nonclinical Studies
300 University Blvd.
Galveston, Texas 77555

PROTOCOL/STUDY NUMBER: STDY-15-00000-TRJC	SPONSOR: NUAIC
☑ TEST ARTICLE ☐ CONTROL ARTICLE	LOT/BATCH NUMBER: 123456789 - abc-test
SUPPLIER/MANUFACTURER OF TEST OR CONTROL ARTICLE: Mickey Mouse Laboratories	
DATE AND TIME RECEIVED: 10Sept 2015 PRINTED NAME:	SIGNATURE
CARRIER AND WAYBILL NUMBER:	
CoA RECEIVED? ☑ YES ☐ NO	MSDS RECEIVED? ☑ YES ☐ NO
PHYSICAL DESCRIPTION of Test/Control Article: White powder	
VOLUME PER CONTAINER (ON LABEL): 4 mg	NUMBER OF CONTAINERS: 1
CONDITION OF PACKAGE UPON RECEIPT: Good	DESCRIPTION OF CONTAINER: good
TEMPERATURE TRACKER INCLUDED? ☐ YES ☑ NO	
RECOMMENDED STORAGE TEMPERATURE: Room Temp 15-30°C	

STORAGE LOCATION: ☑ GNL 6.314 ☐ GNL 6.308 ☐ OTHER _____

Room Temperature	Thermo/Revco 4°C	Thermo/Revco -20°C	Thermo/Revco -80°C
15°C to 25°C ☑	REL2304A Refrigerator	UGL1210A19 Freezer	ULT2586-10-D42 Freezer
	SN: 0115667201140723	SN: U30T-136225-VT	SN: 0125837801080820
	2°C to 8°C ☐	-10°C to -25°C ☐	-70°C to -90°C ☐

DATE AND TIME STORED: 10 Sept 2015 1300	INITIALS: CA
EXPIRATION DATE: 30 July 2016	

COMMENTS: _____

Reviewed by: _____ (Initials and Date)

FORM-LAB-147-v01

Documentation—Incomplete information

Test System #1 - Guinea Mouse CD-1 Male

Ear Notch – No Hole

Procedure	Substance	Date	Time	Dose	Volume	Route	Anesthesia	Performed by	Verified by
Test Article	Chorawet	9.19.15	1:03pm	N/A	0.5 mL	OG	\	B. Roberts	CA 19Sept15
Challenge	GP Virus	22Sept15	8:24am	1.05×10^6	100 µl	IP	\	M. Jones	2015 Sept 22

	CN-2015 Behavior			Appearance			Weight			Blood Draw		
Date	score	time	initials	score	time	initials	grams	time	initials	volume	time	initials
19 Sept 15	1	10:03A	BR	1	10:03A	BR	13.6	10:04A	BR	0.3mL	10:10A	BR
20 Sept 15	1	10:04A	BR	1	10:04A	BR						
21 Sept 15	2	11:17A	BR	1	11:18A	BR						
22 Sept 15	1	7:21A	BR	1	7:23A	BR	13.8	7:25A	BR			
23 Sept 15	2	9:03A	BR	1	9:04A	BR						
24 Sept 15	2	10:23A	BR	2	10:24A	BR						
25 Sept 15	2	8:35A	CA	2	8:36A	CA						
26 Sept 15	3/EU	10:01A	KJ	2/EU	10:03A	KJ	13.2	10:04A	KJ	0.25mL	10:07A	KJ

Comments (Initial and date all comments in this section):

EU = Euthanized by CO_2 or Overexposure to isoflurane

n/a

Reviewd/QC: KJ 26 Sept 2015

Initial Date

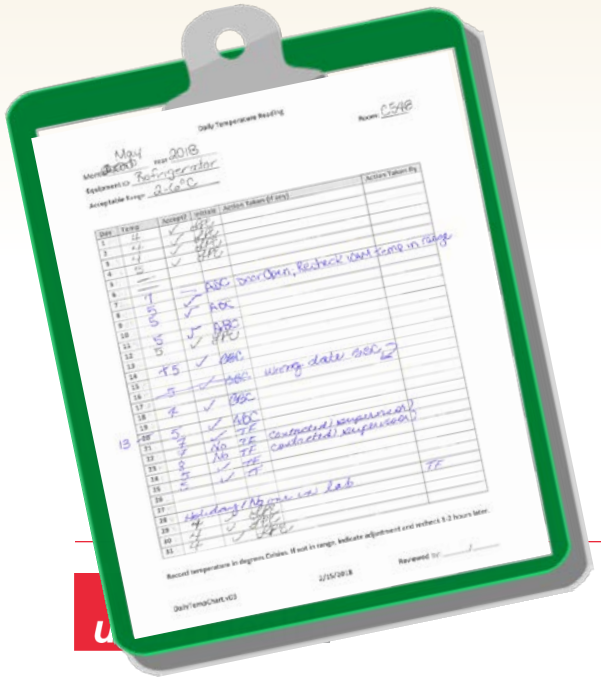
Page 1

FORM-LAB-148-v01

For Use on STDY-15-XXXX-TRJC

Activity 3: Document Review

- ❑ Attributable?
- ❑ Legible?
- ❑ Contemporaneous?
- ❑ Original?
- ❑ Accurate?



Daily Temperature Reading

Month May Year 2018 Room: C548

Equipment ID Refrigerator

Acceptable Range 2-6°C

Day	Temp	Accept?	Initials	Action Taken (if any)	Action Taken By
1	4	✓	LPE		
2	4	✓	LPE		
3	4	✓	LPE		
4	5	✓	LPE		
5	—				
6	—				
7	7	—	ABC	Door Open; Recheck 10AM Temp in range	
8	5	✓			
9	5	✓	ABC		
10					
11	5	✓	ABC		
12	5	✓	LPE		
13					
14	15	✓	BBC		
15					
16	5	✓	BBC	Wrong date BBC	
17					
18	4	✓	BBC		
19					
20 (13)	5	✓	ABC		
21	7	✓	TF		
22	7	No	TF	Contacted supervisor	
23	8	No	TF	Contacted supervisor	
24	5	✓	TF		
25	5	✓	TF		
26					
27					
28	Holiday/No one in lab				TF
29	4	✓	LPE		
30	4	✓	LPE		
31	4	✓	LPE		

Record temperature in degrees Celsius. If not in range, indicate adjustment and recheck 1-2 hours later.

DailyTempChart.v03 2/15/2018 Reviewed by: _____/_____

Documentation—Images

"Falsified the Western blot data demonstrating sPLA2 expression in a time course after ischemia in Figure 1B of the JBC paper and Figure 2A and 2C of the Brain Research paper by rearranging the bands such that the labels do not accurately portray what is in the lanes…"

FINDINGS OF RESEARCH MISCONDUCT

Notice Number: NOT-OD-13-040

Key Dates

Release Date: February 12, 2013

Issued by

Department of Health and Human Services

Purpose

SUMMARY: Notice is hereby given that the Office of Research Integrity (ORI) has taken final action in the following case:

Rao M. Adibhatla, Ph.D., University of Wisconsin: Based on the report of an investigation conducted by the University of Wisconsin (UW) and additional analysis conducted by ORI in its oversight review, ORI found that Dr. Rao M. Adibhatla, Assistant Professor, Department of Neurological Surgery, UW, engaged in research misconduct by falsifying results in two publications supported by National Institute of Neurological Diseases and Stroke (NINDS), National Institutes of Health (NIH), grant R01 NS042008 and in three unfunded applications that Dr. Adibhatla submitted to NINDS, NIH, as R01 NS042008-05, -05A1, and -05A2. The questioned papers are:

1. Adibhatla, R.M., Hatcher, J.F., Larsen E.C. et al. ``CDP-choline Significantly Restores Phosphatidylcholine Levels by Differentially Affecting Phospholipase A2 and CTP:Phosphocholine Cytidylyltransferase after Stroke.' *J. Biol. Chem.* 281:6718-6725, 2006 (hereafter referred to as the ``*JBC* paper'), as the sPLA2-IIA, CCTα, and PLD2 data in Figures 1B, 2A, and 3A, respectively

2. Adibhatla, R.M., & Hatcher, J.F. ``Secretory phospholipase A2 IIA is Up-regulated by TNF-α and IL-1α/β after Transient Focal Cerebral Ischemia in Rat.' *Brain Research* 1134:199-205, 2007 (hereafter referred to as the ``*Brain Research* paper'), as the sPLA2-IIA data in Figures 2A and 2C.

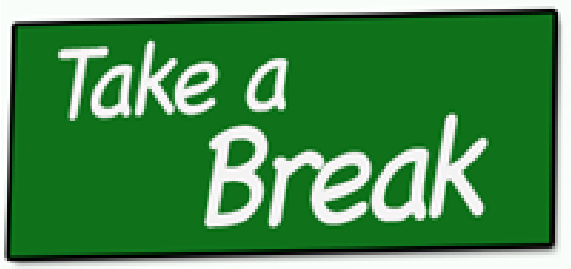
ORI found that Respondent committed research misconduct by falsifying Western blot images as well as quantitative and statistical data obtained from purported scans of the films. The research studied the effect of cerebral ischemia on phospholipid homeostasis in an experimental animal model (SHR rat) of stroke during the course of reperfusion of the ischemic cortex. The falsified Western blot images and derivative quantitative data describe changes in levels of sPLA2-IIAA, CCTα, and of PLD2 during reperfusion in the ischemic cortex.

Specifically, the Respondent:

- Falsified the Western blot data demonstrating sPLA2 expression in a time course after ischemia in Figure 1B of the *JBC* paper and Figure 2A and 2C of the Brain Research paper by rearranging the bands such that the labels do not accurately portray what is in the lanes. He perpetuated the falsification by presenting the quantification of the single falsified Western blot in a bar graph as the average of five (5) replicate Western blots. The result in the paper cannot be substantiated by the actual experiments.
- Falsified the Western blot data demonstrating CCTα expression in a time course assay after ischemia in Figure 2A of the *JBC* paper by rearranging the bands such that the labels do not accurately portray what is in the lanes. He perpetuated the falsification by presenting the quantification of the single falsified Western blot in a bar graph as the average of four (4) replicate Western blots and the six (6) hour time point was further falsified to make the results look better. The result in the paper cannot be substantiated by the actual experiments.
- Falsified the quantification of a Western blot demonstrating PLD2 expression in a time course after ischemia in Figure 3A of the *JBC* paper by claiming a bar graph quantifying a single

Data Integrity Workshop

BREAK…Grab lunch!



Data Integrity Workshop

Change Control

Documentation—Corrections

Making Corrections

- **S**ingle
- **L**ine
- **I**nitial
- **D**ate
- **E**ntry
- **R**eason

EXAMPLE

ID 45924:
~~Active, eating~~ MME 29 May 2018
Active, holding cookie*

*Incorrectly wrote observation for 45923 in animal 45924 record. Error found during QC.
MME 31 May 2018

Group Discussion—Changes

How do you make changes?

- Study plan
- Standardized methods

How do you document changes?

How do you communicate these changes?

Who approves changes?

Data Integrity Workshop

Labeling

Materials and Reagents

Labeling


WATERMELON
PACKED ON
SELL BY
WT.LBS
1.49
1.00
2 05040 50149 8
1.49
08/21
PRICE PER LB.
TOTAL $ PRICE
COMPARE FOODS
1883 MADISON STREET QNS


SLIDES
MICROSCOPE SLIDES
72 PCS


STERILE

Reagent Labeling

Reagent Information

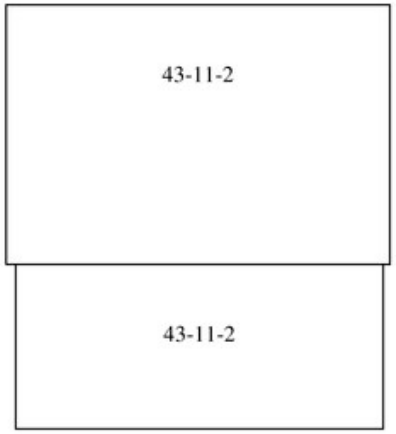
- Supplier / Vendor
- Lot number
- Expiration date
- Storage requirement
- Safety information
- Opened date
- Labeling
  - Mixtures
  - Aliquots

Reagent:	
Date received:	Sign.:
Date opened:	
Opened by:	Sign.:
Store loc.:	
Expiry date:	
Remarks:	

http://www.fao.org/docrep/W7295E/w7295e07.htm

Sample Tracking

Front view of box and lid



Example:
43 - Clinical Center ID#
11 - Frozen shipment number
2 - Box 2 of this shipment

Top View of Box

73								81
64								72
55								63
46								54
37								45
28								36
19								27
10								18
1	2	3	4	5	6	7	8	9

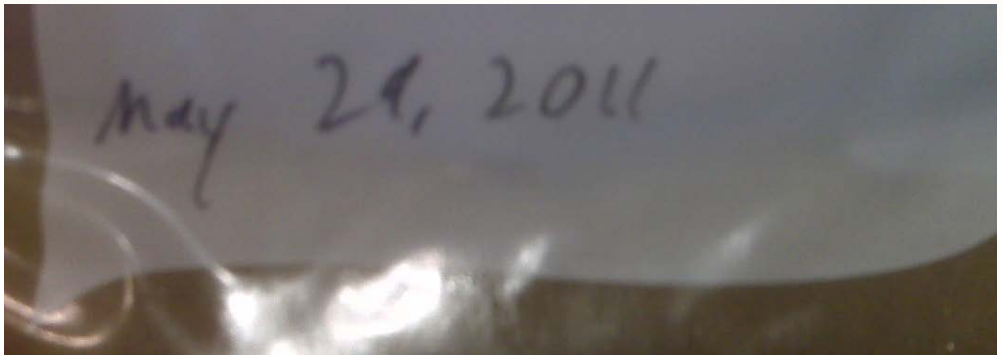
Front

Numbers indicate position numbers inside of storage box

Reagents

What's the date?

- May 21
- May 24
- May 27
- May 29



Reagents

What's the date?

- May 21
- May 24
- May 27
- May 29

Critical Reagents / Supplies

- ❑ Contamination
- ❑ Authentication
- ❑ Potency
- ❑ Sterility
- ❑ Stability

NEWSFOCUS

Cases of Mistaken Identity

Downloaded from http://science.sciencemag.org/ on May 16, 2018

For decades, biologists working with contaminated or misidentified cell lines have wasted time and money and produced spurious results; journals and funding agencies say it's not their job to solve this problem

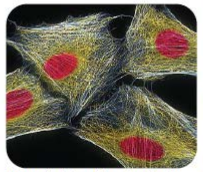
IN THE 1980S, WHEN HE WAS A postdoctoral fellow at the Scripps Research Institute in San Diego, California, Reinhard Kofler received what was supposed to be a human cancer cell line from a collaborator. "We cultured it, we cloned genes into it," he recalls, then "[we] genotyped it and realized it was 100% mouse."

After scores of similar experiences with misidentified cells, Kofler and his colleagues at the Tyrolean Cancer Research Institute in Innsbruck, Austria, now authenticate every line as soon as it arrives at the institute. And periodically afterward, they use a simple, cheap, quick, and reliable DNA fingerprinting technique to verify that each cell line continues to be what it should be. "It's an absolute must now," says Kofler. His lab "repeatedly" encounters problems with cell line contamination, and without this constant vigilance, Kofler says, "I wouldn't be confident about our work."

Not every biologist is so wary. A 2004 survey of nearly 500 biologists by Gertrude Buehring of the University of California, Berkeley, and her colleagues, showed that less than 50% of researchers regularly verify the identities of their cell lines using any of the standard techniques such as DNA fingerprinting. "Everybody is in denial" about the widespread problem of cell line cross contamination, says Charles Patrick Reynolds of the University of Southern California and the Children's Hospital Los Angeles' Institute for Pediatric Clinical Research, who establishes new pediatric cancer cell lines and tests potential cancer drugs on existing lines.

Indeed, many studies have shown that a surprisingly large number of cell lines have become contaminated, often by older, more well-established cancerous cells. For example, according to a 1999 paper by Roderick MacLeod and his colleagues at the German Cell Bank (DSMZ) in Braunschweig, 18% of 252 lines donated to the bank were misidentified or contaminated. The extent of the problem "always seems to come as a surprise for people," says John Masters of University College London, president of the European Tissue Culture Society.

And even though biologists read and hear about cross contamination, "people just think that this is not a problem in *my* lab," says Reynolds. If contaminated cell lines are used merely as "test tubes" to express proteins, a lab's work may not be affected. But, say Masters and others, research with contaminated lines continues to obscure potential drug leads and



Early warning. HeLa cells have contaminated scores of cell lines for more than 4 decades.

Published by AAAS

PLOS ONE

RESEARCH ARTICLE

The ghosts of HeLa: How cell line misidentification contaminates the scientific literature

Serge P. J. M. Horbach, Willem Halffman*

Radboud University, Institute for Science in Society, Nijmegen, The Netherlands

* w.halffman@science.ru.nl

Check for updates

OPEN ACCESS

Citation: Horbach SPJM, Halffman W (2017) The ghosts of HeLa: How cell line misidentification contaminates the scientific literature. PLoS ONE 12 (10): e0186281. https://doi.org/10.1371/journal.pone.0186281

Editor: Wolfgang Glanzel, KU Leuven, BELGIUM

Received: April 21, 2017

Accepted: September 28, 2017

Published: October 12, 2017

Data Availability Statement: Data supporting our analysis have been deposited in the DANS archive (curated by the Dutch Royal Academies of Sciences), and are accessible via http://dx.doi.org/10.17026/dans-2ap-7bnu. This includes the precise search string and the Web of Science search history based on it, along with instructions on how to repeat our search in WoS. However, access to data (i.e., the full list of articles found to be reporting on misidentified cell lines) is conditional upon approval by the research ethics committee of the Science Faculty of the Radboud University Nijmegen (via f.vandermolen@science.ru.nl). The key concern leading to conditional access is that

Abstract

While problems with cell line misidentification have been known for decades, an unknown number of published papers remains in circulation reporting on the wrong cells without warning or correction. Here we attempt to make a conservative estimate of this 'contaminated' literature. We found 32,755 articles reporting on research with misidentified cells, in turn cited by an estimated half a million other papers. The contamination of the literature is not decreasing over time and is anything but restricted to countries in the periphery of global science. The decades-old and often contentious attempts to stop misidentification of cell lines have proven to be insufficient. The contamination of the literature calls for a fair and reasonable notification system, warning users and readers to interpret these papers with appropriate care.

Introduction

The misidentification of cell lines is a stubborn problem in the biomedical sciences, contributing to the growing concerns about errors, false conclusions and irreproducible experiments [1, 2]. As a result of mislabelled samples, cross-contaminations, or inadequate protocols, some research papers report results for lung cancer cells that turn out to be liver carcinoma, or human cell lines that turn out to be rat [3, 4]. In some cases, these errors may only marginally affect results; in others they render results meaningless [4].

The problems with cell line misidentification [5] have been known for decades, commencing with the controversies around HeLa cells in the 1960s [6–10]. In spite of several alarm calls and initiatives to remedy the problem, misidentification continues to haunt biomedical research, with new announcements of large-scale cross-contaminations and widespread use of misidentified cell lines appearing even recently [11–13]. Although no exact numbers are known, the extent of cell line misidentification is estimated between one fifth and one third of all cell lines [4, 14]. (Although currently only 488 or 0.6% of over 80,000 known cell lines have been reported as misidentified, most cell lines are used infrequently [15].) In addition, misidentified cell lines keep being used under their false identities long after they have been unmasked [16], while other researchers continue to build on their results. Considering the biomedical nature of research conducted on these cell lines, consequences of false findings are

utmb Health

Case Study 1—Supplies

You receive a letter from a vendor stating there is a manufacturer's recall on tissue culture flasks, lot number 134804. You check the supply room to discover that you have multiple cases of two different lot numbers—the one recalled and another lot number that has not been recalled. Both lot numbers have been used in the laboratory. You must start an investigation into what might have been impacted by the use of the recalled lot number of tissue flasks…

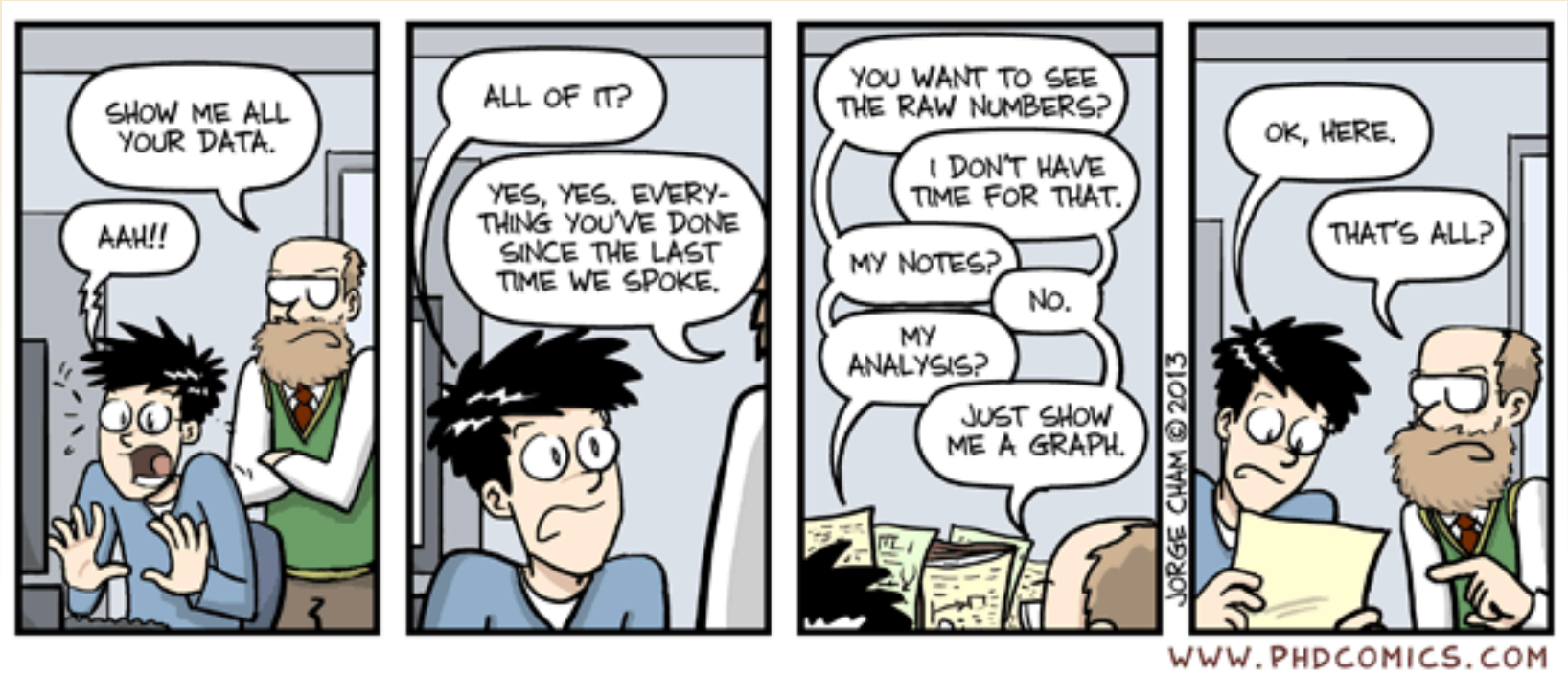
What records might help you determine if the recalled lot number was used?

Data Integrity Workshop

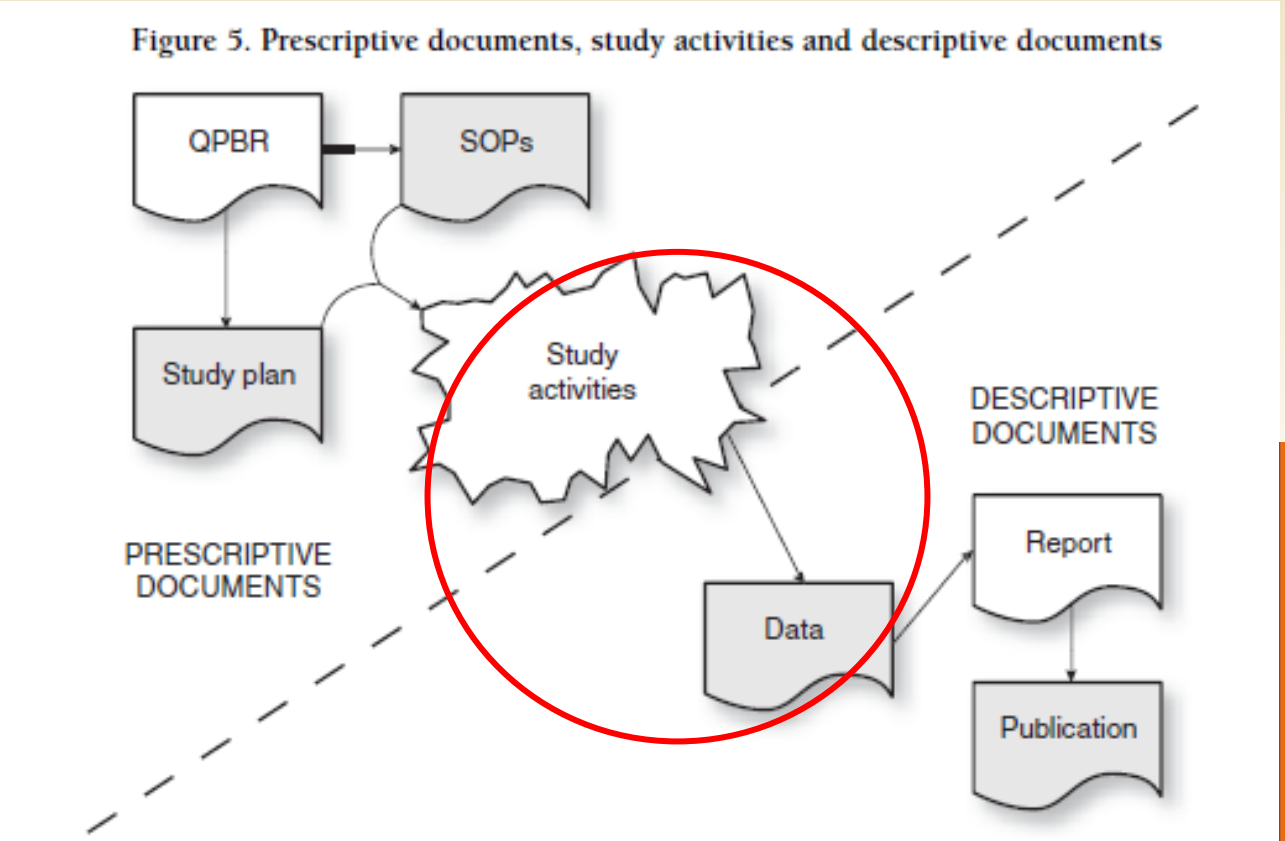
Source (Raw) Data

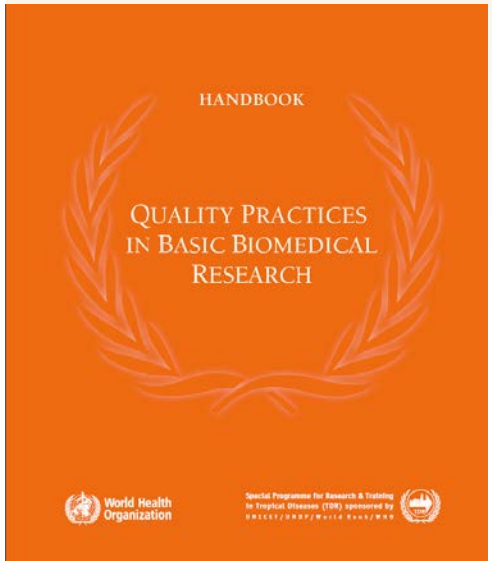
Research Records

Source (Raw) Data



Source (Raw) Data

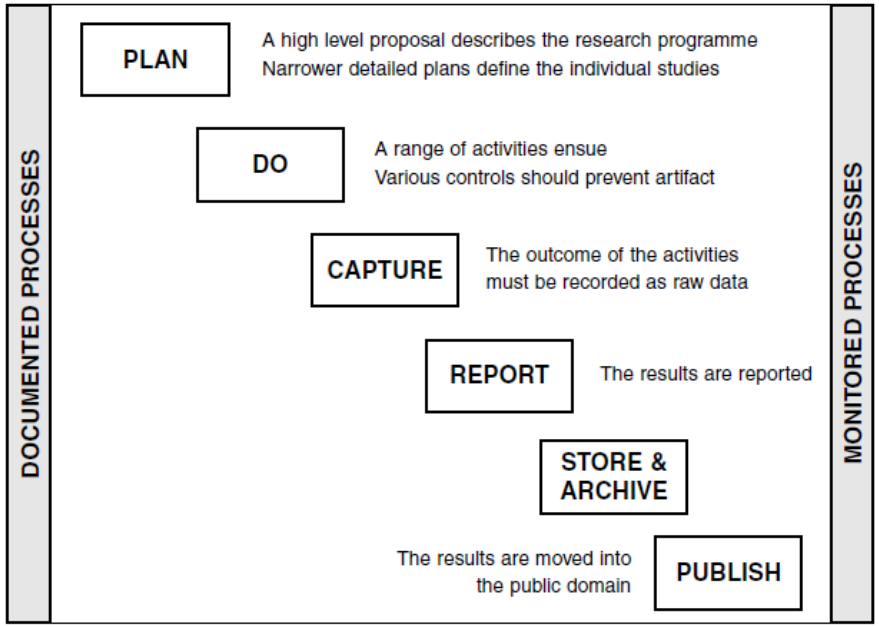




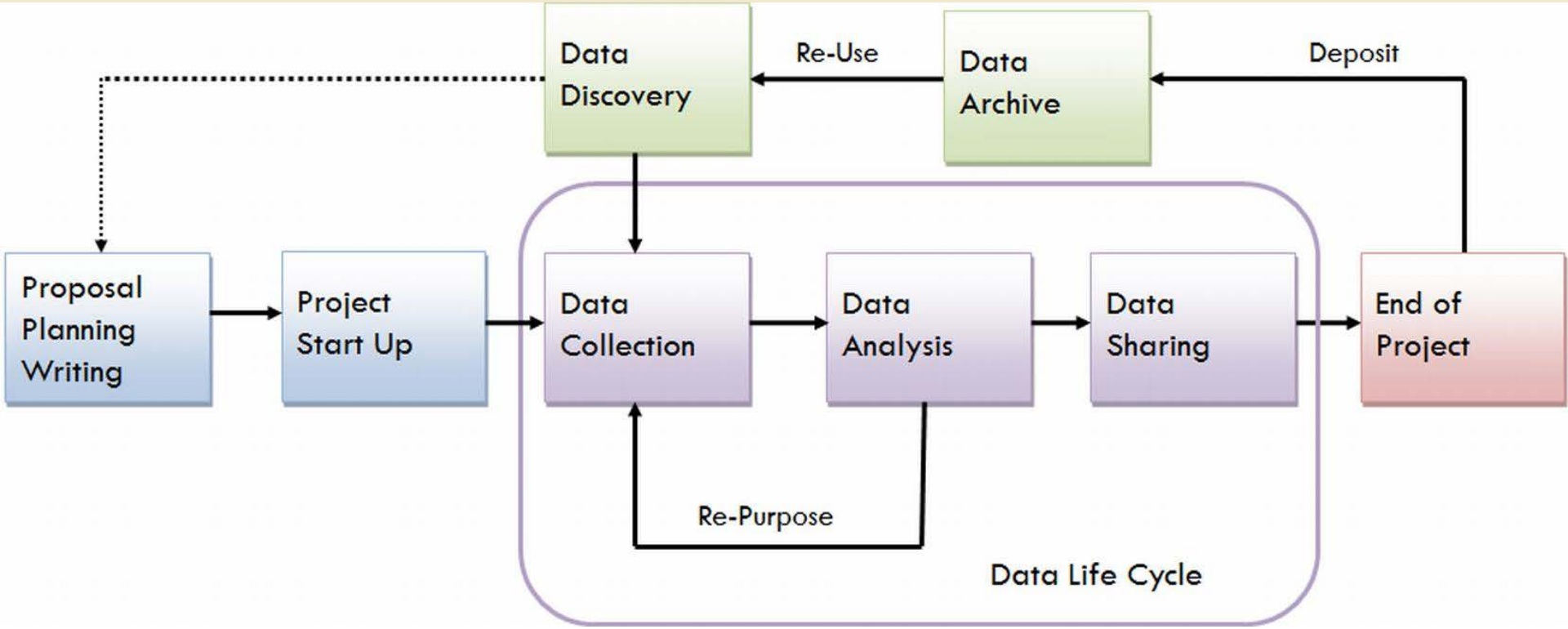
Research Activities

It must be stressed here that the quality practices for biomedical research described in this document do not address the scientific content of a research programme or proposal, but are concerned with the way the research work is organized and planned, performed, recorded, reported, archived, monitored and published. Figure 1 sketches the main steps in this process.

Figure 1. Flow of research activities



Data Lifecycle



http://data.library.virginia.edu/data-management/lifecycle/

Data Lifecycle

- *Who*…is responsible for the data?
- *Who*…will have access to the data?
- *What*…kind(s) of data—and how much?
- *Where*…will the data reside—during and after study completion?
- *When*…(and under what conditions) will the data be shared—during and after study completion?
- *How*…will the data be secured?
- *How*…are changes to data managed and tracked?

What Kind of Data?

- Types (observational, derived, etc.)
- Format (text, numeric, modeling, images, etc.)
- Quantity
- HIPAA
- Proprietary
- Owner

Paper Records—Considerations

- ALCOA
- SLIDER
- Security / Access / Protection
- Language
- Verification (e.g., calculations)
- Data collection forms
- Supportive documents
- Organization & Retention

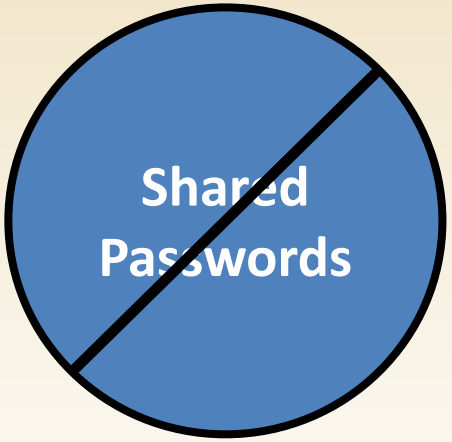
ALCOA+

- Attributable
- Legible
- Contemporaneous
- Original
- Accurate

+Complete, Consistent, Enduring, Readily Available

Electronic Records—Considerations

Electronic Systems



- Accessibility
  - Security / Passwords
- Software Compatibility
- Program Updates
  - Automatic
  - Impact to significant digits
- System Administration / Operating System sustainability
- Backup Procedures
- Retention

Electronic Records—Considerations

Electronic Data

- Quality & Integrity (ALCOA+)
  - Meta data & Audit trails
- Data Migration / Readability
- Transposition Errors

ALCOA+

- Attributable
- Legible
- Contemporaneous
- Original
- Accurate

+Complete, Consistent, Enduring, Readily Available

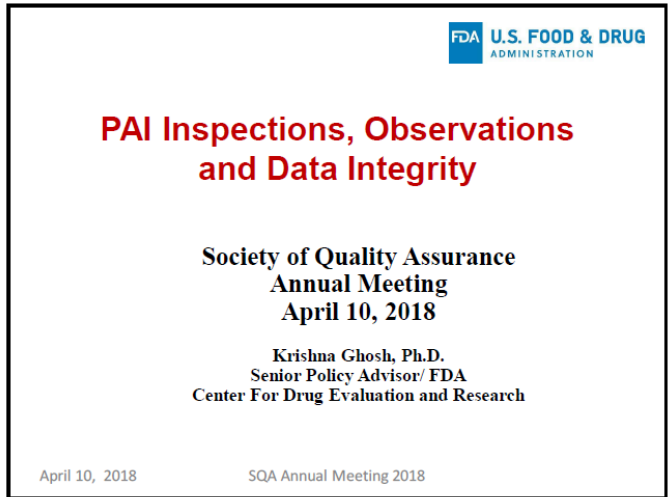
Documentation—Audit Trail

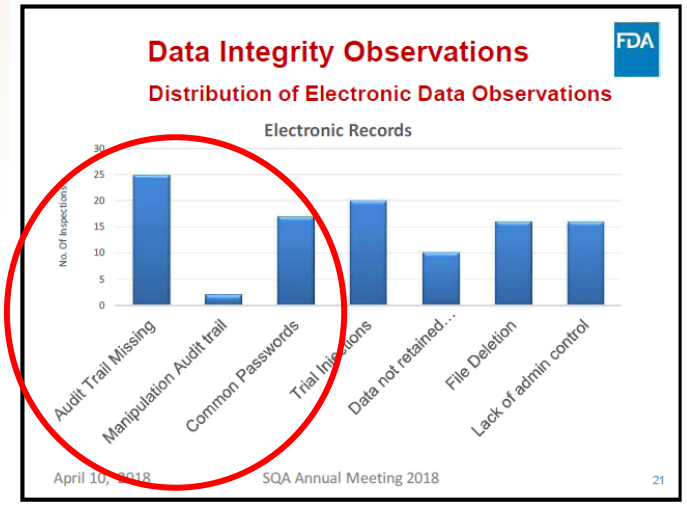
Application	Module	Changed Field	Old Value	New Value	Change Reason	User ID	Date
Documents	Infocard Edit	Vault	ORNCS_LAB001...	delete	Changes made in...	System Administrator...	2-Aug-2016
Documents	Infocard Edit	Document Number	SOP-LAB-001-...	SOP-LAB-001-...	Changes made in...	System Administrator...	2-Aug-2016
Documents	InfoCard	Owner	TRBRASEL	DGOODING	Changes made in...	System Administrator...	2-Aug-2016
Documents	InfoCard	Owner	TRBRASEL	DGOODING	Changes made in...	System Administrator...	2-Aug-2016
Documents	InfoCard	Owner	Matthew McGa...	DGOODING	Changes made in...	System Administrator...	2-Aug-2016
Documents	Infocard Edit	Document Number	SOP-CAL-005-...	SOP-CAL-005-...	Deleted per Jac...	System Administrator...	2-Aug-2016
Documents	Infocard Edit	Vault	ORNCS_CAL005...	delete	Deleted per Jac...	System Administrator...	2-Aug-2016
Documents	InfoCard	File Name	SOP-LAB-003-...	SOP-LAB-003-...	uploaded new fi...	J[redacted]	18-Jul-2016
Documents	Packets	packet_status	In Process	On Hold	wrong main file...	System Administrator...	18-Jul-2016
Documents	Packets	step_status	In Process	On Hold	wrong main file...	System Administrator...	18-Jul-2016
Documents	InfoCard	Title	HOBOware	HOBOware Lig...	Added File-JDA ...	J[redacted]	8-Jul-2016
Documents	InfoCard	File Name	SOP-LAB-001-...	SOP-LAB-001-...	changed file na...	J[redacted]	2-May-2016
Documents	InfoCard	Author	JDABENDR	CHMASSEY	Updated owner a...	J[redacted]	13-Apr-2016
Documents	InfoCard	Owner	JDABENDR	TRBRASEL	Updated owner a...	J[redacted]	13-Apr-2016
Documents	InfoCard	Creator	JDABENDR	CHMASSEY	Updated owner a...	J[redacted]	13-Apr-2016
Documents	InfoCard	Owner	TRBRASEL	DGOODING	Added SOP File-...	J[redacted]	17-Mar-2016
Documents	InfoCard	Title	Spirit Fille...	Use and Main...	Added SOP File-...	J[redacted]	17-Mar-2016
Documents	InfoCard	Document Number	SOP-MCS-000-...	SOP-MCS-000-...	Draft doc preve...	P[redacted]	23-Feb-2016
Documents	InfoCard	Document Number	SOP-MCS-000-...	SOP-MCS-000-...	Draft doc using...	P[redacted]	23-Feb-2016
Documents	InfoCard	Notes	No attachmen...	No attachmen...	Draft doc using...	P[redacted]	23-Feb-2016
Documents	InfoCard	Document Number	SOP-MCS-000-...	SOP-MCS-000-...	Changed Draft b...	P[redacted]	23-Feb-2016
Documents	InfoCard	Document Number	SOP-MCS-000-...	SOP-MCS-000-...	This is a draft...	P[redacted]	23-Feb-2016
Documents	InfoCard	load_time	17 Feb 2016 ...	17 Feb 2016 ...	Replaced the ma...	T[redacted]	17-Feb-2016
Documents	InfoCard	File Name	QAU-000- 000...	QAU-000- 000...	Replaced the ma...	T[redacted]	17-Feb-2016

FDA's Perspective

"Ensuring data integrity is an important component of industry's responsibility to ensure the safety, efficacy, and quality of drugs, and of FDA's ability to protect public health."

--Data Integrity and Compliance with cGMP, draft guidance for industry (April, 2016)





Electronic Data

- ✓ Use security settings on documents to assure no unauthorized changes occur (i.e., protect from potential loss of data/information)
- ✓ Consider software compatibility when adding programs
- ✓ Be aware that program updates may change significant digits (confirm calculations)
- ✓ Consider timing of automatic security updates and determine:
  - o Will changes impact your data?
  - o Will automatic shut-down and restart of your computer result in data loss?
- ✓ Enable audit trail functionality
- ✓ Include a quality control check to identify transposition errors after data transfer/data migration, including after copy/pasting data

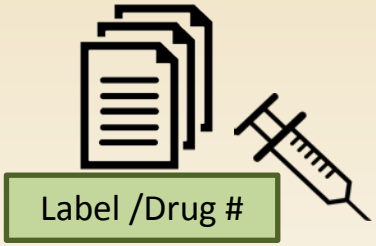
Source Data vs. Tables

Sample	Cq	Cq Mean	Starting Quantity SQ	SQ Mean
1	39.01	38.98	1.03E+03	1.05E+03
1	38.91	38.98	1.09E+03	1.05E+03
1	39.01	38.98	1.03E+03	1.05E+03
2		0.00		0.00E+00
2	38.61	38.95	3.82E+03	3.22E+03
2	39.29	38.95	2.61E+03	3.22E+03
3		0.00		0.00E+00
3	39.08	39.08	2.94E+03	2.94E+03
3		0.00		0.00E+00
4		0.00		0.00E+00
4	39.68	39.83	7.00E+02	6.46E+02
4	39.97	39.83	5.92E+02	6.46E+02
5		0.00		0.00E+00
5		0.00		0.00E+00
5	39.10	39.10	9.78E+02	9.78E+02

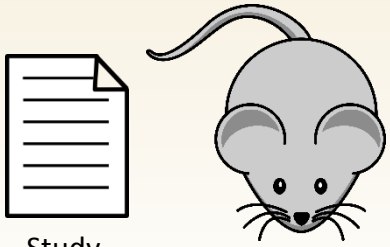
vs.

Animal ID	Cq Mean	SQ Mean
1	38.98	1.05E+03
2	38.95	3.22E+03
3	0.00	<LLOD
4	39.83	<LLOQ
5	0.00	<LLOD

Research Records

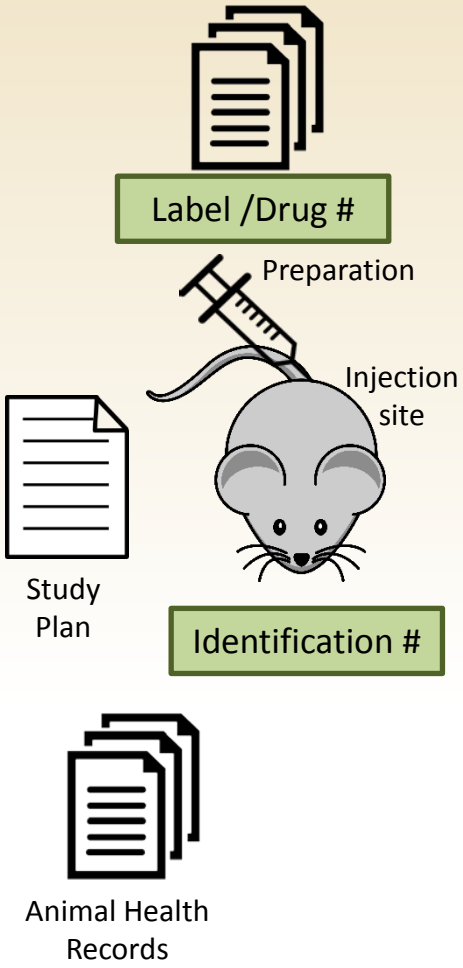


Preparation

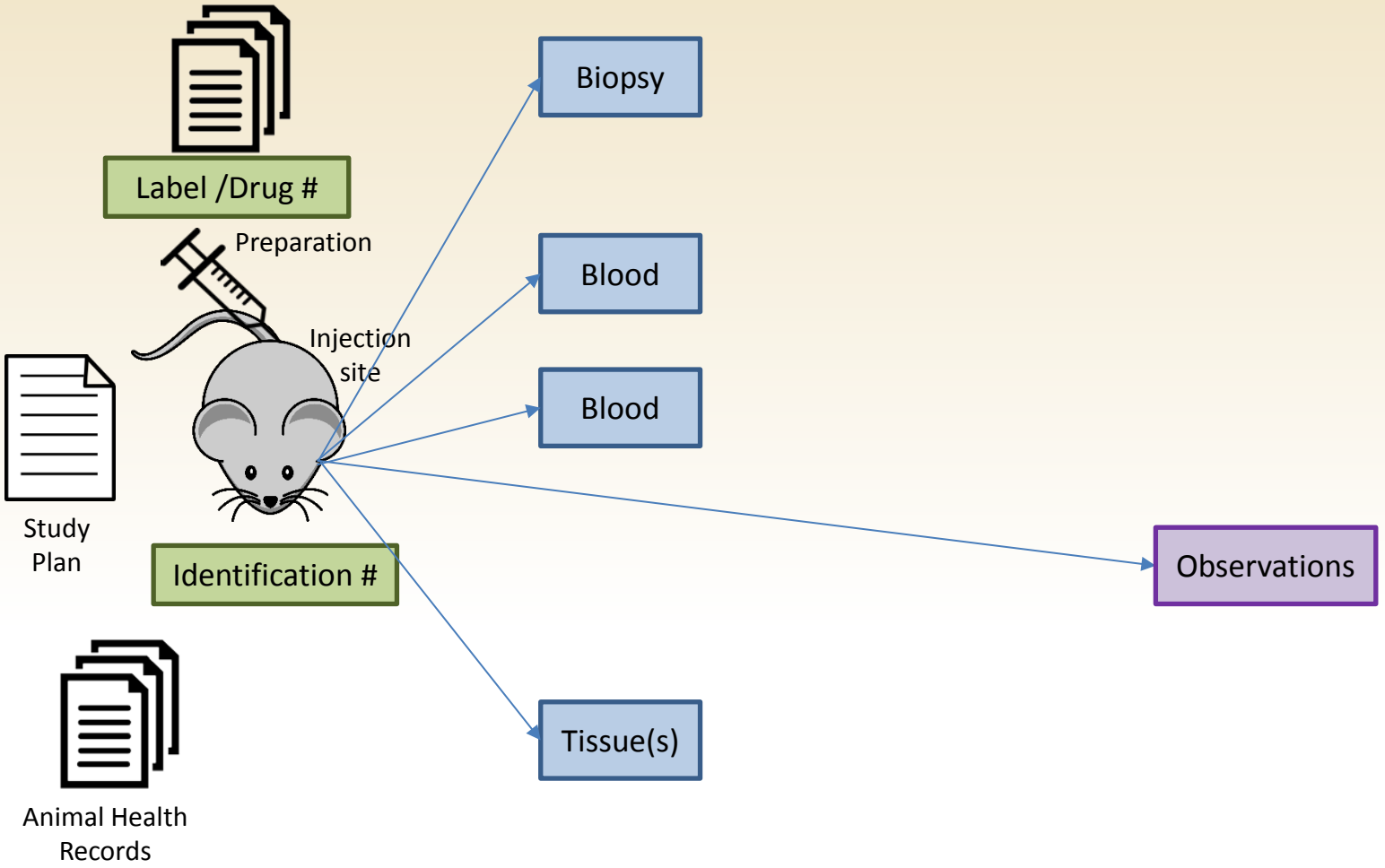


Study Plan

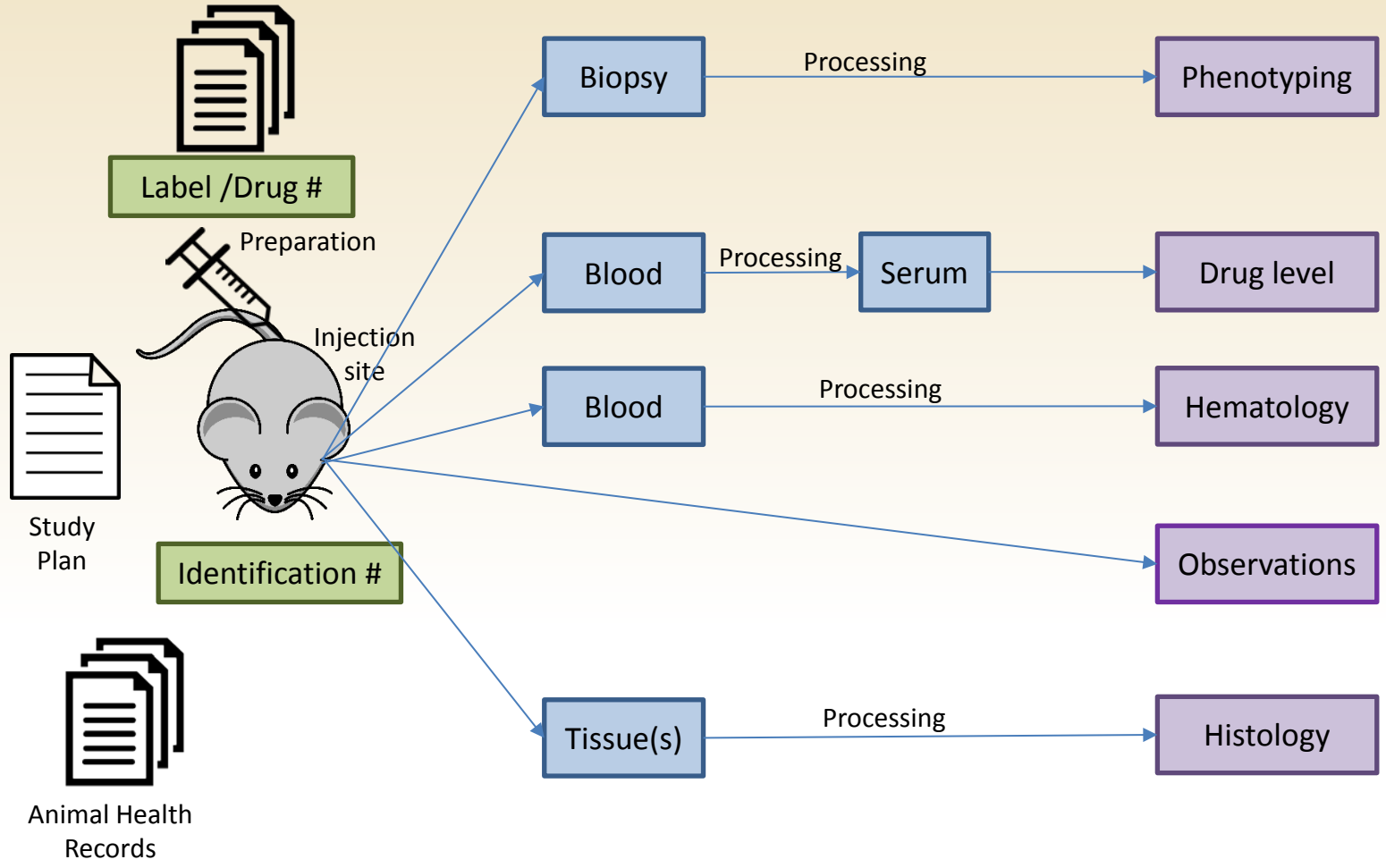
Research Records



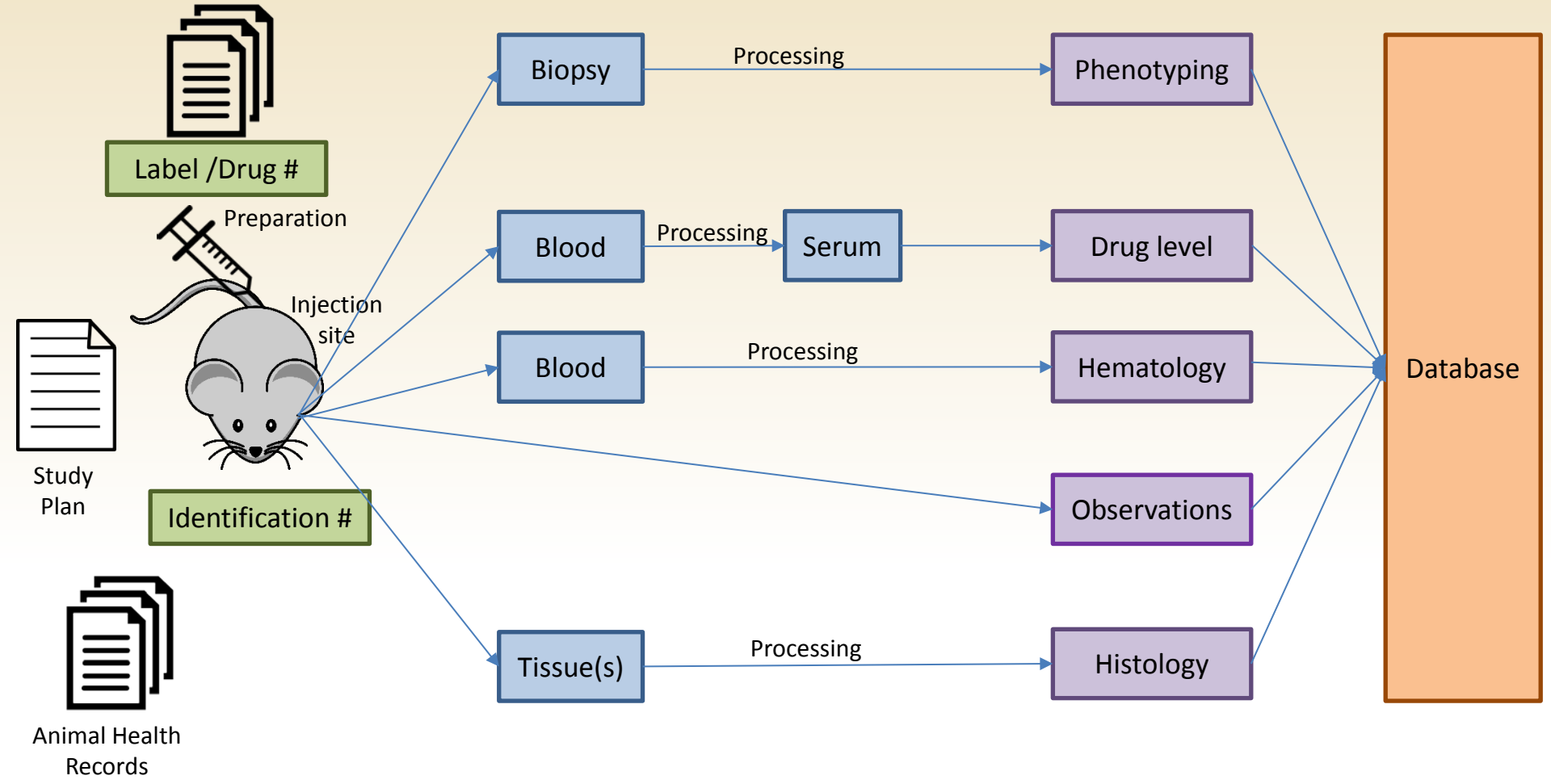
Research Records



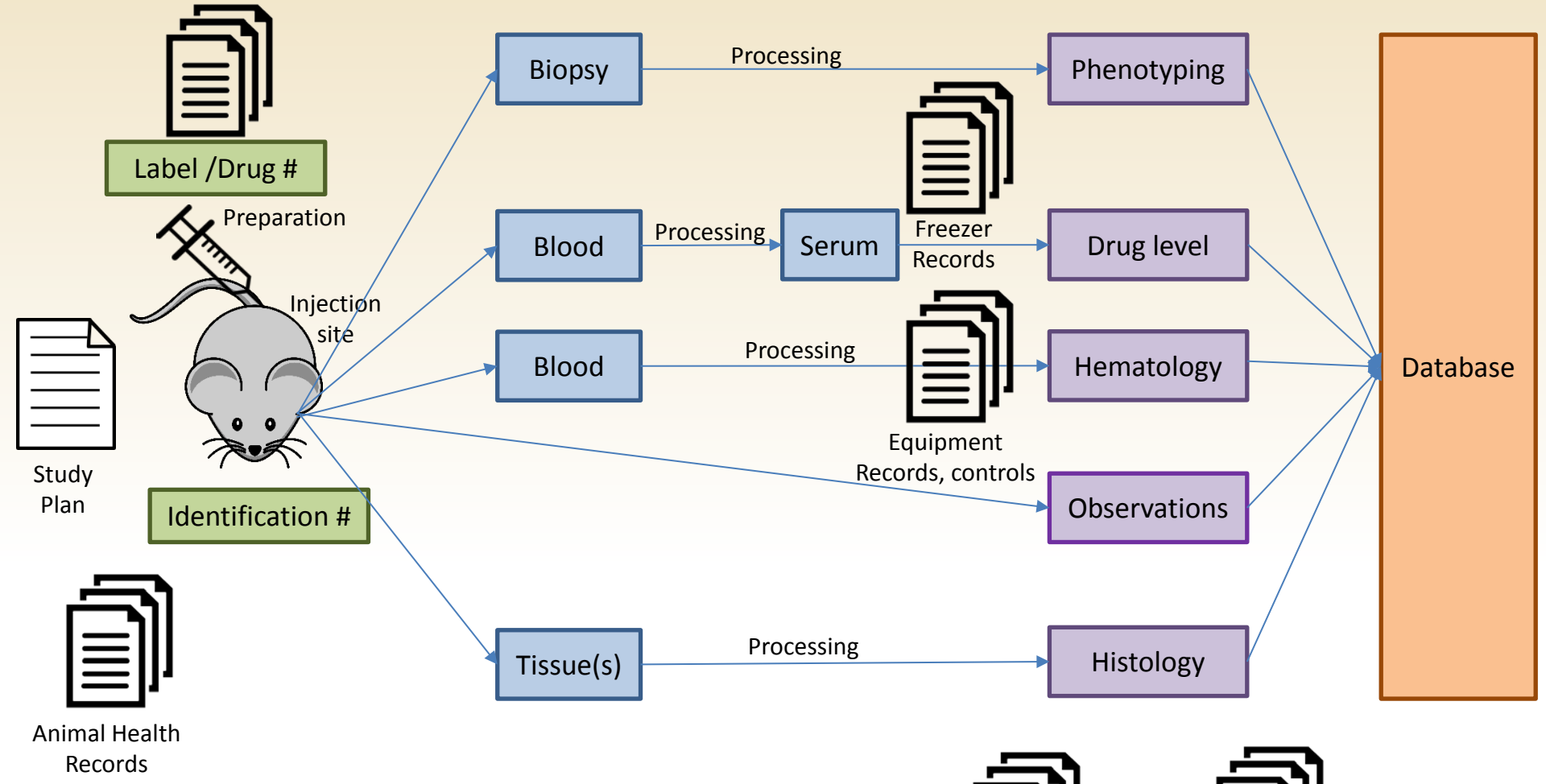
Research Records



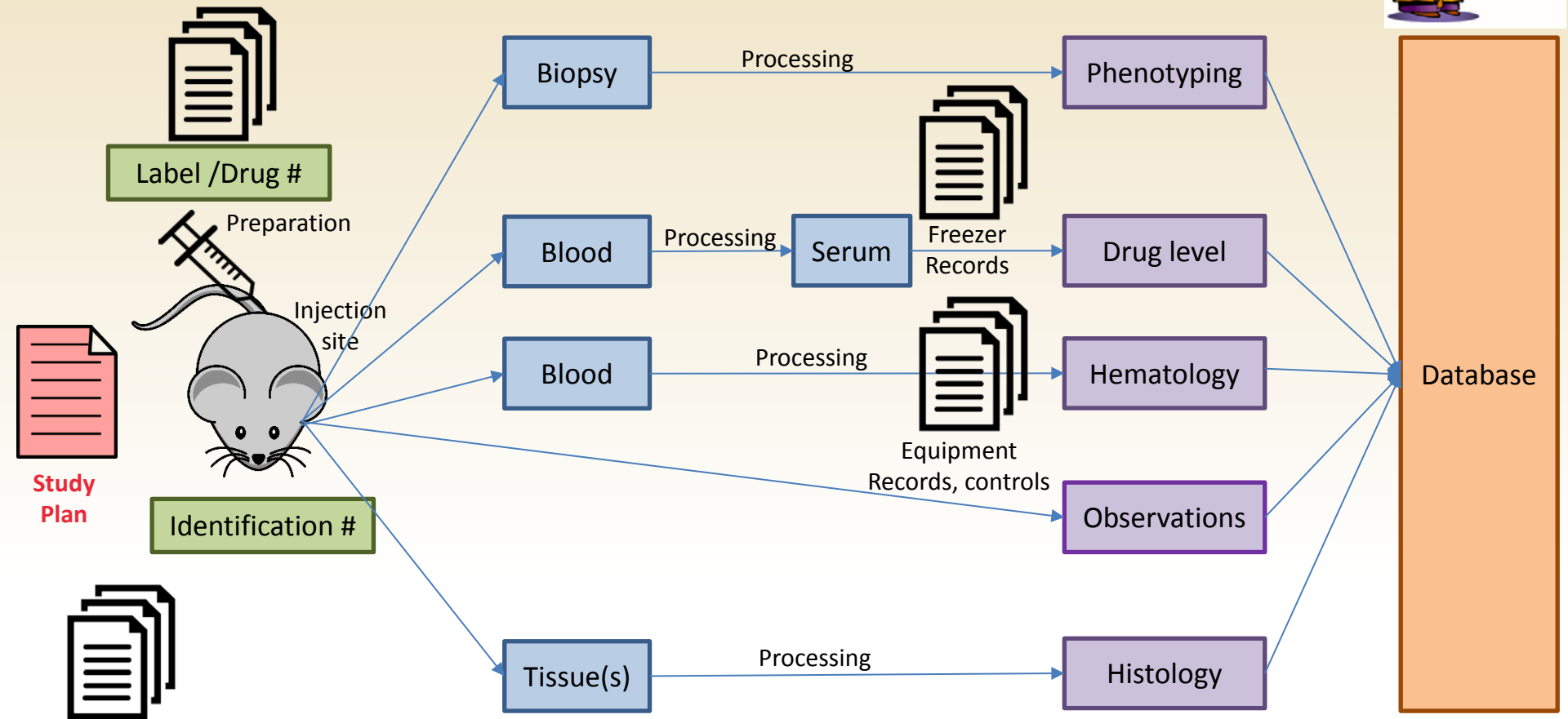
Research Records



Research Records



Research Records



Animal Health Records

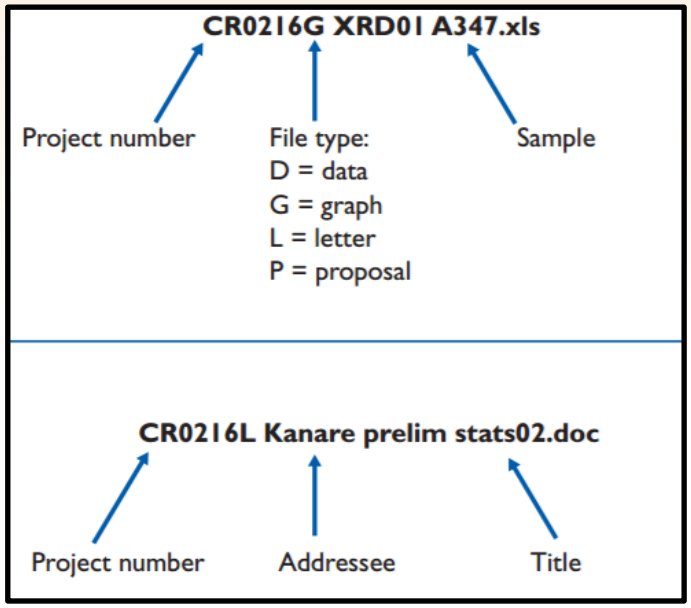
SOPs

Reagents

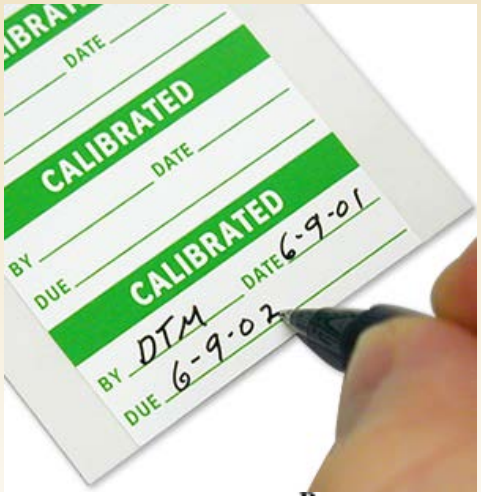
Training

Research Records

Electronic File Organization



Research Records: Documentation vs. Communication



A

59991	59991	2005-08-05	Gekakis	02-32
Mother 153092 C57BL/6J-		Father 130448 B6.ENU-217(9019)		
Strain B6.ENU-217(9019)		F5N1	2005-04-30	

grp	sex	tag	val	ID	Gtyp
0	M	172449	.	172449	1+/+
0	F	172454	.	172454	1+/-
0	F	172455	.	172455	1+/-

PEESTERS
PEESTERS
PEESTERS

B

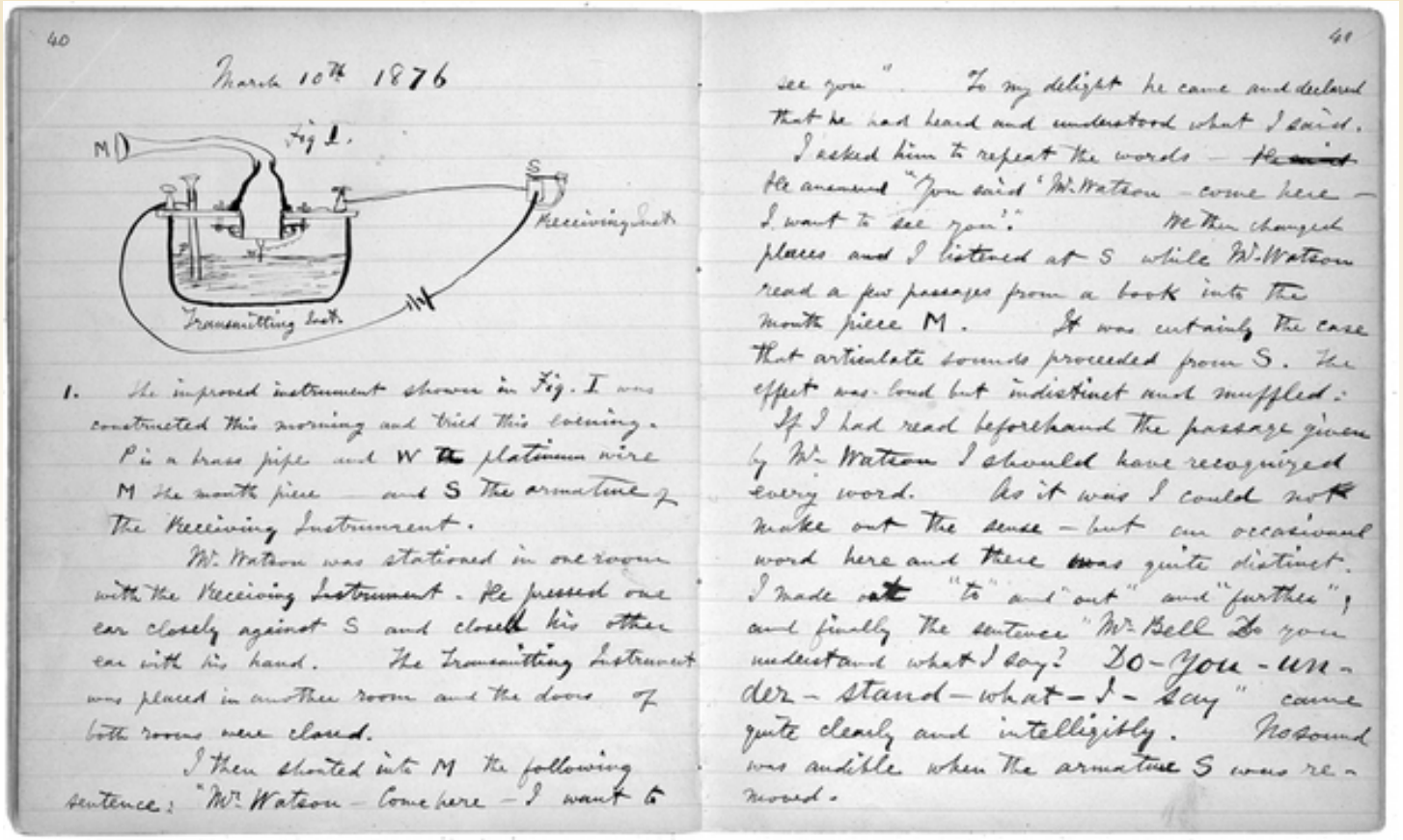
59991	2005-08-05	Gekakis	02-32
M.mother C57BL/6J-	Mother B6.ENU-217(9019)		F5N1
M.father B6.ENU-217(9019)	2005-04-30 172454 172455		0
F.mother C57BL/6J-	Father B6.ENU-217(9019)		F5N1
F.father B6.ENU-217(9019)	2005-04-30 172449		0
2005-08-05	B6.ENU-217(9019)		F6N1

#	P	W	DOB	T:F:M	Comment
1	00-00-0005-09-14		05-08-24	7:5:2	.
2					
3					
4					
5					
6					
7					
8					
9					
10					

Data Integrity Workshop

Laboratory Notebooks

Laboratory Notebooks



40

March 10th 1876

Fig 1.

1. The improved instrument shown in Fig. I 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

41

see you". To my delight he came and declared that he had heard and understood what I said.

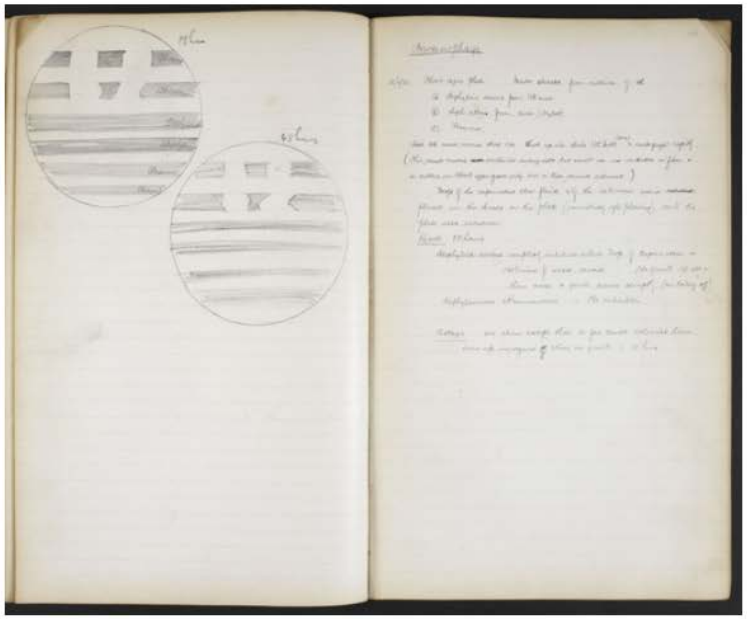
I asked him to repeat the words — ~~he said~~ He answered "You said 'Mr. Watson — come here — I want to see you'." We then changed places and I listened at S while Mr. Watson read a few passages from a book into the mouth piece M. It was certainly the case that articulate sounds proceeded from S. The 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.

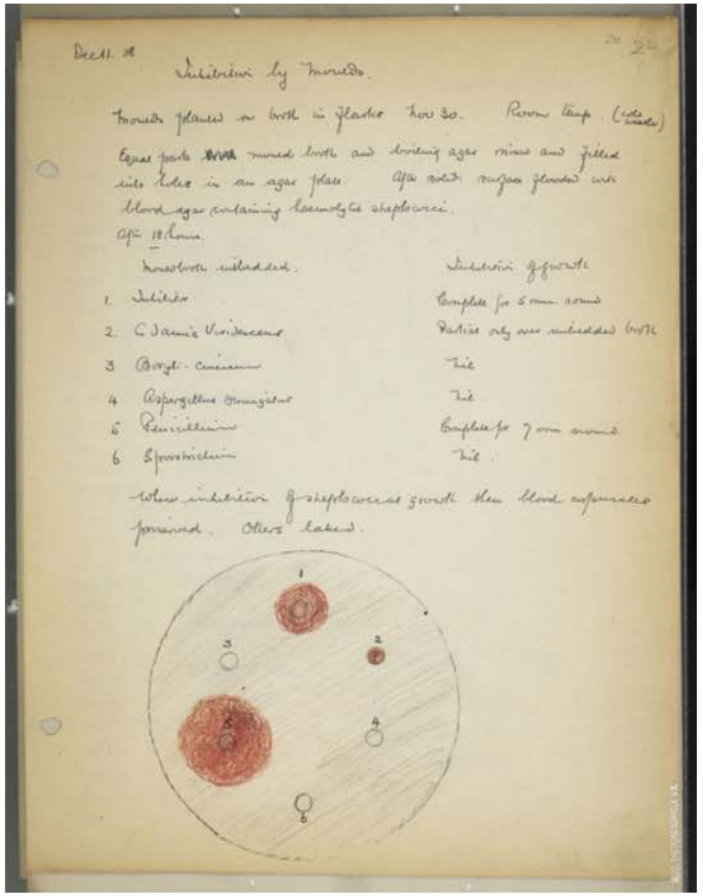
https://aids.harvard.edu/consider-the-lab-notebook/

Laboratory Notebooks

Lab Notebooks

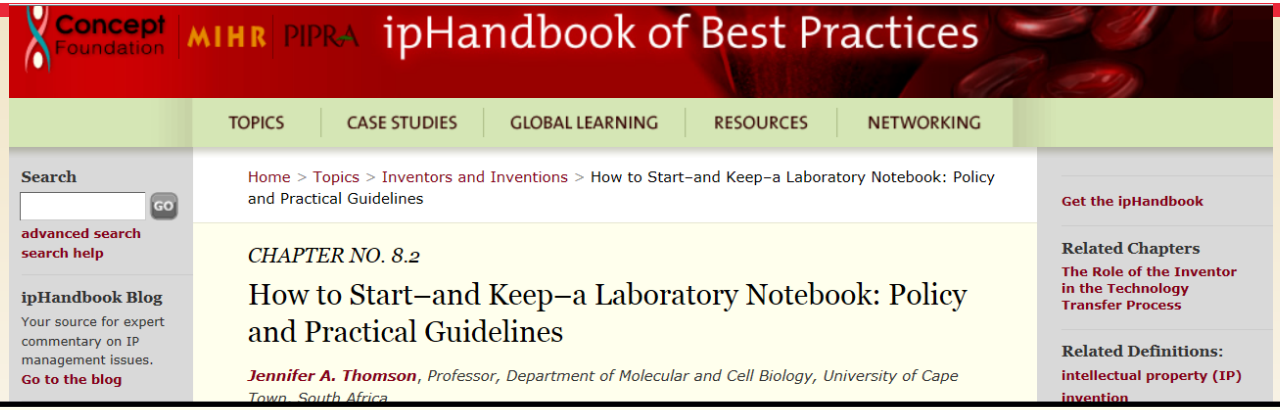


On display at the British Library are some of Fleming's lab books from 1921, when he studied lysosomes. A Lysosome is a component of a eukaryotic cell that has degradative properties. It was used as a naturally occurring antiseptic that can dissolve bacteria.



https://mandiekaiser.weebly.com/alexander-fleming.html

Laboratory Notebooks



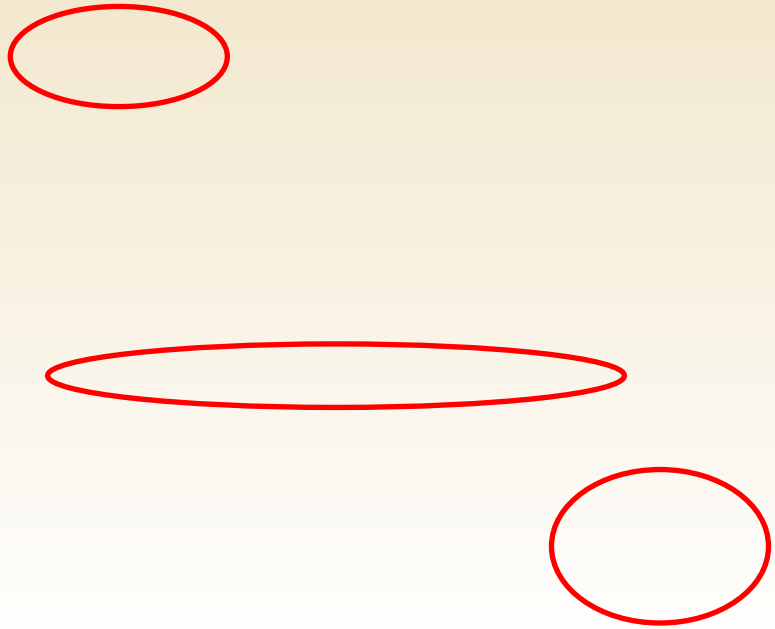
1. What is a Laboratory Notebook?

Although you may think you will remember what you did and why you did a certain experiment in a week's time, YOU WILL NOT! And nor will anyone else in your laboratory. Hence the need for laboratory notebooks. In short, a laboratory notebooks is:

- a daily record of every experiment you do, think of doing, or plan to do
- a daily record of your thoughts about each experiment and the results thereof
- the basis of every paper and thesis you write
- the record used by patent offices and, in the case of disputes, courts of law (in the event you file patents on your findings)
- a record that would enable successive scientists, working on the same project, to pick up where you left off or reproduce your results

Source: http://www.iphandbook.org/handbook/ch08/p02/

Laboratory Notebook—Example



Laboratory Notebooks

- ✓ Maintain an Index at the front of your notebook
- ✓ Assure notebooks are all recorded in same language (English)
- ✓ Sign and date notebook pages
- ✓ Initial and date critical observations and calculations
- ✓ Verify critical calculations
- ✓ Identify (line through) large blank spaces
- ✓ Standardize date annotation

  Example: 08/07/2016

Laboratory Notebooks

- ✓ Affix printouts
  - ✓ Make a copy of Thermal paper read-outs
  - ✓ Date and initial the printout
- ✓ Record manufacturers, lot numbers and expiration dates of critical reagents and supplies

  (Don't mix kit reagents!)

Source: Bing Images

Laboratory Notebooks

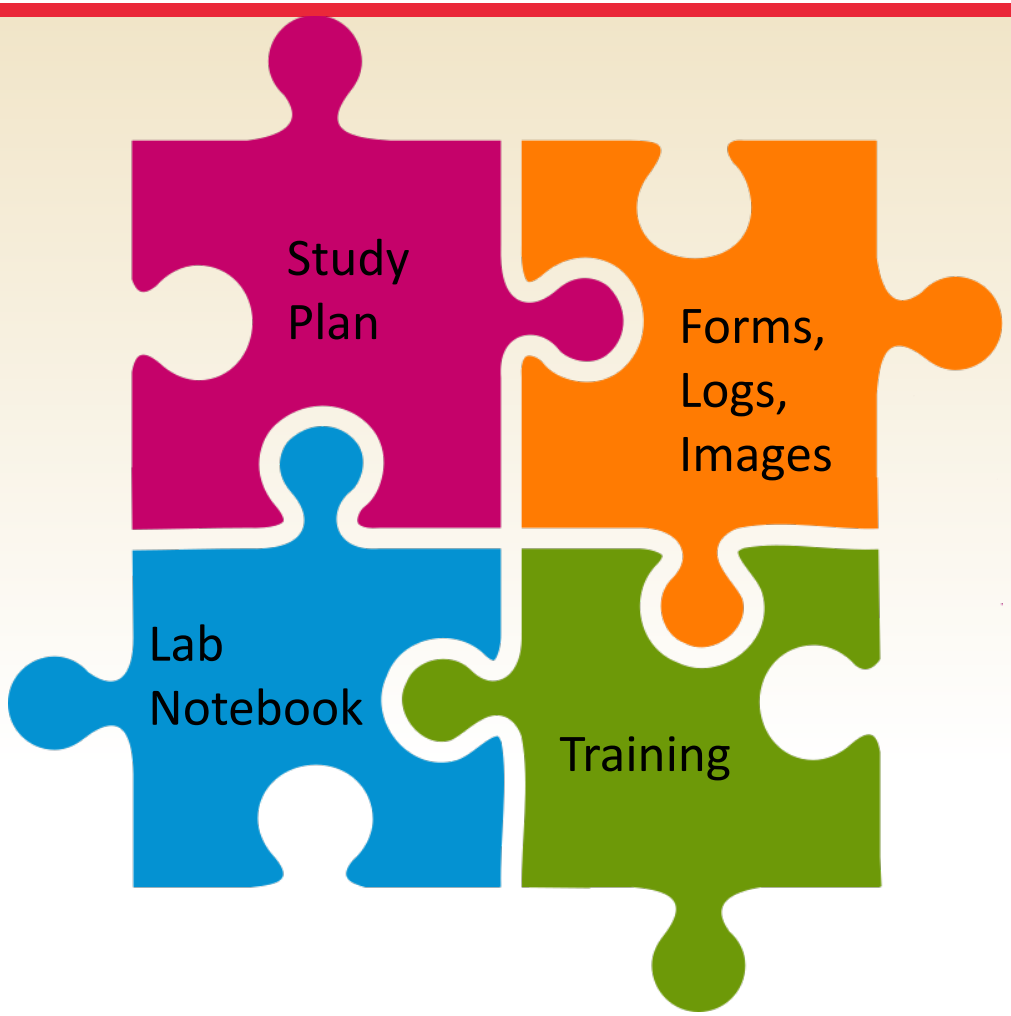
- ✓ Document any procedural changes and unexpected outcomes
- ✓ When not in use, store notebooks in a secure environment and protect them from a potential natural disaster such as fire or flood
- ✓ Be knowledgeable of your Institution's policies on data ownership

Advanced Tip: Implement a periodic peer review to determine if information recorded is complete and communicates clearly how the experiment could be repeated.

Laboratory Notebooks

- ✓ Consider 1 notebook per project
- ✓ Show positive examples to new employees / students / post-docs

Laboratory Notebooks

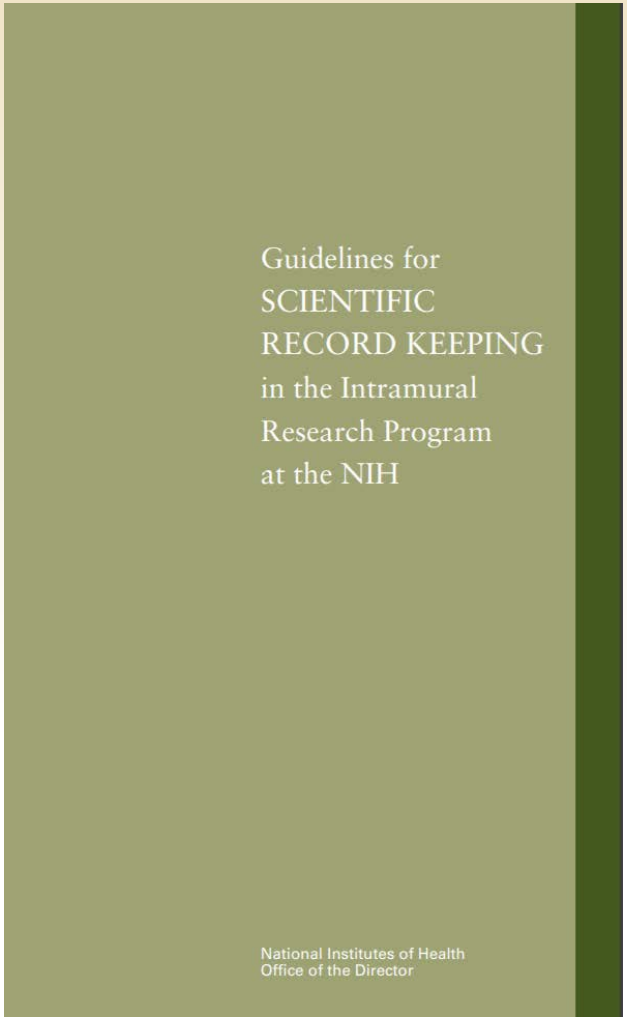


Electronic Laboratory Notebooks

- Customizable
- Templates
- Multi-site
- ALCOA
- Sustainability?
- Updates?

Scientific Record Keeping

"Good science requires good record keeping. Good record keeping promotes both accountability and integrity in research…"



https://oir.nih.gov/sites/default/files/uploads/sourcebook/documents/ethical_conduct/guidelines-scientific_recordkeeping.pdf

Scientific Record Keeping

List 1

Best Practice Principles for Individual Researchers*

Useful (good) research records explain

- what you did,
- when you did it,
- why you did it,
- how you did it,
- who you are (the person creating the record),
- what project(s) it was a part of,
- who thought of it if not you,
- what special materials and instruments you used,
- where you obtained the materials and instruments,
- what happened and what did not happen (data),
- how you manipulated and analyzed the results,
- your interpretation (and the interpretations of others if important), and
- what will be the next steps in the project based on these results.

In addition, good research records

- are legible if handwritten,
- are recorded using reliable materials and tools,
- are well organized (e.g., well labeled, indexed, catalogued, etc.),
- are accurate and complete; they include (1) all original data and important study details (meta-data) and (2) successful and unsuccessful studies and activities,
- describe and date all alterations and changes in records,
- allow repetition of your procedures and studies by yourself and others,
- are accessible (physically and/or electronically) to others both short term and long term,
- are stored and backed-up properly for the short and long term (archiving),
- are witnessed where needed to protect intellectual property rights,
- are in compliance with departmental, institutional, and federal regulatory requirements, with special care given to human and animal research, and
- are the research diaries of the researcher's work and thoughts.

utmb Health

Institutional Issues

Academic Research Record-Keeping: Best Practices for Individuals, Group Leaders, and Institutions

Alan A. Schreier, PhD, Kenneth Wilson, PhD, and David Resnik, PhD, JD

Abstract

During the last half of the 20th century, social and technological changes in academic research groups have challenged traditional research record-keeping practices, making them either insufficient or obsolete. New practices have developed but standards (best practices) are still evolving. Based on the authors' review and analysis of a number of sources, they present a set of systematically compiled best practices for research record-keeping for academic research groups. These best practices were developed as an adjunct to a research project on research ethics aimed at examining the actual research record-keeping practices of active academic scientists and their impact on research misconduct inquiries.

The best practices differentiate and provide separate standards for three different levels within the university: the individual researcher, the research group leader, and the department/institution. They were developed using a combination of literature reviews, surveys of university integrity officials, focus groups of active researchers, and inspection of university policies on research record-keeping. The authors believe these best practices constitute a "snapshot" of the current normative standards for research records within the academic research community. They are offered as ethical and practical guidelines subject to continuing evolution and not as absolute rules. They may be especially useful in training the next generation of researchers.

Acad Med. 2006; 81:42–47.

Good record-keeping is central to the scientific process.[1–4] Good research records encompass much more that just research data. They include but are not limited to planning and protocol descriptions, data manipulations and analysis procedures, personal and group interpretations of the results, and important communications and group decisions among collaborators. Data management is a subset of the broader concept of research record-keeping. Research records are important for managing and planning research, for replicating results, for documenting collaborations, for publishing and peer review, and for complying with governmental and institutional rules and regulations. In recent decades, legal and regulatory uses of research records have become prominent. Research records have long been used to resolve intellectual property disputes.[2] However, research misconduct scandals in the 1980s and 1990s involving falsification and fabrication of research records provoked the federal government to require universities to implement research misconduct policies.[2] Examination of research records is a central feature of inquiries and investigations under such university policies.

We recently conducted a survey of 96 university officials who are responsible for such inquiries and investigations as part of a research project on the impact of research records in research misconduct cases.[5] We found that over half of the officials who reported experience with misconduct cases at their institutions also reported that they had been hampered in their inquires/investigations by inadequate research records. Also, another recent survey of investigators who had been funded by the National Institutes of Health (NIH) on the prevalence of questionable research practices noted that 27% of the 3,247 respondents admitted to "inadequate record-keeping related to research projects."[6]

Given the importance of good research records, it is somewhat surprising that formal standards for such records are the exception rather than the rule in academic research laboratories. Although governments have mandated standards for good research records for certain segments of the research community—most notably in the area of human health and safety research through the stringent regulations of the U.S. Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA)[7,8]—the majority of academic researchers are not constrained by any external set of record-keeping guidelines. In fact, most academic scientists find the mandated FDA record-keeping practices both onerous and unnecessary. Academic researchers prefer informal guidelines rather than formal standards for record-keeping.

During the last half of the 20th century, technological changes in how records are produced, collected, analyzed and stored, coupled with social changes in the nature of research groups, have created new challenges for research record-keeping.[9] Traditional practices for such record-keeping are either no longer sufficient or, at worse, obsolete for the modern researcher. New record-keeping practices have arisen to meet these challenges; however, very little research has been

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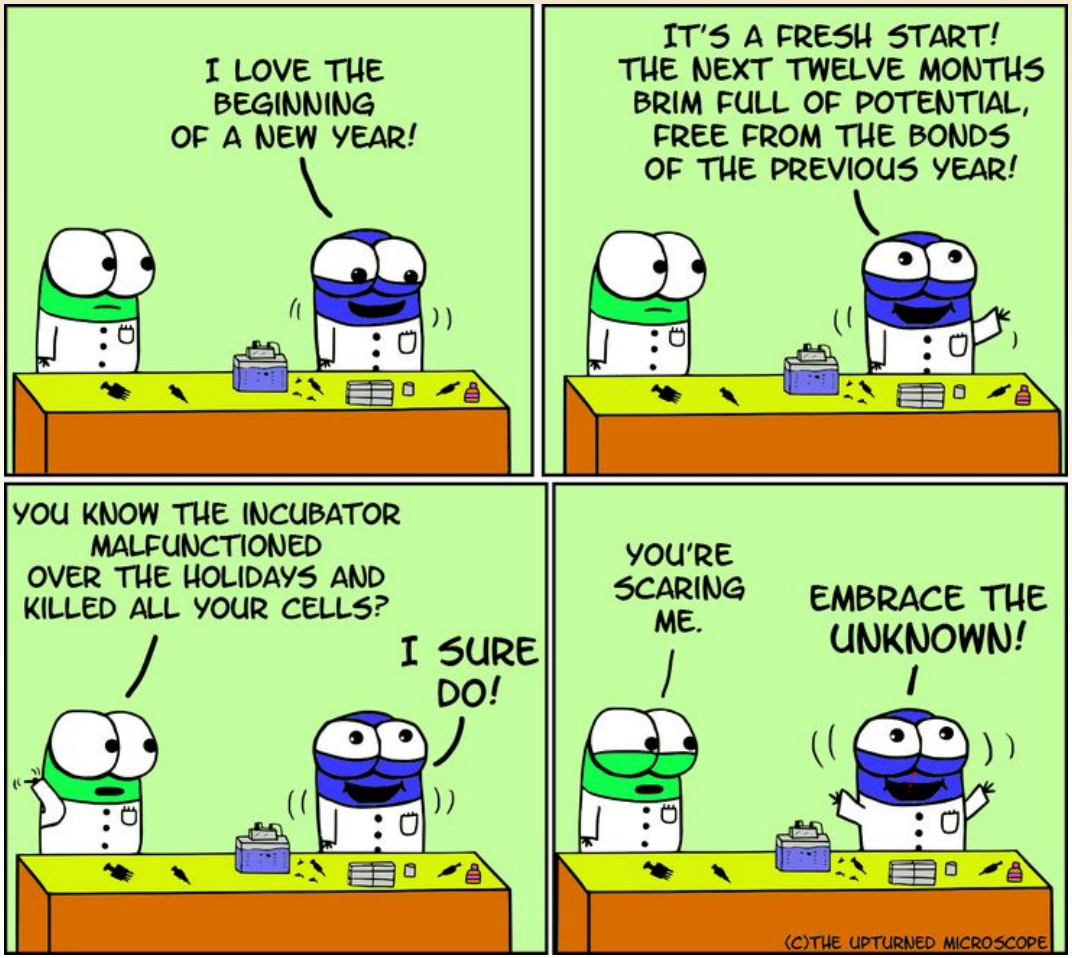
Data Integrity Workshop

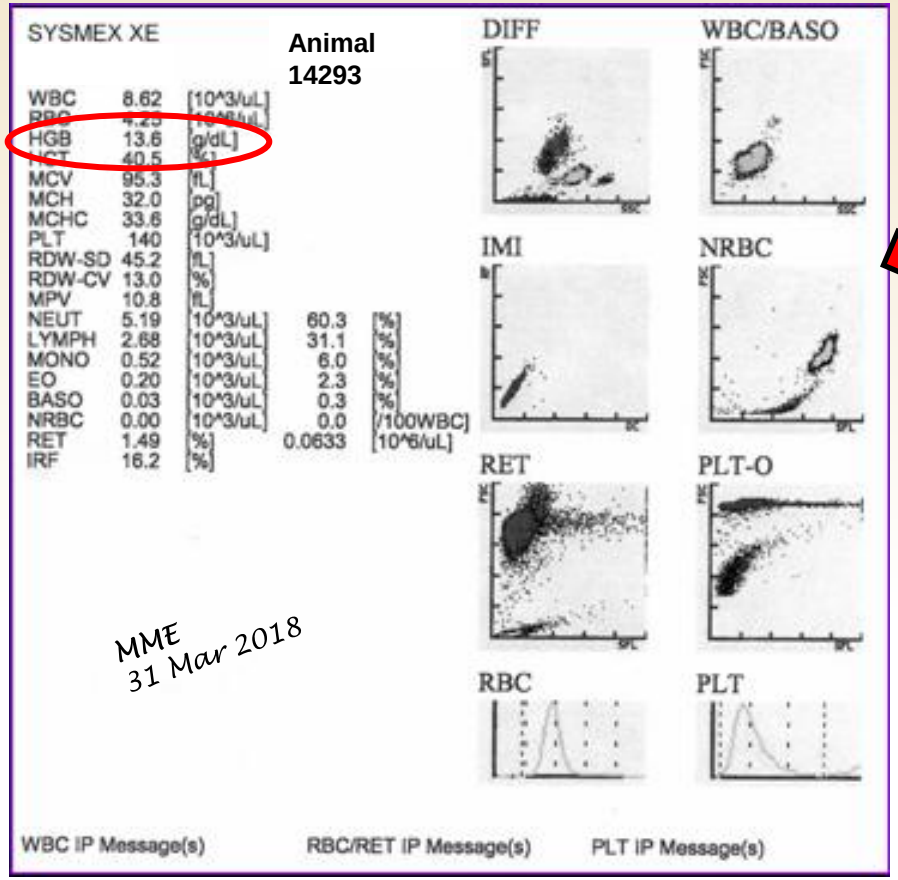
(Potential) Risks to Research

(Potential) Risks to Research



Risks: Transcription Errors

Hemoglobin Value



Animal	HGB
12938	12.2
14039	8.9
14293	3.6
14980	13.8
15209	12.5
15490	9.5
15560	14.0

Source: Google Images

Risks: Natural Disasters

UTHealth
The University of Texas Health Science Center at Houston

ABOUT CAREERS DIRECTORY
SCHOOLS STUDENTS

Media Relations

Media Relations
- Top News Headlines
- Media Relations Team

Impact on Research

By the Numbers

The Impact on Research

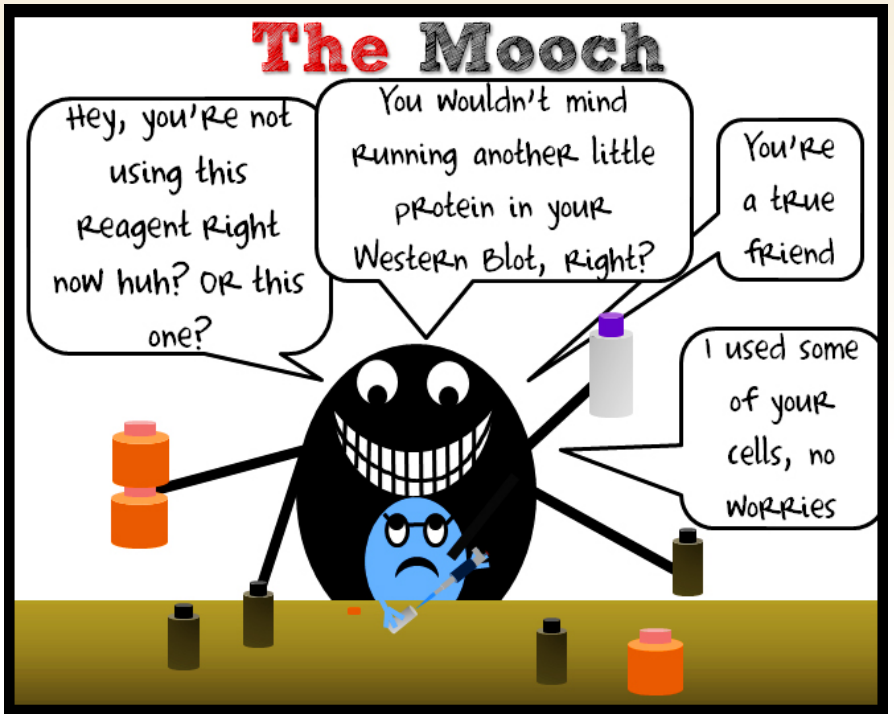
- Emergency Response

- An estimated $105 million in sponsored research awards has been affected.
- All animal-based research has been destroyed.
- Almost 4,000 animals were killed in the flood. The financial loss in animals alone currently is estimated at $7.4 million dollars. These included:
  - Genetically engineered mice bred to be susceptible to cardiovascular disease, asthma, immune deficiency diseases or neurological disorders;
  - Monkeys trained since childhood to do certain cognitive functions for the study of normal and abnormal brain development;
  - Rabbits and rats treated with new drugs for many months to determine the long-term effects of treatment.
- 350 to 400 faculty members and their research projects have been affected. The salary and benefits of many of these individuals are paid through grants representing $2.8 million per month, consuming $120,000 each day the school is closed. Depending upon the reactions of the sponsors of this research, many of these efforts may be lost.
- Losses that could take as long as three to four years to redevelop at a cost of more than $7 million include:
  - Cell cultures developed from human tumors or tissues used to study effects of new drugs or cancer cell growth;
  - Valuable human blood and urine research samples from a variety of diseases that were under investigation;
  - Valuable chemical reagents and unique bacterial strains used to study diseases.
- The cyclotron facility is a total loss. Radioactive chemicals produced here are critical to a number of sophisticated research applications.
- Many faculty are feverishly working in borrowed and leased lab space to meet the requirements of their grants. Displacement of these faculty and their research may take as long as two months.
- Flooding also resulted in significant equipment losses, including MRI machines and the data associated with them. MRI data, compiled over many years, was used to learn how strokes and blood clots form and block vessels. Images were also used to study both Attention Deficit Hyperactivity in children with normal and abnormal brain development and the impact of drug dependence on cognitive functions.

https://www.uth.edu/media/featured/allison/research.htm

Group Discussion—Potential Risks

What are some potential risks to your research?



Case Study 2—Risk to Research

Case Study: Resolution of a Phase Contrast Microscope

Case Overview: An analyst is preparing to count asbestos fibers using phase contrast microscopy to estimate the concentration of airborne asbestos fibers. The result will be used to determine if workers have been exposed to concentrations that exceed permissible exposure limits established by the United States Department of Labor Occupational Safety and Health Administration (OSHA).

Potential Problem: If the resolution is insufficient, fibers may not be seen by the microscopist and therefore, not counted. A falsely low count could result in an inaccurate value that falls within the permissible exposure limit.

System Checks: Since the diameter of the fibers to be counted is small (less than 1 μm), it is important that the microscope is clean, aligned, and checked for the detection limit (or resolution). A glass phase-shift test slide, containing sets of line gratings with varying widths, is used to test the resolution.

Risk Mitigation

Risk Assessment

1. What are the potential risks?
2. What is the likelihood of occurrence
3. What is the impact to your research if the risk occurs?

Risk Analysis

1. Identify the risks that are most likely to occur and that will have the most impact to your work.

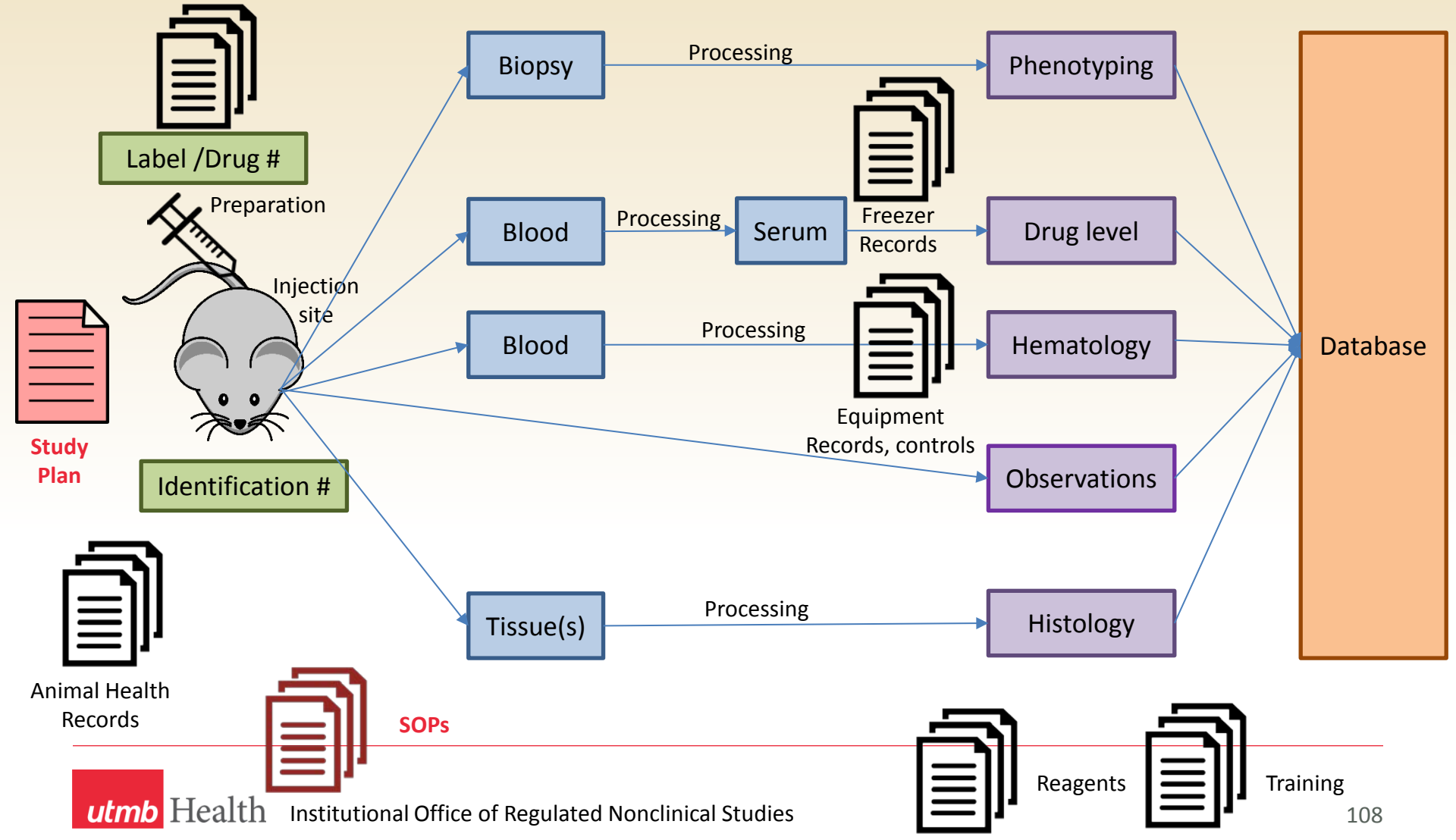
Risk Mitigation:

1. Develop a strategy to address (or reduce likelihood of occurrence of) the risk

Data Integrity Workshop

Quality Management Systems

Research Records



Activity 4: Data Integrity Support at the System Level

https://www.therqa.com/assets/js/tiny_mce/plugins/filemanager/files/Publications/RQA_Quality_Systems_Workbook.pdf

FDA Good Laboratory Practices

21 CFR Part 58 Subpart A—General Provisions

§58.1 Scope.

(a) This part describes good laboratory practices for conducting nonclinical laboratory studies that support or are intended to support applications for research or marketing permits for products regulated by the Food and Drug administration…compliance with this part is **intended to assure the quality and integrity of the** safety **data**…

FDA GLP Regulations (21 CFR Part 58)

PART 58 -- GOOD LABORATORY PRACTICE FOR NONCLINICAL LABORATORY STUDIES

Subpart A -- General Provisions

§58.1 Scope.
§58.3 Definitions.
§58.10 Applicability to studies performed under grants and contracts.
§58.15 Inspection of a testing facility.

Subpart B -- Organization and Personnel

§58.29 Personnel.
§58.31 Testing facility management.
§58.33 Study director.
§58.35 Quality assurance unit.

Subpart C -- Facilities

§58.41 General.
§58.43 Animal care facilities.
§58.45 Animal supply facilities.
§58.47 Facilities for handling test and control articles.
§58.49 Laboratory operation areas.
§58.51 Specimen and data storage facilities.

Subpart D -- Equipment

§58.61 Equipment design.
§58.63 Maintenance and calibration of equipment.

Subpart E -- Testing Facilities Operation

§58.81 Standard operating procedures.
§58.83 Reagents and solutions.
§58.90 Animal care.

Subpart F -- Test and Control Articles

§58.105 Test and control article characterization.
§58.107 Test and control article handling.
§58.113 Mixture of articles with carriers.

Subpart G -- Protocol for and Conduct of a Nonclinical Laboratory Study

§58.120 Protocol.
§58.130 Conduct of a nonclinical laboratory study.

Subparts H-I [Reserved]

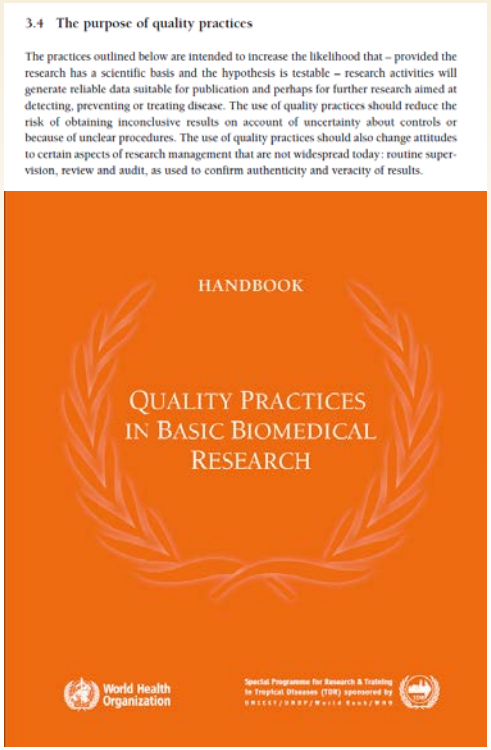
Subpart J -- Records and Reports

§58.185 Reporting of nonclinical laboratory study results.
§58.190 Storage and retrieval of records and data.
§58.195 Retention of records.

Quality Practices

*"(Quality) practices…are intended to increase the likelihood that—provided the research has a scientific basis and the hypothesis is testable—research activities will generate **reliable data** suitable for publication and perhaps for further research aimed at detecting, preventing, or treating disease.*

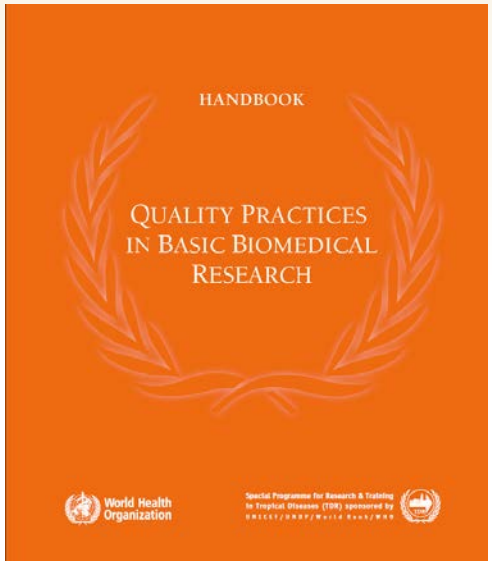
*The use of quality practices should also change attitudes to certain aspects of research management that are not widespread today: routine supervision, review and audit, as used to **confirm authenticity and veracity of results**."*



Quality Practices

Table 3. How sound scientific principles and good quality practices contribute to the credibility of results

	Sound scientific principles	Good quality practices	Credibility of results
Scientific study 1	No	No	No
Scientific study 2	No	Yes	No
Scientific study 3	Yes	No	No
Scientific study 4	**Yes**	**Yes**	**Yes**



Data Integrity Workshop

Culture of Quality &

Closing Thoughts

Who is Responsible?

"The research supervisor—group leader, principal investigator (PI), however he or she is called—is the main person to pass on the tradition of science to the next generation. Senior scientists have an obligation to instill strong ethical and moral values in their progeny."

COMMENTARY

DOI: 10.1002/adsc.201201128

Ethical Conduct in Chemical Research and Publishing

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Abstract: In recent years the incidence of scientific misconduct has increased. While the direct responsibility lies with the individual researcher, the educational role of mentors and research institutions needs rethinking and renewal. Researchers, principal investigators, departments, institutions, funding agencies, chemical societies, publishers, scientific journal editors, referees and editorial board members all have responsibilities in order to maintain the integrity of chemistry within the scientific community and to restore the confidence of the general public in chemistry as a responsible contributor to the solutions of the global problems facing mankind in this century.

Keywords: duplicate publication; ethical standards; plagiarism; retractions; scientific fraud; scientific misconduct; self-plagiarism

1 The Respected Tradition of Chemistry

Chemistry is a basic science with beauty and fascination in itself. At the same time, chemistry is closely involved in society, providing the foundations for areas of applied science such as nutrition, medicine, environment, energy and materials. Collaborations with other disciplines are resulting in many breakthroughs both in the areas of basic and applied research. As chemists, we have a fundamental role to play in society; maintaining our credibility in society depends on our scientific rigor and integrity.

Chemistry has a long tradition. We did not learn to be chemists solely by reading books; when we launch our careers as young scientists, we are heavily influenced by our first mentors. As Polanyi wrote in 1946, "Science is what scientists do."[1] Later in 1964 he wrote, "The authority of science resides in scientific opinion. Science exists as a body of wide-ranging authoritative knowledge only so long as this consensus of scientists continues. It lives and grows only so long as this consensus can resolve the perpetual tension between discipline and originality. Every succeeding generation is sovereign in reinterpreting the tradition of science. With it rests the fatal responsibility of the self-renewal of scientific convictions and methods. To speak of science and its continued progress is to profess faith in its fundamental principles and in the integrity of scientists in applying and amending these principles."[1]

2 Retracted Articles

In recent years there has been growing concern about whether this "self-renewal of scientific convictions and methods" is succeeding. The study carried out by Fang, Steen and Casadevall of all 2,047 retracted biomedical and life-science research publications indexed by PubMed to May 3, 2012, revealed that only 21.3% were due to error, while 67.4% were attributable to scientific misconduct: fraud or suspected fraud (43.4%), duplicate publication (14.2%), and plagiarism (9.8%).[2] This contradicts a common assumption that most retractions are due to errors that have been subsequently discovered. The authors wrote, "Incomplete, uninformative or misleading retraction announcements have led to a previous underestimate of the role of fraud in the ongoing retraction epidemic. The percentage of scientific articles retracted because of fraud has increased ~10-fold since 1975."[2] Secondary sources used by the authors to determine the true causes of retraction included the United States Office of Research Integrity[3] and Retraction Watch.[4]

The geographic patterns in the cases of misconduct were also surprising. Significantly, the ethics of indi-

Research Leaders

List 2

Best Practice Principles for Leaders of Research Groups

Research group leaders should

- set standards for record-keeping practices for individuals in their group in areas such as
  (1) research studies/activities within the group (handwritten and electronic notes, data, and other documentation),
  (2) labeling and cataloging of experimental samples, tangible products of research, etc.,
  (3) communications with collaborating researchers, such as letters, e-mails, minutes of meetings (face-to-face or teleconference), etc.,
- provide/assure that group members receive training in record-keeping practices,
- provide motivation by emphasizing the benefits of good records and the problems associated with poor records,
- provide examples of well-maintained records and good record-keeping practices,
- clarify data and research record ownership and access rights,
- perform periodic reviews of the records of the members of your group,
- delegate, as needed, oversight and training duties for group records to senior members of your group and perform periodic checks on the performance of these duties and modify/reassign duties as needed,
- provide the tools (paper-based notebooks or electronic hardware/software),
- establish temporary storage areas for records in use (both paper and electronic) and appropriate backup facilities/methods,
- require adherence to group record-keeping standards by group members,
- promote communication of research information within the group,
- have a plan to assure the transmission of important research information (accessible and understandable records/notebooks) from departing group members,
- require adherence to departmental, institutional, and legal requirements,
- seek to assure the long-term accessibility of records for a set period of time (archiving) after completion of the research, and
- update records standards as needed.

utmb Health

Institutional Issues

Academic Research Record-Keeping: Best Practices for Individuals, Group Leaders, and Institutions

Alan A. Schreier, PhD, Kenneth Wilson, PhD, and David Resnik, PhD, JD

Abstract

During the last half of the 20th century, social and technological changes in academic research groups have challenged traditional research record-keeping practices, making them either insufficient or obsolete. New practices have developed but standards (best practices) are still evolving. Based on the authors' review and analysis of a number of sources, they present a set of systematically compiled best practices for research record-keeping for academic research groups. These best practices were developed as an adjunct to a research project on research ethics aimed at examining the actual research record-keeping practices of active academic scientists and their impact on research misconduct inquiries.

The best practices differentiate and provide separate standards for three different levels within the university: the individual researcher, the research group leader, and the department/institution. They were developed using a combination of literature reviews, surveys of university integrity officials, focus groups of active researchers, and inspection of university policies on research record-keeping. The authors believe these best practices constitute a "snapshot" of the current normative standards for research records within the academic research community. They are offered as ethical and practical guidelines subject to continuing evolution and not as absolute rules. They may be especially useful in training the next generation of researchers.

Acad Med. 2006; 81:42–47.

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Questions to ask….

- ❑ Are my studies reconstructable?
- ❑ Are all study activities documented?
- ❑ Does documentation follow ALCOA principles?
- ❑ Do we follow the study plans?
- ❑ Do we follow standardized methods?
- ❑ Do we maintain all source data?
- ❑ Are controls included?
- ❑ Are conditions established for acceptance and rejection of data?
- ❑ Do we have a defined approach to manage exceptions…or deviations…or changes…?

Next steps…

- ✓ Implement the principles of ALCOA and SLIDER (including language and dates)
- ✓ Verify critical calculations
- ✓ Standardize procedures/methods wherever possible (use for training!)
- ✓ Leverage laboratory (team) meetings for pre-planning and risk mitigation
- ✓ Develop a plan for data management (including file nomenclature)
- ✓ Leverage annual performance evaluation (for goals) and take the opportunity to review training
- ✓ Create logs and/or checklists (e.g., reagents, equipment maintenance, training, etc.)

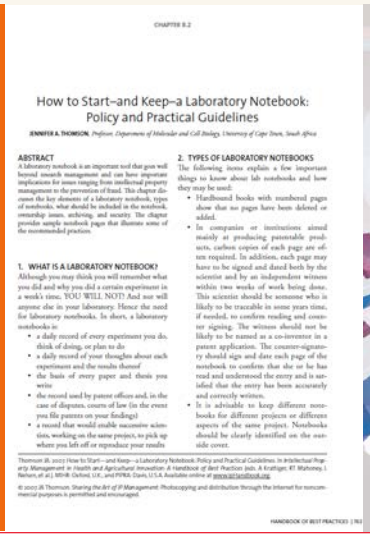
References / Tools

http://www.who.int/tdr/publications/training-guideline-publications/handbook-quality-practices-biomedical-research/en

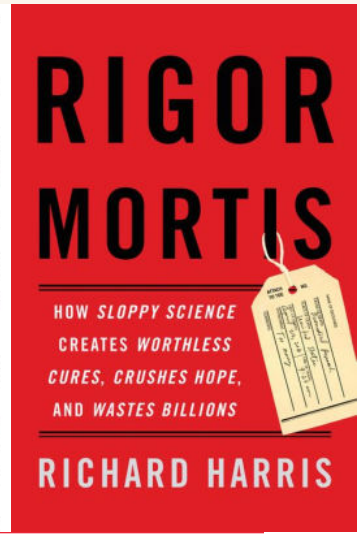
http://www.iphandbook.org/handbook/ch08/p02/

https://www.therqa.com/assets/js/tiny_mce/plugins/filemanager/files/Publications/RQA_Quality_Systems_Workbook.pdf

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3943904/


How to Start–and Keep–a Laboratory Notebook: Policy and Practical Guidelines


Academic Research Record-Keeping: Best Practices for Individuals, Group Leaders, and Institutions



THANK YOU!

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