Data Analytics in Clinical Data Management using Stata

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STATA Conference

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AGENDA

1. Understanding Clinical Trials
2. About Clinical Data Management
3. Statistical Analysis in Clinical Research
4. Stats Software – Evaluation Criteria
5. STATA – Features and Benefits
6. Conclusion

Understanding Clinical Trials

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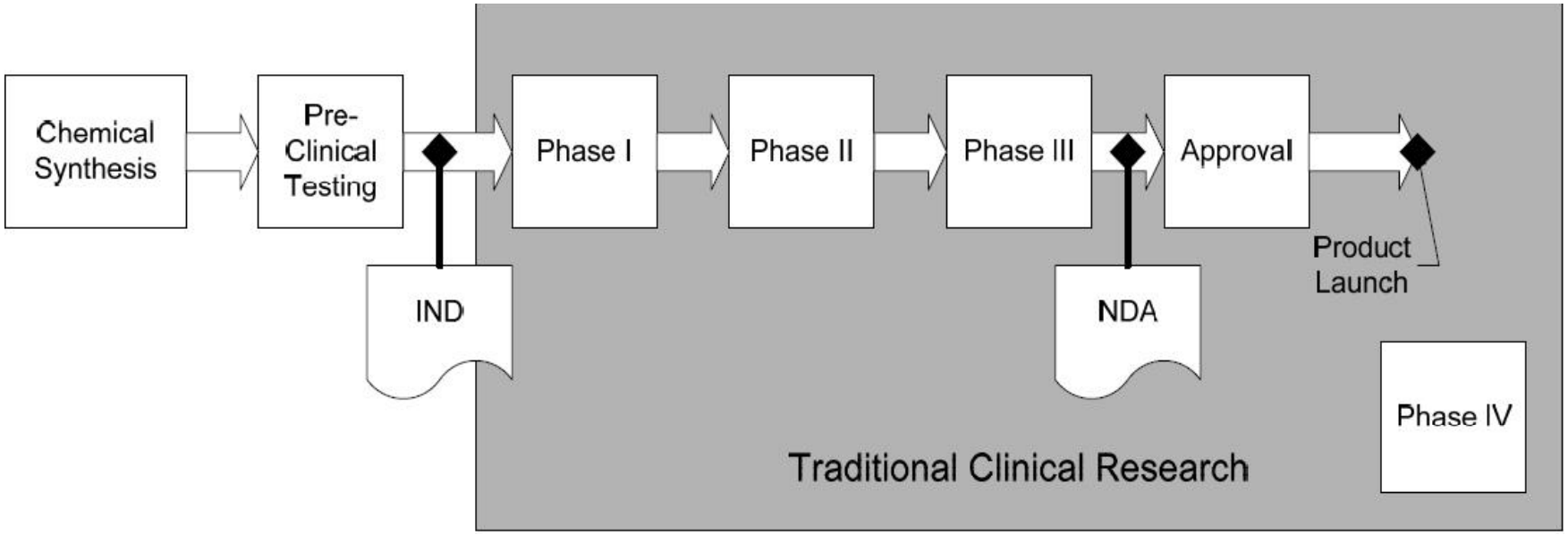
Drug development life cycle



8-12 years
$750-$802 million
20 years patent protection

Drug discovery and preclinical development

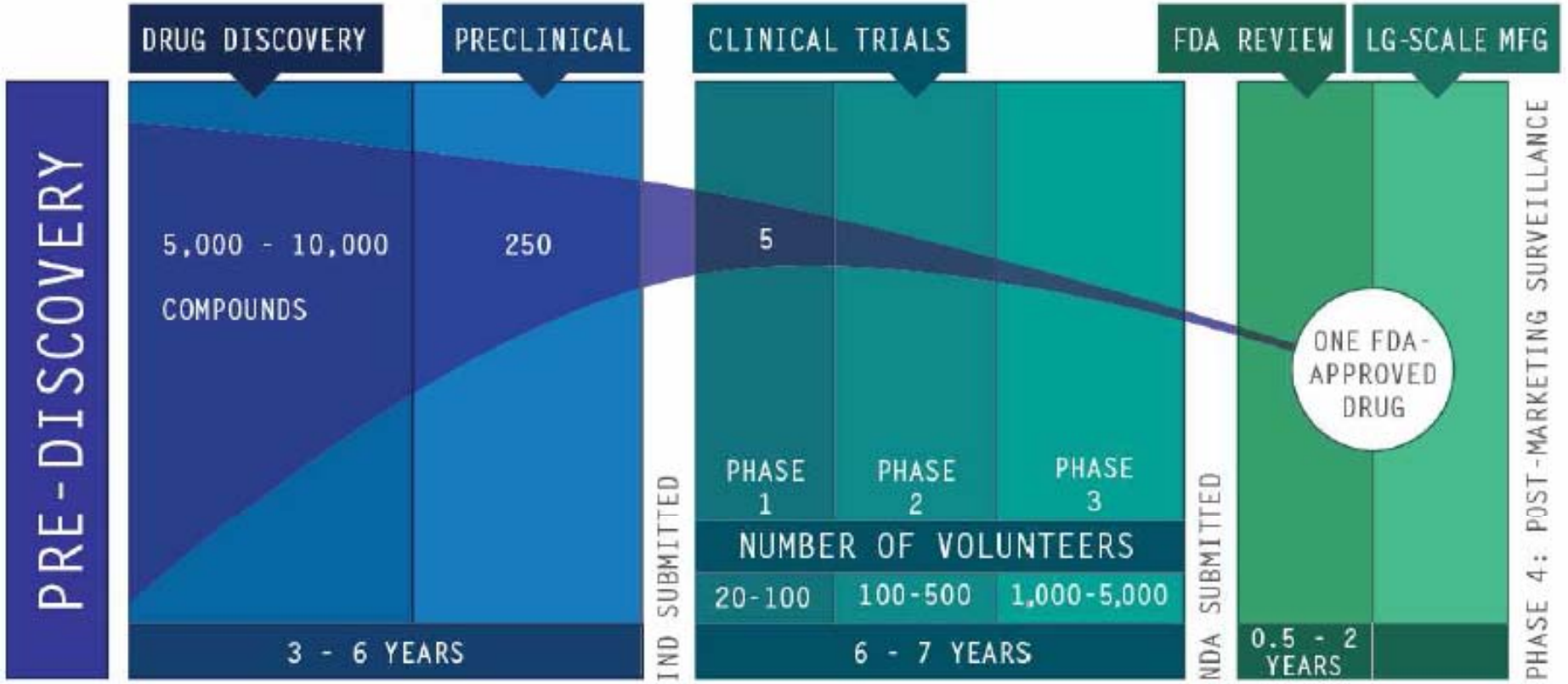
Pre-discovery
Goal: Understand the disease and choose a target molecule.
How: Scientists in pharmaceutical research companies, government, academic and for-profit research insititutions contribute to basic research.

3 - 6 YEARS

Discovery
Goal: Find a drug candidate.
How: Create a new molecule or select an existing molecule as the starting point. Perform tests on that molecule and then optimize (change its structure) it to make it work better.

Preclinical
Goal: Test extensively to determine if the drug is safe enough for human testing.
How: Researchers test the safety and effectiveness in the lab and in animal models.

Drug Development Process



Basel Institute for Clinical Epidemiology and Biostatistics, University of Zürich

Clinical Research

- Clinical research involves working with human subjects to answer questions relevant to their well-being
- Patient oriented research is where the ‘rubber meets the road’!

Hypothesis

- Hypothesis is a tentative construct to be proved or disproved according to the evidence
- The hypothesis is sometimes expressed as a null hypothesis

Study Types

- Will you test a hypothesis or describe a phenomenon?
- Observational
  - Longitudinal
  - Cross-sectional
- Randomized, double-blind, parallel group, placebo controlled trial

Epidemiology *vs.* RCT

- Epidemiology allows the study of the real world and the development of hypothesis regarding disease states
- Randomized, controlled trials allow the rigorous testing of hypothesis in a well characterized manner that is less real world in nature

Study Design

- Study Population
  - Age
  - Gender
  - Ethnicity/Race
  - Disease characteristics
  - Exclusions
  - Number
  - Stratification
  - Randomization

Human Subjects

- The safety and rights of human subjects must be protected
  - Study Design
  - Institutional Review Board
  - Informed consent
  - Data Safety Monitoring/Medical Monitors

Phase I Studies

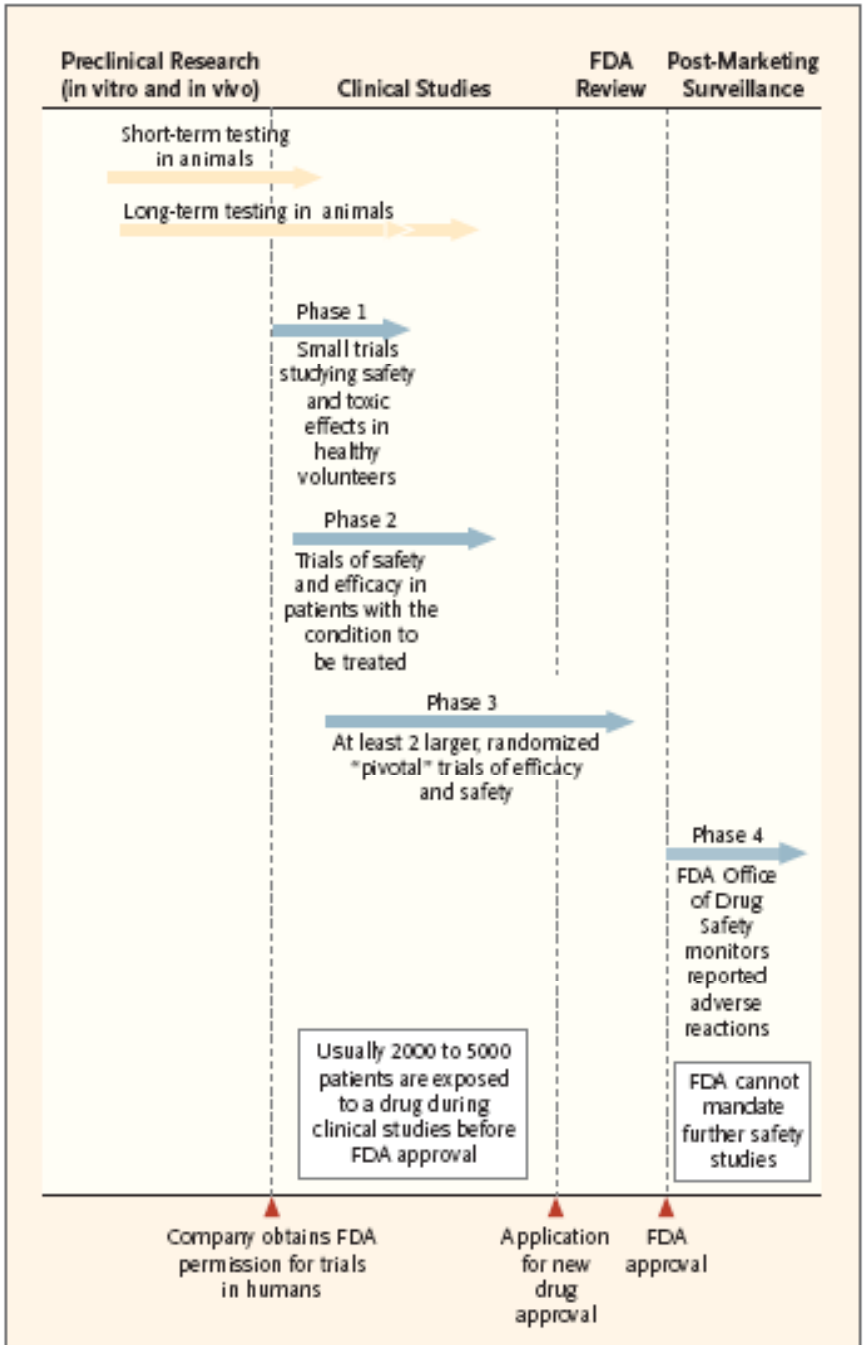
- Assess drug safety and tolerability
- Healthy volunteers, then those with target disease
- Pharmacokinetics
  - Absorption
  - Metabolism
  - Excretion
- Dose escalation
- 70% of new drugs pass this phase

Phase II Studies

- Assess drug efficacy
- Usually randomized, controlled trials with smaller numbers up to several hundred subjects
- Test different therapeutic strategies
- Use surrogate variables and are usually short term
- Only 1/3 get past phase II

Phase III Trial

- **Objective :** To compare experimental or new therapies with standard therapy or competitive therapies.
- Very large, expensive studies
- Required by FDA for drug approval
- If drug approved, usually followed by Phase IV trials to follow-up on long-range adverse events – concern is safety


Preclinical Research (in vitro and in vivo)
Clinical Studies
FDA Review
Post-Marketing Surveillance
Short-term testing in animals
Long-term testing in animals
Phase 1
Small trials studying safety and toxic effects in healthy volunteers
Phase 2
Trials of safety and efficacy in patients with the condition to be treated
Phase 3
At least 2 larger, randomized "pivotal" trials of efficacy and safety
Phase 4
FDA Office of Drug Safety monitors reported adverse reactions
Usually 2000 to 5000 patients are exposed to a drug during clinical studies before FDA approval
FDA cannot mandate further safety studies
Company obtains FDA permission for trials in humans
Application for new drug approval
FDA approval

Clinical Trial Model

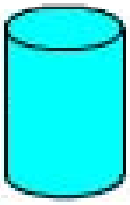
STUDY CENTERS

DATA PAPER CRF FROM SITES/HOSPITALS SENT TO SCAN

DATA ENTERED INTO ORACLE DATABASE

ENTERED DATA CLEANED/VALIDATED

LOGICAL CHECKS IN ORACLE RUN



BOTH AUTOMATED VALIDATIONS AND MANUAL DISCREPANCY RESOLVED

INVESTIGATOR ANSWERS QUERY FAXED TO HIM

FREEZING OF DATABASE AFTER ALL DATA IS CLEAN

AFTER FREEZING BIOSTATICIANS DO ANALYSIS

FINAL ANALYSIS DONE FOR SAFETY AND EFFICACY

About Clinical Data Management

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CONCEPTUAL MODEL OF CLINICAL DATA MANAGEMENT

Clinical Trial Design

Protocol Review

Site and Investigator Selection

Patient Recruitment

Data Entered into CDMS

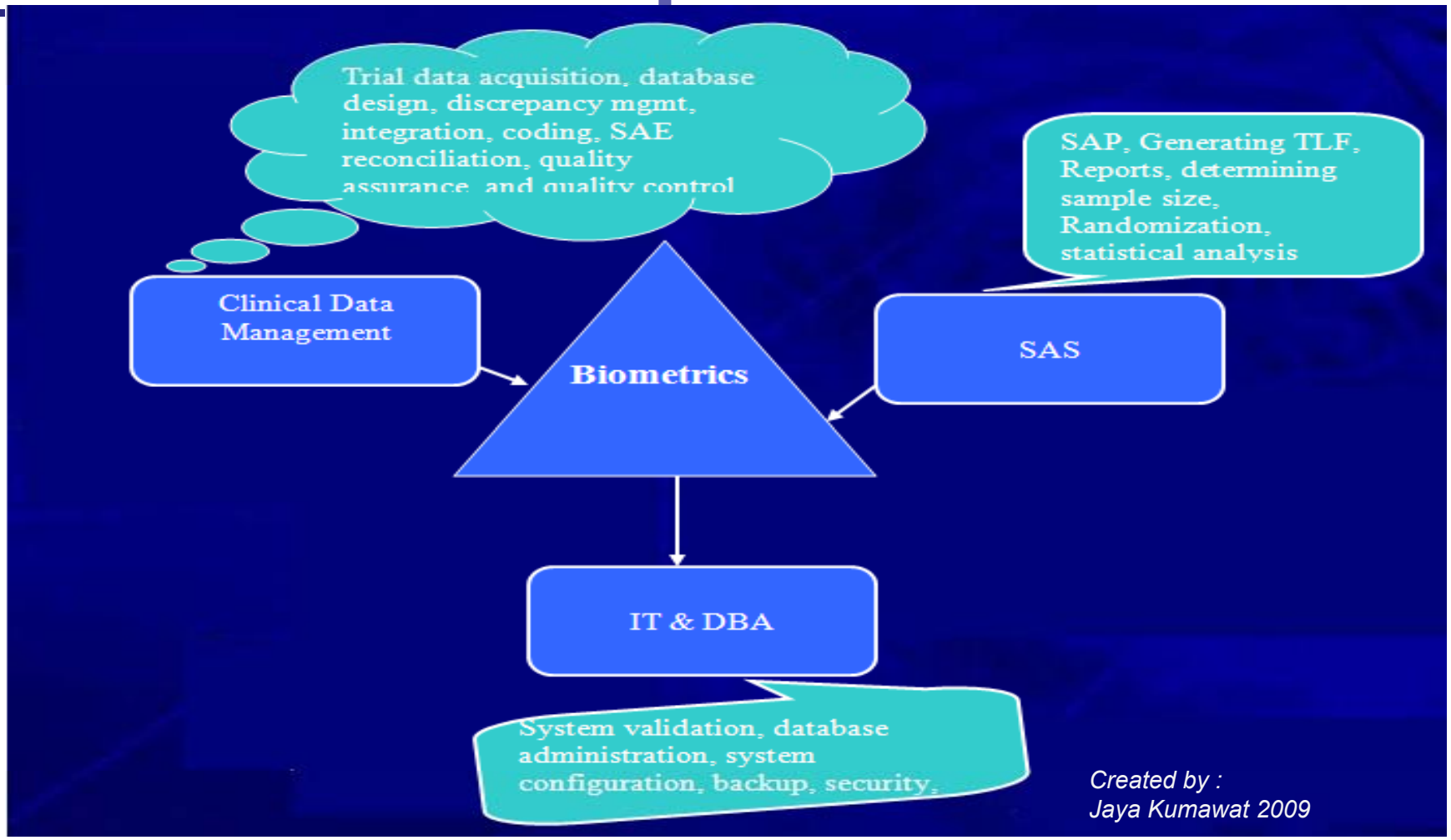
Data Cleaning

Raw Data Extraction

Statistical Analysis

Presentation/Publication Report /Regulatory submissions

Biometrics – A Broad Perspective



Technology

The CDM Industry is guided by the philosophy that technology is not an add-on to clinical trial processes; it is the

backbone.

Technology - CDMS

What is a CDMS?

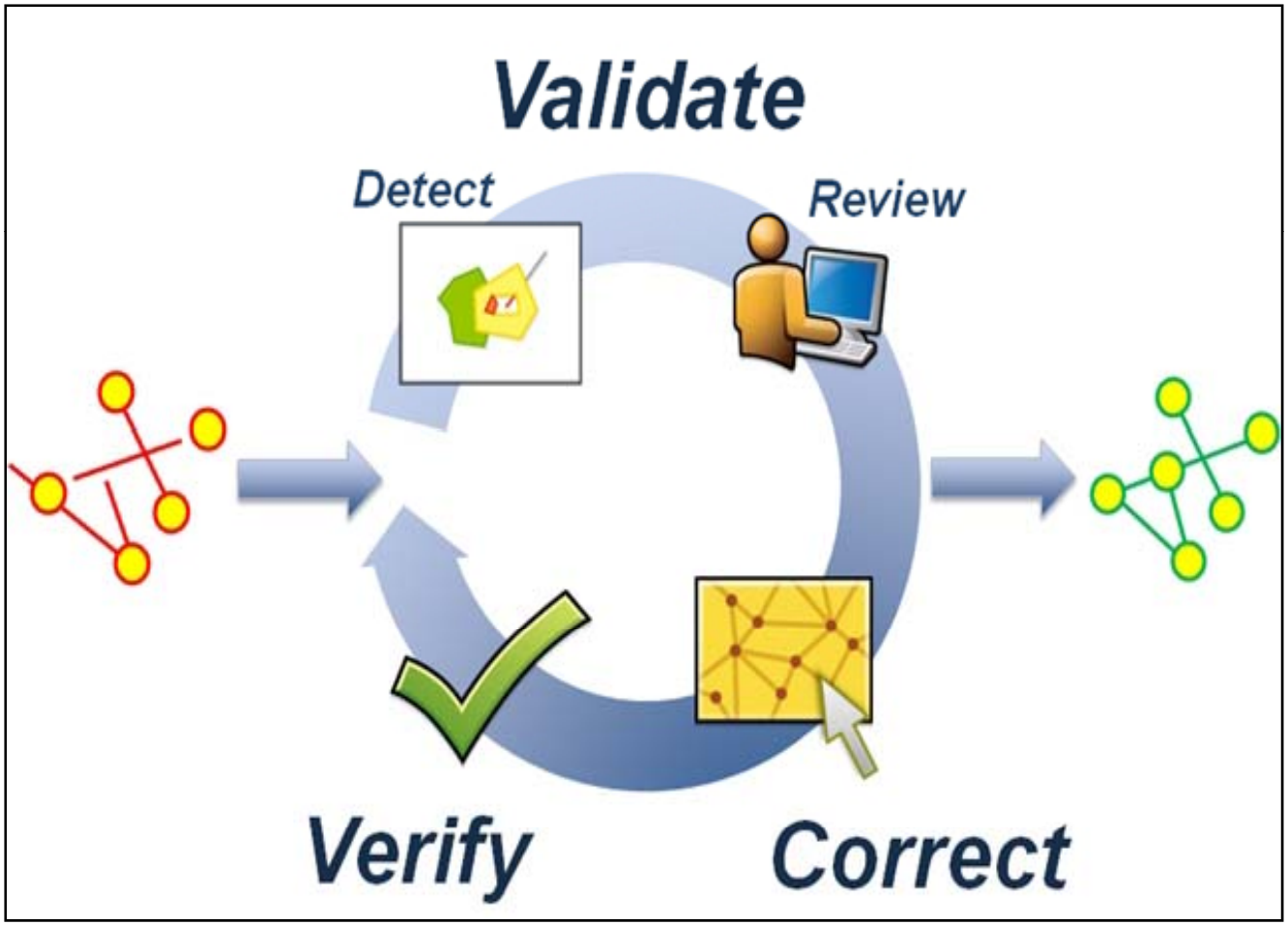
- **A flexible relational database system for**
  - **Capturing,**
  - **Storing, and**
  - **Processing clinical trial data**

HE WILL BE SHOT DEAD/KILLED!!

Data Entry

Batch Data Load

Data Validation

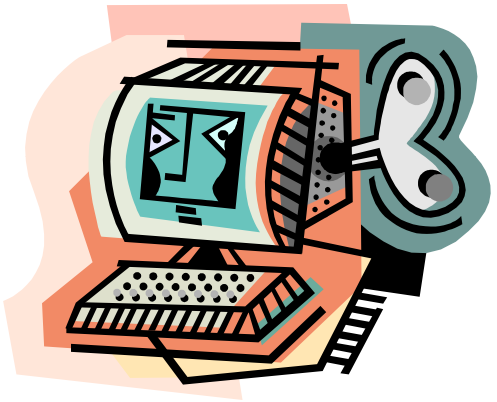


Data

- Data are the facts you measure
- They should be carefully recorded in an unbiased manner
- They should be measured in a manner that minimizes random variation
- They should be derived from the operational definitions you have developed

Data Validation

- Do the data make sense?
- Look critically at the data
  - Highest and lowest values
  - Data entry errors
  - Distribution: Normal or skewed
- Check selected data entries with original data forms



Data Interpretation

- Do not interpret/analyze data until after study is completed
- Do not 'unblind' subjects until the study is completed other than for safety reasons
- Do not interpret/analyze data until after data has been validated and the data set closed

CDM – Compliance, Standards & Regulatory

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Understanding the Environment

International Regulations/ Guidelines

- **Code of Federal Regulations**
  - **HIPAA**
  - **FDA**
    - **21 CFR Part 11**
    - **IRB**
    - **….**
- **ICH**

- **GCP/GCDMP**
- **Sponsor specific**
- **Local regulations**
- **Etc, etc, etc**

GCP
Standards for data

CDISC

GCDMP

Quality Assurance
ICH E6

Compliance

- **compliance** with 21 CFR part 11: security, audit trail, version control
- **Validation** - accuracy, reliability, consistent intended performance and the means to discern invalid or altered records
- **Restriction of system access** to only authorized individuals
- **Secure, computer-generated, time-stamped audit trails** to record operator entries and action to create, modify and delete electronic records – retained for required period and available for agency review and copying
- **Operational system checks** to enforce permitted sequencing of steps and events as appropriate
- **Authority checks** for use, e-signature, access of input and output device, altering a record and performing operation at hand
- **PDUFA III** - The '***Prescription Drug User Fee Act'*** (PDUFA) was a law passed by the United States Congress in 1992 which allowed the Food and Drug Administration (FDA) to collect fees from drug manufacturers to fund the new drug approval process.

Related Standards

- ICH – The International Conference on Harmonization has been compiling a series of guidelines for the preparation, design, conduct, and reporting of clinical trials with an aim to harmonize the interpretation and application of technical guidelines and requirements for product registration.

- CDISC
  - Operational Data Model (ODM) - operational support of data collection .
  - Study Data Tabulation Model (SDTM) – data tabulation data sets
  - Case Report Tabulation Data Definition Specification (CRTDDS - aka
  - define.xml)
  - Laboratory Data Model (Lab)
  - Standard for Exchange of Non-clinical Data (SEND)
  - Analysis Data Model (ADaM) – analysis data structures
  - And others.. LAB, SEND

But why standards??????

- Reviewer's efficiency.
- FDA Repository
- Standard software tools for viewing and analyzing.
- Streamline the flow of data from collection through submission, facilitating data interchange b/w partners and providers.

Statistical Analysis in Clinical Research

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Statistical Considerations in Clinical Research

- Sample Size determination.
- Randomization
- SAP(Statistical Analysis Plan)
- Manual Discrepancy Management
- Generating Table, Listings, Figures.
- Data Conversions into CDISC (SDTM & ADaM) Models.
- Analysis and Reporting (including XMLs for FDA submissions).

Stats Software – Evaluation Criteria

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Criteria 1 :21CFR Part 11

- **Stata is verifiably accurate**
- When you submit new drug applications (NDAs), the U.S. Food and Drug Administration (FDA) requires you to verify the validity of your data and analyses.
- According to this document, to demonstrate the validity of the software used for an NDA, you must have :
  - a written design specification
  - a test plan
  - test results.

Stata provides all the three

Criteria 2: Used for Clinical Research ??

Stata is widely used in the medical community, including many hospitals and medical schools. In addition, the Centers for Disease Control uses Stata frequently.

Online resource to STATA users :

- *Dalla Lana School of Public Health, University of Toronto*
- *Department of Epidemiology, University of Albany*
- *Department of Psychology, Stockholm University & National Institute for Psychosocial Medicine*
- *Department Community Health & General Practice, Trinity College, Dublin, Ireland*
- *Ontario Cancer Institute, Princess Margaret Hospital*
- *University of North Carolina Chapel Hill*
- *Harvard School of Public Health*

Criteria 3: Programming Required?

- No in-depth programming skills are necessary for the primary usage of Stata. If a user wishes to write their own command, they will need some experience.

- There are many useful topics here and they are presented in an intuitive way. The manuals provided with your license (in PDF format) are also very valuable.

Criteria 4:Support for Regulatory/FDA Submission

Can STATA generate SAS transport files(.XPT) required for FDA submissions?

Answer:

- Stata can read and write SAS XPORT format datasets natively, using the fdause and fdasave commands.
- STATA can export a dataset in FDA (SAS XPORT) format using the -fdasave- command.
- You can also read in a SAS XPORT file into Stata with the -fdause- command.

Criteria 5: CDISC Compliance

- How will the software support ADaM. Does it have built in CDISC SDTM and ADaM libraries?

- Stata has no direct link to ADaM, and it hasn't been tested in this environment though no problems anticipated.

Criteria 6: Generation of XML files

- How will the software support generation of Data Definition Files like the define.xml.

- Stata can write datasets to .xml format using -xmlsave-, or you can write to text format for spreadsheets using -out sheet-.

Sample xml file generated from STATA

```
<?xml version="1.0" encoding="US-ASCII" standalone="yes"?>
<dta>
<header>
<ds_format>113</ds_format>
<byteorder>LOHI</byteorder>
<filetype>1</filetype>
<nvar>12</nvar>
<nobs>74</nobs>
<data_label>1978 Automobile Data</data_label>
<time_stamp>26 Jul 2013 12:55</time_stamp>
</header>
<descriptors>
<typelist>
<type varname='make'>str18</type>
<type varname='price'>int</type>
<type varname='mpg'>int</type>
<type varname='rep78'>int</type>
<type varname='headroom'>float</type>
<type varname='trunk'>int</type>
<type varname='weight'>int</type>
<type varname='length'>int</type>
<type varname='turn'>int</type>
<type varname='displacement'>int</type>
<type varname='gear_ratio'>float</type>
<type varname='foreign'>byte</type>
</typelist>
<varlist>
```

Criteria 7: Cost Assessment

- Breaks the market monopoly of other statistical tools.
- No Annual License.
- Reasonably priced.

Criteria 8: Training/learning resources.

- STATA can arrange for an online training at corporate level on a need basis.
- Huge amounts of online training documentations available.
- a pdf help file has been installed within the software.

Criteria 9: Support for biostatistics / epidemiology features

- Comprehensive coverage of biostatistics/epidemiology .
- The capabilities include all the standard functionalities required viz. dataset filtering, transformation, merging, statistical models, great graphics and other biostatistical tests.

Criteria 10: Miscellaneous Factors

- Maintenance & support.
- Ethics/ principles/ honesty.
- GUI , ease of use, intuitive.
- Updates/patches.
- Multi platform support i.e. Linux, Macintosh, windows.

STATA – Features and Benefits as explored and supported for Clinical Research

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1. Data imports

- Imports data in all possible formats:
  a) MsExcel.
  b) CSV.
  c) ASCII
  d) .xpt
  e) .xml

  f) (perhaps some others….)

2. Data Transformations (E.g.: merge , append)

mydata1

	country	year	y	y_bin	x1	x2	x3
1	A	2000	1343	1	.28	-1.11	.28
2	A	2001	-1900	0	.32	-.95	.49
3	A	2002	-11	0	.36	-.79	.7
4	A	2003	2646	1	.25	-.89	-.09
5	B	2000	-5935	0	-.08	1.43	.02
6	B	2001	-712	0	.11	1.65	.26
7	B	2002	-1933	0	.35	1.59	-.23
8	B	2003	3073	1	.73	1.69	.26
9	C	2000	-1292	0	1.31	-1.29	.2
10	C	2001	-3416	0	1.18	-1.34	.28
11	C	2002	-356	0	1.26	-1.26	.37
12	C	2003	1225	1	1.42	-1.31	-.28

mydata2

	country	year	x4	x5	x6	order
1	A	2000	10	1	9	1
2	A	2001	7	1	9	2
3	A	2002	7	9	4	3
4	A	2003	1	2	3	4
5	B	2000	0	5	6	5
6	B	2001	5	8	5	6
7	B	2002	9	4	5	7
8	B	2003	1	5	1	8
9	C	2000	4	5	4	9
10	C	2001	6	9	6	10
11	C	2002	6	5	3	11
12	C	2003	7	3	3	12

```
merge 1:1 country year using mydata2

    Result                           # of obs.
    -----------------------------------------
    not matched                             0
    matched                                12  (_merge==3)
    -----------------------------------------
```

- Make sure one dataset is loaded into Stata (in this case mydata1), then use merge.
- Make sure to map where the using data is located (in this case mydata2, for example "c:\folders\data\mydata2.dta")*.

NOTE: For Stata 10 or older:

1) Remove the 1:1
2) Sort both datasets by all the ids and save before merging

	country	year	y	y_bin	x1	x2	x3	x4	x5	x6	order	_merge
1	A	2000	1343	1	.28	-1.11	.28	10	1	9	1	matched (3)
2	A	2001	-1900	0	.32	-.95	.49	7	1	9	2	matched (3)
3	A	2002	-11	0	.36	-.79	.7	7	9	4	3	matched (3)
4	A	2003	2646	1	.25	-.89	-.09	1	2	3	4	matched (3)
5	B	2000	-5935	0	-.08	1.43	.02	0	5	6	5	matched (3)
6	B	2001	-712	0	.11	1.65	.26	5	8	5	6	matched (3)
7	B	2002	-1933	0	.35	1.59	-.23	9	4	5	7	matched (3)

3. Ability to handle Diff -> Types of Data – (1)

- ***Discrete Data-*** limited number of choices
  - Binary: two choices (yes/no)
    - Dead or alive
    - Disease-free or not
  - Categorical: more than two choices, not ordered
    - Race
    - Age group
  - Ordinal: more than two choices, ordered
    - Stages of a cancer
    - Likert scale for response
      - E.G. strongly agree, agree, neither agree or disagree, etc.

Types of Data – (2)

- ***Continuous data***
  - Theoretically infinite possible values (within physiologic limits) , including fractional values
    - Height, age, weight
  - Can be interval
    - Interval between measures has meaning.
    - Ratio of two interval data points has no meaning
    - Temperature in Celsius, day of the year).
  - Can be ratio
    - Ratio of the measures has meaning
    - Weight, height

Support for Types of Data – Why Important ??

- The type of data defines:
  - The summary measures used
    - Mean, Standard deviation for continuous data
    - Proportions for discrete data
  - Statistics used for analysis:
    - Examples:
      - T-test for normally distributed continuous
      - Wilcoxon Rank Sum for non-normally distributed continuous

Descriptive Statistics

- Characterize data set
  - Graphical presentation
    - Histograms
    - Frequency distribution
    - Box and whiskers plot
  - Numeric description
    - Mean, median, SD, interquartile range

Numeric Descriptive Statistics

- Measures of central tendency of data
  - Mean
  - Median
  - Mode
- Measures of variability of data
  - Standard Deviation
  - Interquartile range

Descriptive Statistics Example

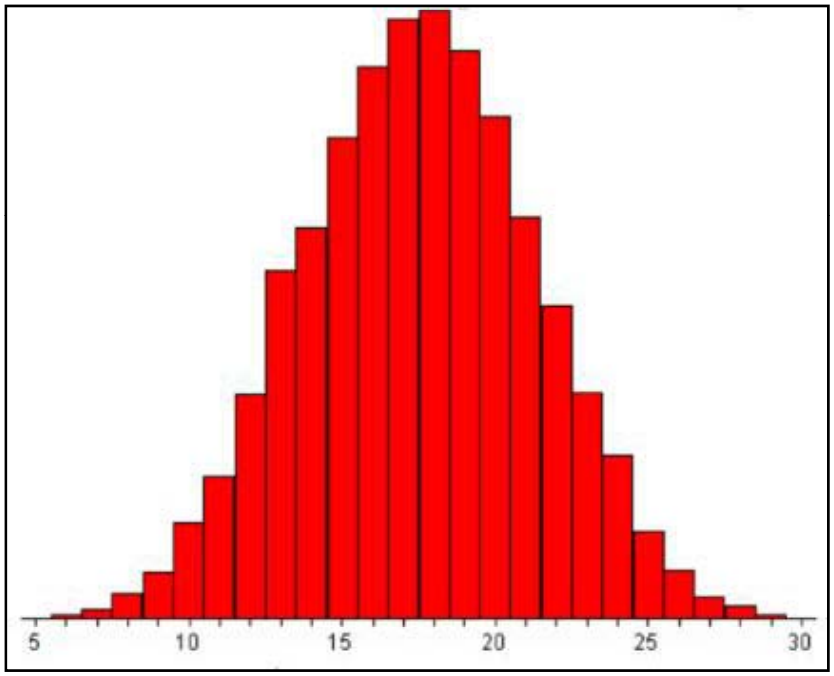
```
. summarize
```

Variable	Obs	Mean	Std. Dev.	Min	Max
id	30	15.5	8.803408	1	30
lastname	0				
firstname	0				
city	0				
state	0				
gender	0				
studentsta~s	0				
major	0				
country	0				
age	30	25.2	6.870226	18	39
sat	30	1848.9	275.1122	1338	2309
averagesco~e	30	80.36667	10.11139	63	96
heightin	30	66.43333	4.658573	59	75
newspaperr~k	30	4.866667	1.279368	3	7

Zeros indicate string variables

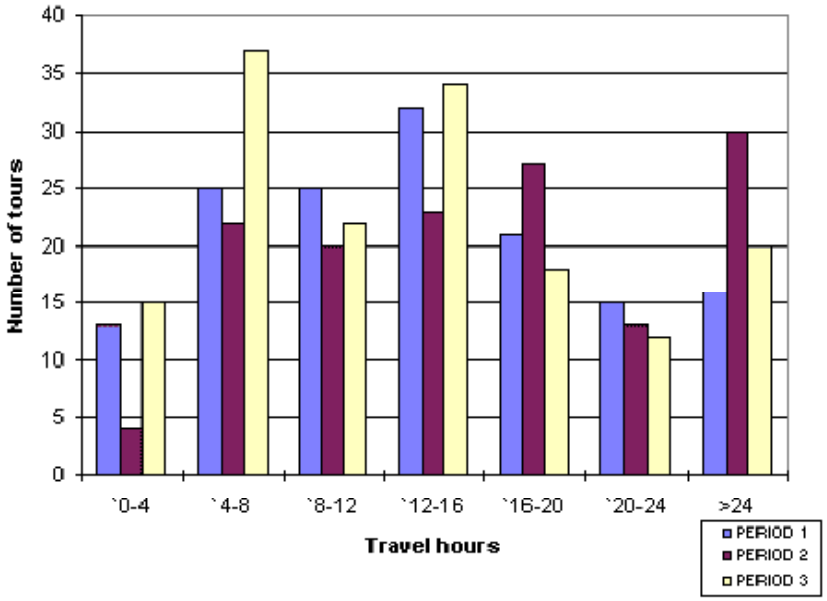
Use 'min' and 'max' values to check for a valid range in each variable. For example, 'age' should have the expected values ('don't know' or 'no answer' are usually

Histogram - Continuous Data



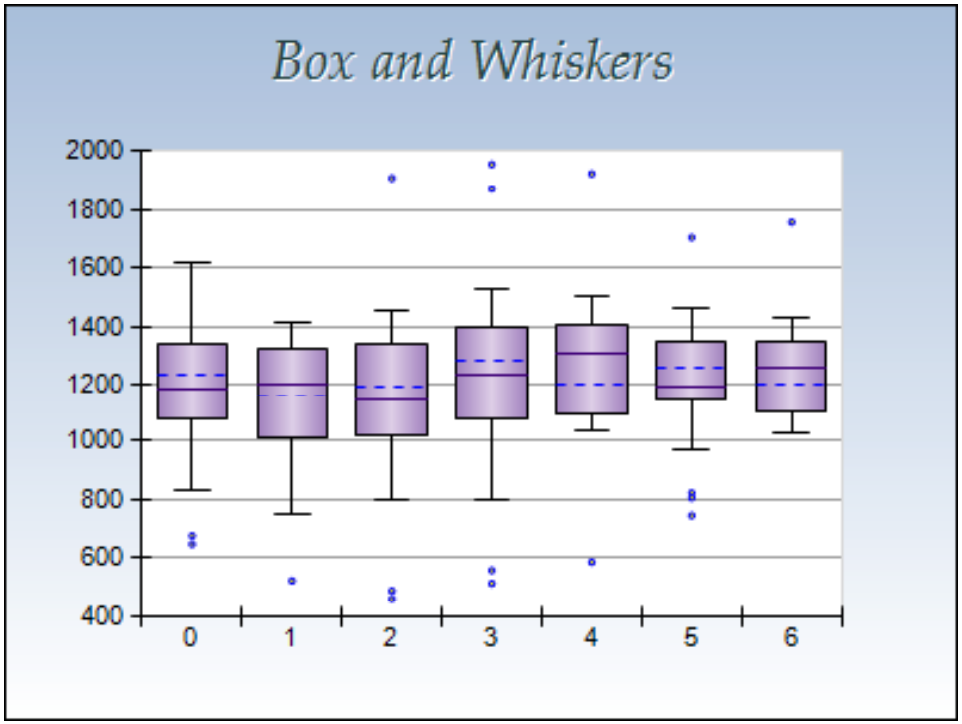
No segmentation of data into groups

Frequency Distribution



Segmentation of data into groups
Discrete or continuous data

Box and Whiskers Plots



Useful for presenting comparative data graphically

Standard Error

- Standard error measures the precision of the estimate of a population parameter provided by the sample mean or proportion.

Standard Error Significance

- Significance:
  - Is the basis of confidence intervals
  - A 95% confidence interval is defined by
    - Sample mean (or proportion) ± 1.96 X standard error
  - Since standard error is inversely related to the sample size:
    - The larger the study (sample size), the smaller the confidence intervals and the greater the precision of the estimate.

Confidence Intervals

- May be used to assess a single point estimate such as mean or proportion.

- Most commonly used in assessing the estimate of the difference between two groups.

Confidence Interval

Table 1
Mean Values of Baseline Characteristics and Short-term Outcomes

	No. of Patients	Mean ± SE	95% CI
Baseline characteristics			
Age (y)	100	43.0 ± 0.52	41.9–44.0
Body mass index (kg/m^2)	83	26.9 ± 0.44	26.0–27.7
Baseline uterine volume (cm^3)	96	628 ± 34.1	560–695
Baseline fibroid volume (cm^3)	96	150 ± 15.7	118–181
Baseline fibroid-specific QOL symptom score	98	54.1 ± 2.19	49.8–58.5
Baseline fibroid-specific QOL total score	98	52.3 ± 2.24	47.9–56.8
Ethnic background (%)			
African-American	61		
Caucasian	34		
Other	5		
Short-term outcome measures			
Maximum VAS score in hospital	99	3.03 ± 0.26	2.50–3.55
Maximum VAS score first week	92	4.89 ± 0.26	4.38–5.4
Maximum temperature in hospital (°C)	91	37.1 ± 0.05	37.1–37.2
Maximum temperature first week (°C)	93	37.4 ± 0.05	37.4–37.5
Symptom summary score			
First week	90	26.6 ± 1.73	23.2–30.1
Week 2	96	5.93 ± 0.34	5.25–6.60
Week 3	87	4.68 ± 0.38	3.92–5.44
Week 4	90	4.86 ± 0.41	4.04–5.68
Weeks 2–4	83	15.3 ± 0.85	13.6–17.0
Number of PCA doses attempted	96	70.6 ± 6.72	57.2–83.9
Number of PCA doses given	97	28.1 ± 1.62	25.6–32.0
Total PCA dose (normalized to morphine mg)	98	46.7 ± 3.48	39.8–53.6
Total ondansetron dose (mg)	98	3.43 ± 0.36	2.71–4.15
Total promethazine dose (mg)	98	12.3 ± 1.41	9.53–15.1
Total number of oxycodone/acetaminophen tablets	92	10.7 ± 1.19	8.32–13.0
Total number of ibuprofen tablets	91	17.9 ± 0.58	16.8–19.0

Commonly reported in studies to provide an estimate of the precision of the mean.

P values

- The probability that any observation is due to chance alone assuming that the null hypothesis is true
  - Typically, an estimate that has a p value of 0.05 or less is considered to be “statistically significant” or unlikely to occur due to chance alone.
  - The P value used is an arbitrary value
    - P value of 0.05 equals 1 in 20 chance
    - P value of 0.01 equals 1 in 100 chance
    - P value of 0.001 equals 1 in 1000 chance.

ERRORS

- Type I error
  - Claiming a difference between two samples when in fact there is none.
    - Remember there is variability among samples- they might seem to come from different populations but they may not.
  - Also called the α error.
  - Typically 0.05 is used

ERRORS

- Type II error
  - Claiming there is no difference between two samples when in fact there is.
  - Also called a β error.
  - The probability of not making a Type II error is 1 - β, which is called the power of the test.
  - Hidden error because can't be detected without a proper power analysis

(Pearson's) Chi-Squared ($\chi 2$) Test

- Used to compare observed proportions of an event compared to expected.
- Used with nominal data (better/ worse; dead/alive)

Example that uses 4 test in a single command:

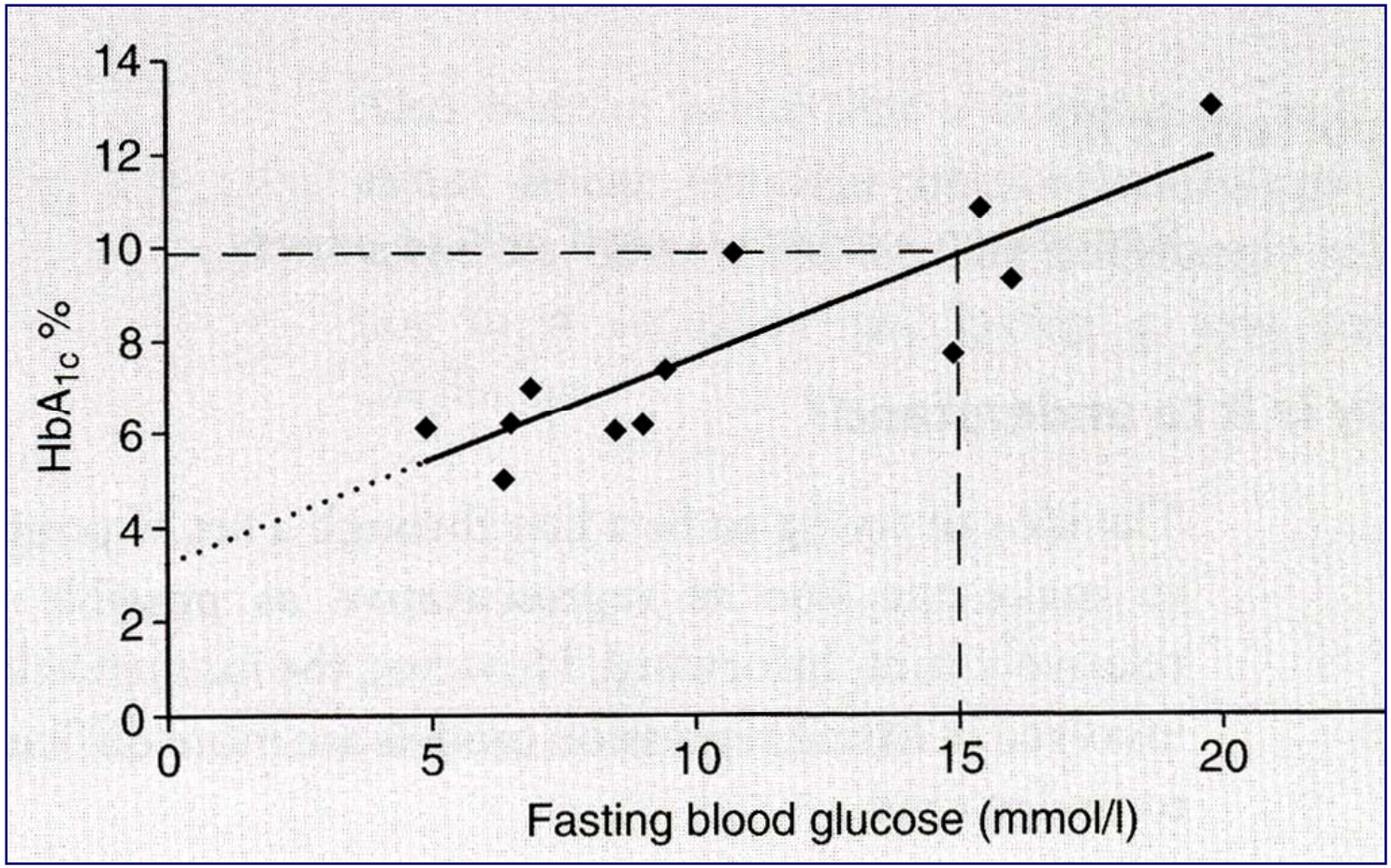
". tab ecostatu1 gender, column row nokey chi2 lrchi2 V exact gamma taub"

- Chi-Squared ($\chi 2$) Test
- Fisher's exact
- Gamma and taub (*Kruskal's γ (gamma))*
- Cramer's *V*

RECODE of ecostatu (Status of Nat'l Eco)	Gender of Respondent Male	Female	Total
Well	427	392	819
	52.14	47.86	100.00
	67.99	52.62	59.65
Bad	196	343	539
	36.36	63.64	100.00
	31.21	46.04	39.26
Not sure/ref	5	10	15
	33.33	66.67	100.00
	0.80	1.34	1.09
Total	628	745	1,373
	45.74	54.26	100.00
	100.00	100.00	100.00

Pearson chi2(2) =	33.5266	Pr =	0.000
likelihood-ratio chi2(2) =	33.8162	Pr =	0.000
Cramér's V =	0.1563		
gamma =	0.3095	ASE =	0.050
Kendall's tau-b =	0.1553	ASE =	0.026
Fisher's exact =			0.000

Correlation



Source: Harris and Taylor. Medical Statistics Made Easy

Conclusions

Conclusion

- Do **NOT** follow the rest of the world because your requirements and budgets may be altogether different.

- Understand your statistical requirements first and then make the choice for an appropriate and best fit stats software.

The Roads not Taken

Two roads diverged in a yellow wood,
And sorry I could not travel both….

….I took the one less traveled by,
And that has made all the difference.”

- Robert Frost