An Overview of Clinical Trials, Early Phase trials, Statistical Methods and Safety Issues

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UCLA

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Outline

1 Overview of Designs in Health Care Studies

1.1 Common Studies in the Health Sciences

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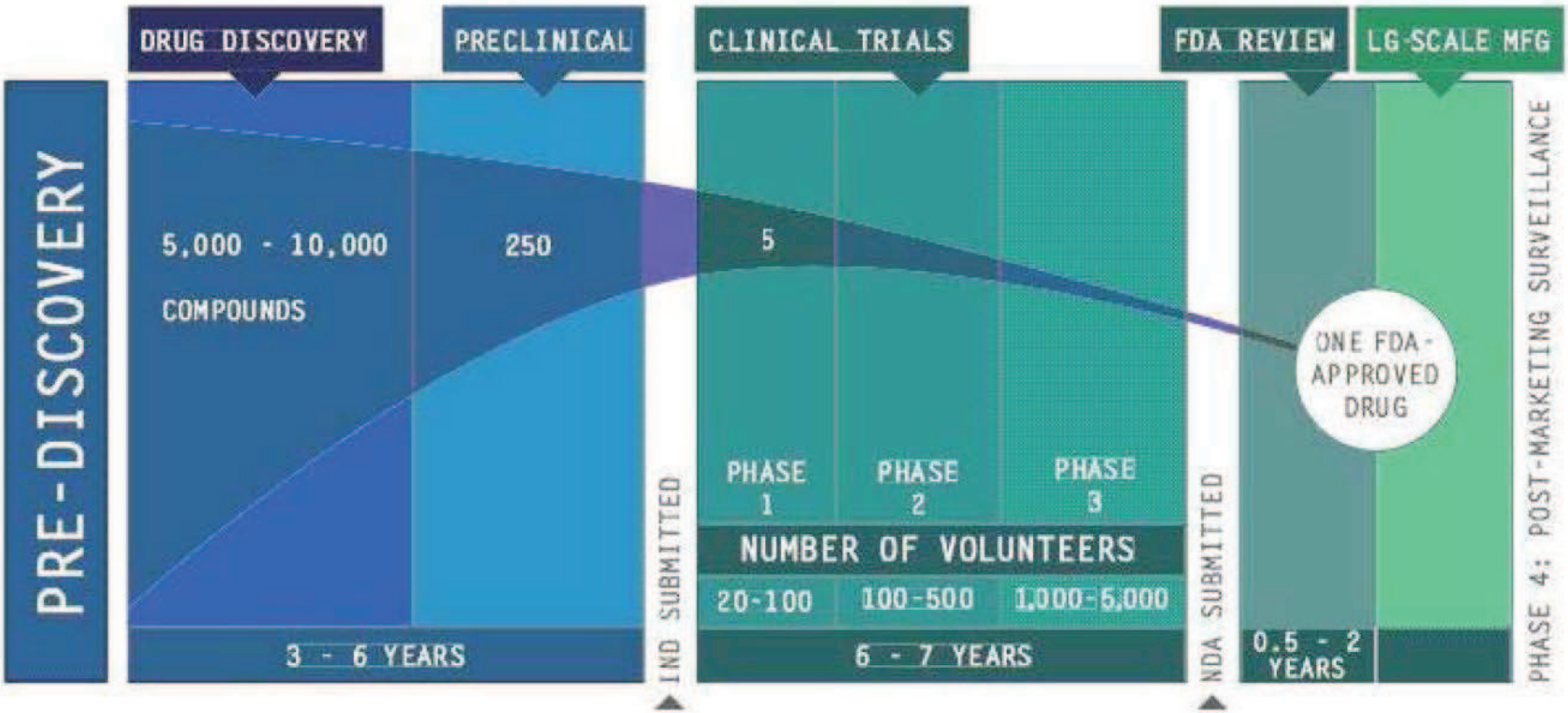
1.2 The Drug Discovery Cycle



McDOUGALL SCIENTIFIC
INSIGHTS YOU CAN TRUST

1.3 Staggering Cost of Developing Drugs (Herper, Forbes, 2012)

Research Spending Per New Drug

Company	Ticker	Number of drugs approved	R&D Spending Per Drug ($Mil)	Total R&D Spending 1997-2011 ($Mil)
AstraZeneca AZN -0.84%	AZN	5	11,790.93	58,955
GlaxoSmithKline GSK -0.50%	GSK	10	8,170.81	81,708
Sanofi SNY +%	SNY	8	7,909.26	63,274
Roche Holding RHHBY +% AG	RHHBY	11	7,803.77	85,841
Pfizer PFE +0.14% Inc.	PFE	14	7,727.03	108,178
Johnson & Johnson	JNJ	15	5,885.65	88,285
Eli Lilly & Co.	LLY	11	4,577.04	50,347

1.4 Clinical Trials

- A clinical trial is a research study to answer specific questions about a new medical treatment (medicine/drug, medical device, new therapies, vaccines), or new ways of using known treatments. Clinical trials are used to determine whether such new treatments are both safe and effective or non-inferior.

- Carefully conducted clinical trials are the fastest and safest way to find treatments that work in people. A clinical trial is one of the final stages of a long and careful research process. Studies are done with patients to find out whether promising approaches to disease prevention, diagnosis, and treatment are safe and effective.

- Historical details and information on clinical trials are available at many websites, commerical or otherwise, see for example, http://www.availclinical.com/clinical-study/clinical-trials-history/

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Need for a RCT

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- Grace[2] (1996) reviewed 53 studies of portacaval shunt operation for portal hypertension; 75% of the 32 uncontrolled trials were strongly positive; 0% of the 6 well-controlled trials reported strongly positive results - 3 moderately positive

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- publication bias
- Other issues include compliance, administrative problems
- These are not statistical biases that arise from estimators. For example, if s^2 is the sampling variance estimator, s is biased for estimating the standard deviation σ. However, we still can obtain an unbiased estimator for σ. Missing data is a constant problem.

1.8 Phases of Clinical Trials

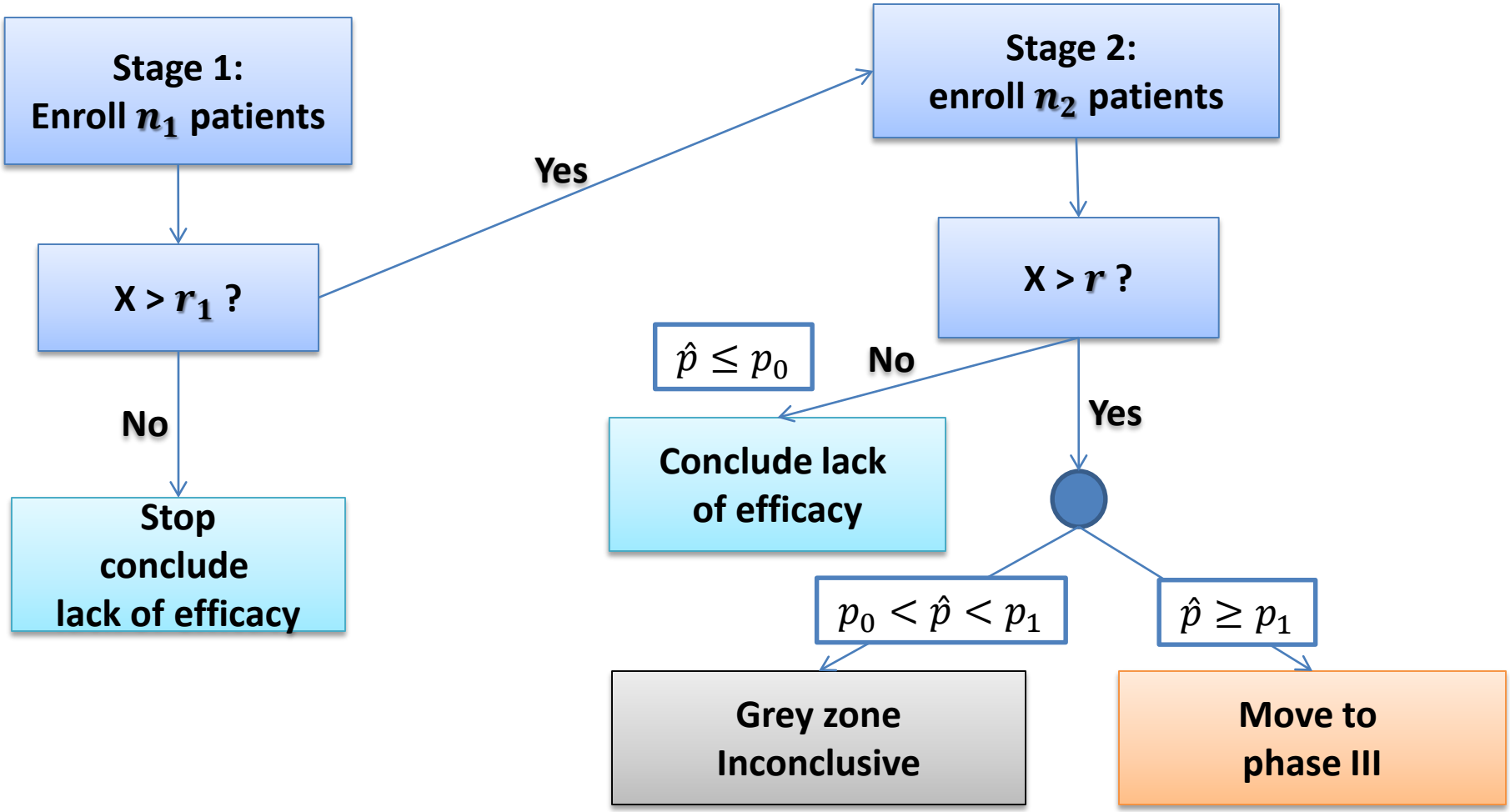
- Phase I Trials: These first studies in people evaluate how a new drug should be given, how often, and what dose is safe. A phase I trial usually enrolls only a small number of patients, sometimes as few as a dozen.

- Phase II Trials: A phase II trial continues to test the safety of the drug, and begins to evaluate how well the new drug works.

- Phase III Trials: These studies test a new drug, a new combination of drugs, or a new surgical procedure in comparison to the current standard. Phase III trials often enroll large numbers of subjects and assign them to one of the treatment groups.

Simon's Two-Stage Designs

- X: the number of responders



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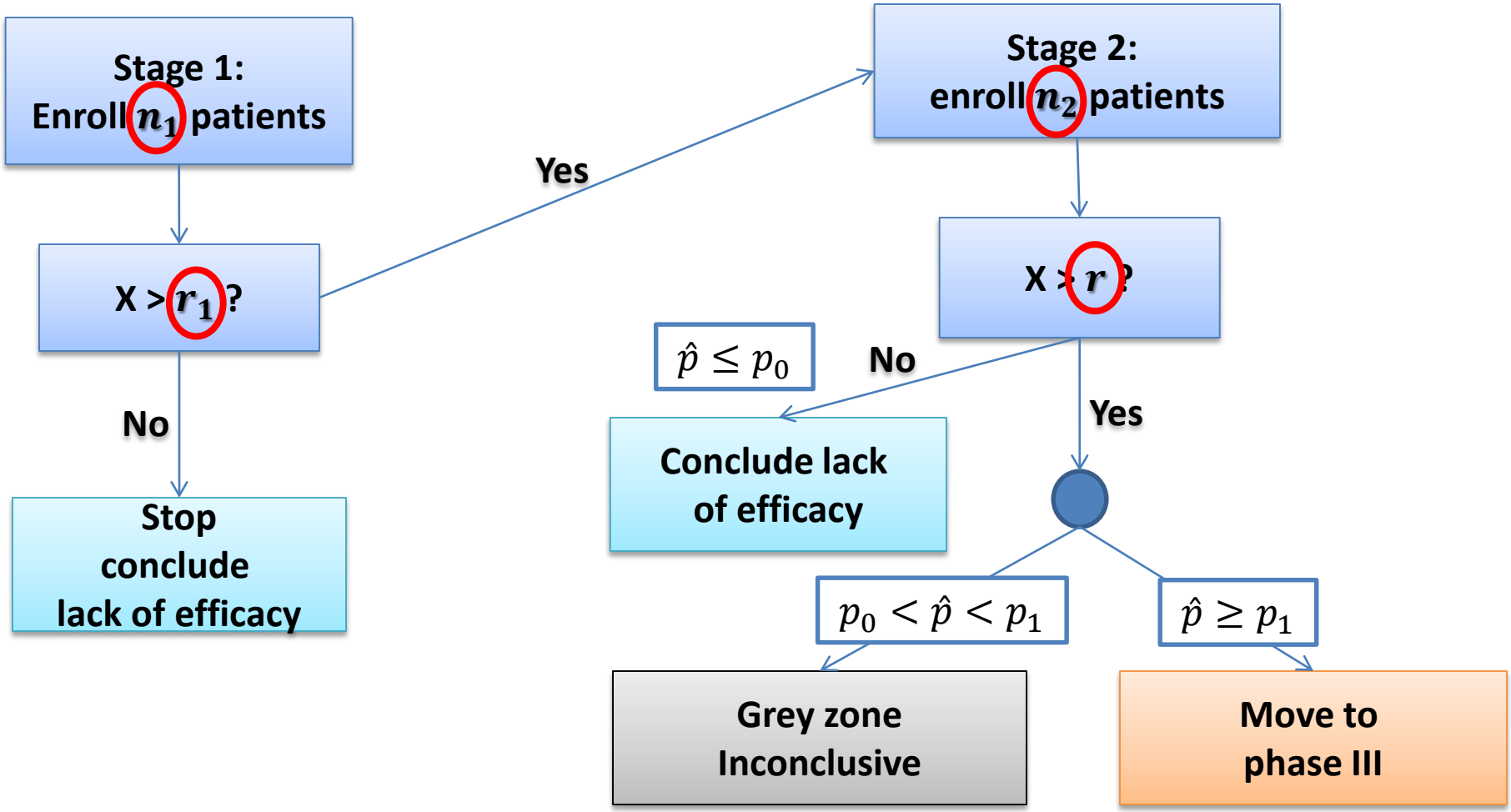
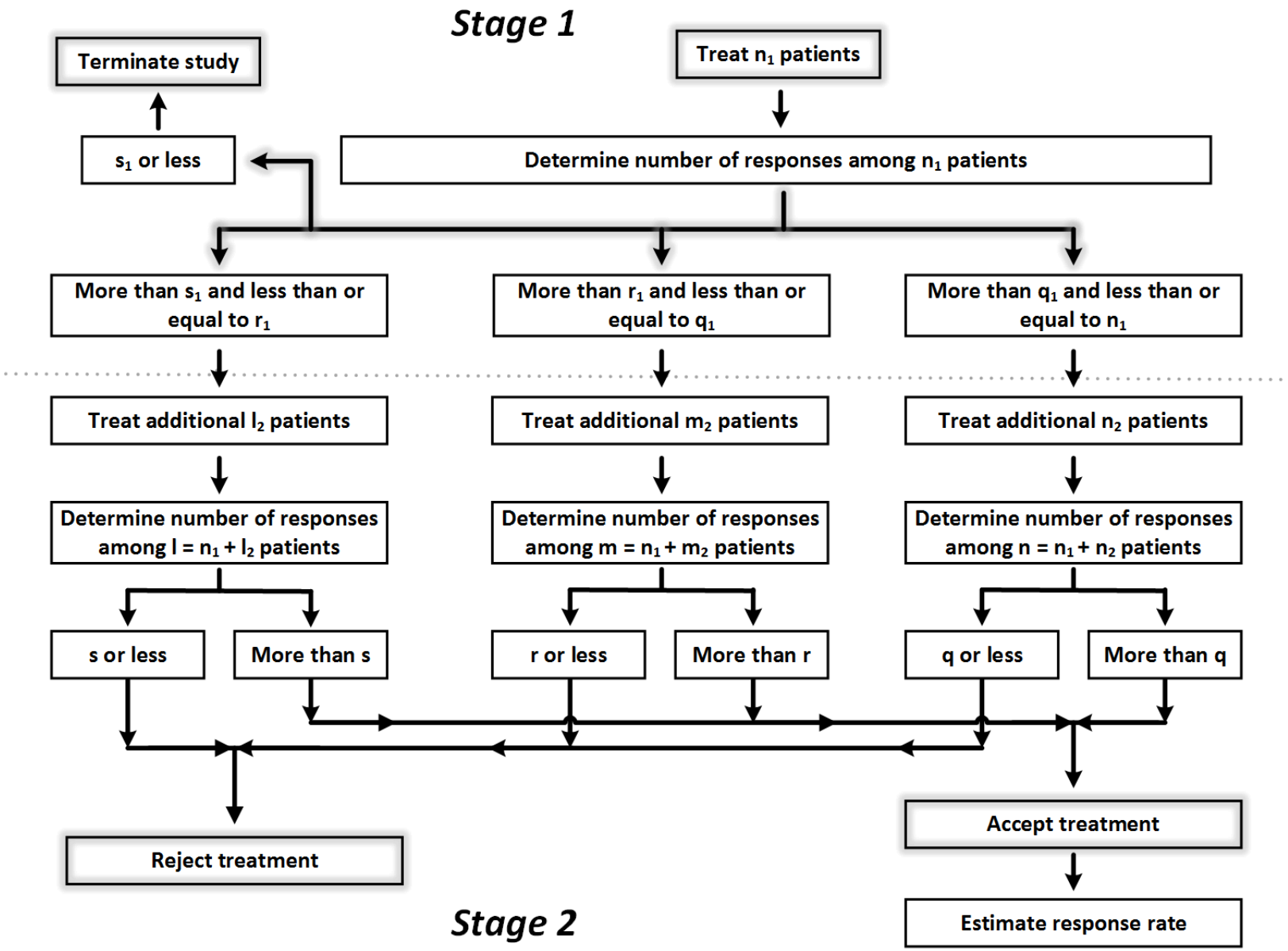


1.10 An Extended 2-stage Adaptive Phase II Design (Kim and Wong, 2016)



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- Metha, et al. (Circulation, 2016) discusses choice of design strategies for CV research.

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- The site http://www.ich.org/ for the International Conference on Harmonization (ICH) provides important guidelines to standardize technical requirements for registering medical products

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- Detecting safety issues are generally problematic, especially in early phase trials!
- Sullivan and Hamadeh (Chapter 17 of Jiang and Xia) provides an overview of safety evaluation and quantitative approaches during preclinical and early phases of drug development.

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- Connor (2015, chapter 7 of Jiang and Xia) provides an adaptive trial for finding optimal sample size when the true event rate is unknown subject to type 1 error specification in a confirmatory study on CV events.

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- Other drugs like Rosiglitazone are prescribed with tighter restrictions after discovering that it produced higher CV risk
- Result in more stringent drug safety requirements on new drugs; eg. new diabetes drug must, in addition to efficacy, demonstrate it is heart safe

3. Statistical Methods for Detecting Safety Issues

- Graphical Tools
- Systematic Reviews and Meta-analysis
- Safety Surveillance and Signal Detection Process
- Bayesian Adaptive Trials for Drug Safety (Chapter 2 of Jiang and Xia - Bayesian Design for Evaluating CV Risk)
- False Discovery Rate for Evaluating Clinical Safety Data (Mehrotra and Heyse, SMMR, 2004)
- Several others as well...

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- Next few slides are taken from

https://www.ctspedia.org/do/view/CTSpedia/StatGraphHome

Graphics Best Practices

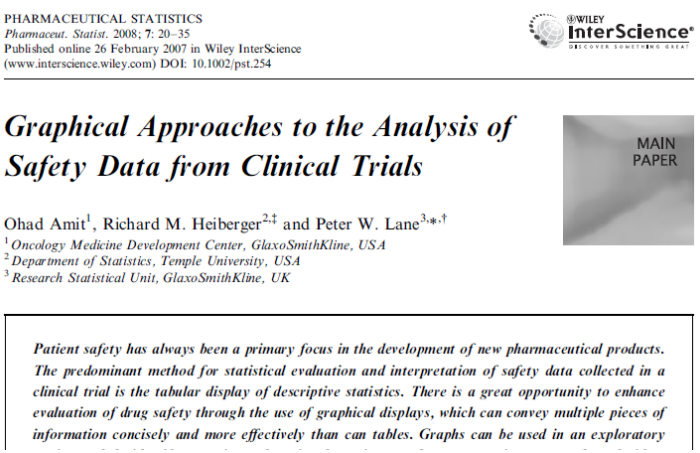
1. **Content** Every graph should stand on its own
2. **Communication** Tailor each graph to its primary communication purpose
3. **Information** Maximize the data-to-ink ratio
4. **Annotation** Provide legible text and information
5. **Axes** Design axes to aid interpretation of a graph
6. **Styles** Make symbols and plot lines distinct and readable
7. **Colors** Make use of color if appropriate for the medium of communication
8. **Techniques** Use established techniques to clarify the message
9. **Types of plots** Use the simplest plot that is appropriate for the information to be displayed

http://www.ctspedia.org/do/view/CTSpedia/BestPractices

Endorsed by General Principles subteam, FDA/Industry/Academia Safety Graphics Working Group
Adapted from GlaxoSmithKline Graphics Principles

How to Make Quality Graphs More Quickly?
Use Standard Graphs for Common Safety Questions

- Two references:
  - Graphical approaches to the analysis of safety data from clinical trials (Amit, Heiberger & Lane, 2008)



PHARMACEUTICAL STATISTICS
Pharmaceut. Statist. 2008; **7**: 20–35
Published online 26 February 2007 in Wiley InterScience
(www.interscience.wiley.com) DOI: 10.1002/pst.254

WILEY InterScience

Graphical Approaches to the Analysis of Safety Data from Clinical Trials

MAIN PAPER

Ohad Amit[1], Richard M. Heiberger[2,‡] and Peter W. Lane[3,*,†]
[1] *Oncology Medicine Development Center, GlaxoSmithKline, USA*
[2] *Department of Statistics, Temple University, USA*
[3] *Research Statistical Unit, GlaxoSmithKline, UK*

Patient safety has always been a primary focus in the development of new pharmaceutical products. The predominant method for statistical evaluation and interpretation of safety data collected in a clinical trial is the tabular display of descriptive statistics. There is a great opportunity to enhance evaluation of drug safety through the use of graphical displays, which can convey multiple pieces of information concisely and more effectively than can tables. Graphs can be used in an exploratory

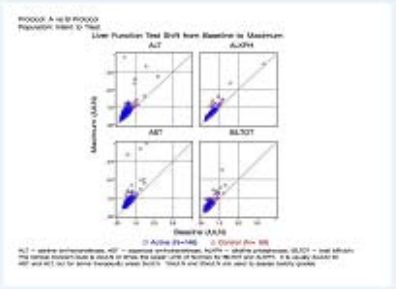
  - FDA/Industry/Academia Safety Graphics Working Group
    - Each graph entry in the wiki has a description of use, sample program code & data
    - The wiki is searchable, has a glossary and many other features
    - ctspedia.org/StatGraphHome

Graphs that answer common lab questions

Baseline and Trending over Time

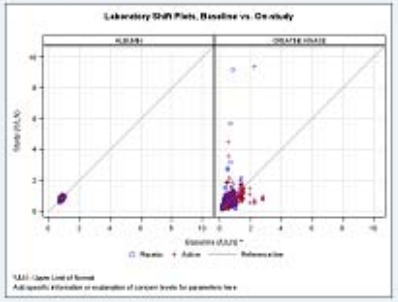
1. What are the changed and percent changes from baseline over time? ie, are abnormal lab values a result of an abnormal baseline or have values changed on study?

Example 1



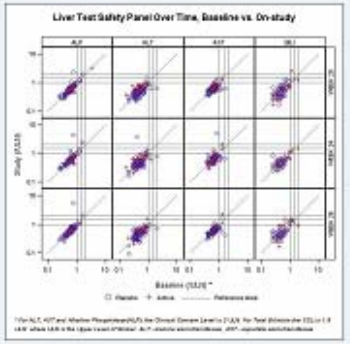
Click here for Example 1 Data

Example 2



Click here for Example 2 Data

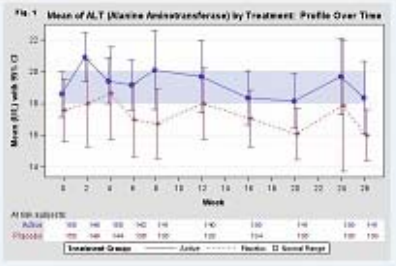
Example 3



Click here for Example 3 Data

2. Is there a temporal relationship between treatment and lab values?

Example 1



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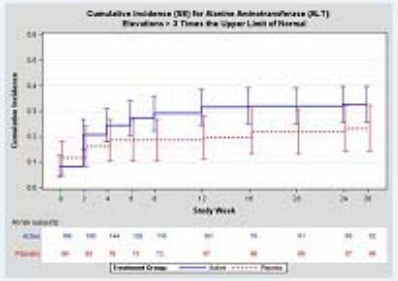
Example 2



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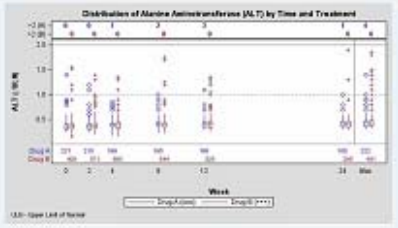


Click here for Example 3 Data

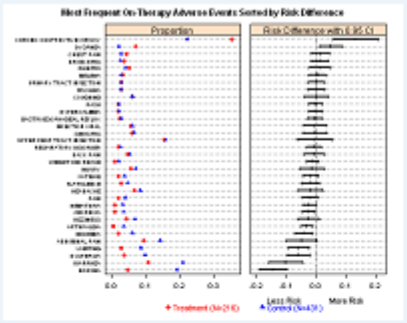
See more questions and graphs at ctspedia.org/StatGraphHome

Contributed by Safety Graphics Working Group Lab/Liver subteam, lead by Robert Gordon, J&J

Graphs that answer common adverse event questions

1. Which AEs are elevated in treatment vs. control? Which AE could be a safety signal?

Example 1



Click here for Example 1 Data

Example 2

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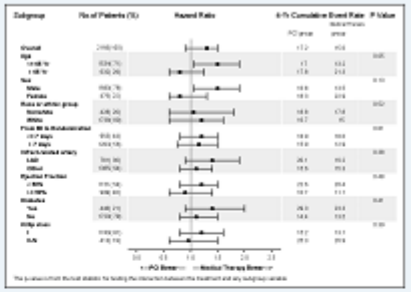
Example 3

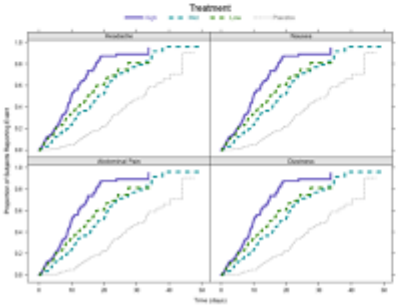


Click here for Example 3 Data

2. What is the risk trend of an Adverse Event of Special Interest?

3. Is there a difference in the time to the first event across treatment groups?

Example 1



Click here for Example 1 Data

See more questions and graphs at ctspedia.org/StatGraphHome

Contributed by Safety Graphics Working Group AE subteam, lead by Qi Jiang, Amgen & Liping Huang, CSL Behring

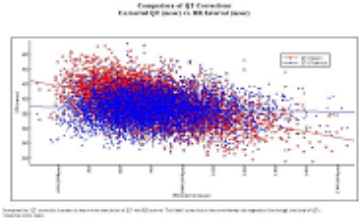
Graphs that answer common ECG/Vital Signs questions

1. What are the longitudinal trends in the data?

2. Are there outlier individuals that have large changes or raw values?

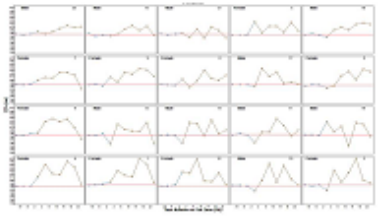
Click here for more information

3. How do the different QT correction compare w.r.t relationship with RR?



Click here for more information

4. How do individuals' values track over time?



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Contributed by Safety Graphics Working Group ECG/Vitals subteam, lead by Rich Anziano, Pfizer

3.7 Steps in a Meta-analysis

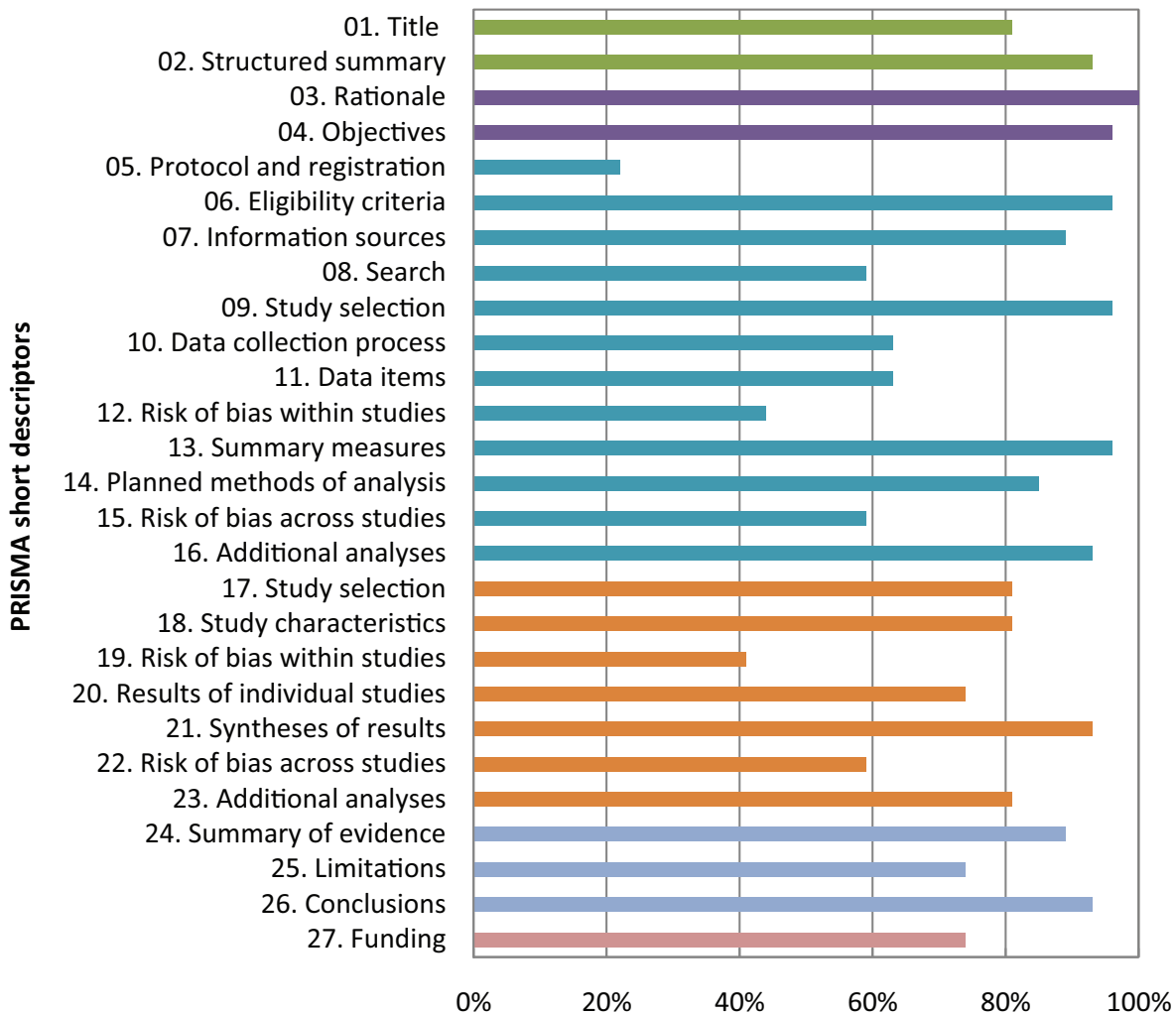
- Eligibility criteria
- Search Strategy
- Study Selection
- Data Collection and analysis
- Methodological quality of included studies
- All cause and cause-specific mortality
- Risk factors across underlying conditions
- Adverse events

Reference: Mills E. J., et al. (2010). Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170255 patients from 76 randomized trials. Q J Med.:An International Journal of Medicine.

3.8 Further guidelines: QUOROM and PRISMA

- Quality of Reporting of Meta-Analyses (QUOROM, 2009)
- Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, 2009)
- Both aim to provide a more regulated and systematic framework that requires certain ingredients or details in the report.
- Meta-analysis is commonplace in heart study; one example is Singh, et al. (2011). Risk of serious adverse CV events associated with Varenicline: a systematic review and meta-analysis, CMAJ, 183(12), 1859-1366.

3.9 An Empirical Assessment of Quality of Recent Meta-Analyses Reports from High Impact Journals



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- There are Good Clinical Practices and adherence to these principles, including adequate human subject protection is universally recognized as a critical requirement to the conduct of research involving human subjects.
- I gave an overview of clinical trials and a quick review on the importance of discovering safety issues.
- Only some statistical methods for detecting safety issues in clinical data are mentioned briefly here; there are more. Keep diligently alert to new methods for evaluating safety issues.

4.2 References

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