# CLINICAL TRIALS

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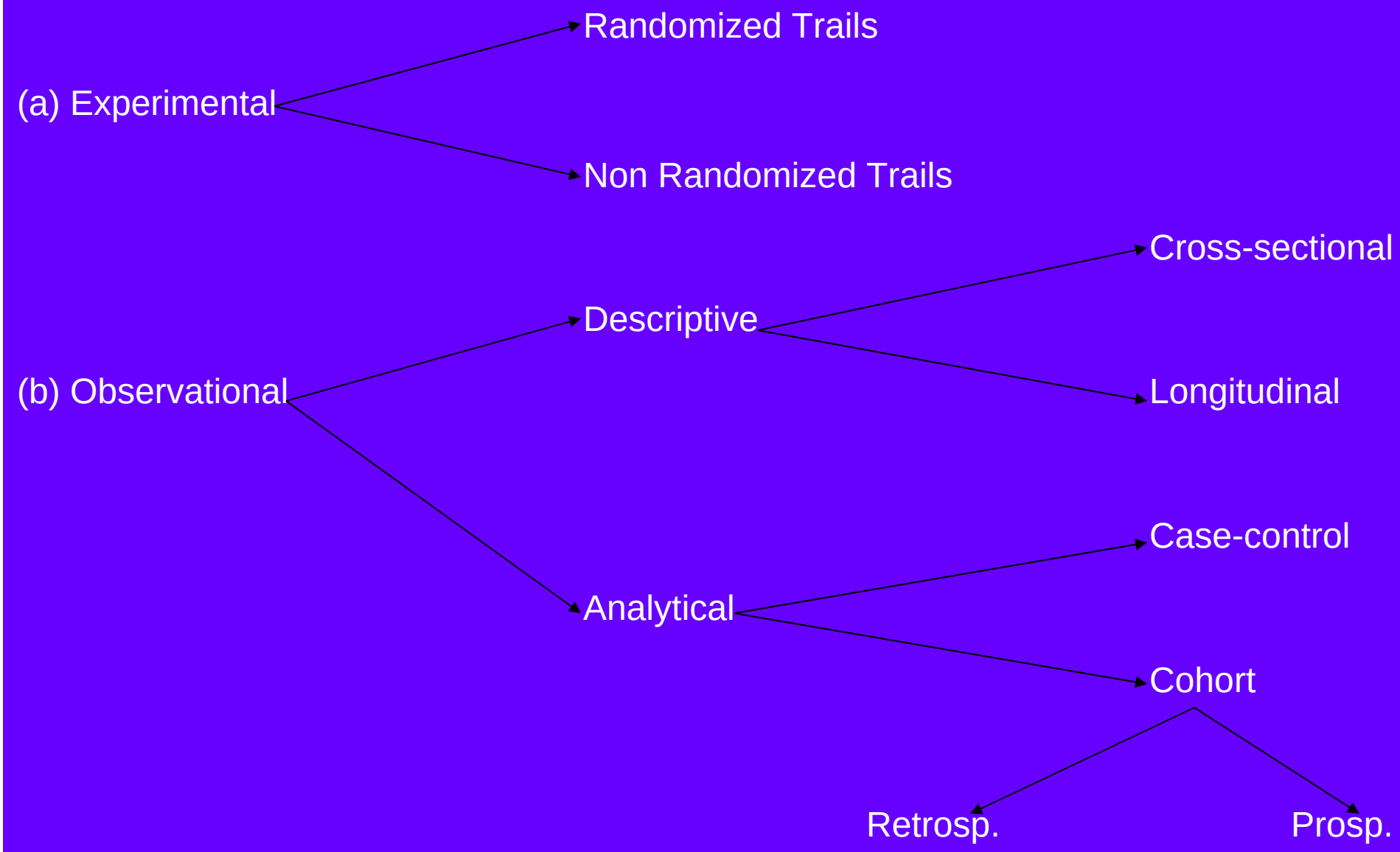
# Types of Studies:-



# CLINICAL TRIALS

- Meaning be experimental studies:
- Problems in experimental studies:
  - Cost
  - Ethical issues
  - Feasibility
- Types of experimental studies:
  - Randomized
  - Non-randomized
- Animal Studies & Human experiments:
  - In animal studies disease in animals is experimentally reproduced for testing efficacy of preventive and therapeutic measures.
  - Human experiments are conducted to investigate disease etiology and efficacy of the measures.

# RANDOMIZED CONTROL TRIAL (RCT):

- RCT is an experimental study to evaluate methods of treat/prevention involving random process of allocation (to patients or randomly allocation of patients to different measures).

## DEFINITION:

- Carefully planned and ethically designed study (experiment) with the aim of answering questions concerning effectiveness of different regimens, a surgical procedure or method of treatment, or therapeutic regimen administered to patients.

## NEED:

- Evaluation of safety and efficacy of therapies.
- Opportunities to screen new drug
- To detect differences between drugs or methods of treatment

# TYPES OF RCT

**Therapeutic:**

- To compare efficacy of a new drug with the best of current treatment (diet, surgery, physiotherapy, ionizing radiation)

**Prophylactic:** To measure effectiveness of preventive measures (weight reduction, contract, immunization, fortification of food stuffs)

**Why Placebo?** To separate the effect of the therapy on trial from the suggestive element introduced giving any treatment, placebo a pharm. inert or harmless substance or procedure made to resemble the drug or medical procedure under evaluation is used

## CLINICAL TRIALS:

- A type of RCT (a prospective planned, ethically designed expt) to compare the effectiveness of different regimens or methods of treatment in human subjects.

## NEED FOR CLINICAL TRIALS:

- Evaluation of safety and efficacy
- Opportunity to screen new drugs
- To detect differences of responses and advantages

## BIAS IN CLINICAL TRIALS:

- Systemic difference at admission
- Differential practice in follow-up
- Differential assessment of outcome
- Differential exclusion or withdrawal

## METHODS OF REDUCING BIAS:

- Randomization
- Blinding
- Uniform handling of procedures

Single Blind Trail : the patient is unaware which treatment he / she is receiving.

Double-blind trail: Neither the patient nor the doctor assessing the response is aware which specific treatment is given. Double blind trials avoid physician's or patient's potential bias.

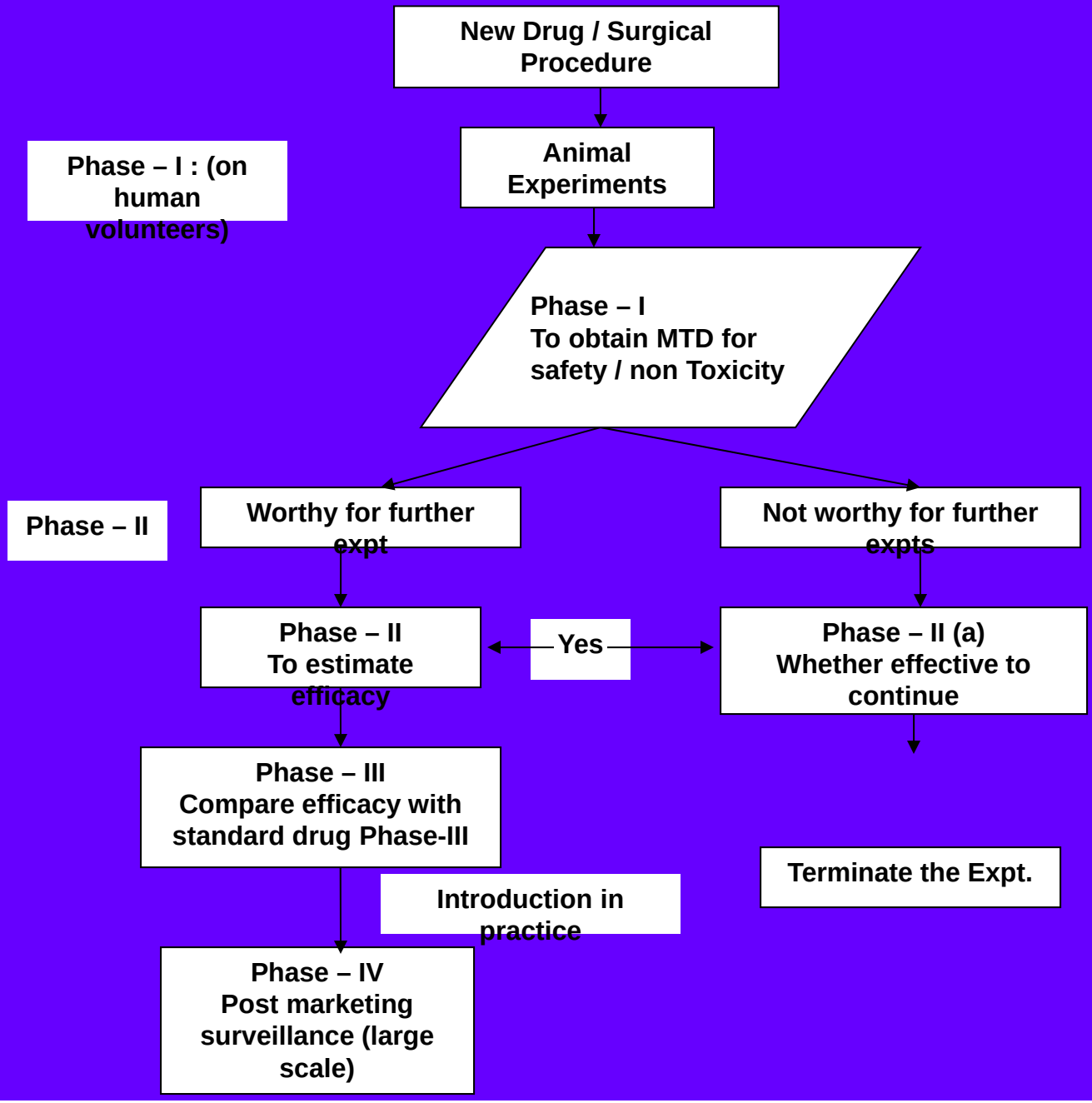
# The basics: What is a randomized controlled trial?

- Simplest definition: Individuals are allocated at random to receive one of several interventions (at least two total).
- RCT's are comparative studies (in contrast to case series studies that do not make comparisons between groups)
- RCT's are experimental—the intervention is controlled by the investigator

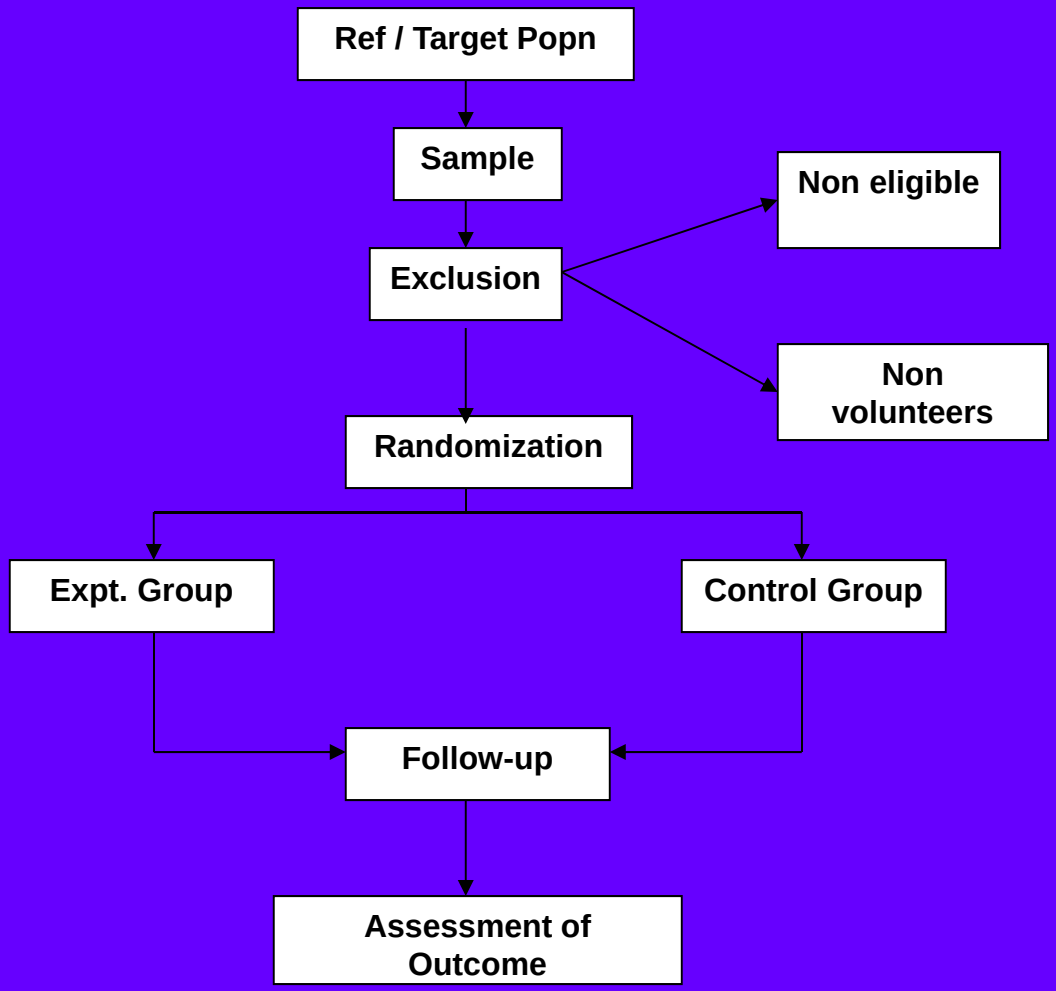
# Phase I, II, III, IV (human) trials

- Phase I
  - Conducted after animal safety established
  - Tend to focus primarily on human safety
  - Focus on proper dosing and metabolism
  - Participants sometimes include the investigators, terminal patients, employees—often NOT people with the disease the drug is designed to treat
  - Often neither randomized nor controlled—these are more like case series studies

# SEQUENCE / PHASES OF CLINICAL TRIALS



# LAYUOUT OF AN RCT



The essential feature of a trail is comparison of one experimental group receiving the treatment being evaluated and another group (control) being given the standard treatment, or if there is no generally accepted therapy, no treatment or placebo.

# Types of RCT's—classifcation schemes

- Based on the type of interventions being evaluated
- Based on how participants are exposed to interventions
- Based on the number of participants
- Based on whether goal is evaluation of superiority vs. equivalence
- Based on whether investigators and/or participants know which intervention is being studied (blinding)
- Based on whether the preferences of non-randomized individuals are considered

# Types of RCT's—classification schemes

- Based on the aspects of interventions being evaluated
  - Explanatory and pragmatic trials
  - Efficacy and effectiveness trials
  - Phase I, II, III trials

# Explanatory vs. pragmatic trials

- Explanatory trials
  - Address whether or not an intervention works
  - Strict inclusion criteria; highly homogenous groups
  - Example:  study of hypertension that only enrolls 40-50 year olds with no history of drug treatment
  - Intended to yield as clean a result as possible
- Pragmatic (or management) trials
  - Designed to test both whether the intervention works but under circumstances mimicking clinical practice
  - Sometimes will involve one drug vs. another rather than placebo

# Efficacy vs. effectiveness

- Efficacy—does the intervention work in the people who actually receive it?
  - These trials tend to be explanatory
  - Goal here is high compliance
- Effectiveness—how does the intervention work in those offered it
  - Tend to be pragmatic

# Superiority vs. equivalence trials
# (equivalence trial slides courtesy of Starley Shade)

- Superiority trials
  - Intended to determine if new treatment is different from (better than) placebo or existing treatment (active control).

- Equivalence trials
  - Intended to determine that new treatment is no worse than active control.
    - We can never assess absolute equivalence.
    - We can only assess no difference within a prescribed margin.

# Why do an equivalence trial?

- Existing effective treatment
- Placebo-controlled trial unethical
  - Life-threatening illness.
- New treatment not substantially better than existing treatment.
  - May have fewer side effects, greater convenience, lower cost, higher quality of life, or provide an alternative or second line therapy.

# Hypotheses

- Superiority trials
  - Null hypothesis is that there is no difference between treatments.
  - Alternative hypothesis is that the new treatment is different from (two-sided) or better than (one-sided) control.

# Hypotheses

- Equivalence trials
  - Null hypothesis and alternative hypotheses are reversed.
    - Null hypothesis is that difference between treatments is greater than X.
    - Alternative hypothesis is that difference between treatments is less than X.

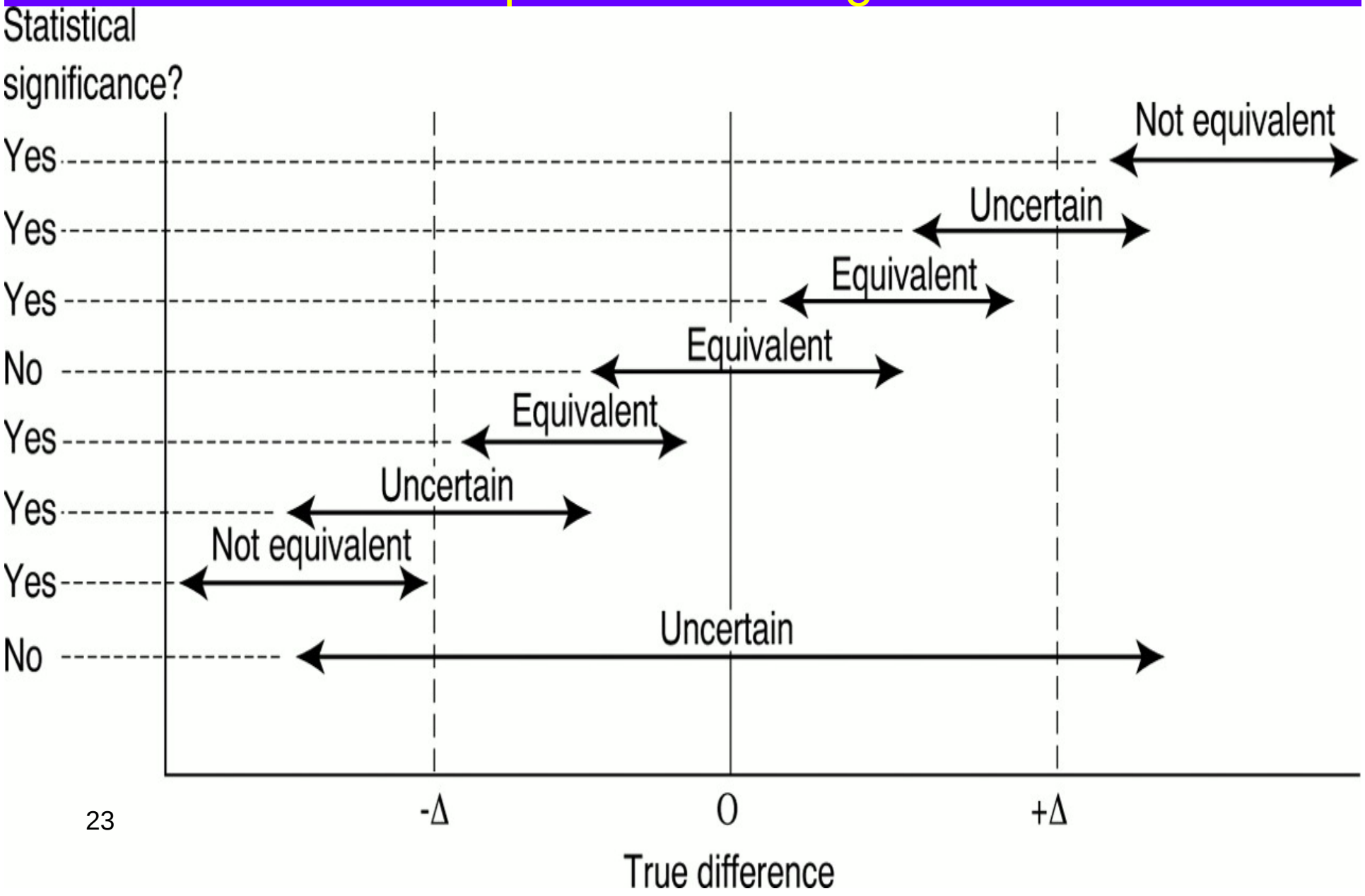
# Equivalence margin

- If confidence interval lies entirely within the equivalence margin, then equivalent.
- If confidence interval lies entirely outside the equivalence margin, then one drug is superior.
- If confidence interval crosses the equivalence margin, then inconclusive results.

# How to set equivalence margin

- Superiority trials set sample size to detect a “clinically significant” difference.
- Equivalence trials set sample size to establish “clinically insignificant” difference.
- “Clinically insignificant” determined by information outside of the trial.
  - May be a source of great controversy.
  - Has a large impact on sample size.

# Equivalence margin



# Challenges in design

- Necessity of a gold standard for existing therapy (active control).
  - May not exist if multiple existing treatments.
- Necessity to establish equipotent doses of new treatment and active control.
  - Requires prior testing of multiple doses of each drug.
  - Difficult to know if smaller prior study not conducted.

# Challenges in design

- Best condition for new therapy may not match previous research for active control.
  - Testing of new therapy as second line treatment.

# Bias in equivalence trials

- In superiority trials, incomplete follow-up, low compliance, and co-interventions tend to bias results toward the null.

- In equivalence trials, these biases increase the likelihood accepting the alternative hypothesis of no difference between groups.

# Bias in equivalence trials

- Incomplete follow-up
  - May limit observed response and therefore bias results toward no difference.
- Low compliance
  - May limit observed response and therefore bias results toward no difference.
- Co-interventions
  - May create ceiling in response and therefore bias results toward no difference.

**Outcome Measures:** **Response:**

- Death, recovery, disability, pain, recurrence

**Meaning by Placebo:**

- Pharmacologically inert / harmless medical procedure or substance, made to reasonable the drug / procedure under evaluation.

**Why Placebo:**

- To separate the effect of treat on trail from the suggestive element introduced by giving any treatment.

# Trial classification: Efficacy

- Assessment of equivalence does not insure efficacy.
  - Both drugs could be equally ineffective.
- Evidence of efficacy must come from:
  - Outside the study, or
  - An additional placebo arm.

# Efficacy

- The desire to establish efficacy using information outside of the study
  - Creates pressure to make equivalence studies mirror the methods of the original placebo controlled trials of the active control.
  - However, this may not put the investigational drug in the best light.
    - The target of the two drugs may differ.

# Efficacy

- The desire to establish efficacy using an additional placebo arm
  - Continues the ethical debate about the use of placebos.
    - Some proportion of patients will not receive active drug.

# Phase I, II, III, IV

- Phase II trials
  - Intervention is given to those who actually have disease
  - Aim is to evaluate different doses
  - Often not randomized

## How are quality assessments used?

- Clinicians may use assessments to determine how to apply results to their practice
- Journals may use assessments to determine publication
- Researchers may use assessments to influence new research
- General public (?)  - recent example of anti depressants and suicide among teens

# Essentials of reporting and interpreting individual trials (Jadad ch 5)

- 30 years of empiric evidence supporting the idea that there is a gap between what trials should vs. do report for a reader to fully interpret the quality of a trial
- Key elements of a trial for a reader
  - Is the topic interesting?
  - Are the results likely to be unbiased?
  - Can we use the results?
  - Are the results important enough to remember?

# Key elements when reviewing a trial

- What was the sampling frame?
- What were the exclusion/inclusion criteria?
- Was the setting relevant (generalizability)?
- What were the interventions—how given and by whom?
- Are the details of randomization and blinding provided?
- What were the outcomes of interest and how were they measured? By whom?
  - Were the outcome assessors blinded?

# Key elements of a trial (cont.)

- Were the results properly analyzed?
  - Statistical tests
  - Statistical significance
  - *A priori* sample size and/or *post hoc* power statement (elaborate)
  - Was intention to treat analysis used?
  - Were sub-groups defined *a priori*?
- Is the flow of participants in the trial shown?

- Reducing bias in trials
  - One example: efforts to limit direct funding by the developers of the intervention
- More trials to address clinically relevant questions
- More precise results in trials
  - Too many small, imprecise studies are done
  - Would we be better off with fewer, more definitive RCT's?
- Improving the ways that trials are presented and understood by the public
  - Should (basic) interpretation of scientific results be taught in schools?

# Improving trials (cont.)

- Registering trials at inception
- Publishing trials soon after completion, and regardless of results
- Trials are more systematically captured in systematic reviews and meta-analyses
- Make trials more easily accessible
- Decision makers need to learn how to interpret trials
- Despite 50 years of improvement, most trials are biased, too small, or trivial

# PREPARATION OF A PROTOCOL: (Plan of RCT).

- Aims
- Review and significance of study
- Duration of the trail (period of entry & follow-up)
- Patient population
  - Inclusion
  - Exclusion
- Experimental design

- Treatment administration
  - Number of treatments involved,
  - Treatment allocation ratio in different groups (1:1 or 1:2 randomly)
  - Treatment management / allocation / administration
- Comparability of patients in different groups (by randomization)
- Clinical, lab procedures and data to be collected

- Criterion for response and toxicity
- Frequency of interim analysis
- Statistical considerations [sample size, randomization design of trail, analysis strategies etc]
- Informed consent (ethical issues)
- Data collection forms
- References
- Responsible investigators


THANK YOU