

# Part I: Introduction

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**Essentials of Randomized Clinical Trials  
SCT Pre-Conference Workshop – Philadelphia, PA  
May 18, 2014**

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## Introduction to Randomized Clinical Trials

### Outline I

- **Historical perspective**
- **Rationale for randomized clinical trials**
  - Rationale for randomization
  - The equipoise issue
  - To blind or not to blind?
- **Key issues in the design of a RCT:**
  - What is the study question? Defining hypothesis, objectives and end-points
  - Defining selection criteria: generalizability vs. homogeneity
  - Selecting the control group: the placebo vs. “usual care” issue

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## Introduction to Randomized Clinical Trials

### Outline II

- **The different phases of a RCT**
- **Basic RCT Designs**
  - Parallel, cross-over, factorial and cluster designs
  - Large Simple Trials
  - Comparative Effectiveness trials
  - Superiority, Equivalence and Non-Inferiority trials
- **Key elements of a RCT Protocol**
- **Some ethical considerations**
  - Informed Consent Process
  - Patient safety issues

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### Historical perspective

*I raised myself very early to visit them when beyond my hope I found those to whom I had applied the digestive medicament, feeling but little pain, their wounds neither swollen nor inflamed, and having slept through the night. The others to whom I had applied the boiling oil were feverish with much pain and swelling about their wounds. Then I determined never again to burn thus so cruelly the poor wounded by arquebuses.*

*Ambroise Paré (1510 – 1590)*

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### Historical perspective

#### Lind's Scurvy Study

Nb of Patients: 12

Test Treatments:

Cyder, 1qt/day  
Elixir vitriol, 25 gutts, 3 times/day  
Vinegar, 2 tsp, 3 times/day  
Bigness of nutmeg 3 times/day  
orange (2) ; lemon (1) /day

Control Treatment

Sea-water, ½ pt/day

Follow-up: 6 days

Outcome: fit for duty

*Lind's Treaty on Scurvy, 1753*

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## Historical perspective

### Key Dates in the History of RCT

- 1747 Lind's Scurvy experiment
- 1800 Waterhouse's smallpox experiments
- 1863 Gull's use of Placebo Treatment
- 1923 Fisher's 1<sup>st</sup> application of randomization
- 1931 1<sup>st</sup> use of randomization (and blindness) in a clinical trial
- 1946 Nuremberg Code for Human Experimentation
- 1962 Hill AB Statistical Methods of Clinical and Preventive Medicine
- 1979 Society for Clinical Trials
- 2006 Clinical and Translational Science Awards (CTSAs) program
- 2009: The Recovery Act (ARRA) provides \$1.1 billion for Comparative Effectiveness Research.

*From Curtis L. Meinert. Clinical Trials, Oxford University Press 1986 1-7*

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## Randomized Clinical Trials

### Some Terminology

- **Clinical Trial:**
  - An experiment testing medical (e.g. drug, surgical procedure, device or diagnostic test) treatments on human subjects
    - Experiment: a series of observations made under conditions controlled by the scientist
    - Prospective (≠ case-control study)
    - Comparative (≠ cohort study)
    - Involves human subjects
  - A research activity that involves administration of a "test treatment" to some "experimental unit" in order to evaluate that treatment

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## Randomized Clinical Trials

### Some More Terminology

- **Randomization:** the process of assigning patients to treatment using a random process (such as a table of random numbers)
- **Randomized controlled clinical trial (or randomized clinical trial-RCT):**
  - Clinical trial with at least one control treatment and one test treatment
  - In which the treatment administered are selected by a random process

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## Randomized Clinical Trials

### Why Randomize?

- To find out which (if any) of two or more interventions is more effective
- Produce comparable groups
  - Protect against both known and unknown/unmeasured confounders (prognostic factors)
  - Eliminate treatment selection bias
- Best to establish causality
- Can define “Time zero”

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## Randomized Clinical Trials

### Why Randomize?

- Necessary to detect small but clinically important treatment differences
- Protect against possible time trends in:
  - Patient population and disease characteristics
  - Diagnostic methods and supportive care
- Provides a valid basis for statistical tests of significance

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## Randomized Clinical Trials

Why Randomize: The Hormone Replacement Therapy Story



### Postmenopausal estrogen therapy and cardiovascular disease. Ten-year follow-up from the nurses' health study

(N Engl J Med 1991, 325: 756-762)

**METHODS.** We followed 48,470 postmenopausal women, 30 to 63 years old... During up to 10 years of follow-up (337,854 person-years), we documented 224 strokes, 405 cases of major coronary disease (nonfatal myocardial infarctions or deaths from coronary causes), and 1263 deaths from all causes.

**RESULTS.** After adjustment for age and other risk factors, the overall relative risk of major coronary disease in women currently taking estrogen was 0.56 (95 percent confidence interval, 0.40 to 0.80...

**CONCLUSIONS.** Current estrogen use is associated with a reduction in the incidence of coronary heart disease as well as in mortality from cardiovascular disease, but it is not associated with any change in the risk of stroke.

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## Randomized Clinical Trials

Why Randomize: The Hormone Replacement Therapy Story



June 26, 1995

### ESTROGEN FOREVER?

The prevailing medical view is that most should stay on estrogen for the long haul ...

At the turn of the century, women died soon after their ovaries quit." Now they live to face heart disease, osteoporosis, increased fractures -- problems that may be prevented in part by taking estrogen...

There may be other risks and other advantages of HRT, but what doctors know is limited by the type of research that has been done. Instead of setting up a group of women on HRT and a carefully matched control group that does not take hormones, studies like the Nurses trial simply look at populations of women who made their own choice whether to take estrogen. "the problem with this.. is that women who take hormones go to doctors more, eat well, exercise and are in better health generally than women who don't take hormones." Thus it is hard to tell whether their lower rates of heart disease or colon cancer or fractures reflect HRT or these other healthy habits.

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## Randomized Clinical Trials

Why Randomize: The Hormone Replacement Therapy Story



Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results From the Women's Health Initiative Randomized Controlled Trial

Writing Group for the Women's Health Initiative Investigators

(JAMA 2002; 288: 321-333)

**Design** Estrogen plus progestin component of the Women's Health Initiative, a **randomized controlled primary prevention trial** (planned duration, 8.5 years) in which 16608 postmenopausal women aged 50-79 years with an intact uterus at baseline were recruited by 40 US clinical centers in 1993-1998.

**Interventions** Participants received **conjugated equine estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, in 1 tablet (n = 8506) or placebo (n = 8102).**

**Main Outcomes Measures** The primary outcome was **coronary heart disease (CHD)** (nonfatal myocardial infarction and CHD death), with **invasive breast cancer as the primary adverse outcome.** A global index summarizing the balance of risks and benefits included the 2 primary outcomes plus stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, and death due to other causes.

**Conclusions** **Overall health risks exceeded benefits** from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal US women. All-cause mortality was not affected during the trial. The risk-benefit profile found in this trial is not consistent with the requirements for a viable intervention for primary prevention of chronic diseases, and **the results indicate that this regimen should not be initiated or continued for primary prevention of CHD.**

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**Randomized Clinical Trials**  
 Why Randomize: The Hormone Replacement Therapy Story



July 22, 2002

A large, federally funded clinical trial, part of a group of studies called the Women's Health Initiative (WHI), has definitively shown for the first time that the hormones in question--estrogen and progestin--are not the age-defying wonder drugs everyone thought they were. As if that weren't bad enough, the results, made public last week, proved that taking these hormones together for more than a few years actually increases a woman's risk of developing potentially deadly cardiovascular problems and invasive breast cancer, among other things.

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**Randomized Clinical Trials**  
 When Randomize?

- Is there equipoise?
  - *Definition:* A state of genuine uncertainty on the part of the clinical investigators regarding the comparative therapeutic merits of each arm of the trial
  - Trial options must be consistent with *standard of care:* if state of genuine uncertainty exists randomization is an acceptable option
- Importance of the informed consent process
  - Accept risk of new treatment
  - Accept concept of randomization
  - Informed about alternative treatment options

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**Randomized Clinical Trials**  
 When Randomize?

- Finding “window of opportunity”
  - Too early
    - Not enough “preliminary” evidence :biological plausibility, epidemiologic studies
    - Intervention not “mature” enough (e.g. surgical technique)
  - Too late: intervention already established in clinical practice
- Changing Clinical Practice Guidelines

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## Randomized Clinical Trials

### To Blind or not to Blind?

- **Definition:** concealment (masking) to the patient (single blind), investigator (double) and the monitors (triple) of the identity of the intervention.  
(Opposite = unblinded or open trial)
- **Goal:** avoid bias (systematic error= anything that does not occur by chance!)

*The more subjective the intervention, the more important the blinding!*

Bias can occur at any stage of the study: patient assignment, data collection, event ascertainment...

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## Randomized Clinical Trials

### To Blind or not to Blind?

- Unblinded trial
  - May be the only option: strategies of treatment (drug vs. surgery) behavioral interventions...
  - “True” blinding may be hard: expected biological effect of intervention
  - Easier to carry out and less expensive but...  
*Risk of bias generally outweigh benefits!*
- Alternative to blinding intervention (if not possible): blind outcome assessment

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## Randomized Clinical Trials

### What is Randomization?



From Furberg BD and Furberg CD. *Evaluating Clinical Research*. Springer Ed. I-21

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## Introduction to Randomized Clinical Trials

### Outline I

- **Historical perspective**
- **Rationale for randomized clinical trials**
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  - The equipoise issue
  - To blind or not to blind?
- **Key issues in the design of a RCT:**
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## Elements of a RCT

### What is the Study Question (Who-What-When)?

- Primary question tests the hypothesis
- Hypothesis must include:
  - *Population studied*
  - *Primary outcome of interest*
  - *Intervention studied*
  - *Period of observation*
- Objective: phrase the research question in concise, quantitative terms

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## Elements of a RCT

### Primary and Secondary Objectives

- Primary objective needs to be defined (determine sample size)
- Secondary objective needs to be:
  - *Defined a priori (avoid post hoc "fishing expedition")*
  - *Chosen parsimoniously (avoid false positive)*
- Primary vs. secondary:
  - *Question of greatest interest/relevance*
  - *Consider feasibility (e.g. mortality vs. morbidity)*

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## Elements of a RCT

### The Endpoints

- Quantitative measurement required by the objectives (= outcome, response variable)
- Event/condition the trial is designed to ameliorate, delay, prevent...
- Primary endpoint: need to be clearly and rigorously defined (*what is survival?*)
- Endpoints defined by type of measurement used:
  - Discrete, dichotomous (*dead or alive?*), count, time to event
  - Continuous (*BP change*), ordered (*toxicity*)

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## Elements of a RCT

### The Endpoints: what makes a good Primary Endpoint?

- Must answer the primary question (*Co-primary?*)
- Frequency of occurrence must be known in control (determine sample size)
- Must be able to estimate treatment effect: clinical relevance (*minimum desired effect to change practice?*)
- Must be assessed/evaluable in all participants
- Can be measured accurately/reliably/objectively
  - Blinded randomization
  - Blinded assessment (*soft end point?*)
- All patients must be evaluated (no post randomization exclusion/no lost to follow up)

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## Elements of a RCT

### Composite Endpoints

- Considered to have occurred if any one of several different outcomes are observed (mortality, myocardial infarction and stroke)
  - ↑Event rate (↑power/↓sample size)
  - ↓Study duration
  - Overall "index" (risk/benefit)
- Need to account for:
  - Correlation (causal pathway?)
  - Noise?
  - Missing data
  - Adjudication?

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**Elements of a RCT**  
**Surrogate Endpoints**

- “A test, measurement, score, or some other similar variable that is used in place of a clinical event in the design of a trial, or in summarizing results from it.”
- Believed to be correlated with clinical event
- Perceived utility in yielding detectable treatment difference

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**Elements of a RCT**  
**Surrogate Endpoints**

**Advantages**

- Smaller sample size
- Endpoint earlier than ideal endpoint
- Easier
- Less costly

**Disadvantages**

- Not well correlated to ideal endpoint
- Mechanism of action unclear
- Less acceptable
- Less clinical relevance

**NO SURROGATE for Safety**



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**Elements of a RCT**  
**Surrogate Endpoints: Examples**

Disease	Definitive Endpoint	Surrogate Endpoint
CVD	MI	Cholesterol level
	CHD	Carotid IMT
	Heart Failure	BNP
	Stroke	Blood pressure
Cancer	Mortality	Tumor size reduction
Prostate Cancer	Overall Survival	PSA decline
HIV Infection	AIDS/Death	CD4+ count
Glaucoma	Vision Loss	Intraocular pressure

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## Elements of a RCT

### What is the Study Question?

— IT AIN'T EASY TO FIND THE RIGHT ANSWER WHEN YOU DON'T KNOW WHAT YOU'RE LOOKING FOR.



From Furberg BD and Furberg CD. *Evaluating Clinical Research*. Springer Ed.

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## Elements of a RCT

### Defining the Study Population

- Subset of population with disease/condition of interest
- Patients enrolled = subset of study population defined by the eligibility criteria
- Inclusion criteria: Define “at risk” population
  - Less inclusive (= more homogeneous population): potential for benefit increase
    - but need to understand mechanism of action of intervention
    - Cannot generalize to other “subgroups”
  - More inclusive (= more heterogeneous population):
    - Increase generalizability
    - But may dilute effect of intervention (increase sample size)
  - Select group more likely to benefit from intervention
    - Higher risk: increase number of events, decrease sample size
    - But: are results applicable to lower risk?

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## Elements of a RCT

### Defining the Study Population

- **Exclusion criteria:**
  - Insure patient safety (risk/benefit in specific subgroups)
  - Assess competitive risk
  - Assess likelihood of adherence to protocol and intervention

**Eligibility criteria will be defined by goal of trial: efficacy vs. effectiveness trial?**

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## Elements of a RCT

Defining the Study Population: Homogeneity vs. Generalizability

### Homogeneity

- Divergent subgroup of patients (i.e., “atypical” patients) can distort findings for the majority
- Restriction of population reduces “noise” and allows study to be done in a smaller sample size
- Restrict population to homogenous group

### Generalizability

- At the end of the study, it will be important to apply findings to the broad population of patients with the disease
- It is questionable to generalize the findings to those excluded from the study
- Have broad inclusion criteria “welcoming” all



From: Virginia Howard

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## Elements of a RCT

Defining the Study Population: Efficacy vs. Effectiveness trial

Characteristic	Efficacy Trial	Effectiveness Trial
Goal	Test biological question	Assess “real life” effect of intervention
No participants	< 1,000	> 10,000
Cohort	Homogeneous	Heterogeneous
Data collection	Extensive	Limited
Focus of inference	Internal validity	Generalizability
Eligibility criteria	Strict	Broad

From: Steven Piantadosi. *Clinical Trials. A Methodologic Perspective.* John Wiley & Sons, Inc 1997

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## Elements of a RCT

Choosing an Effectiveness Design

- **Define the *question*:** What is the purpose of the trial?
  - Does the intervention work when applied in usual practice?
- **Define the *setting*:** under which conditions will the trial results be applicable?
  - Ideal setting vs. normal practice?
- **How are *participants* selected?**
  - Eligibility criteria mostly defined by the condition of interest
- **Outcomes of interest?**
  - Direct relevance to practice
  - Will influence clinical decisions and/ health policy decisions

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## Randomized Clinical Trials

### Nature of "Intervention"

- Drug (or drug regimen)
- Surgical procedure
- Medical device
- Therapeutic modality (radiation, biologic therapy, etc)
- Diet
- Behavioral intervention (education)
- Clinical approach to diagnosis, treatment, symptom management, palliative care, etc. (e.g. strategy)

The common denominator: there is a choice between two alternative approaches; uncertain which is preferable (e.g. equipoise)

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## Randomized Clinical Trials

### Selecting the Control Group

- Four different types:
  - Placebo
  - No Treatment
  - Different doses or regimens of the treatment
  - Different active treatment (including usual care)
- Control group will be classified based on:
  - Type of treatment used
  - Method of assignment in control group
  - May be more than one control!

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## Randomized Clinical Trials

### Selecting the Control Group: The Placebo Issue

- **Definitions**
  1. **Clinical:** "A substance having no pharmacological effect but given merely to satisfy a patient who supposes it to be a medicine"  
*Goal: to distinguish pharmacological effects from the effects of suggestion*
  2. **Research:** "A substance having no pharmacological effect but administered as a control in testing experimentally or clinically the efficacy of a biologically active preparation."  
*Goal: to obtain an unbiased assessment of the result of an experiment*

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## Randomized Clinical Trials

### Placebo Control: Scientific Justification

- Minimize subject and investigator bias (when used with randomization and blinding)
- Maximize likelihood of establishing efficacy: encourage optimal conduct of the trial: decrease “incentive” for poor trial conduct (drop-outs, cross-overs, etc)
- Enable distinction between adverse effects of drug/intervention and disease
- Allow for measurement of true effect size: account for the “*placebo effect*”

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## Randomized Clinical Trials

### The Active Control

- **Positive control:** new therapy compared to known active therapy (randomized, can be blinded)
  - Goal: effectiveness or non-inferiority
  - Based on assumption that previous treatment shown to be effective! (external validation needed)
- **Challenges:**
  - Effect size and safety assessment more difficult
  - Larger sample size
  - Many possible bias: non adherence, concomitant therapies, randomization of inappropriate patients

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## Randomized Clinical Trials

### Usual Medical Care as Control Group

- State of equipoise: is there a “standard of care”?
- Potential advantages:
  - Increase relevance
  - Increase external validity
  - Increase practicality
- Interpretation of evidence:
  - Is usual care validated by research? Is there a consensus on what is “usual care”?
  - Adherence to guidelines/evidence-based care?

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**Introduction to Randomized Clinical Trials**  
**Outline II**

- **The different phases of a RCT**
- **Basic RCT Designs**
  - Parallel, factorial, cluster and cross-over designs
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  - Superiority, Equivalence and Non-Inferiority trials
- **Key elements of a RCT Protocol**
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**The Different Clinical Trial Phases**  
**Phase I**

- First in humans
- Small, uncontrolled
- Healthy volunteers/failed conventional therapy
- Dose-escalation protocols
- Tolerability/toxicity study: Maximum Tolerated Dose (MTD)
- Dose-response models

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**The Different Clinical Trial Phases**  
**Phase II**

- Test biologic activity/effect
- Estimate rates of adverse events
- Performed in patients with disease/condition of interest
- With or without comparison group
- Strict eligibility criteria

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## The Different Clinical Trial Phases

### Phase II

- Phase IIa
  - Small scale feasibility studies
  - Intermediate endpoints
- Phase IIb
  - Comparative, randomized
  - Intermediate endpoints

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## The Different Clinical Trial Phases

### Phase III

- Determine the effectiveness (overall benefit/risk-cost assessment) of new therapies relative to standard therapy
- Large sample size
- Multicenter
- Superiority, equality, equivalence or non inferiority

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## The Different Clinical Trial Phases

### Descriptive Terminology

- **Early phase/development:**
  - Translational trials (e.g. from lab to clinic)
  - Mechanistic trials
    - Treatment mechanism
    - Dose finding/dose ranging studies
- **Middle development**
  - Safety and activity: probability of benefit?
  - May be randomized (remove selection bias, temporal trends)
  - Intermediate/surrogate outcomes
  - Small sample size

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## The Different Clinical Trial Phases Descriptive Terminology

- **Late development**
  - Comparative studies
    - Treatment efficacy (IIb/III)
    - “Pivotal” trials
    - Large scale/simple trials
    - Superiority or equivalence
  - Late Safety Studies
    - Estimate of incidence of rare serious side effects
    - Very large sample size
    - Causality inference?

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## The Different Clinical Trial Phases Phase IV

- Long term surveillance studies (“post marketing”) for safety
- New dosing regimens/indications
- Look for rare side effects
- Often non randomized

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## The Different Clinical Trial Phases Summary

Phase	Features	Purpose
I	First Administration of new therapy in humans	Exploratory: determine if further investigation is possible
II	Early trials in patients	Dose-response relationship Adverse Events PK/PD Studies
III	Large scale comparative trials	Clinical efficacy/effectiveness Regulatory approval
IV	Monitoring in clinical practice	Post marketing surveillance Rare adverse events

*From: Antman EM, Califf RM, Clinical Trials and meta-analysis  
Cardiovascular therapeutics, WB Saunders 1996*

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# Introduction to Randomized Clinical Trials

## Outline II

- The different phases of a RCT
- **Basic RCT Designs**
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# Basic RCT Designs

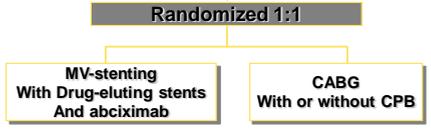
## Parallel Design



### FREEDOM Design

Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease

**Eligibility:** DM patients with MV-CAD eligible for stent or surgery  
**Exclude:** Patients with acute STEMI, cardiogenic shock



Am Heart J 2008;155:215-23 I-53

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# Basic RCT Designs

## Cross Over Design

- Participant = own control
- Randomize: order of treatment for each patient (e.g. AB vs. BA)
- Advantages
  - Reduce variability  $\implies$  Reduce Sample Size
  - Detect difference in response in individual patient
- Disadvantages
  - Order of treatment should not matter
  - No carry over of effect  $\implies$  test for interaction

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## Basic RCT Designs Factorial Design

- **Advantage:**
  - Two trials for (almost) the price of one
  - Design is best if: two intervention have different mechanisms of actions or different outcomes (e.g. cancer for A and CV disease for B)
- **Disadvantages:**
  - Need to test for possibility of interaction (e.g. A differs based on the presence or absence of B)
  - Test for interaction not very powerful
  - Need to consider gain in cost vs. increased complexity, recruitment and adherence issues and potential for adverse events

I-58

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## Basic RCT Designs Cluster Design

- Cluster design= group randomization
- Group= schools, clinics, villages...
- Sample size: based on number of groups (not individuals)
  - Need to be adjusted by factor  $N_m$  (where N= number of cluster each of size m)
  - Need to take into account within-cluster correlation of response (correlation= loss of efficiency)
- Analysis:
  - Cannot use classic statistical methods (correlation)
  - Random effect model
  - Use sensitivity analyses

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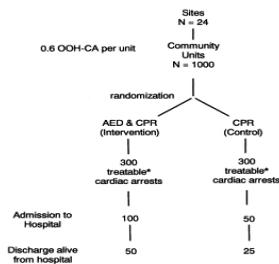
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## Basic RCT Designs Cluster Design: The Public Access Defibrillation (PAD) Trial



\*Treatable arrests are considered to be those witnessed or discovered shortly after collapse.

Resuscitation. 2003 Feb;56(2):135-47

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## Basic RCT Designs Comparative Effectiveness Trials

- Comparative effectiveness is a type of health care research that compares the results of one approach for managing a disease to the results of other approaches.
- Usually compares two or more types of treatment, such as different classes of drugs, for the same disease. Can compare types of surgery or other kinds of medical procedures and tests.
- CER is designed to *inform health care decisions* by providing evidence on the effectiveness, benefits, and harms of different treatment options.

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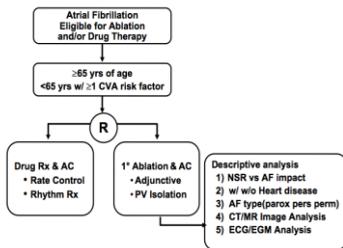
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## Basic RCT Designs Comparative Effectiveness Trials

### CABANA Trial Design



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## Basic RCT Designs Superiority, Non Inferiority and Equivalence Trials

- **Superiority trial**
  - Is (new) intervention better than no (placebo) intervention or standard intervention?
  - Goal: Demonstrate a difference!
- **Non inferiority trial**
  - Is new intervention *not worse* than standard? (not less effective, but safer, cheaper, etc.)
  - Goal: Demonstrate that new intervention is not worse than the standard by a prespecified  $\Delta$  (minimum clinically significant difference)
- **Equivalence trial**
  - Are the effects of the two interventions very similar?
  - Goal: Demonstrate that the two interventions are not different by more than the prespecified  $\Delta$

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## Introduction to Randomized Clinical Trials

### Outline II

- The different phases of a RCT
- Basic RCT Designs
  - Parallel, cross-over, factorial and cluster designs
  - Large Simple Trials
  - Comparative Effectiveness Trials
  - Superiority, Equivalence and Non-Inferiority trials
- **Key elements of a RCT Protocol**
- Some ethical considerations
  - Informed Consent Process
  - Patient safety issues

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## Key elements of a RCT Protocol

### Study Design: Preliminary Considerations

- Demonstrate need for trial
- Establish study objectives
- Choose best approach to problem/question
  - Small vs. large?
  - Less is more!
- Objectives ≠ study goals
  - Objectives: statement about question to answer
  - Goals: what you need to achieve to answer the question

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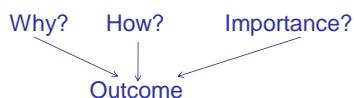
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## Key elements of a RCT Protocol

### Study Design: Framing the Question

- Toxicity? Efficacy? Effectiveness?
- Feasibility
- Proof of concept
- Pilot study



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## Key elements of a RCT Protocol Study Design: Key Steps to Follow

1. Establish study objectives
2. Choose basic study design
3. Determine primary and secondary outcomes
4. Choose type of control
5. Determine need/feasibility of blinding
6. Choose randomization procedure
7. Sample size and power
8. Determine screening, baseline, treatment and follow-up periods
9. Choose patient population
10. Establish treatment modalities

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## Introduction to Randomized Clinical Trials Outline II

- **The different phases of a RCT**
- **Basic RCT Designs**
  - Parallel, cross-over, factorial and cluster designs
  - Large Simple Trials
  - Comparative Effectiveness Trials
  - Superiority, Equivalence and Non-Inferiority trials
- **Key elements of a RCT Protocol**
- **Some ethical considerations**
  - *Informed Consent Process*
  - *Patient safety issues*

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## Ethical Issues Specific to Clinical Trials

- Special ethical concerns because treatment is determined by chance
- The arms of the clinical trial must be in clinical equipoise
- Principle of non maleficence, withholding proven treatment from control group
- Periodic analysis of interim data by independent Data and Safety Monitoring Board

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**Some Ethical Considerations  
Informed Consent Process**

- Purpose of the trial
- Nature of the trial
- Procedures of the trial
- Risks and potential benefits and alternatives to participating
- Procedures to maintain confidentiality
- Assurances and contact information

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**Some Ethical Considerations  
Informed Consent Issues**

- Withdrawal
  - Participant is free to withdraw at any time
- New findings
  - Obligation to tell participant of any significant new findings that may affect his/her willingness to continue
- Potential for coercion
- Undue inducement/Exploitation

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**Some Ethical Considerations**

Health Information Portability and Accountability Act (HIPAA)

- Research subjects must sign an authorization form that describes the use and disclosure of their protected health information (PHI) for research purposes
- HIPAA authorization wording may be part of informed consent document or a separate form
- Subject must be given signed copy of form with HIPAA disclosure information
- <http://privacyruleandresearch.nih.gov/>

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## Some Ethical Considerations

### Responsibilities of Individual Investigators

- Handling and reporting adverse events promptly, completely and accurately
- Taking personal responsibility for the veracity of all reports in which the investigator is mentioned
- Being objective and evenhanded when reporting results and problems to colleagues
- Maintaining scientific detachment and caution when reporting to the public
- Reporting malfeasance and misconduct (data fraud e.g. fabrication or falsification of data)

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## Some Ethical Considerations

### Summary Principles of Ethical Clinical Trials

- Collaborative partnership
- Scientific value
- Scientific validity
- Fairness of subject selection
- Favorable risk – benefit
- Independent Review
- Informed consent
- Respect for enrolled subjects

*Emanuel et al. JAMA 2000; 283:2701*

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## Some Ethical Considerations

### Where to Go for More Info

- **Human Subjects Research Protection**
  - <http://www.hhs.gov/ohrp/>
  - Training: <http://phrp.nihtraining.com/users/login.php>
- **Registry of clinical Trials and Background:**
  - <http://clinicaltrials.gov/>
- **Regulations and Ethical Guidelines:**
  - <http://ohsr.od.nih.gov/guidelines/index.html>
  - 45 CFR 46 Protection Of Human Subjects
  - [Guidelines for Conduct of Research Involving Human Subjects at NIH \(Gray Booklet\) \(pdf file\)](#)
  - [The Belmont Report Ethical Principles and Guidelines for the Protection of Human Subjects of Research](#)
  - [Nuremberg Code Directives for Human Experimentation](#)
  - [World Medical Association Declaration Of Helsinki](#)
- **NIH bioethics Resources:** <http://bioethics.od.nih.gov/index.html>

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## Randomized Clinical Trials Some key Points

- **Important**
  - in evaluating interventions for the prevention, diagnosis, and treatment of disease
  - Important to obtain unbiased comparisons of interventions
- **Ethical**
  - in the presence of uncertainty (equipoise)
  - present the best choice of therapeutic options to the patients
- **Robust**
  - large trials recommended to increase reliability
- **Applicable to studies of efficacy and of effectiveness**
- **Can answer more than one question at a time (factorial trials and other designs)**
- **In some situations, can randomize entire groups (e.g., communities, medical practices)**

I-76

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## Randomized Clinical Trials Some Key References

- Fundamental of Clinical Trials. Lawrence M Friedman, Curt D Furberg, David L DeMets. Springer Verlag Editors
- Clinical Trials: Design, Conduct and analysis. Curtis L Meinert. Oxford University Press
- Successful randomized trials. A Handbook for the 21th Century. Michael Domanski, Sonja McKinlay. Lippincott Williams & Wilkins
- Principles and Practice of Clinical Research. John I Galin. Academic press
- Guide to Clinical Studies and Developing Protocols. Bert Spilker. Raven press
- Clinical Trials. A Methodological Perspective. Steven Piantadosi. John Wiley & Sons, Inc.

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## Randomized Clinical Trials Why Randomize?



"Mind you, only one doctor out of ten recommends it."

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## Additional Slides

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## Elements of a RCT

Protocol: Table of contents (I/IV)

- Abstract
- I. STUDY HYPOTHESIS
- II. INTRODUCTION AND BACKGROUND
- III. OBJECTIVES OF THE STUDY
  - A. Primary objective
  - B. Secondary objective
- IV. STUDY ENDPOINTS
  - A. Primary Endpoint
  - B. Secondary Endpoints
- V. STUDY DESIGN
- VI. PATIENT SELECTION
  - A. Inclusion criteria
  - B. Exclusion Criteria
- VII. INFORMED CONSENT PROCEDURE

I-80

## Elements of a RCT

Protocol: Table of contents (II/IV)

- VIII. RANDOMIZATION PROCEDURE
- IX. ADMINISTRATION OF STUDY DRUG
- X. DATA MANAGEMENT, QUALITY ASSURANCE & MONITORING PROCEDURES
  - A. Data collection and management
  - B. Monitoring reports
    1. Executive Committee
    2. Steering Committee
    3. Data and Safety Monitoring Board
  - C. Quality Assurance
- XI. STATISTICAL ANALYSES
  - A. Primary endpoint
  - B. Sample size and power
  - C. Subgroup and secondary analyses
  - D. Interim analyses

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## Elements of a RCT

Protocol: Table of contents (III/IV)

- **XII. STUDY ORGANIZATION**
  - A. Sponsor
  - B. Steering Committee
  - C. Clinical Trial Center
  - D. Data and Safety Monitoring Board
- **XIII. SUBSTUDIES AND ANCILLARY STUDIES**
  - A. Introduction
  - B. Ancillary studies
  - C. Databank studies
  - D. Application review process
  - E. Data storage and analysis

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## Elements of a RCT

Protocol: Table of contents (IV/IV)

- **XIV. PUBLICATION POLICY**
  - A. Data analysis and release of results
  - B. Review process
  - C. Primary outcome papers, abstracts and presentations
- **XV. CLOSEOUT PROCEDURES**
  - A. Interim
  - B. Reporting of Study Results
- **XVI. REFERENCES**

### Appendices

- Mode Informed Consent
- Conflict of Interest Policies

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## Basic RCT Designs

Large Simple Trials

- Provide a more reliable estimate of the effect of intervention
- Needed to uncover smaller treatment effects  
*That are important in common conditions*
- Increase generalizability  
*But limit data collection/subgroups and secondary analyses*
- Decrease cost by simplifying design and management  
*But need strong randomization procedures and reliable outcomes assessment*

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