CLINICAL TRIALS
BASIC DESIGN CONSIDERATIONS

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DISCLOSURES

- NONE

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OVERVIEW OF THERAPEUTIC INTERVENTION TRIALS LECTURES

- BASICS OF CLINICAL TRIAL DESIGN - SPIES
- DEVELOPING A THERAPEUTIC TRIAL PROTOCOL - SHIELDS
- MEASURING OUTCOMES FROM THERAPY TRIALS - SOULEN

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LEARNING OBJECTIVES

- UNDERSTAND BASIC DESIGNS OF THERAPY TRIALS
- UNDERSTAND OPTIONS FOR PATIENT SELECTION
- UNDERSTAND METHODS TO MANAGE SAMPLE SIZE WITH INTERIM ANALYSES AND ADAPTIVE TRIAL DESIGNS
- UNDERSTAND ELEMENTS OF INTERNAL AND EXTERNAL VALIDITY

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BASIC QUESTION IN THERAPY TRIALS

- PICO Acronym
  - In a specified population (P)
  - The intervention of interest (I)
  - Comparison (standard Intervention) (C)
  - Outcome (O)
  - Timing (T)
  - Setting (S)

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BASIC CONSIDERATIONS IN STUDY DESIGN

- Patient selection
  - Source population
    - Inclusion and exclusion criteria
- Defining Intervention and comparator
- Patient allocation method
- Defining and measuring outcome – clinical and imaging
  - Primary outcome measure
  - Secondary outcome measures
  - Adverse event recording
- Sample size calculation and analysis plan

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NON-RANDOMIZED DESIGN

CASE SERIES

- RETROSPECTIVE CASE SERIES
  - DATA INCOMPLETE, CASE INCLUSION BIAS, NO CONTROLS
- PROSPECTIVE CASE SERIES WITH HISTORICAL CONTROLS
  - SUBJECT TO SELECTION BIAS IN CONTROLS
- CASE SERIES WITH BEFORE AND AFTER WITHIN SUBJECT CONTROL
  - CANNOT ASSESS PLACEBO EFFECT AND ANY IMPROVEMENT THAT WOULD OCCUR WITHOUT INTERVENTION.
- ALL APPROACHES HAVE MULTIPLE OPPORTUNITIES FOR INTRODUCTION OF BIAS

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NON-RANDOMIZED DESIGN

NON-RANDOMIZED COMPARATIVE PROSPECTIVE STUDIES

- IMPROVED OPPORTUNITY FOR PARALLEL ASSESSMENT OF SUBJECTS AND CONTEMPORANEOUS CONTROLS.
- DATA DEFINITIONS AND COLLECTION CAN BE MORE COMPLETE
- CAN COMPARE SUBJECTS AND CONTROLS FOR SIMILARITIES.
- SELECTION BIAS STILL KEY PROBLEM.
- ASSESSORS, PATIENTS USUALLY NOT BLINDED.
- CAN USE PROPENSITY-MATCHING OR PROPENSITY WEIGHTING, WHICH POTENTIALLY REDUCE BIAS IN ASSESSING OUTCOMES

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RANDOMIZED CLINICAL TRIALS

- GOLD STANDARD FOR ASSESSMENT OF CLINICAL EFFICACY
- TWO PRIMARY BENEFITS
  - CONTROLS SELECTION BIAS
  - BEST MEANS OF ASSIGNING THE KNOWN AND UNKNOWN POTENTIAL CONFOUNDERS IN EACH ARM.
- ALLOWS FOR APPROPRIATE APPLICATION OF STATISTICAL MODELS.

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INTERNAL AND EXTERNAL VALIDITY

- INTERNAL VALIDITY
  - DID THE STUDY AS EXECUTED ANSWER THE QUESTION THE STUDY WAS INTENDED TO ANSWER?
  - KEY ISSUE IS CONTROLLING BIAS THAT MIGHT BE INTRODUCED DURING CONDUCT OF THE STUDY
- EXTERNAL VALIDITY
  - THE EXTENT TO WHICH THE STUDY'S RESULTS WOULD BE BE REFLECTED IN OUTCOMES IN THE BROADER POPULATION
  - KEY ISSUE IS THE STUDY POPULATION AND HOW IT COMPARES TO THE GENERAL POPULATION

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INTERNAL VALIDITY

- DETERMINANTS OF INTERNAL VALIDITY IN A THERAPEUTIC TRIAL:
  - INCLUSION AND EXCLUSION CRITERIA EXPLICIT AND ADHERED TO.
  - FLOW OF SUBJECTS THROUGH STUDY RECORDED.
  - POWER ANALYSIS TO DETERMINE PROPER NUMBER OF SUBJECTS.
  - RANDOM ALLOCATION OF SUBJECTS, MANAGED TO MINIMIZE BIAS
  - BLINDED ASSESSMENT OF BOTH CLINICAL AND IMAGING OUTCOMES.
  - INTENTION TO TREAT ANALYSIS.

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INCLUSION AND EXCLUSION CRITERIA

- SHOULD BE CREDIBLE AND APPLICABLE IN GENERAL PRACTICE
  - THE MORE THEY MIRROR THE POTENTIAL CANDIDATES FROM THE BROADER POPULATION, THE GREATER THE EXTERNAL VALIDITY.
- IF CRITERIA NOT CLEAR-CUT AND UNEQUIVOCAL, SELECTION CREEP CAN OCCUR
  - EXAMPLES OF VAGUE LANGUAGE:
    - UNRESECTABLE CANCER
    - FAILED MEDICAL THERAPY
    - LIFE EXPECTANCY OF LESS THAN . . .

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RANDOMIZATION

- Conducted after inclusion criteria are met and study consent obtained.
- Process needs to be managed carefully to avoid introduction of bias
  - Treatment assignment masked to as many participants as feasible.
    - Patients, nursing staff, imagers, pathologists, interventionalists.
    - If assignment must be revealed, should be at last moment when team is committed to treatment.
  - Should be handled by a third party not part of the study team.
    - Random number generators, sealed opaque envelopes

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RANDOMIZATION SCHEMES

- Simple
  - Each assignment is independent of the previous and the next.
- Blocked
  - Blocks of assignment of varying lengths.
    - Blocks of 2, 4, 6, 8 mingled.
    - Provides for balanced assignment over a fixed number of participants.
      - May be used to avoid very uneven numbers of patients in each treatment group. Most important in small studies.
    - Length of blocks varied and kept secret- prevents guessing as to which assignment is next.

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RANDOMIZATION

- Stratification
  - Dividing the assignment groups by some important clinical parameter.
    - Race, age group, gender, study center, disease severity, etc.
    - Assures equal numbers among important subgroups.
  - Usually only 2 groups or 3 groups stratified.
- Can combine stratification and blocking
  - Will have different blocking groups for each subgroup.

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RANDOMIZATION

- May use unequal allocation of subjects
  - 1:2 or 1:3
  - Helpful when one treatment inherently more attractive to potential subjects
  - Applicable when a well-studied standard therapy is used as control.
    - There may be less need for data regarding safety on standard therapy than the new therapy, so fewer standard therapy patients may be needed.

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INTENTION TO TREAT ANALYSIS

- ANALYSIS BASED ON HOW PARTICIPANTS WERE RANDOMLY ASSIGNED, REGARDLESS OF WHETHER EACH IS ACTUALLY TREATED AS RANDOMIZED.
- A KEY COMPONENT OF INTERNAL VALIDITY: IT IS INHERENTLY UNBIASED.
- NON-ADHERENCE IS NOT RANDOM- PROVIDES INSIGHT INTO DESIRABILITY OF EACH TREATMENT
- IF USE "AS TREATED" OR "PER PROTOCOL "ANALYSIS, WILL BE EXCLUDING PATIENTS WHO MAY BE DIFFERENT FROM THOSE WHO ARE INCLUDED.

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THERAPEUTIC STUDY DESIGNS

- PARALLEL
  - TWO GROUPS RANDOMIZED, TREATED AND FOLLOWED AS TWO GROUPS.
- CROSSOVER
  - TWO GROUPS RANDOMIZED, EACH STARTS ONE TREATMENT AND THEN AT A DESIGNATED TIME POINT, THEY CROSSOVER AND RECEIVE THE OTHER TREATMENT.
  - MAY NEED A WASHOUT PERIOD PRIOR TO STARTING DRUG OR THERAPY 2, TO ALLOW FOR EFFECTS OF DRUG ONE TO WEAR OFF.
  - CAN BE USED IN SHAM-CONTROLLED TRIALS IN SHAM GROUP ONLY

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CHOICE OF CONTROL

- PLACEBO
  - RELATIVELY EASY TO IMPLEMENT IN DRUG TRIALS.
  - EASY STANDARD FOR APPROVAL OR ACCEPTANCE OF A NEW DRUG.
    - SHOULD NOT BE USED IF OTHER EFFECTIVE SIMILAR DRUGS ARE ALREADY APPROVED.
- SHAM THERAPY
  - SOME THERAPIES DO NOT HAVE A PLACEBO AND IN SOME CASES A SHAM PROCEDURE PROTOCOL CAN BE USED
  - MOST FEASIBLE WHEN A MINIMALLY-INVASIVE THERAPY WOULD OTHERWISE HAVE TO BE COMPARED TO A STANDARD OPERATION
    - SURGERY VS MINIMALLY-INVASIVE TRIALS NOTORIOUSLY DIFFICULT TO RECRUIT TO

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CHOICE OF CONTROL
ACTIVE CONTROLS

- CONTROL RECEIVES ANOTHER THERAPY RATHER THAN PLACEBO
  - MOST ETHICAL APPROACH IS A CURRENT STANDARD OF CARE
- CAN RAISE PROBLEMS FOR ANALYSIS
  - SHOULD THE NEW TREATMENT BE BETTER THAN THE OLD?
    - MAY NOT BE FEASIBLE IF GOLD STANDARD IS HIGHLY EFFECTIVE.
    - IT MAY BE NEW THERAPY IS LESS INVASIVE, LESS EXPENSIVE, OR OTHERWISE ADVANTAGEOUS, BUT IS NOT BETTER.
      - SHOULD CHOOSE PRIMARY OUTCOME BASED ON THE PERCEIVED ADVANTAGE OF THE NEW THERAPY

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TRIAL DESIGN

- SUPERIORITY
  - IDEAL IF A SIGNIFICANT IMPROVEMENT OVER CONVENTIONAL THERAPY ANTICIPATED FOR NEW TREATMENT.
- EQUIVALENCE
  - NEED TO HAVE MINIMAL DIFFERENCE BETWEEN GROUPS, WHICH MAY REQUIRE LARGE NUMBER OF SUBJECTS.
- NON-INFERIORITY TRIALS
  - THE NEW THERAPY IS NOT WORSE THAN CURRENT.
  - INVESTIGATOR DECIDES THE MARGIN THAT IS ACCEPTABLE FOR NON-INFERIORITY, BUT MUST BE DONE A PRIORI.

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CLASSIC CLINICAL TRIAL STAGE DEFINITIONS

- PHASE 1 – SINGLE ARM 15 TO 30 PTS
  - DOSING ASSESSMENT (ESCALATION) STUDIES
  - "FIRST IN MAN" EXPLORATORY STUDIES
  - INITIAL ASSESSMENT OF SAFETY
  - CLINICAL FEASIBILITY OF A THERAPY
- MAY BE STAGED – PHASE IA AND IB
  - IF SAFE IN A VERY LIMITED GROUP, CAN EXPAND GROUP TO SIZE SUFFICIENT TO GATHER MEANINGFUL PRELIMINARY DATA
- GOALS
  - WHAT IS THE MAXIMAL TOLERATED DOSE AND RECOMMENDED DOSE FOR PHASE II?
  - IS A LARGER PHASE II TRIAL SAFE?
  - PRELIMINARY DATA INTENDED TO ALLOW PLANNING FOR PHASE II (EG SAMPLE SIZE).

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CLASSIC CLINICAL TRIAL DEFINITIONS

- PHASE II TRIALS
  - LARGER COHORT, POSSIBLY BROADENED INCLUSION CRITERIA
  - SAFETY AND INITIAL ASSESSMENT OF EFFICACY
- COMPARISON ARM MAY BE INCLUDED
  - PHASE IIA - MAY USE HISTORIC CONTROLS, CONCURRENT CONTROLS
    - GOAL IS TO ASSESS SUITABILITY FOR LARGER PHASE III TRIAL FOR DRUGS
  - PHASE IIB – LARGER, RANDOMIZED TYPICALLY
    - IN DEVICE EVALUATION, OFTEN IS THE PIVOTAL OR KEY TRIAL IN FDA SUBMISSION
    - IN DRUG EVALUATIONS, MAY BE COMBINED WITH PHASE III TRIALS.

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CLASSIC CLINICAL TRIAL DEFINITIONS

- PHASE III
  - LARGE PIVOTAL TRIALS FOR NEW DRUGS OR INTERVENTIONS
  - TYPICALLY SEVERAL HUNDRED PATIENTS
  - NATIONAL OR INTERNATIONAL STUDIES
  - ALWAYS RANDOMIZED, USUALLY COMPARED TO CURRENT STANDARD THERAPY
  - INFREQUENTLY DONE FOR MEDICAL DEVICES OR INTERVENTIONAL PROCEDURES
  - MORE COMMON IN RADIATION THERAPY, ONCOLOGY, CARDIOLOGY

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CLASSIC CLINICAL TRIAL DEFINITIONS

- PHASE IV TRIALS
  - POST-MARKET SURVEILLANCE STUDIES OVER MANY YEARS, WITH MINIMAL DATA GATHERED FROM LARGE NUMBERS OF PATIENTS
    - MONITORING USE AND OUTCOMES IN REGULAR PRACTICE
  - NOW COMMONLY MANDATED BY FDA
  - BEST MEANS OF DETECTING RARE SIDE EFFECTS, COMPLICATIONS
  - REAL-WORLD EFFECTIVENESS

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LIMITATIONS OF THE PHASE I-III STRUCTURE

- FIXED PROTOCOLS RIGID AND SEQUENTIAL
  - AS A RESULT, STUDIES ARE SLOW TO BE COMPLETED AND PRACTICE MAY ADVANCE BEFORE COMPLETION.
  - SAMPLE SIZE ESTIMATE MAY NOT BE ACCURATE
- INTERIM ANALYSES OFTEN NOT INCLUDED BECAUSE OF POTENTIAL LOSS OF STATISTICAL POWER DUE TO MULTIPLE ANALYSES

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INTERIM ANALYSES FOR PHASE II TRIALS

- RANGE OF DESIGNS TO LIMIT STUDY CONTINUATION IF FUTILE
  - GEHAN – REJECTS AN INEFFECTIVE TREATMENT EARLY IF FIRST N NUMBER OF SUBJECTS HAVE NO BENEFIT.
  - FLEMING – EARLY TERMINATION WHEN INTERMEDIATE ANALYSIS AFTER SPECIFIED NUMBER OF SUBJECTS SHOWS EXTREME RESULTS EITHER IN FAVOR OR AGAINST TREATMENT.
  - SIMON –
    - OPTIMAL DESIGN: MINIMIZES THE NUMBER OF PATIENTS TREATED IF NULL HYPOTHESIS IS TRUE
    - MINIMAX DESIGN: DETERMINES MINIMAL SAMPLE SIZE FOR THE WHOLE TRIAL.
- NEED STATISTICIAN TRAINED IN DESIGN TO PLAN

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EXAMPLE OF OBRIEN- FLEMING METHOD

- PRE-PLANNED INTERIM ANALYSES
- BILATERAL VERSUS UNILATERAL FEMORAL ACCESS FOR UAE: RESULTS OF A RANDOMIZED COMPARATIVE TRIAL*
  - PRIMARY OUTCOME: FLUOROSCOPY TIME

Planned Analyses	Number of Patients	Required P Value
1ST	22	0.0071
2ND	52	0.0227
3RD	94	0.0416

  - AFTER 2ND ANALYSIS, REQUIRED SIGNIFICANT LEVEL ACHIEVED AND STUDY ENDED
  - (13 MIN VERSUS 16.6 MIN, P = 0.0033)

*Costantino M, et al J Vasc Interv Radiology 2010; 21:829-835

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ADAPTIVE TRIAL DESIGNS

- TRADITIONAL STUDIES USE FREQUENTIST STATISTICS – USING NULL HYPOTHESIS TESTING
- USE BAYESIAN METHODS TO ADJUST STUDY IN REAL-TIME
  - PRE-STUDY PRIOR PROBABILITY OF THE ESTIMATE OF TREATMENT EFFECT IS CHANGED AS DATA FROM THE STUDY IS GATHERED TO ESTIMATE A NEW POSTERIOR PROBABILITY
- ADAPTIVE DESIGNS REQUIRE CAREFUL PLANNING WITH KNOWLEDGEABLE TRIALISTS AND BIOSTATISTICIANS.

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ADAPTIVE METHODS - APPLICATIONS

- RESPONSE ADAPTIVE RANDOMIZATION
  - INTERIM ANALYSES CAN ALLOW ADJUSTMENT OF ALLOCATION RATIOS TO FAVOR TREATMENTS WITH MORE FAVORABLE INTERIM RESULTS
- SAMPLE SIZE RE-ADJUSTMENT
  - AS INITIAL OUTCOMES ARE OBTAINED, CAN INCREASE OR DECREASE SAMPLE SIZE AND IMPROVE TRIAL EFFICIENCY AND ACCURACY
- SEAMLESS DESIGNS
  - ALLOW IMMEDIATE CONTINUATION OF ONE PHASE INTO ANOTHER TO INCREASE EFFICIENCY
- ADAPTIVE ENRICHMENT
  - MODIFICATION OF ELIGIBILITY CRITERIA TO FOCUS ON SUBGROUPS WITH FAVORABLE OUTCOMES

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REALISTICALLY

- MOST YOUNG INVESTIGATORS WILL FOCUS ON SMALL STUDIES TESTING A NEW IDEA
  - DOES THIS PROPOSED INTERVENTION HAVE ANY BENEFIT?
  - DOES THIS PROPOSED INTERVENTION HAVE SIGNIFICANT RISK?
  - DOES THIS COMBINATION OF TREATMENTS WORK ANY BETTER THAN THE STANDARD TREATMENT ALONE?
- MANY OF THESE PRELIMINARY STUDIES DO NOT FIT NEATLY INTO THE PHASE I– IV FRAMEWORK, BUT LIKELY MOST ARE PHASE I OR II ISH.

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RESEARCH QUESTIONS WORTH CONSIDERING

- DOES DEVICE A WORK BETTER THAN DEVICE B FOR A STANDARD THERAPY?
  - BOTH DEVICES ARE FDA CLEARED BUT HAVE NOT BEEN COMPARED
- WHAT SUBPOPULATIONS RESPOND BEST TO MY INTERVENTION?
  - ROLE OF BIOMARKERS AS PREDICTORS OF RESPONSE OR COMPLICATIONS FROM INTERVENTIONS IS IMPORTANT
- WHAT PRELIMINARY TESTING OR FOLLOW-UP PROTOCOL IS BEST FOR A GIVEN INTERVENTION?
- WHAT PERI-PROCEDURAL MANAGEMENT APPROACH WORKS BEST FOR MY INTERVENTION?

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CONSORT STATEMENT

REPORTING RANDOMIZED TRIALS

- PARTICIPANTS ELIGIBILITY STATED AT THE TIME OF STUDY DESIGN, ALONG WITH EXCLUSION CRITERIA.
- THE INTERVENTIONS ARE DESCRIBED IN DETAIL.
- PRIMARY AND SECONDARY OUTCOME MEASURES DEFINED.
- STATISTICAL ANALYSIS PLAN DETAILED DEFINED PRIOR TO START OF STUDY

•Maher D, Schulz KF, Altman D. The CONSORT Statement: Revised recommendations for Improving the quality of reports of parallel-group randomized trials. JAMA 2001;285:1987-1991

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CONSORT STATEMENT

REPORTING RANDOMIZED TRIALS

- FLOW OF PATIENTS THROUGH STUDY PROVIDED IN FLOW CHART.
  - NUMBER SCREENED, QUALIFIED, RANDOMIZED, TREATED, AND ASSESSED AT EACH STAGE OF FOLLOW-UP.
- DATES OF RECRUITMENT PROVIDED
- BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS PROVIDED AND COMPARED.

•Maher D, Schulz KF, Altman D. The CONSORT Statement: Revised recommendations for Improving the quality of reports of parallel-group randomized trials. JAMA 2001;285:1987-1991

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CONSORT STATEMENT

REPORTING RANDOMIZED TRIALS

- ADVERSE EVENTS ASSESSED AND REPORTED EQUALLY FOR BOTH GROUPS.
- ANCILLARY ANALYSES TAKE INTO ACCOUNT MULTIPLICITY OF ANALYSES.
  - LESS WEIGHT PUT ON CONCLUSIONS FROM SECONDARY ANALYSES.
- DISCUSSION INCLUDES:
  - INTERPRETATION OF RESULTS AND GENERALIZABILITY
  - DISCUSSION OF LIMITATIONS, POTENTIAL BIASES.
  - DISCUSSION OF THE EVIDENCE IN CONTEXT OF OTHER STUDIES, CURRENT KNOWLEDGE.

•Maher D, Schulz KF, Altman D. The CONSORT Statement: Revised recommendations for Improving the quality of reports of parallel-group randomized trials. JAMA 2001;285:1987-1991

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ONCE YOUR PROTOCOL IS DONE . . .

- IRB APPROVAL
- ON OCCASION, FDA IDE OR IND
- REGISTER THE TRIAL ON CLINICALTRIALS.GOV

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SUMMARY

- Most investigators will start with Phase I-II trials but including sound design principles will improve validity of results.
- Internal validity should be primary goal of study design.
- Newer adaptive models may have applicability in many settings.
- CONSORT Statement a useful tool both for designing and reporting studies, even those that are not randomized.

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