Clinical Trial Design

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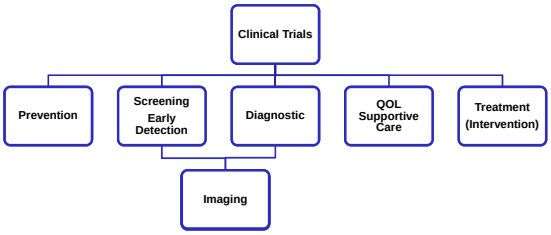
Agenda

- Types of clinical trials
- Clinical Trial design general principles and terminology
- Phase I – III clinical trial designs

Types of Clinical Trials



Prevention Trials

- Evaluate better ways to prevent disease in people who have never had the disease or to prevent a disease from returning
  - Evaluate the effectiveness of ways to reduce the risk of cancer
  - Enroll healthy people at high risk for developing cancer
- 2 types of trials:
  - Action studies – "do something"
  - Agent studies – "take something"

Screening Trials

- Test the best way to detect certain diseases or health conditions
  - Assess new means of detecting cancer earlier in asymptomatic people
- Tools:
  - Tissue sampling/procurement
  - Laboratory tests, including genetic testing
  - Imaging tests
  - Physical exams
  - History, including family hx (pedigree)

Diagnostic Trials

- Discover better tests or procedures for diagnosing a particular disease or condition
  - Develop better tests or procedures to identify a suspected cancer earlier or more accurately
- Tools:
  - Imaging tests
  - Laboratory correlative studies/tumor marker

Imaging Trials

- Scientific question being asked is aimed at understanding if or how a specific imaging test can best be used to:
  - Screen
  - Diagnose
  - Direct the treatment of a disease
  - Monitor the response to a therapy for a disease

Supportive Care/QOL Trials

- Explore ways to improve comfort and the quality of life for individuals with a chronic illness
  - Evaluate improvements in comfort of and quality of life (QOL) for people who have cancer
  - Seek better therapies or psychosocial interventions for subjects
- Focus on subjects AND families or caregivers

"Treatment" Clinical Trials

- Test:
  - New intervention
  - New combination of drugs
    - Approved + investigational
    - Investigational + investigational
  - New approaches to:
    - Surgery
    - Radiation therapy
  - New approaches to combination therapies

Study Design: Selected Considerations

- Randomization
- Stratification
- Control Group
- Superiority, equivalence, or non-inferiority
- Mask/blind
- Number of Arms
- Number of Stages
- Endpoints
- Single vs. Multi-Center
- Phase

Randomized Controlled CT

- Compare outcomes of trial group and control group following an intervention
- Most powerful tool to assess efficacy
- Controlled, randomized, double-blind trials are the "Gold Standard" in clinical research
- Simple or Complex using software programs

Randomization

Advantages

- Difference is *because* of the intervention
- Minimizes investigator bias
- Allows stratification within treatment groups

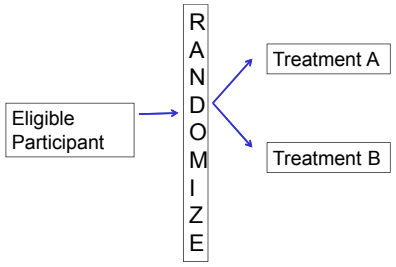
Disadvantages

- Results not always generalizable
- Recruitment
- Acceptability of Randomization Process
- Administrative Complexity

Randomization: Other Considerations

- Intent-to-treat analysis may be used
  - Compares participants in the groups they were originally randomized to whether they completed intervention or not
- Data Safety Monitoring Board (DSMB) for interim analysis

Parallel Design…



…Parallel Design

Low dose vs. higher dose

Randomization (n=50)

25 — 25

New Agent/ Intervention Low Dose

New Agent/ Intervention Higher Dose

Placebo (Inactive) vs agent

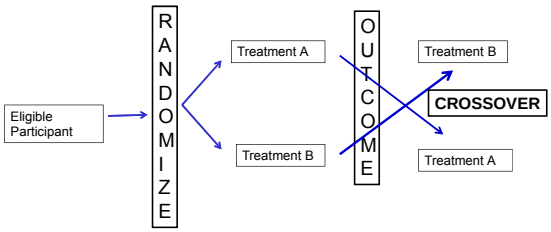
Randomization (n=50)

25 — 25

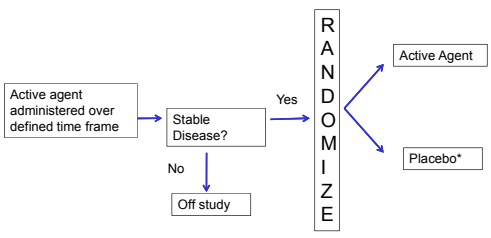
New agent alone or + placebo

New agent + standard of care

Crossover Design



Randomized Discontinuation Design



* Patients with progressive disease on placebo can switch back to active agent.

Stratification…

- Partitioning subjects by factor other than the treatment
- Examples of stratification factors include:
  - Demography: gender, age
  - Disease severity, risk factors
  - Prior treatments
  - Concomitant illness

…Stratification

Advantages

- Offers most precision of treatment effect by keeping variability:
  - Within strata as small as possible
  - Between-strata as large as possible
- Avoid imbalance in the distribution of treatment groups within strata
- Protect against Type I and Type II errors

Disadvantages

- Gains (power/efficiency) that can occur with stratification is often small, particularly once (# subjects) / (# treatments) > 50
- More costly
- More complicated trial
  - Greater opportunity to introduce randomization error

Stratification after Randomization

- Easier and less costly to implement
- Often *nearly* as efficient
- May be less convincing
- Cannot correct for cases of extreme imbalance or confounding of covariates

Control Group

- Group of research participants who do not receive the treatment being studied
- Distinguishes treatment outcomes from outcomes caused by other factors:
  - Natural progression of disease
  - Observer/patient expectations
  - Other treatment

Choosing a Control Group

- Standard therapies are available for the study population
- Goal of the study
- Significance of the control group
- Ethical considerations

Types of Controls

- External control
  - Historical control
- Concurrent Controls
  - Placebo control
  - No treatment control
  - Dose-response control
  - Active Control
  - Same time period another setting

Taken from: ICH HARMONISED TRIPARTITE GUIDELINE:CHOICE OF CONTROL GROUP AND RELATED ISSUES IN CLINICAL TRIALS, E10

Historical Control

- Control group was treated at different time
  - Outcome compared with previous series of comparable subjects
- Non-randomized
- Rapid, inexpensive, good for initial testing of new intervention
- Vulnerable to biases:
  - Different underlying populations
  - Criteria for selecting patients
  - Patient care
  - Diagnostic or evaluating criteria

Placebo Control

- Used as a control treatment
- Includes:
  - Inactive or sham treatment
  - Best standard of care if "placebo" unethical
- May need matched placebo controls
  - Patients and investigators cannot decode the treatment

Active Control

- Investigational drug is compared with a known active drug
- Often used for life-threatening or debilitating disease and/or an effective therapy already exists
- Need to determine if study outcome is to show a difference between the treatments or not

Superiority vs. Non-Inferiority

Superiority Design

- Demonstrates that new treatment is superior to the control than the control or standard
- Type of controls
  - No treatment
  - Best standard of care

Non-inferiority Design

- Demonstrates that the new treatment is similar in efficacy to a known effective treatment
- Types of controls
  - Most active control
  - Some historical

Masking/Blinding

- Minimize potential investigator and subject bias
- Most useful when there is a *subjective* component to treatment or evaluation
- Assures that subjects are similar with regard to post-treatment variables that could affect outcomes
- May be only way to obtain an objective answer to a clinical question

Feasibility of Masking

- Ethical
  - Should not result in any harm or undue risk
- Practical
  - May be impossible to mask some treatments
- Compromise
  - Sometimes partial masking can be sufficient to reduce bias (e.g., radiologist)

Types of Masking/Blinding

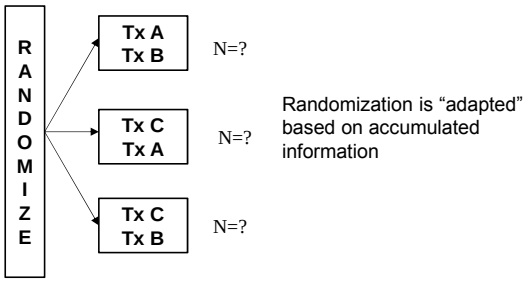
- Single Blind
  - Patient does not know treatment
- Double Blind*
  - Neither patient nor health care provider know treatment
- Triple Blind
  - Patient, physician and statistician/monitors do not know treatment

**Double-blind recommended when possible*

Adaptive Design

- Use of accumulated data to decide how to modify aspects of the ongoing study without effecting validity and integrity of trial
- FDA Draft Guidance Document 2010
  - *Adaptive Design Clinical Trials for Drugs and Biologics*
  - Prospectively planned modification of one or more aspects of the study design and hypotheses based on analysis of data (usually interim data)

Adaptive Designs



Study Arms & Stages

- Arms (# of groups/interventions)
  - Single Arm
    - Compare change from baseline
  - Two or more arms
    - Compare outcomes in the different groups
- Stages
  - One-stage
  - Multi-stage

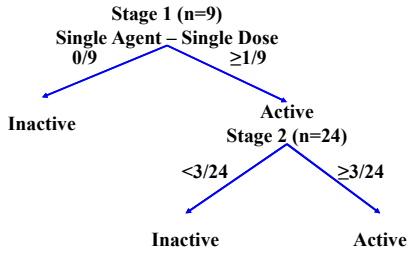
One-stage Design

- Used when time-dependent endpoints are considered
- Early stopping rules usually incorporated for:
  - Lack of efficacy
  - Unacceptable toxicity
- Need good historical control data

Multi-Stage Designs

- Frequentist
  - Gehan 2-Stage
  - Simon 2-Stage Optimal
  - Simon 2-Stage Minimax
  - Fleming 1-stage
  - Gehan-Simon 3-Stage
  - Randomized Phase 2
  - Constant Arc-Sine
  - Randomized Discontinuation
- Bayesian
  - Thall-Simon-Estey
  - 1-Stage Bayesian
  - 2-Stage Bayesian
    - Tan Machin
    - Heitjan
- Adaptive
- Multiple Outcomes

Standard 2 Stage Design



Two-stage design with early stopping rule for efficacy or futility

Endpoints

- Primary
- Secondary
- Direct
- Surrogate

Primary & Secondary Endpoints

- Primary
  - Most important, central question
  - Ideally, only one
  - Stated in advance
  - Basis for design and sample size
- Secondary
  - Related to primary
  - Stated in advance
  - Limited in number

"Direct" Endpoints

- Clinically meaningful endpoints that directly measure how subject:
  - Feels
  - Functions, or
  - Survives
- Endpoints that characterize the clinical outcome of interest
  - Objective: survival, disease exacerbation, clinical event
  - Subjective: symptom score, "health related quality of life"
- Customarily, the basis for approval of new drugs

Surrogate Endpoints

- Endpoints used as alternative to desired or ideal clinical response to save time and/or resources
- Surrogate for clinical benefit
  - Laboratory measure or a physical sign intended used as substitute for a direct endpoint
- Surrogate endpoints can be used for drug approval:
  - if well validated, or
  - under Subpart H: "accelerated approval" for serious and life-threatening illnesses; 1992

Examples of Surrogates

Surrogate	Condition/Disease
arterial blood pressure	CVA, MI, heart failure
Cholesterol and triglyceride levels	atherosclerotic disease
Increased IOP	Loss of Vision
Blood sugar	Survival/complications of DM
Disease-free survival; time to progression; progression free survival	Cancer survival

Surrogate Endpoints: Potential Pitfalls

- Unless validated, relationship between surrogate and direct benefit may not be causal
- True risk:benefit ratio may not be clear
- Drugs may have other unfavorable effects, apart from effect on surrogate
- Use of validated surrogate for study of drugs with different mechanisms of action
- Surrogate creep

Phase I Goals

- Determine dosing in humans
- Assess safety
- Evaluate PKs and PDs
- Explore drug metabolism and drug interactions

Phase I Additional Goal(s)

- Also used to:
  - Evaluate new treatment schedule
  - Evaluate new drug combination strategy
  - Evaluate new multi-modality regimen

May provide early evidence of response, but *NOT* primary aim

Phase I Subjects

General

- Healthy volunteers
- Patients
  - Used when drug is known or expected to be toxic; cytotoxic agents, biological agents
- Special populations (elderly, renal impairment)
- Small numbers
  - 15 – 30
  - <100

Cancer Specific

- Usually many cancer types (e.g. solid tumors)
- Refractory to standard therapy
- No remaining standard therapy
- Adequate organ function
- Adequate performance status

Phase I Standard Design

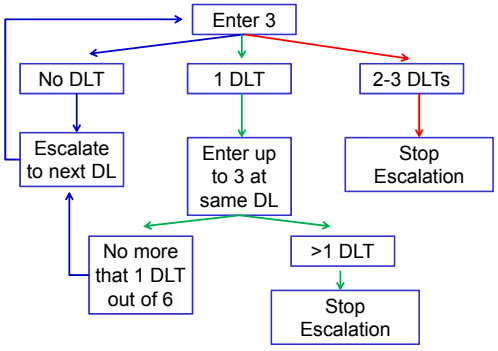
- Open label, non-randomized, dose escalation
- Low starting dose
  - 1/10th the lethal dose (LD10) in the most sensitive species tested = dose at which 10% of the animals die
  - Unlikely to cause serious toxicity
  - Pediatric dose starts at 80% of adult MTD
- 3-6 patients per cohort
- Increase dose gradually
  - Most common scheme is a Modified Fibonacci

Classic Modified Fibonacci Dose Escalation Scheme

% Increase Above Preceding Dose:

Level 1: Starting dose
Level 2: 100% increase from Level 1
Level 3: 67% increase from Level 2
Level 4: 50% increase from Level 3
Level 5: 40% increase from Level 4
Levels 6+: 33% increase from Level 5+

3 + 3 Study Design



Alternate Designs

Accelerated design

- 1 subject enrolled per DL until grade 2 toxicity then return to the 3 + 3 design

OBD

- Find dose that is considered to safe and have optimal biologic effect (OBD)
- Optimize "biomarker" response within safety constraints

Intrapatient Dose Escalation

- Once a DL has been proven "safe" then subjects at lower levels are able to escalate to the "safe" level
- Subject used as own control and can escalated to higher DL if lower level tolerated

Phase I Endpoints

- Dose Limiting Toxicity (DLT)
  - General DLT Criteria:
    - ≥ Grade 3 non-heme toxicity
    - Grade 4 neutropenia lasting longer than 5 days
    - Grade 4 thrombocytopenia
  - Typically the DLT is defined for the first course/cycle
- Maximum Tolerated Dose (MTD)
  - Highest dose level at which ≤1/6 patients develop a DLT

Phase I Limitations

- Questionable risks without benefits
- Initial patients may be treated at low (sub-therapeutic) doses
- Slow to complete trial (need to find fairly healthy advanced cancer patients)
- Toxicity may be influenced by extensive prior therapy
- Inter-patient variability
- MTD definition is imprecise
- Minimal data about cumulative toxicity since only the first cycle/course is taken into consideration for a DLT

Phase II Goals

- Provide initial assessment of efficacy or 'clinical activity'
  - Screen out ineffective drugs
  - Identify promising new drugs for further evaluation
- Further define safety and toxicity

Phase II Subjects

- ~100 subjects (100-300)
- More homogenous population that is deemed likely to respond based on:
  - phase I data
  - pre-clinical models, and/or
  - mechanisms of action
- Subject needs to have measurable disease
- May limit number of prior treatments

Phase 2 Designs

- Most common
  - 2 stage design w/ early stopping rule
- Randomized designs
  - Want to explore efficacy
  - Not willing to invest in phase III (yet)
  - Want some "control" or "prioritization"

Phase II Endpoints

- Response
  - Complete Response (CR)
  - Partial Response (PR)
  - Stable Disease (SD)
  - Progressive Disease (PD)
- Additional safety data

Phase II Limitations

- Lack of activity may not be valid
- Measurable disease required

Phase III Goals

- Efficacy compared to standard therapy
  - Activity demonstrated in Phase II study
- Further evaluation of safety

Phase III Subjects

- Hundreds to thousands of subjects
- Single cancer type
- May be front-line therapy
- Well-defined eligibility criteria
- Internal control group
- Multi-institutional participation necessary to reach targeted accrual goals

Phase III Standard Design

- Randomized +/- blinding/masking

Phase III: Endpoints

- Efficacy
  - Overall survival
  - Disease-free survival
  - Progression-free survival
  - Symptom control
  - Quality of life

Phase III: Limitations

- Difficult, complex, expensive to conduct
- Large number of patients required
- Incorporation of results into front-line therapy in community is often slow and incomplete

FDA Cancer Approval Endpoints

- Overall survival
- Endpoints based on tumor assessments
- Symptom endpoints (PROs)
- FDA Guidance: *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics*

Overall Survival

- Time from randomization until death
- Intent-to-treat population

Endpoints: Tumor Assessments…

- **Disease-free survival**
  - Randomization until recurrence of tumor or death from any cause
  - Adjuvant setting after definitive surgery or radiotherapy
  - Large % of patients achieve CR after chemo
- **Objective response rate (ORR)**
  - Proportion of patients with reduction of tumor size of a predefine amount and for a minimum time period
  - Measure from time of initial response until progression
  - Sum of PRs + CRs
  - Use standardized criteria when possible

…Endpoints: Tumor Assessments

- **Progression free survival (PFS)**
  - Randomization until objective tumor progression or death
  - Preferred regulatory endpoint
  - Assumes deaths are r/t progression
- **Time to Progression (TTP)**
  - Randomization until objective tumor progression, excluding deaths
- **Time-to-treatment failure (TTF)**
  - Randomization to discontinuation of treatment for any reason (PD, toxicity, death, etc.)
  - Not recommended for regulatory drug approval

Endpoints: Symptom Assessment

- Time to progression of cancer symptoms
- FDA Guidance: *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*
- Tools/surveys
- Issues:
  - Missing data
  - Infrequent assessments

Questions