Clinical Trial Design

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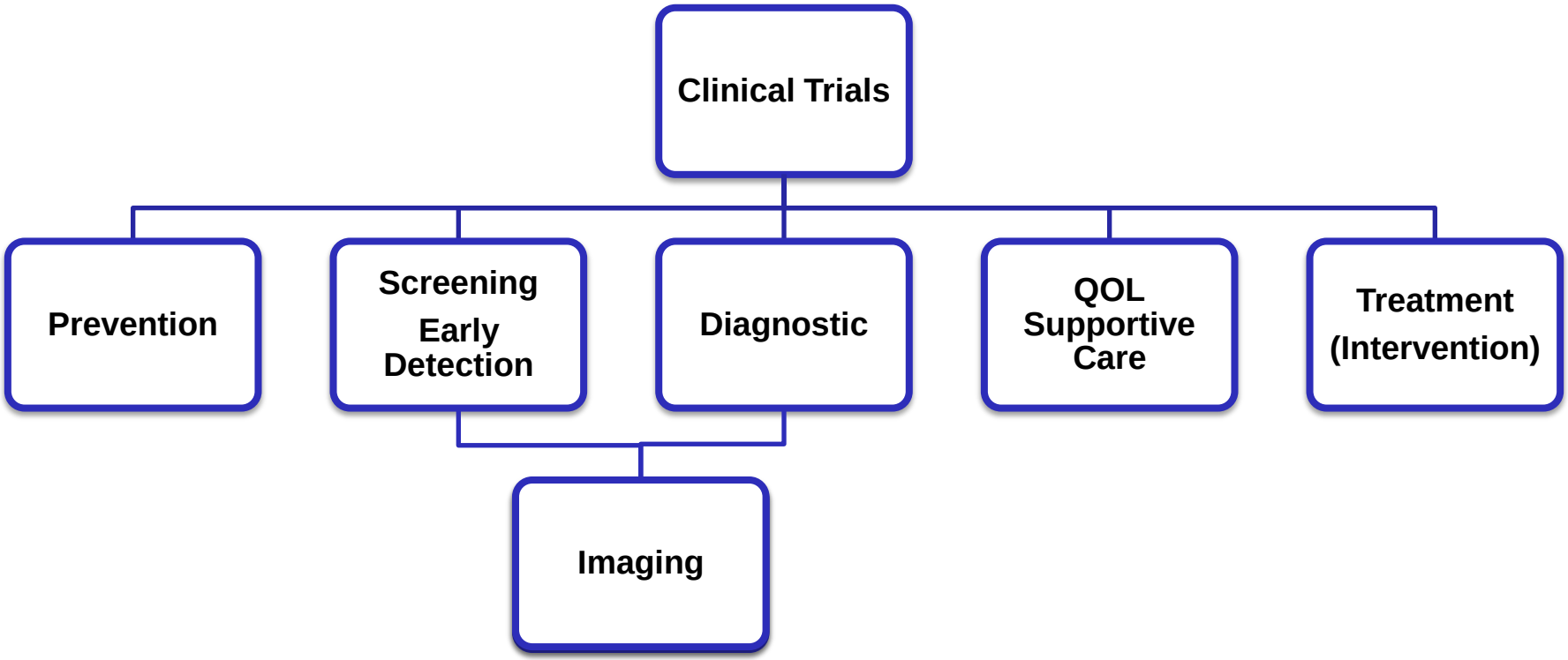
Agenda

- 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

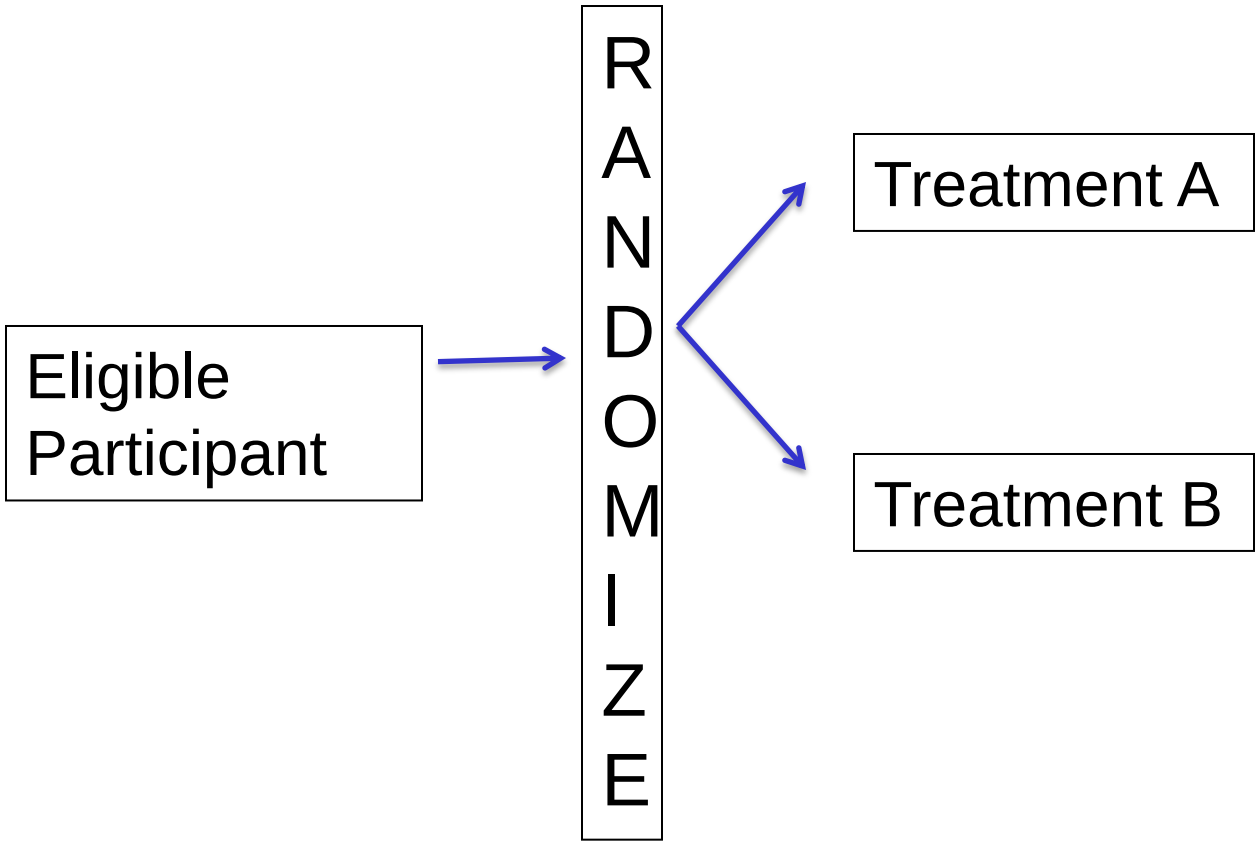
Disadvantages

- 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

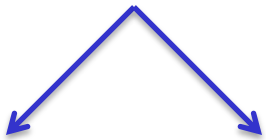
Parallel Design…



…Parallel Design

Low dose vs. higher dose

Randomization (n=50)



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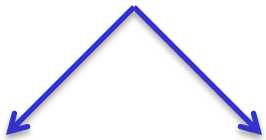
New Agent/ Intervention Low Dose

New Agent/ Intervention Higher Dose

Placebo (Inactive) vs agent

Randomization (n=50)



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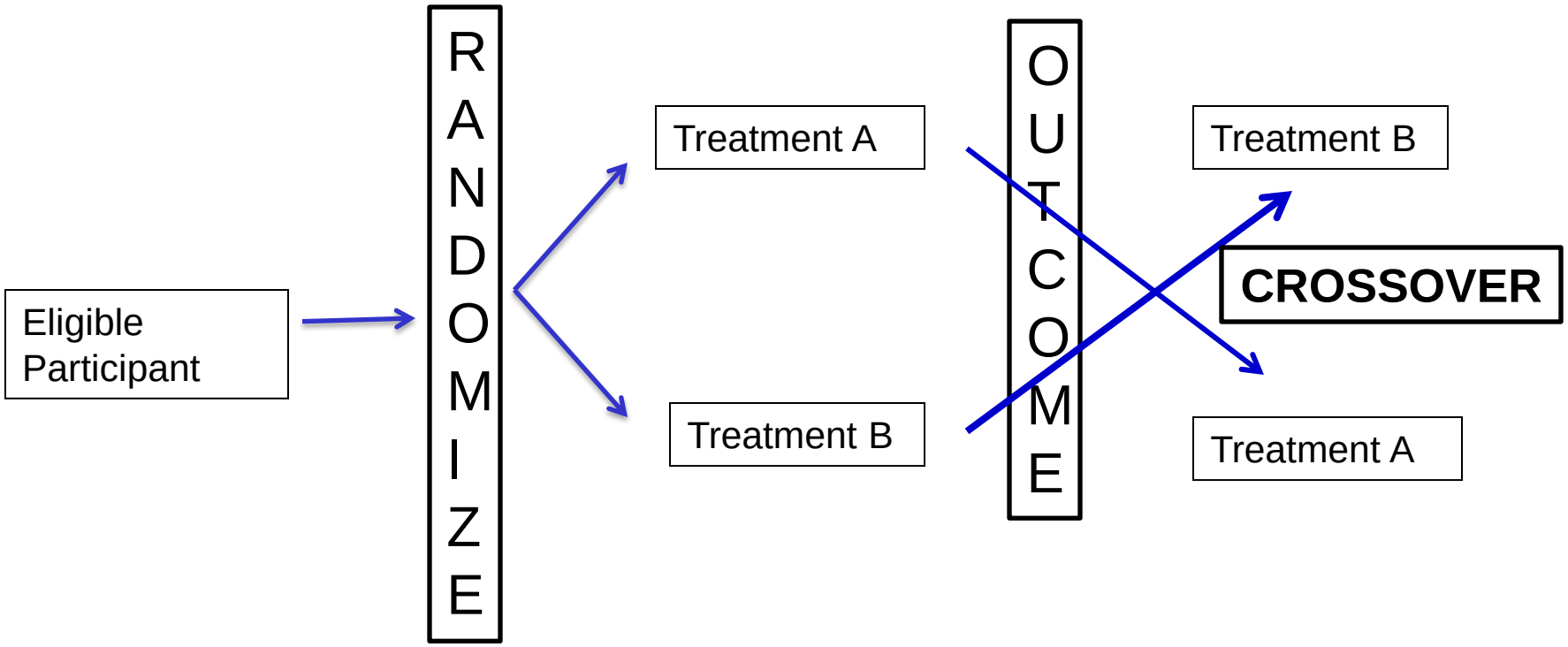
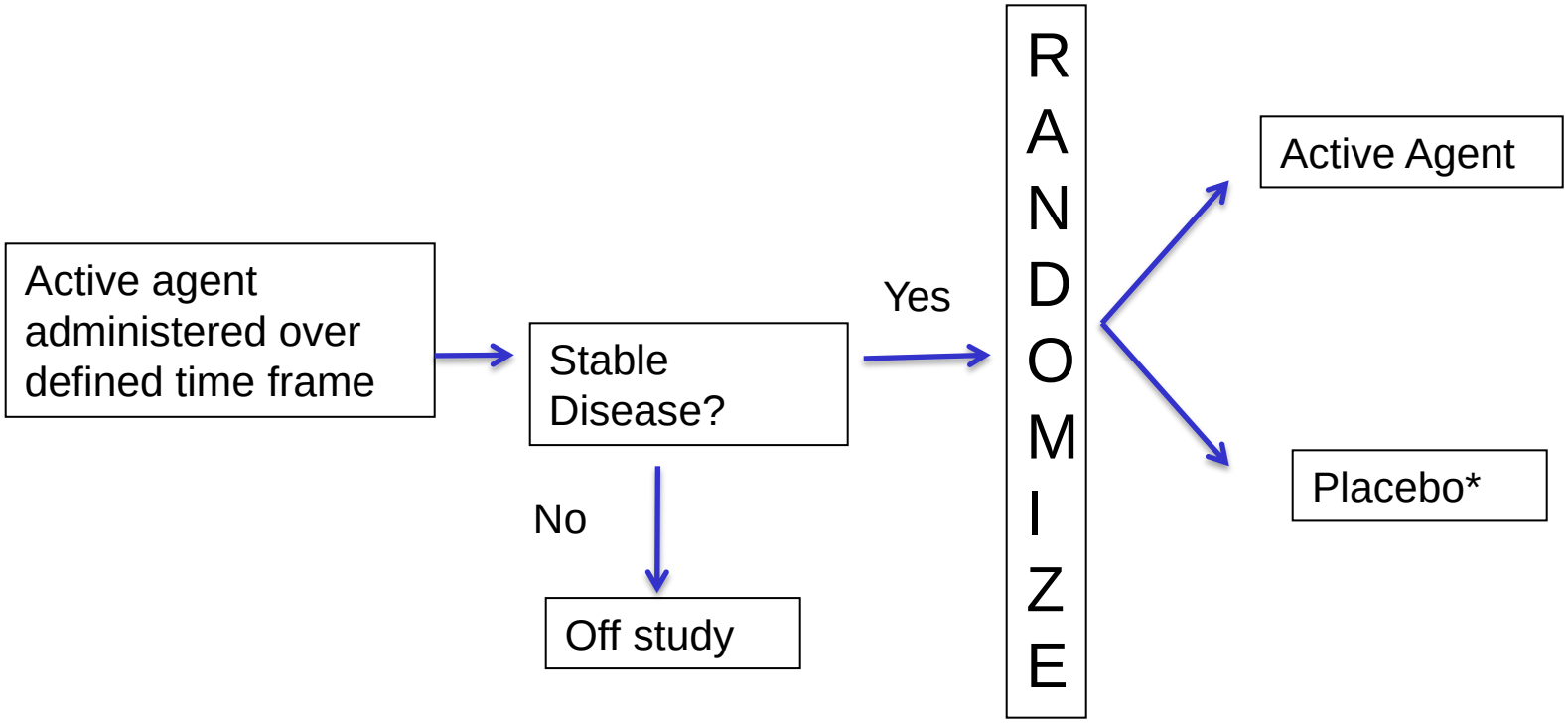
New agent alone or + placebo

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

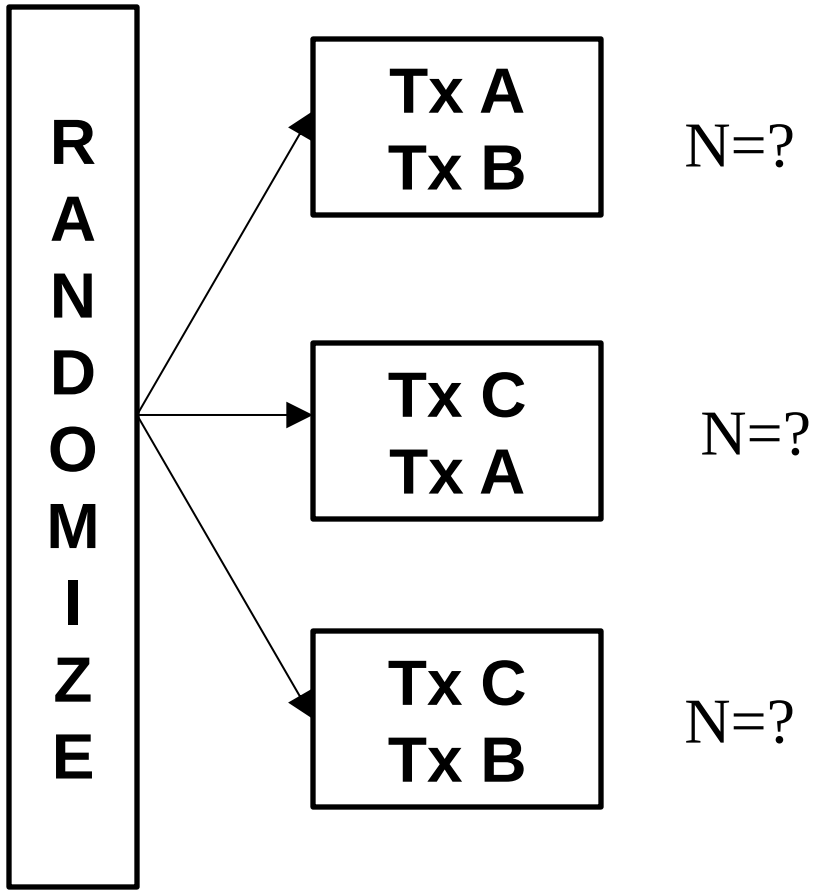
**Double blind recommended when possible*

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



Randomization is “adapted” based on accumulated information

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

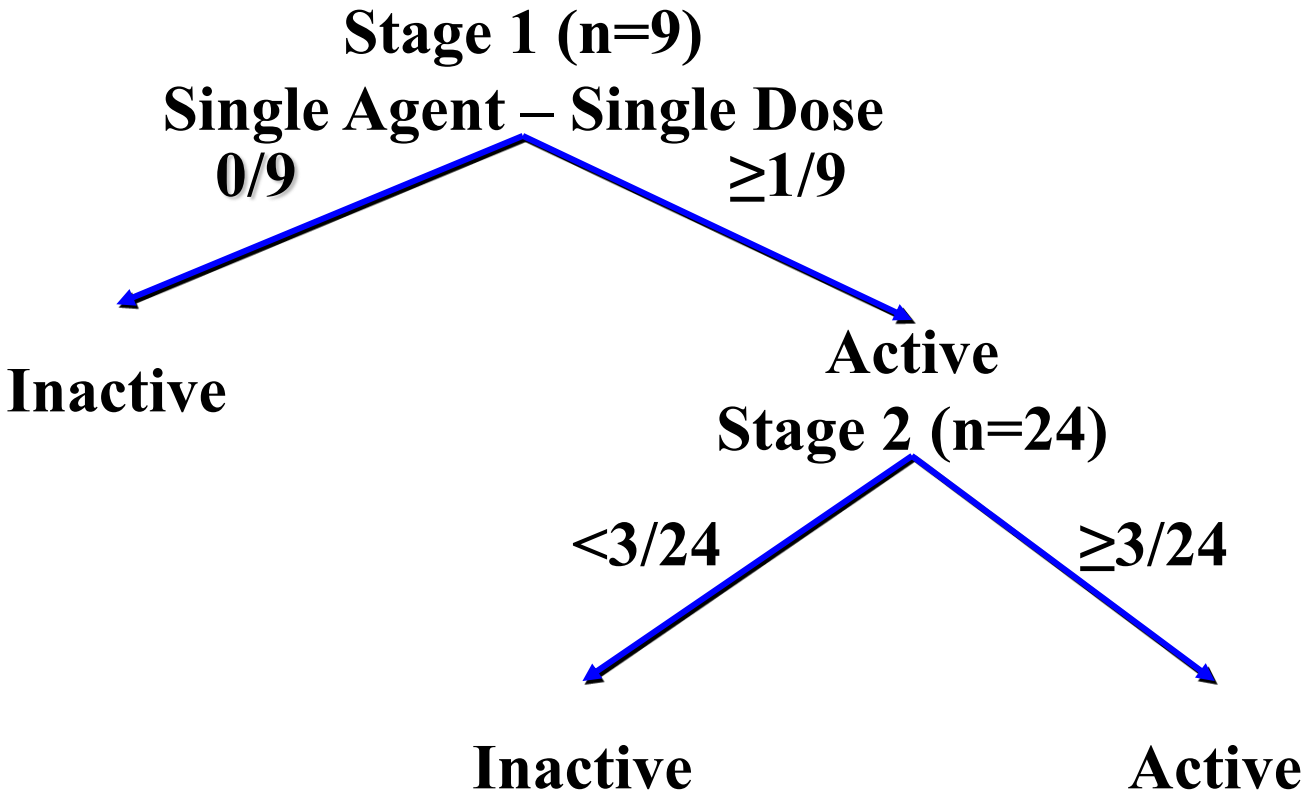
One-stage Design

- 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

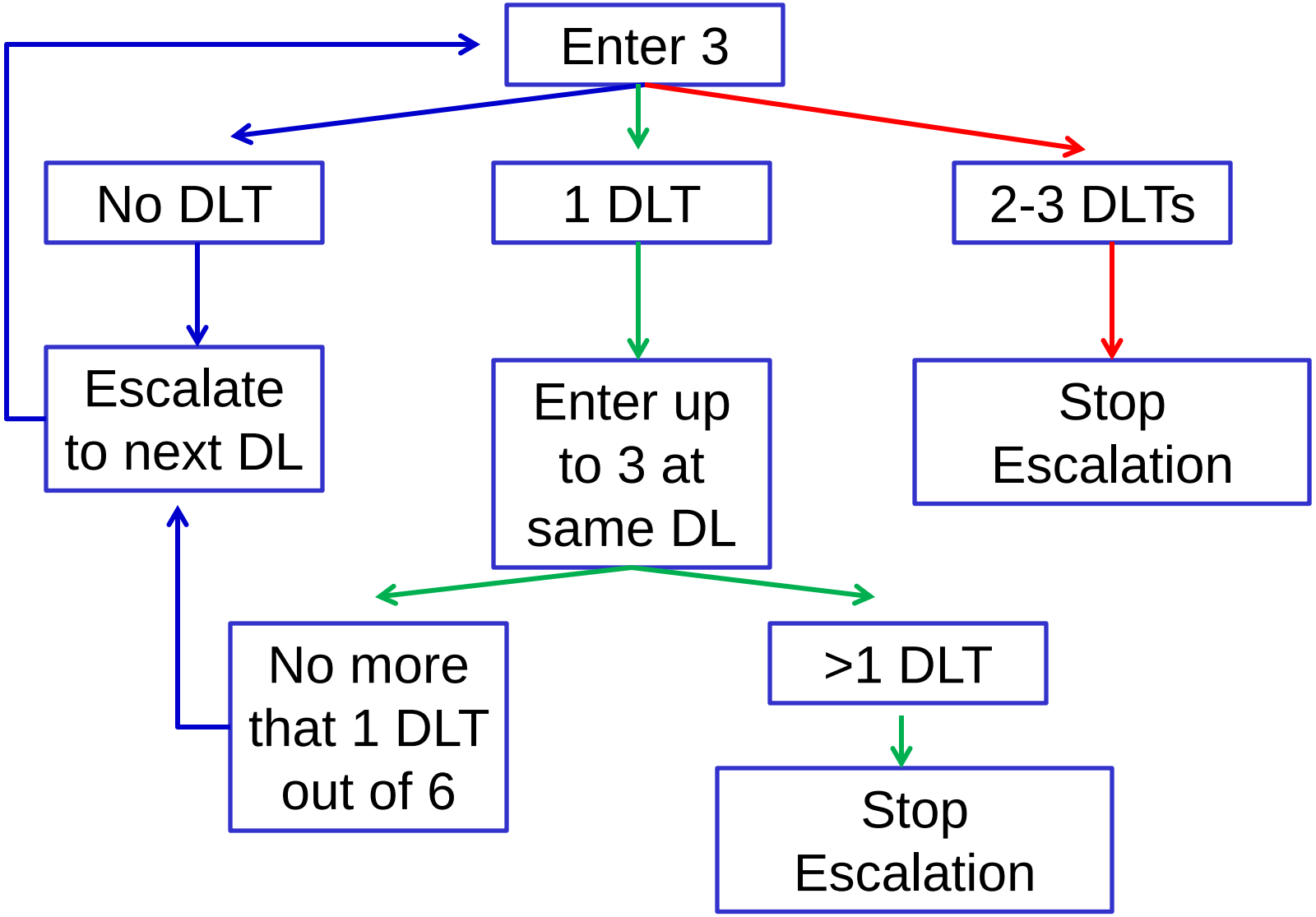
Level 3: 67% increase from Level 2

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