Randomized Controlled Studies

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Clinical Trials

- Designed to study response to an intervention under experimental conditions
- One or multiple arms
- Uncontrolled or controlled
- Superiority or equivalence (non-inferiority)
- Open label or blinded
- Randomized trials, adaptive designs, pragmatic trials

Why Randomized Controlled Trials (RCT)?

Patients enrolled in clinical trials can have improved short-term outcomes, even if the treatment is ineffective

- **Potential sources of 'benefit'**
  - **Enrollment of lower-risk patients**
  - **Use of standardized protocols and improved supportive care**
  - **Greater effort to prevent or manage adverse events**
- **Hawthorne or placebo effect**
  - **Hawthorne effect: changes in physicians' or patients' behavior, because of being observed, resulting in improved outcomes**
  - **Placebo effect: benefit derived not from the treatment itself but from the patients' expectations of benefit**

What are the key elements in a randomized trial?

- Hypotheses and aims
- Study population
- Trial design
- Randomization
- Endpoints
- Sample size
- Data analyses

Safety and Efficacy of Magic Pill A in NASH

Hypotheses and Aims

- **Sound hypotheses**
  - **Is there any physiologic basis / background data to support that magic pill A would have an effect in reversing pathophysiology of NASH and/or in ameliorating NASH liver injury?**
- **Clearly defined, measurable, realistic aims**
  - **How to define efficacy – symptoms, labs, histology, clinical outcomes?**
  - **Histology – decrease in NAS score or fibrosis score or both, by how much, when?**
  - **Should potential negatives be considered? Adverse events, costs…**

Study Population

- **Which patients to study?**
  - **Inclusion criteria**
  - **Exclusion criteria**
  - **Which tests needed prior to enrollment**
    - **To confirm diagnosis and to assess baseline severity: liver biopsy, Fibroscan, MR?**
    - **When should those tests be done: window period before enrollment?**
    - **What should the test results be: minimum NAS / fibrosis score?**

Inclusion Criteria

- **Demographics: age limit?**
- **Liver disease:**
  - **NAFLD vs. NASH**
  - **Minimum NAS / fibrosis score**
  - **Cutoffs for non-invasive tests?**

Exclusion Criteria

- Other liver diseases: HBV, HCV, alcohol – how much?
- Prior treatment – bariatric surgery, liposuction?
- Concomitant medications?
- Decompensated liver disease?
- Lab criteria – blood counts, hepatic panel, creatinine, A1c, lipid panel?
- Comorbid medical conditions that might impact response, safety, compliance or life-expectancy

Enrollment of Participants

- **Source of patients – referral base, feasibility**
- **Screening log – Patients with same condition but not enrolled**
  - **Reasons for not enrolling: ineligible (which criteria), patient refusal (why)**
  - **Are the enrolled patients similar to those not enrolled (demographics, disease characteristics)? Can results be generalized?**
  - **No. enrolled / no. screened – is the intervention applicable to the patient population?**

Trial Design – Intervention

- No. of treatment arms
- Test treatment
- Control: active treatment or placebo?
  - Is it ethical to use placebo?
  - Is it feasible to use placebo? Impact on enrollment?
  - Is it important to use placebo? Subjective vs. objective endpoint? Likelihood of spontaneous improvement?
  - Is blinding possible?

Trial Design - Intervention

- **Experimental and control arms**
  - **Duration of treatment**
  - **Dose regimen**
  - **Route of administration**
  - **Management of adverse events, criteria for dose reduction / termination**

Randomization

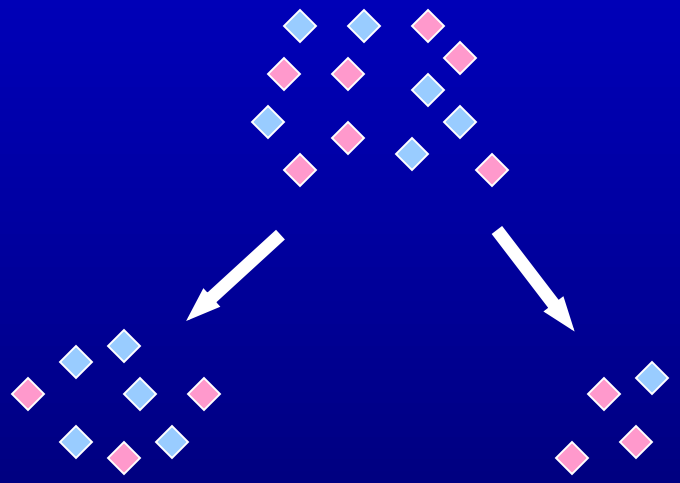
- Purpose – to minimize imbalances in baseline characteristics between treatment groups
- Allocation concealment – prevent prediction of treatment assignment resulting in selection bias
  - Selected patients not enrolled or
  - Certain patients enrolled out of sequence: deferred enrollment

Randomization Methods

- **Randomization methods:** flip a coin, random draw, computer generated random numbers
- **Allocation concealment:** opaque sealed envelopes, allocation by central office
- **Timing of randomization:** after confirmation of eligibility, treatment initiation visit scheduled, and treatment ready to begin
  - Patients randomized but not started on treatment need to be included in intention to treat (ITT) analyses

Simple Randomization

Study Population (n=12)



Treatment A (n=8)

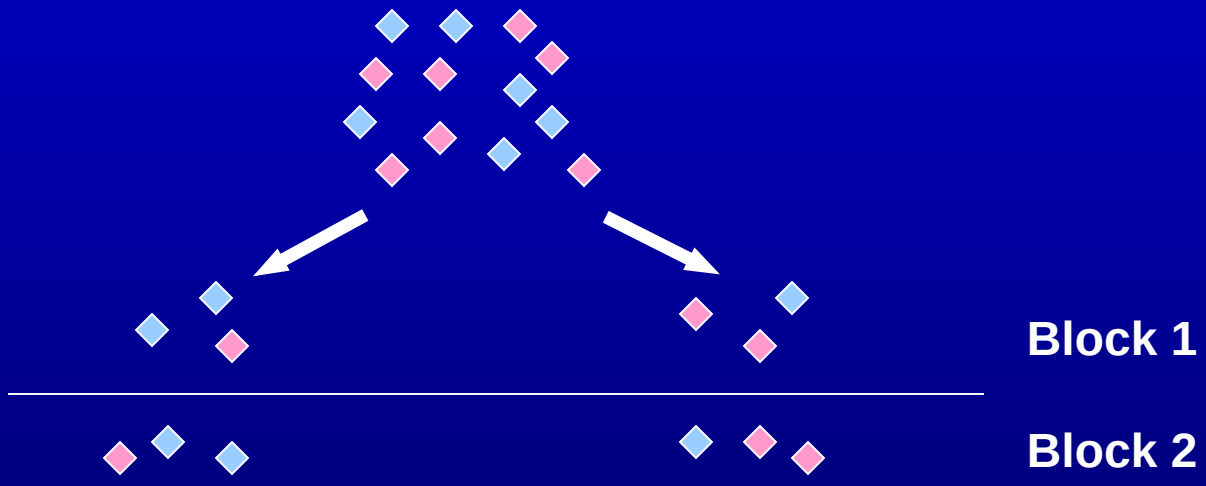
Treatment B (n=4)

With small sample size, there can be

- unequal number in each treatment arm
- unequal distribution of prognostic factors in each arm
- chronological bias – one treatment predominantly assigned earlier

Blocked Randomization

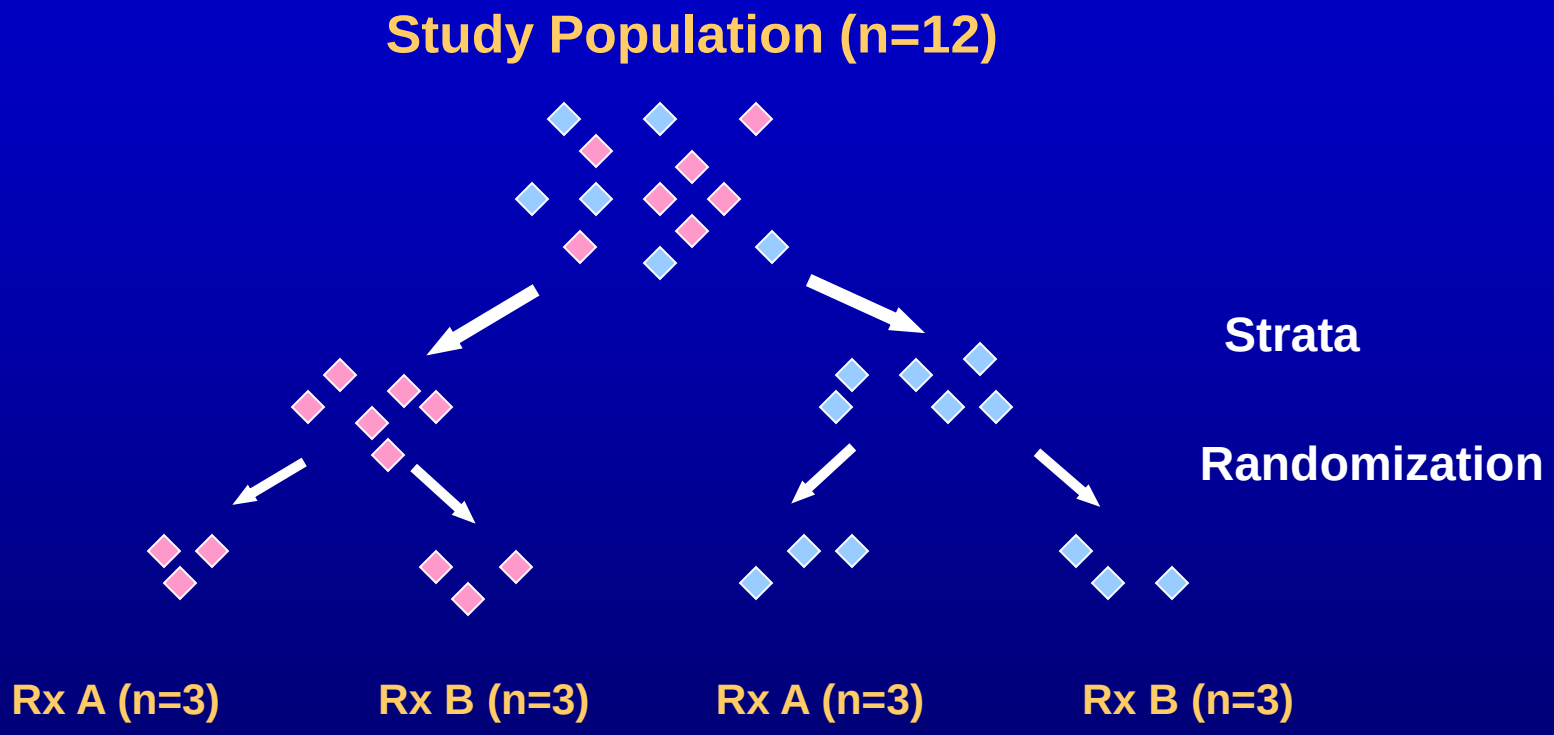
Study Population (n=12)



Treatment A (n=6) **Treatment B (n=6)**

Randomization occurs in blocks - Maintain equal or nearly equal no. in each treatment arm but distribution of prognostic factors not necessarily even. Block size may be constant or varied to decrease investigators' ability to predict treatment assignment

Stratified Randomization



Prognostic stratification avoids imbalance between treatment arms
Excessive stratification increases complexity of trial administration, randomization and analyses, risk of too few patients in some strata

Blinding of Treatment Assignment

- **Purpose – minimize bias in assessing efficacy and safety, maximize retention in trial**
- **Blinding of treatment assignment**
  - **Feasibility: route of administration, side effect profile**
  - **Matched placebo**
- **Blinding of test results**
  - **Tests blinded to patients only or to patients and investigators?**
  - **Blinding of efficacy results only or safety results also?**
  - **Ethical? Feasible? Retention?**

Safety and Efficacy Assessment

- **Visit schedule:** frequent enough to capture necessary data but not excessively burdensome
- **Efficacy assessment** – objective, measurable
  - Primary endpoints
  - Secondary endpoints
  - Timing of assessment
- **Safety assessment**
  - Subjective: directed vs. undirected questioning
  - Objective: labs
  - Management plan for adverse events / treatment failure
- **Measure of compliance** – subject diary, return bottles/pill count, drug levels

Endpoints

Primary endpoint – objective, measurable, and achievable

- Timing of assessment and method of assessment must be predefined
- Improvement in NASH: based on histology, non-invasive assessment?
  - Histology: decrease NAS / fibrosis scores or both by how much or to less than X? Patients with missing or inadequate biopsies will be counted as nonresponders
  - Non-invasive assessment: reproducibility, validity as surrogate?

Secondary endpoints

- Other measures of efficacy e.g. symptoms, labs
- Measures of safety
- Predictors of response

Sample Size Estimate

- To maximize the chance of detecting a significant difference between treatments when there is one, to avoid false positive or false negative results
- No. of patients needed to enroll to detect a significant difference with sufficient power (>80%)
- Predicated on projected response rates to investigational treatment vs. control
  - Estimation of response need to be scientifically based and realistic
- Adjustment for drop outs
- Adjustment for interim analyses

Analyses of Efficacy

- **Intention to treat (ITT)**
  - Include all patients randomized, problem when drop out rate is high or different among treatment arms
  - Modified ITT – include only patients who received at least one dose
- **Per protocol / As treated**
  - Include only patients who received treatment or who received adequate dose or duration of treatment
  - Patients who were available for assessment of primary endpoint
  - More accurate assessment of efficacy when adequate dose or duration of treatment is received but over estimate treatment effect for all patients in whom treatment is intended

Data Analyses

- Meet with statistician early on, during trial design
- Definition of endpoints
- Sample size
- Pre-determined analysis plan including subgroup analysis, missing data

Regulatory / Safety / Budget Issues

- Registration of trial, e.g. clinicaltrials.gov (many journals require this)
- IRB or ethics committee approval
- Informed consent
- Adverse event reporting
- Independent Data and Safety Monitoring Board
- Budget, funding, conflict of interest

Protocol template and instructions on how to write a clinical trial protocol can be found at:

http://osp.od.nih.gov/office-clinical-research-and-bioethics-policy/clinical-research-policy/clinical-trials