Principles of Clinical Trials

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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.
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• Potential sources of ‘benefit’
  – Enrollment of lower-risk patients with minimal comorbidities
  – 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 protocol?

- Background and rationale for study
- Hypotheses and aims
- Study population – inclusion and exclusion criteria
- Trial design – intervention and comparison, randomization
- Endpoints – what, when and how
- Sample size and data analysis plan
Safety and Efficacy of Magic Pill A in NASH
Introduction

• Study rationale
  – Why is this study important

• Background
  – Review literature on standard of care for the disease
  – Provide preliminary data on the intervention to be studied: in vitro, animal and human data on efficacy, safety, clinical pharmacology

• Risk/Benefit assessment
  – Known potential risks and benefits
  – Justification of potential risks, measures to minimize risks
Hypotheses

• **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?
Endpoints

- **Primary** – which effect, how it will be measured and when
  - Preferably one primary endpoint, basis for concluding whether study objective is met and for sample size calculations
  - Clinically relevant, reliable test/method to measure effect
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• **Secondary**
  • Provide supportive information about effect of intervention
  • Examples: efficacy at different time point or in pre-defined subsets, dose-response effect, predictors of response, safety measures, patient reported outcomes
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- **Exploratory**
  - May include clinically important events that are expected to be infrequent or hypotheses generating
Study Population

• Which patients to study?
  – Inclusion and exclusion criteria
  – Consider generalizability of results
  – Consider availability of participants
  – 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

• Every participant must satisfy all criteria
• Demographics: age limit?
• Diagnosis of disease
• Staging of disease
• Informed consent
Exclusion Criteria

- All participants meeting any of the criteria must be excluded
- 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
- Pregnancy
Recruitment and Retention

• **Source of patients** – where and how will potential participants be identified: patient registry, electronic medical records, advertising (IRB approval)

• **Strategies to meet sample size**

• **Screening log** – Patients with same condition but not enrolled. Are enrolled patients similar to those not enrolled?
Consort Diagram

1. Enrollment
   - Assessed for eligibility (n=\_)
     - Excluded (n=\_)
       - Not meeting inclusion criteria (n=\_)
       - Declined to participate (n=\_)
       - Other reasons (n=\_)
     - Randomized (n=\_)

2. Allocation
   - Allocated to intervention (n=\_)
     - Received allocated intervention (n=\_)
     - Did not receive allocated intervention (give reasons) (n=\_)
       - Excluded from analysis (give reasons) (n=\_)
   - Allocated to intervention (n=\_)
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     - Did not receive allocated intervention (give reasons) (n=\_)

3. Follow-Up
   - Lost to follow-up (give reasons) (n=\_)
   - Discontinued intervention (give reasons) (n=\_)
   - Lost to follow-up (give reasons) (n=\_)
   - Discontinued intervention (give reasons) (n=\_)

4. Analysis
   - Analysed (n=\_)
     - Excluded from analysis (give reasons) (n=\_)
   - Analysed (n=\_)
     - Excluded from analysis (give reasons) (n=\_)
Trial Design – Intervention

- **Participating sites:** no., location
- **Design:** single vs. multiple arms, cross-over, adaptive, etc
- **Test treatment:** dose, route, duration, criteria for dose modification/termination
- **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? Safety assessment
  - Is blinding possible?
Randomization

- **Purpose:** to minimize imbalance in patient characteristics between groups
- **Methods:** computer generated random numbers, blocks, stratification
- **Concealment:** prevent prediction of treatment assignment resulting in selection bias
- **Timing:** 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 analysis
Study Assessments and Procedures

- Study visit table
- Timing of each visit and visit window: visits frequent enough to capture necessary data but not excessively burdensome
- Clinical assessments including physical exam, concomitant medications, comorbidities
- Tests and procedures: specify methods, e.g. liver steatosis by Fibroscan or MR PDFF
- Assessment of adverse events: definition, methods of assessment, management
- Questionnaires, patient reported outcomes
Study Intervention

• Study drug dispensing
• Adherence
  – To intervention: diaries, electronic monitoring, drug levels…
  – To protocol: study visits, tests
• Concomitant therapy
  – Which medications are restricted
• Rescue therapy
  – For treatment failure or for adverse events
Statistical Considerations

- Statistical hypotheses
- Sample size determination
- Populations for analyses
- Statistical analyses
  - General plan
  - Specific plan for each primary, secondary and exploratory endpoints, and safety analyses
  - Describe how missing data will be handled
  - Describe subgroup and interim analyses if applicable
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Meet with statistician early during planning of trial not after completion of trial
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
Primary Efficacy Endpoint

• Objective, measurable, and achievable
• Define timing and method of assessment
• Improvement in NASH
  – Based on histology, MR or other tests
  – Histology
    • Central read or local read?
    • Decrease NAS or fibrosis score or both, decrease by how much or to less than what?
    • Patients with missing or inadequate biopsies will be counted as non-responders in ITT analysis
  – Non-invasive assessment: reproducibility, validity as surrogate?
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
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: