1. Specifying the study setting and objectives

1.0 Background
   ▶ Where will we end up?:
     (a) The treatment indication
     (b) Inference upon trial completion
   ▶ The scientific method

1.1 Defining the study population

1.2 Defining the study question
   (a) Defining the interventions: What is the treatment?
   (b) Phase I-IV clinical trials
   (c) Statistical structure of the outcome space
   (d) 1-sided versus 2-sided questions

1.3 Case study (Rocket-AF trial)
1.2 The Study Question

(a) What is a treatment?

- In addition to the actual compound that will be tested, a treatment includes:
  - Dose and delivery method
  - Schedule and duration of treatment
  - Other ancillary or supportive treatments

- A treatment is also targeting a disease:
  - Bacterial versus viral infections
  - Type of cancer; cancer stage

- The treatment is also given to particular types of patients:
  - Newly diagnosed versus recurrent patients
  - Patients who have failed other treatments
  - Patients with combinations of diseases (HIV and KS)

- Its targeted impact; for example:
  - Relief of headache
  - Reduction of risk for myocardial infarct
  - Prolongation of life

- Notice that all of the above elements are also key to the “indication" (per earlier discussion).
1.2 The Study Question

(b) Phase I-IV clinical trials

New therapies are usually evaluated in a phased sequence of studies. The phases provide a conceptual framework for organizing the scientific objectives of the study.

- See Piantadosi Chapter 6 (esp: sections 6.3-6.5)
- Terminology (nonstandard but thoughtful):

<table>
<thead>
<tr>
<th>Developmental Stage</th>
<th>Terminology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Old</td>
</tr>
<tr>
<td>Early</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Phase I</td>
</tr>
<tr>
<td></td>
<td>↓</td>
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<tr>
<td></td>
<td>↓</td>
</tr>
<tr>
<td>Middle</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>Phase IIa</td>
</tr>
<tr>
<td></td>
<td>Phase IIb</td>
</tr>
<tr>
<td></td>
<td>Phase III</td>
</tr>
<tr>
<td></td>
<td>Phase IV</td>
</tr>
<tr>
<td></td>
<td>Large simple</td>
</tr>
</tbody>
</table>
1.2 The Study Question

(b) Phase I-IV clinical trials

New therapies are usually evaluated in a phased sequence of studies. The phases provide a conceptual framework for organizing the scientific objectives of the study.

- Epidemiologic studies (non-experimental)
- Pre-clinical studies (not with human subjects)
- “Pilot” studies
  - Not appropriate for estimating or comparing either biological or clinical effects.
  - May be used to develop or test procedures:
    - Testing randomization procedures.
    - Testing dataflow and data capture
    - Learning how to run an assay.
    - Testing whether or not a survey is easily understood.
1. Setting and Objectives

1.1 The study population
   (a) Treatment indication
   (b) Inference upon completion

1.2 The study question
   (a) What is the treatment?
   (b) Phase I-IV trials
   (c) Nature of the clinical question
   (d) 1-sided vs 2-sided questions

1.3 Case study: Rocket-AF

(b) Phase I-IV clinical trials

Phase I: preliminary safety and dose-finding studies

- Goals:
  - Pharmacokinetics.
  - Ruling out major adverse events.
  - Dose determination.
  - Device configuration.

- Methods:
  - Dose escalation or device alteration.
  - Subjects not necessarily from target population.
  - Subjects might have failed all standard therapies.
  - Uncommon to have a concurrent control group.
**Phase II: Preliminary efficacy and safety evaluation**

- **Goal:**
  - Show toxicity is acceptably low.
  - Screen for evidence of efficacy prior to larger trials.

- **Methods:**
  - Study population more closely reflects target population.
  - Dose (treatment) is the same as the dose that will be used in subsequent trials.
  - Endpoint may be a surrogate (biological marker) for the true clinical endpoint (e.g., CD4 cell count vs survival).
  - Historical or concurrent controls may be used.
  - Typically small (< 100 patients).
(b) Phase I-IV clinical trials

<table>
<thead>
<tr>
<th>Phase III: Full-scale efficacy trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Goal:</strong></td>
</tr>
<tr>
<td>▶ Evaluate clinical efficacy.</td>
</tr>
<tr>
<td>▶ Confirm suitably low toxicity.</td>
</tr>
<tr>
<td><strong>Methods:</strong></td>
</tr>
<tr>
<td>▶ Study population closely reflects target population.</td>
</tr>
<tr>
<td>▶ Concurrent (randomized) control group.</td>
</tr>
<tr>
<td>▶ Primary outcome: clinical efficacy.</td>
</tr>
<tr>
<td>▶ Sufficiently large to answer the clinical/scientific question.</td>
</tr>
<tr>
<td><strong>Common applications:</strong></td>
</tr>
<tr>
<td>▶ Establish efficacy of new treatment; i.e.,:</td>
</tr>
<tr>
<td>Superiority over no treatment.</td>
</tr>
<tr>
<td>Superiority over an existing treatment.</td>
</tr>
<tr>
<td>▶ Establish equivalence with current treatment; i.e.,:</td>
</tr>
<tr>
<td>Two-sided equivalence: bioequivalence.</td>
</tr>
<tr>
<td>One-sided equivalence: non-inferiority</td>
</tr>
<tr>
<td>(perhaps superior on a secondary endpoint).</td>
</tr>
<tr>
<td>▶ Establish harm of existing treatment.</td>
</tr>
</tbody>
</table>
(b) Phase I-IV clinical trials

Phase IV: Effectiveness trials (post-marketing surveillance)

- **Goal:**
  - Determine if estimated effects are actually observed in routine clinical use.
    - E.g., AIDS vaccine which is less than fully protective might cause an increase in AIDS because vaccinated individuals resume high-risk behavior.
  - Detect rare adverse events.
  - Assess long-term outcome.

- **Methods:**
  - Study population is the target population.
  - Rarely with a randomized control group; usually monitoring studies.
  - Can be very large with long-term follow-up.
Example: Irinotecan for Lung Cancer

- Small-cell lung cancer:
  - Worse prognosis than non-small-cell lung cancer.
  - Usually treated with cisplatin chemotherapy.
- Irinotecan (new chemotherapy drug):
  - Good biological rationale
  - Has shown strong anti-tumor properties in experimental tumor models.
  - Has been active against leukemia, lymphoma, and several common solid tumors.
  - Dose-limiting toxicities include leukopenia and diarrhea.
(b) Phase I-IV clinical trials

Example: Irinotecan for Lung Cancer

- What would you do??
  - Phase I study:
  - Phase II study:
  - Phase III study:
Irinotecan example (con’t):

**Phase I:**


- **Study Design:** Dose escalation 3 patients per group with 5 additional patients at maximum tolerated dose.

- **Outcome variables:**
  - Toxicity (leukopenia, anemia, nausea/vomiting, diarrhea): graded I-IV
  - Pharmacokinetics (plasma concentration versus time)
  - Tumor response (CR, PR, NR)

- **Primary explanatory variable:**
  - Drug dose?

- **Results:**
  - Maximum tolerated dose: 90 mg/m²
  - Dose limiting toxicity: Diarrhea
  - Pharmacokinetic profiles
Irinotecan example (con’t):

Phase II:

Study Design: 75 patients all receive the same treatment. Dose reduced to 80\(mg/m^2\).

Outcome variables:
- Tumor response (CR, PR, NR) and response duration.
- Patient survival.
- Toxicity (neutropenia, leukopenia, anemia, diarrhea): graded I-IV

Primary explanatory variable:
- Local versus extended disease.
Irinotecan example (con’t):

**Phase II (con’t):**

**Results:**

- **Response rates:**
  - Overall: 84% (CR + PR); 29% (CR)
  - Extended disease: 83% (CR + PR); 30% (CR)
  - Local disease: 86% (CR + PR); 29% (CR)
  - Toxicity: Major (grade 3 or 4) toxicities in most patients; 2 deaths.
Irinotecan example (con’t):

Phase III:

Study Design: Randomized controlled trial including 154 patients.

Outcome variables:
- Survival
- Toxicity: (severe or life threatening myleosuppression)

Explanatory variable:
- Drug (irinotecan versus etoposide)

Results:
- Significant improvement in survival with irinotecan when compared with etoposide
- Toxicity was more frequent with etoposide
## Irinotecan Example

### Summary of published trials

  - Design: Dose escalation (14 patients)
  - Outcome: Grade 3-4 toxicities (leukopenia, diarrhea)
  - Primary explanatory: Dose level
  - Covariate: None

- **Phase II: J. Clinical Oncology (1998) 16:1068-1074**
  - Design: Single arm (75 patients)
  - Outcome: Tumor response; grade 3-4 toxicities.
  - Primary explanatory: Extended vs local disease.
  - Covariate: None

  - Design: Randomized controled trial (154 patients) (irinotecan vs etoposide)
  - Outcome: Survival
  - Primary explanatory: Treatment group
  - Covariate: None
# Phase I-III trials

## Design elements from Phase I-III

<table>
<thead>
<tr>
<th></th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endpoints</strong></td>
<td>Tolerance</td>
<td>Safety bioactivity</td>
<td>Efficacy safety</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>Short</td>
<td>Moderate</td>
<td>Longer</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>Non-target</td>
<td>Target</td>
<td>Target</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Dose finding</td>
<td>Study dose</td>
<td>Study dose</td>
</tr>
<tr>
<td><strong>Comparison</strong></td>
<td>Across doses</td>
<td>Historical or randomized</td>
<td>Randomized</td>
</tr>
<tr>
<td><strong>Sample Size</strong></td>
<td>Very small</td>
<td>Moderate</td>
<td>Large</td>
</tr>
</tbody>
</table>
Another example: Iloprost for prevention of lung cancer

What would you do?

- Pre-clinical studies:

  - Phase I study:

  - Phase II study:

  - Phase III study:

  - Phase IV study:
1. Setting and Objectives

1.1 The study population
(a) Treatment indication
(b) Inference upon completion

1.2 The study question
(a) What is the treatment?
(b) Phase I-IV trials
(c) Nature of the clinical question
(d) 1-sided vs 2-sided questions

1.3 Case study: Rocket-AF

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## Phase I-IV trials

### Phases in other settings

- **Surgery**
  - Phase I: Refining procedures/technique, safety.
  - Phase II: Safety; preliminary efficacy data (short term and/or biological outcomes).
  - Phase III: Definitive efficacy trial, confirm safety.
  - Phase IV: ‘Post-market' effectiveness; long-term safety.

- **Device evaluation**:
  - Phase I: Device refining, safety.
  - Phase II: Safety; preliminary efficacy data.
  - Phase III: Definitive efficacy trial, confirm safety.
  - Phase IV: Post-market effectiveness; long-term safety.

- **Chemoprevention**:
  - Phase I: Dose-finding; short-term tolerability.
  - Phase II: Tolerability and biological efficacy.
  - Phase III: Cause-specific mortality; all-cause mortality.
  - (Phase IV: Extend the target population.)
Phase I-IV trials

Phases in other settings

- Diagnostic tests (biomarker development; Pepe, M, JNCI, 2001)
  - Phase I: Preclinical exploration
  - Phase II: Clinical assay and validation (prevalent case-control study)
  - Phase III: Retrospective longitudinal (incident case-control study)
  - Phase IV: Prospective screening (extend and type of disease detected; false referral rate estimated)
  - Phase V: Disease control (screening with the biomarker reduces disease mortality).
1.2 The Study Question

Recall our outline:

(a) What is the treatment?
(b) Phase I-IV clinical trials:
   ▶ Overview and definition of phases
   ▶ Efficiency of phased approach
(c) Nature of the clinical question:
   ▶ The conceptual structure of parameter space
   ▶ Which decisions are relevant:
     ▶ Superiority, non-superiority
     ▶ non-inferiority, inferiority
     ▶ bio-equivalence
     ▶ approximate equivalence
   ▶ Non-inferiority trials require careful consideration
   ▶ Examples
(d) 1- versus 2-sided questions
(c) Nature of the Clinical Question

- Recommendations for/against a therapy will be based on how we define:
  - Superiority
  - Clinically important superiority
  - Inferiority
  - Clinically important inferiority
- These clinical effects must be formally defined in terms of the parameter(s) that measures treatment effect.

- Notes:
  - In general I will use $\theta$ to denote the true treatment effect (e.g., often with 2 treatments, $\theta = \theta_1 - \theta_0$).
  - For simplicity I will assume larger values of $\theta$ denote better outcomes.
Conceptually, the investigator team must divide parameter space into the following regions:

\[
\begin{align*}
\theta > \theta_\emptyset & \Rightarrow \text{Benefit} \\
\theta > \theta_+ & \Rightarrow \text{Clinically important benefit} \\
\theta \leq \theta_\emptyset & \Rightarrow \text{Harm} \\
\theta < \theta_- & \Rightarrow \text{Clinically important harm}
\end{align*}
\]
(c) Nature of the Clinical Question: Structuring parameter space

- Clinically Important Harm: $\theta_-$
- No Difference: $\theta_{null}$
- Clinically Important Benefit: $\theta_+$
- Inferiority: $\theta < \theta_-$
- Superiority: $\theta > \theta_+$
- Clinical Inferiority: $\theta < \theta_-$
- Clinical Superiority: $\theta > \theta_+$
(c) Nature of the Clinical Question: Structuring parameter space

Example 1: Phase III iloprost chemoprevention trial

- **Background:** Lung cancer is the leading cause of cancer death in both men and women in the United States with a dismal 5-year survival rate of < 15%. There are no established screening tests for the early detection of lung cancer and less than 25% of patients present with surgically curable disease (stages I and II). Active smoking accounts for 85-87% of all new lung cancer cases and more than 50% of new cases were diagnosed in former smokers. Therefore, improved success in decreasing lung cancer rates will rely not only on smoking prevention and cessation, but also on effective chemopreventive strategies.

- **Clinical question:** Several possibilities including:
  - Can iloprost be used to prevent lung cancer among former smokers?
  - Will use of iloprost improve longevity of former smokers?
Example 1: Phase III iloprost chemoprevention trial (con’t)

- **Study treatments**: Daily Iloprost versus placebo (Note: a more complete specification is required.)
- **Study population**: Several possibilities including:
  - Former smokers with more than 20 pack-years of smoking.
  - Stage 1A lung cancer patients with complete resection.
  - Head and neck cancer patients with no disease.
- **Scientific objective**: To determine whether oral iloprost prevents lung cancer.
- **Outcome measures**: Several possibilities including:
  - Time to lung cancer (or new primary lung cancer)
  - Time to death from cancer
  - Time to death from any cause
(c) Nature of the Clinical Question: Structuring parameter space

Example 1: Phase III iloprost chemoprevention trial (con’t)

- **Statistical hypotheses** Suppose that we measure treatment effects by time to a new primary tumor.
  - $\theta_1 =$ hazard of getting a new primary tumor with iloprost treatment
  - $\theta_0 =$ hazard of getting a new primary tumor with iloprost treatment
  - **Defining $\theta$:**
    - Almost always: $\theta = \theta_1 / \theta_0$ so smaller $\theta$ favors iloprost.
    - In this lecture I will use: $\theta = \theta_0 / \theta_1$ so larger $\theta$ favors iloprost.
Example 2: Molecular guided therapy for heart failure

- Background: Patients who present with heart failure are started on beta-blocker therapy. If their ejection fraction has not improved to greater than 35% after one month of therapy, then are often given an implantable defibrillator. This procedure is used in about 90% of heart failure patients. After 12 months most of those patients have not needed the defibrillator, and most (80%) have ejection fraction above 35%.

- Clinical question: Can a molecular expressions be used to predict the patients who should and should not receive implantable defibrillators?

- Study interventions:
  - Standard care (implantable defibrillator as above).
  - Molecular expressions determine who needs the device.
Example 2: Molecular guided therapy for heart failure (con’t)

- **Study population**: Patients with newly diagnosed heart failure.

- **Scientific objective**: Determine whether molecular guided care is as effective as current standard of care.

- **Outcome measures**: Several possibilities:
  - Correct diagnose of who needed the implantable defibrillator at 12-months (ejection fraction above 35%) – Pepe Phase IV
  - Risk of clinical events including MI, hospitalization, death – Pepe Phase V
(c) Nature of the Clinical Question: Structuring parameter space

Example 2: Molecular guided therapy for heart failure (con’t)

▶ Statistical hypotheses: Suppose the primary outcome is a clinical event rate.
  ▶ $\theta_1 =$ hazard of event with molecular guided care
  ▶ $\theta_0 =$ hazard of event with standard care
  ▶ Defining $\theta$:
    ▶ Almost always: $\theta = \theta_1 / \theta_0$ so smaller $\theta$ favors MGC.
    ▶ In this lecture I will use: $\theta = \theta_0 / \theta_1$ so larger $\theta$ favors MGC.
Example 3: Chinese complementary foods trial

► Background: In infants, solid foods are usually introduced at about 6-months of age. In developing regions of the world, those “complementary foods” are often nutrient deficient; particularly in their micronutrient content. Several trials have shown that supplementation with iron and zinc micronutrients result in increased growth and decreased disease morbidity in infants. Most complementary cereals in the US and other developed countries contain micronutrient fortification, but fortified cereals are not readily available in most developing regions. Meats contain a lot of good micronutrients, but are not usually recommended for infants as a complementary food.

► Public health question: Is there benefit to introducing meat as a complementary food in developing regions of the world?
Example 3: Chinese complementary foods trial

- **Interventions:**
  - Ground pork
  - Fortified cereal
  - Standard rice cereal

- **Study population:** Infants age 6-18 months in a developing region of China (Xichou, Kunming province)

- **Scientific objective:** Determine whether meat is as good as fortified cereal, and better than unfortified cereal when fed as a complementary food from 6 to 18 months.
(c) Nature of the Clinical Question: Structuring parameter space

**Example 3:** Chinese complementary foods trial

- **Outcome measures:** Linear growth, cognitive development, disease morbidity
- **Statistical hypotheses:** The primary outcome is linear growth (change in length from 6-months to 18-months)
  - $\theta_M =$ Mean change in length with meat
  - $\theta_F =$ Mean change in length with fortified cereal
  - $\theta_C =$ Mean change in length with cereal (unfortified)
  - $\theta_{MF} = \theta_M - \theta_F$
  - $\theta_{MC} = \theta_M - \theta_C$
  (Larger values of $\theta_{MF}$ or $\theta_{MC}$ favor meat.)
(c) Nature of the Clinical Question: Structuring parameter space

- What should we decide with an infinite sample size ($\theta$ is known)?

Potential trial results (infinite sample size)

<table>
<thead>
<tr>
<th>No Difference ($\theta_{null}$)</th>
<th>Clinically Important Benefit ($\theta_+$)</th>
<th>Clinically Important Harm ($\theta_-$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inferiority ($\theta &lt; \theta_{-}$)</td>
<td>Superiority ($\theta &gt; \theta_+$)</td>
<td>No Difference ($\theta_{null}$)</td>
</tr>
</tbody>
</table>

- Phase I-IV trials
- Nature of the clinical question
- 1-sided vs 2-sided questions

1. Setting and Objectives
1.1 The study population
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(a) What is the treatment?
(b) Phase I-IV trials
(c) Nature of the clinical question
(d) 1-sided vs 2-sided questions
1.3 Case study: Rocket-AF
(c) Nature of the Clinical Question:
Structuring parameter space

What should we decide with an infinite sample size ($\theta$ is known)?

<table>
<thead>
<tr>
<th>Case</th>
<th>Iloprost</th>
<th>MGC</th>
<th>CCF ($\theta_{MC}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Recommend</td>
<td>Recommend</td>
<td>Recommend</td>
</tr>
<tr>
<td>B</td>
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<td></td>
</tr>
<tr>
<td>C</td>
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<tr>
<td>H</td>
<td>Reject</td>
<td>Reject</td>
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</tr>
</tbody>
</table>
(c) Nature of the Clinical Question: Structuring parameter space

What should we decide with an infinite sample size ($\theta$ is known)?

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<tr>
<td>A</td>
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</tr>
<tr>
<td>B</td>
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<td>Recommend</td>
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</tr>
<tr>
<td>C</td>
<td>Recommend?</td>
<td>Recommend</td>
<td>Meat/Cereal</td>
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<td>Reject</td>
<td>Cereal</td>
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</table>
(c) Nature of the Clinical Question: Structuring parameter space

- What should we decide with an infinite sample size ($\theta$ is known)?
- Comments:
  - The question-marks on the above decisions can be a result of:
    - The clinical "importance" of a difference, which is difficult to quantify.
    - Nature of the primary endpoint (e.g., linear growth is a surrogate for behavioral development and disease morbidity).
    - Need to consider the effects on secondary endpoints.
    - Potential for long-term effects that could not be measured in this trial.
- Bottom line:
  - There are grey-areas in parameter space.
  - These will affect the design (e.g., non-inferiority trials).
- Remark: A question that cannot be answered with an infinite amount of data cannot be answered with a finite amount of data.
(c) Nature of the Clinical Question:
Structuring parameter space

- What should we decide with a finite sample size ($\theta$ is estimated with uncertainty)?

Potential trial results (confidence intervals)

- No Difference $\theta_{null}$
- Clinical Inferiority $\theta < \theta_-$
- Clinical Superiority $\theta > \theta_+$
- Clinically Important Harm
- Clinically Important Benefit

<table>
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<th>No Difference $\theta_{null}$</th>
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<tbody>
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<td>Inferiority $\theta &lt; \theta_-$</td>
<td>Clinical Superiority $\theta &gt; \theta_+$</td>
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<tr>
<td>Potential trial results (confidence intervals)</td>
<td></td>
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</tbody>
</table>

Date: 9 Sep 2015
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1.3 Case study: Rocket-AF
   - (c) Nature of the clinical question
     - (d) 1-sided vs 2-sided questions
(c) Nature of the Clinical Question: Structuring parameter space

What should we decide with an infinite sample size ($\theta$ is estimated with uncertainty)?

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<td>Cereal</td>
</tr>
<tr>
<td>H</td>
<td>Reject</td>
<td>Reject</td>
<td>Cereal</td>
</tr>
</tbody>
</table>
(c) Nature of the Clinical Question: Types of Decisions

- Superiority/non-superiority studies
  - Application: Evaluating new therapies to determine if they increase benefits.
  - Defining Hypotheses:
    - Inferiority: $\theta \leq \theta_0$
      (Decide for superiority if inferiority is rejected)
    - Clinical Superiority: $\theta \geq \theta_+$
      (Decide against superiority if clinical superiority is rejected)
  - Example: Comparison of Iloprost to placebo for cancer prevention:
    - (Defining $\theta = \theta_0 / \theta_1$)
      Inferiority: $\theta \leq 1.0$
      Clinical superiority: $\theta \geq 2.0$
    - (Defining $\theta = \theta_1 / \theta_0$)
      Inferiority: $\theta \geq 1.0$
      Clinical superiority: $\theta \leq 0.5$
(c) Nature of the Clinical Question: Types of Decisions

- Non-inferiority/inferiority studies
  - **Applications:**
    - Evaluating new therapies to determine if they are non-inferior to existing therapy.
    - Evaluating existing therapies to determine if they are harmful.
  - **Defining Hypotheses:**
    - Clinical Inferiority: \( \theta \leq \theta \) (Decide for non-inferiority if clinical inferiority is rejected)
    - Superiority: \( \theta \geq \theta_0 \) (Decide against non-inferiority if superiority is rejected)
  - **Example:** MGC versus standard care for heart failure:
    - (Defining \( \theta = \theta_0/\theta_1 \))
      - Clinical Inferiority: \( \theta \leq 0.75 \)
      - Superiority: \( \theta \geq 1.0 \)
    - (Defining \( \theta = \theta_1/\theta_0 \))
      - Clinical Inferiority: \( \theta \geq 1.33 \)
      - Superiority: \( \theta \leq 1.0 \)
(c) Nature of the Clinical Question: Types of Decisions

▶ Equivalence studies
  ▶ Application:
    ▶ Evaluating therapies to determine if they can be used interchangeably.
    ▶ (If not, then to select the best therapy.)
  ▶ Defining Hypotheses:
    ▶ Clinical inferiority ($\theta \leq \theta_-$)
    ▶ Clinical superiority ($\theta \geq \theta_+$)
    ▶ Equality ($\theta = \theta_0$)
  ▶ Decisions
    Decide equivalence if reject both clinical inferiority and superiority.
    Decide treatment A better than B if reject inferiority (of A).
    Decide treatment B better than A if reject superiority (of A).

▶ Example: CCF: Meat versus cereal (unfortified):
  ▶ (Recall: $\theta_{MC} = \theta_M - \theta_C$)
    Clinical Inferiority (of meat): $\theta_{MC} \leq -0.055 \text{ cm/mo}$
    Clinical Superiority (of meat): $\theta_{MC} \geq 0.055 \text{ cm/mo}$
    Equality: $\theta_{MC} = 0$
(d) One- versus two-sided questions

The nature of study questions fall into two categories

1. One-sided questions:
   - Superiority/non-superiority questions:
     \[ H_0 : \theta \leq \theta_0 \]
     \[ H_+ : \theta \geq \theta_+ \]
   - Inferiority/non-inferiority (or approximate equivalence) questions:
     \[ H_0 : \theta \geq \theta_0 \]
     \[ H_- : \theta \leq \theta_- \]

2. Two-sided questions:
   - Equivalence (bioequivalence) questions:
     \[ H_+ : \theta \geq \theta_+ \]
     \[ H_0 : \theta = \theta_0 \]
     \[ H_- : \theta \leq \theta_- \]

(Notice that equivalence questions are simultaneously asking a superiority and an inferiority question.)
1. Setting and Objectives

1.1 The study population
   (a) Treatment indication
   (b) Inference upon completion

1.2 The study question
   (a) What is the treatment?
   (b) Phase I-IV trials
   (c) Nature of the clinical question
   (d) 1-sided vs 2-sided questions

1.3 Case study: Rocket-AF