Bios 6649: Clinical Trials - Statistical Design and Monitoring

1. Scientific setting

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
1.2 The Study Question

Outline section 1.2:

(a) What is the treatment? Defining a treatment indication.
(b) Phase I-IV clinical trials
(c) Nature of the clinical question
(d) 1- versus 2-sided questions
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

- All of the above elements can be viewed as the elements of an “indication"
(a) What is the treatment?

Specifying the Treatment Indication

- New therapies are approved for a particular indication.
  - Most often this is viewed as a class of conditions (diseases) and a type of patient.
- The treatment indication should really be viewed as the formal definition of the treatment. As such it should include:
  - A disease
  - A population of patients
  - The treatment
  - The desired outcome
(a) What is the treatment?

Specifying the Treatment Indication

- **Disease:**
  - Diseases can be defined by symptoms (COPD), causal agents (meningococcal meningitis), or treatment (MDR tuberculosis).
  - The definition of a disease often changes with factors unrelated to the disease (e.g., new treatments or a new categorization of symptoms).

- **Population of patients:**
  - The target patient population is similarly dynamic.
  - Example: better diagnostic tools may detect cancer at earlier stages or make it easier to detect later-stage disease.
(a) What is the treatment?

**Specifying the Treatment Indication**

- **Treatment:**
  - The way in which a treatment is delivered may change.
  - New formulations may allow oral instead of IV delivery, which might extend the use to other populations or other forms of the disease.
  - Ancillary treatments (standard of care) is always changing.

- **Desired outcome**
  - Primary clinical outcomes versus surrogate outcomes (Vioxx; mammography; colon cancer screening)
  - Unanticipated or anticipated beneficial (sildenafil citrate) or harmful (rosiglitazone) effects.
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.

- Piantadosi terminology (nonstandard but thoughtful):

<table>
<thead>
<tr>
<th>Developmental Stage</th>
<th>Terminology</th>
<th>Descriptive Terminology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>None</td>
<td>Translational</td>
</tr>
<tr>
<td></td>
<td>Phase I</td>
<td>Treatment mechanism, TM</td>
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<tr>
<td></td>
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<td>Dose-finding, DF</td>
</tr>
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<td>Dose-ranging</td>
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<tr>
<td>Middle</td>
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<td>Comparative, CTE</td>
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<td></td>
<td>Phase IIb</td>
<td></td>
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<td></td>
<td>Phase III</td>
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<td>Phase IV</td>
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<td></td>
<td>Large simple</td>
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<td>Late</td>
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</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.
(b) Phase I-IV clinical trials

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### 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.
(b) Phase I-IV clinical trials

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

Phase III: Full-scale efficacy trial

- **Goal:**
  - Evaluate clinical efficacy.
  - Confirm suitably low toxicity.

- **Methods:**
  - Study population closely reflects target population.
  - Concurrent (randomized) control group.
  - Primary outcome: clinical efficacy.
  - Sufficiently large to answer the clinical/scientific question.

- **Common applications:**
  - Establish efficacy of new treatment; i.e.,:
    Superiority over no treatment.
    Superiority over an existing treatment.
  - Establish equivalence with current treatment; i.e.,:
    Two-sided equivalence: bioequivalence.
    One-sided equivalence: non-inferiority
    (perhaps superior on a secondary endpoint).
  - Establish harm of existing treatment.
(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 $mg/m^2$
  - Dose limiting toxicity: Diarrhea
  - Pharmacokinetic profiles
Irinotecan example (con’t):

**Phase II:**
**Reference:** Phase II study of irinotecan combined with cisplatin in patients with previously untreated small-cell lung cancer (J. Clinical Oncology 1998 16:1068-1074).

**Study Design:** 75 patients all receive the same treatment. Dose reduced to $80 \text{mg/m}^2$.

**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
## Summary of published trials

<table>
<thead>
<tr>
<th>Phase</th>
<th>Journal</th>
<th>Year</th>
<th>Design</th>
<th>Primary explanatory</th>
<th>Covariate</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Br. J. Cancer</td>
<td>1993</td>
<td>Dose escalation (14 patients)</td>
<td>Dose level</td>
<td>None</td>
<td>Grade 3-4 toxicities (leukopenia, diarrhea)</td>
</tr>
<tr>
<td>II</td>
<td>J. Clinical Oncology</td>
<td>1998</td>
<td>Single arm (75 patients)</td>
<td>Extended vs local disease</td>
<td>None</td>
<td>Tumor response; grade 3-4 toxicities.</td>
</tr>
<tr>
<td>III</td>
<td>NEJM</td>
<td>2002</td>
<td>Randomized controlled trial (154 patients)</td>
<td>Treatment group</td>
<td>None</td>
<td>Survival</td>
</tr>
</tbody>
</table>
## 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</td>
<td>Efficacy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>bioactivity</td>
<td>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

<table>
<thead>
<tr>
<th>What would you do?</th>
</tr>
</thead>
<tbody>
<tr>
<td>▶ Pre-clinical studies:</td>
</tr>
<tr>
<td>▶ Phase I study:</td>
</tr>
<tr>
<td>▶ Phase II study:</td>
</tr>
<tr>
<td>▶ Phase III study:</td>
</tr>
<tr>
<td>▶ Phase IV study:</td>
</tr>
</tbody>
</table>
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:**

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

Structuring parameter space

- Conceptually, the investigator team must divide parameter space into the following regions:

\[
\begin{align*}
\theta > \theta_0 & \implies \text{Benefit} \\
\theta > \theta_+ & \implies \text{Clinically important benefit} \\
\theta \leq \theta_0 & \implies \text{Harm} \\
\theta < \theta_- & \implies \text{Clinically important harm}
\end{align*}
\]
(c) Nature of the Clinical Question

Structuring parameter space

- Clinically Important Harm: \( \theta_- \)
- No Difference: \( \theta_{null} \)
- Clinically Important Benefit: \( \theta_+ \)

- Inferiority
- Superiority

- Clinical Inferiority: \( \theta < \theta_- \)
- Clinical Superiority: \( \theta > \theta_+ \)

1. Scientific setting
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
(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?
(c) Nature of the Clinical Question

Structuring parameter space

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.
(c) Nature of the Clinical Question

Structuring parameter space

**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.
(c) Nature of the Clinical Question

Structuring parameter space

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.
## (c) Nature of the Clinical Question

### Structuring parameter space

**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?
(c) Nature of the Clinical Question

Structuring parameter space

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)
  - $\theta_M = \text{Mean change in length with meat}$
  - $\theta_F = \text{Mean change in length with fortified cereal}$
  - $\theta_C = \text{Mean change in length with cereal (unfortified)}$
  - $\theta_{MF} = \theta_M - \theta_F$
  - $\theta_{MC} = \theta_M - \theta_C$
  (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)?

<table>
<thead>
<tr>
<th>Potential trial results (infinite sample size)</th>
<th>No Difference</th>
<th>Clinically Important Benefit</th>
<th>Clinically Important Harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>θ &lt; θ_ (Inferiority)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>θ = θ_ (No Difference)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>θ &gt; θ_ (Superiority)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Inferiority: $\theta < \theta_-$
- No Difference: $\theta = \theta_0$
- Superiority: $\theta > \theta_+$

- Cases A to H represent different outcomes and sample results.
### (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></td>
<td>Recommend</td>
</tr>
<tr>
<td>B</td>
<td></td>
<td>Recommend</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
<td>Recommend</td>
</tr>
<tr>
<td>D</td>
<td></td>
<td></td>
<td>Reject</td>
</tr>
<tr>
<td>E</td>
<td></td>
<td></td>
<td>Reject</td>
</tr>
<tr>
<td>F</td>
<td></td>
<td></td>
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<tr>
<td>G</td>
<td></td>
<td></td>
<td>Reject</td>
</tr>
<tr>
<td>H</td>
<td>Reject</td>
<td></td>
<td>Reject</td>
</tr>
</tbody>
</table>

Bios 6649: Clinical Trials

1. Scientific setting
   1.2 The study question
      (a) What is the treatment?
      (b) Phase I-IV trials
   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)?

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<th>CCF ($\theta_{MC}$)</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>Recommend</td>
<td>Recommend</td>
<td>Meat</td>
</tr>
<tr>
<td>B</td>
<td>Recommend</td>
<td>Recommend</td>
<td>Meat</td>
</tr>
<tr>
<td>C</td>
<td>Recommend?</td>
<td>Recommend</td>
<td>Meat/Cereal</td>
</tr>
<tr>
<td>D</td>
<td>Reject?</td>
<td>Recommend</td>
<td>Meat/Cereal</td>
</tr>
<tr>
<td>E</td>
<td>Reject</td>
<td>Reject?</td>
<td>Cereal/Meat</td>
</tr>
<tr>
<td>F</td>
<td>Reject</td>
<td>Reject</td>
<td>Cereal/Meat</td>
</tr>
<tr>
<td>G</td>
<td>Reject</td>
<td>Reject</td>
<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

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 ($\theta_{null}$)
- Clinically Important Benefit ($\theta_+$)
- Clinically Important Harm ($\theta_-$)
- Inferiority ($\theta < \theta_-$)
- Superiority ($\theta > \theta_+$)

A
B
C
D
E
F
G
H

Inferiority
Superiority

Potential trial results (confidence intervals)
(c) Nature of the Clinical Question

<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>Meat</td>
</tr>
<tr>
<td>B</td>
<td>Recommend</td>
<td>Recommend</td>
<td>Meat</td>
</tr>
<tr>
<td>C</td>
<td>Recommend?</td>
<td>Recommend</td>
<td>Meat/Cereal?</td>
</tr>
<tr>
<td>D</td>
<td>Reject</td>
<td>Recommend</td>
<td>Meat/Cereal</td>
</tr>
<tr>
<td>E</td>
<td>Reject</td>
<td>Reject?</td>
<td>Cereal/Meat</td>
</tr>
<tr>
<td>F</td>
<td>Reject</td>
<td>Reject</td>
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<tr>
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<td>H</td>
<td>Reject</td>
<td>Reject</td>
<td>Cereal</td>
</tr>
</tbody>
</table>

Structuring parameter space

- What should we decide with an infinite sample size ($\theta$ is estimated with uncertainty)?
(c) Nature of the Clinical Question

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

Structuring parameter space

- 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

Structuring parameter space

- 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: $\theta_{MC} = 0$
(c) Nature of the Clinical Question

Structuring parameter space

- 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.)
### 1.3 Case study (Rocket-AF trial)

#### Setting

**Disease:** Atrial fibrillation is an irregular (uncoordinated) beating of the upper chambers of the heart leading to:
- Poor circulation
- Pooling of blood in the upper chambers
- Increased risk of clot and stroke

**Causes:** Hypertension, previous heart attack, abnormal heart valve, congenital, (and others).

**Standard treatment:**
- Cardioversion (reset the rhythm) followed by drugs or further procedures.
- Prevent blood clots (warfarin or heparin).
  - Warfarin is a vitamin k antagonist; lack of vitamin k inhibits formation of many clotting factors.
  - Must carefully monitor warfarin to assure against bleeding.
  - Heparin (Enoxaparin) is injectable anti factor Xa agent.

**Novel oral anticoagulants for prevention of clots**
- NOAC’s:
  - Are convenient (oral).
  - Inhibit other parts of the coagulation chain.
  - Rivaroxaban is a new anti factor Xa agent.
1.3 Case study (Rocket-AF trial)

Clinical Development

- PubMed lists 1095 publications discussing rivaroxaban (Xarelto) since 2005
- These include publications regarding
  - Pre-clinical pharmacology, interactions with other drugs (e.g., aspirin)
  - Animal studies and studies in healthy volunteers (single-dose PK studies)
  - Phase I/II studies regarding dose and pharmacokinetics
  - An extensive (and ongoing) phase III program:
    - EINSTIEN: Treatment of symptomatic VTE and PE
    - RECORD1: Thromboprophylaxis in hip arthroplasty.
    - RECORD2 & RECORD3: Thromboprophylaxis in knee arthroplasty.
    - ROCKET-AF: VTE prevention and bleeding prevention in AF patients
1.3 Case study (Rocket-AF trial)

ROCKET-AF design overview

- Components of the indication:
  - **Patient population and disease**: Patients with nonvalvular atrial fibrillation
  - **Treatments**: 20 mg once daily, or 15 mg/day for patients with CrCl 15-50 mL/min.
  - **Anticipated outcome**: Reduce risk of stroke and systemic embolism.

- **Xarelto AF indication (per http://www.xareltohcp.com)**: XARELTO is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. There are limited data on the relative effectiveness of XARELTO and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well controlled.
1.3 Case study (Rocket-AF trial)

ROCKET-AF design: Study population

- Study population (pg 884 and pp 8-11 of appendix):
  - Eligibility:
    - Men or women $\geq$ 18 years with non-valvular AF
    - Moderate to high risk of stroke
    - Females must be postmenopausal, unable to have children, or assure adequate birth control.
  - Exclusions (major categories):
    - Cardiac-related conditions
    - Hemorrhage risk-related criteria
    - Concomitant conditions and therapies
    - Study participation and follow-up related criteria.

- Discussion: How is the target population likely to differ from the study population?
1.3 Case study (Rocket-AF trial)

ROCKET-AF design: Study treatments (paper pg 884, and protocol)

- Rivaroxaban:
  - 20 mg daily or 15 mg daily (if Cr clearance 30-49ml per min)
  - Plus placebo to match warfarin
- Warfarin
  - Dose to get targeted INR of 2.0 to 3.0
  - Placebo to match Rivaroxaban group.
- Notice sham dose-adjustment to maintain blinding:
  - Random dose titration increments with placebo as necessary.
  - Why is this necessary?
1.3 Case study (Rocket-AF trial)

ROCKET-AF design: Study outcomes (pg 885 and protocol)

- **Efficacy:**
  - Primary: Composite of stroke, and/or systemic embolism
  - Secondary:
    - Stroke, systemic embolism, or cardiovascular death.
    - Stroke, systemic embolism, cardiovascular death, or MI.
    - Individual components of the composites.

- **Safety:**
  - Principal: Major and non-major clinically-relevant bleeding events.

(Notice independent endpoint adjudication committee)
1.3 Case study (Rocket-AF trial)

ROCKET-AF design: Study outcomes (pg 885 and protocol)

- Outcome parameterization
  The outcome is not fully defined until we choose the parameter measuring the treatment effect in each treatment group (functional of the outcome distribution) and the contrast between groups that measures the difference between treatments.
  - Parameterization:
    * Functional:
      \( \theta_1 = \text{hazard of an event with Rivaroxaban} \);
      \( \theta_0 = \text{hazard of an event with Warfarin} \)
    * Contrast: \( \theta = \frac{\theta_1}{\theta_0} \)

- Notes on the analysis:
  - Intention-to-treat includes all randomized patients
  - Per-protocol analysis excludes patients who did not comply with treatment
  - A per-protocol analysis was pre-specified as the primary analysis because of the non-inferiority design:
    - A sloppy trial may bias the result toward the null (i.e., a false non-inferiority conclusion)
    - Both analyses are always reported
1.3 Case study (Rocket-AF trial)

ROCKET-AF design: Study outcomes (pg 885 and protocol)

- Structuring the outcome space:
  - Suppose $\theta = \frac{\theta_0}{\theta_1}$ (i.e., large values favor Rivaroxaban)
  - How should we structure the outcome space (c.f., section 1.2)?

![Diagram showing the structuring of the outcome space with different regions labeled for clinical important harm, no difference, and clinical important benefit.](image-url)
### 1.3 Case study (Rocket-AF trial)

#### ROCKET-AF design: Study outcomes (pg 885 and protocol)

- **Structuring the outcome space:**
  - Suppose $\theta = \frac{\theta_0}{\theta_1}$ (i.e., large values favor Rivaroxaban)
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