

## Biost 524: Design of Medical Studies

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### Lecture 1: Course Organization; Scientific Setting

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## Lecture Outline

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- Course Structure
- Perspective and Goals (MaFDA)
- Overview of Setting
  - Medical setting
  - Scientific setting

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## Course Overview

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## Course Structure

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- Instructors: Susanne May Ph.D. and Scott S. Emerson, M.D., Ph.D.
- TA: TBN
- Time and Place:
  - Lectures: 8:00 - 9:20 am MW HSB T625
- Class web pages
  - [www.emersonstatistics.com/b524/](http://www.emersonstatistics.com/b524/)

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## Assumed Prior Knowledge

- Scientific curiosity
- Statistical coursework
  - Introductory applied statistics
    - Biost 511 or 517
    - (Biost 512 or 518)

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## Textbooks

- Friedman LM, Furberg CD and DeMets DL: *Fundamentals of Clinical Trials*
- Ellenberg S, Fleming TR and DeMets DL: *Data Monitoring Committees: A Practical Perspective*
- Pocock SJ: *Clinical Trials: A Practical Approach*

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## Old Dogs, New Tricks

- Recording of Lectures: Camtasia
  - Audio and computer video on web
- No guarantees
  - “Mistakes happen”

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## Computer Software

- Minimal use of software
  - Possibly of use for sample size calculation and evaluation of study design
- Students may use any program that will do what is required, however
  - Scott will make available a package in R for those who want to use it

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## Grading

- .....
  - 10% Homeworks
    - Review of an article and answering questions
    - Written and / or in class
    - Other
  - 75% Group project
    - Design of a clinical trial
  - 15% Protocol review committee
    - Critique of another group's project

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## Class - Organization

- .....
  - Questions?

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## Perspective - Goals

- .....
  - MaFDA – volunteer for notes....
  - Setting:
    - Pretend that we have colonized Mars
    - You are part of the people on Mars
    - People on Mars want to establish their own FDA equivalent (MaFDA)
    - Three companies approach the MaFDA for approval
  - Your job:
    - Describe broad goals for MaFDA
    - Establish main guidelines / principles for MaFDA

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## Perspective - Goals

- .....
  - No prerequisites
  - Not a test
  - Big picture....

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## Perspective - Goals

- .....
- Three companies approach the MaFDA for approval
- Company 1
  - seeks approval for an anti-nausea drug for pregnant women
- Company 2
  - seeks approval for an antiarrhythmic for patients with out-of-hospital cardiac arrest to be used by prehospital providers
- Company 3
  - seeks approval for ???

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## Perspective - Goals

- .....
- Questions?

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## Topics

- .....
- Medical / scientific setting
- Design of clinical trials
  - Phases of investigation; types of studies
  - Specific aims; endpoints
  - Target population
    - Inclusion / exclusion criteria
  - Treatment
    - Intervention / comparison groups
  - Recruitment; informed consent
  - Retention; compliance
  - Protocol

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## Topics

- .....
- Conduct of clinical trials
  - Data collection / management
  - Monitoring: QA / QC, safety
- Analysis of clinical trials
  - Statistical analysis plan
  - Reporting results
- Ethical aspects

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## Overview

### Medical Setting

#### Where am I going?

- Ultimately, we perform clinical studies in order to address medical needs
- We thus want to be able to
  - classify the types of questions we answer in a clinical trial, and
  - understand the reasons one type of question might be more important / appropriate than another.

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## Overall Goal

- “Drug discovery”
  - More generally
    - a therapy or preventive strategy
      - drug, biologic, device, behavior
    - for some disease
    - in some population of patients
- Medical diagnosis / prognosis
  - Evaluation of methods

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## Typical Chronology

- Observational epidemiology of disease, risk
- Preclinical experiments
  - Laboratory, animal studies of mechanisms, toxicology
- Clinical trials
  - Safety for further investigations / dose
  - Safety of therapy
  - Measures of efficacy
  - Confirmation of efficacy / effectiveness
- Synthesis and quantification of evidence
- Adoption of new treatment indication

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## The Enemy

- “Let’s start at the very beginning, a very good place to start...”

- Maria von Trapp

(as quoted by Rodgers and Hammerstein)

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## First Consideration

- Where do we want to be?
  - Find a new treatment that improves health of individuals
    - “Personalized medicine”
      - “Person” as fixed effects
      - “Person” as random effects
  - Find a new treatment that improves health of the population
    - Treatments administered to a community
    - Treatments tested on a population

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## Treatment “Indication”

- Disease
  - Putative cause vs signs / symptoms
    - May involve method of diagnosis, response to therapies
- Population
  - Restrict by risk of AEs or actual prior experience
- Treatment or treatment strategy
  - Formulation, administration, dose, frequency, duration, ancillary therapies
- Outcome
  - Clinical vs surrogate; timeframe; measurement

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## Disease

- A moving target heavily influenced by treatment
  - Then: “fevers”
  - Now: “MRSA-related pneumonia”
- Trends over place and time in definition because
  - Symptoms
    - Cultural / geographic effects, earlier recognition, symptomatic treatments, comorbidities
  - Signs
    - New diagnostic modalities, other prevention strategies (e.g., TB vaccine) and treatments
  - Unmet need
    - Effective treatment already discovered for subset

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## Definition of Disease

- Specify the disease targeted by the therapy
  - Scientifically
    - Putative cause of constellation of symptoms
    - Symptoms / signs from multiple causes
  - Clinically
    - Diagnostic criteria
      - Incident vs prevalent
      - Symptoms
        - » Intensity, frequency, duration, response to treatment
      - Signs
        - » Method of measurement
        - » Magnitude, reproducibility
    - Prior treatment history

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## Population

- Treatment indications may be restricted to a specific population
  - Demographics: age, sex
  - Genetics: drug metabolism
  - Comorbid conditions
    - Drug metabolism: renal, liver disease
    - Drug side effects: cardiovascular disease, bleeding
  - Prior treatment history: resistance to alternatives
  - Vulnerable populations
    - Pediatrics, pregnancy

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## Definition of Treatments

- Full description
  - Formulation of treatment
  - Dose, administration, frequency, duration
  - Rules for responsive dosing (e.g., insulin)
- Include plans for
  - Treatment of adverse events
  - Dose reduction
  - Dose discontinuation
- Ancillary treatments
  - Prescribed vs allowed vs prohibited

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## Outcomes

- The desired beneficial response from the treatment
  - Clinical outcomes
    - Prolonged survival
    - Quality of life
  - Surrogate outcomes
    - Improvement in some risk factor believed to be predictive of a good clinical outcome
- Definition
  - Method of measurement
  - Timeframe

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## Diagnostic Test “Indication”

- Disease
  - Putative cause vs eventual outcomes
- Population
  - Identify risk factors (prevalence)
  - Eliminate known false positives, false negatives
- Test or testing strategy
  - Formulation, administration, method of measurement
- Outcome
  - Sensitivity, specificity
  - Predictive value of positive, negative

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## Prognostic Test “Indication”

- .....
- Disease
  - Clinical diagnosis
- Population
  - Identify risk factors (prevalence)
  - Eliminate known false positives, false negatives
- Test or testing strategy
  - Formulation, administration, method of measurement
- Outcome: Clinical event or survival
  - Sensitivity, specificity
  - Predictive value of positive, negative

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## Clinical Decision for Diagnosis

- .....
- What test provides the best information for a patient
  - Based on what we know about the patient?
  - Based on what we know about the test?

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## Clinical Decision for Treatment

- .....
- What is the best treatment to give a patient
  - Based on what we know about the patient?
  - Based on what we know about the treatment?

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## Second Consideration

- .....
- Synthesize and evaluate evidence for a therapy
  - Analysis and interpretation of clinical studies
- Evidence Based Medicine (PICO)
  - Patient population
    - Disease and population characteristics
  - Intervention
    - Precise description of treatment strategy
  - Comparator
    - Alternatives in the absence of the new treatment
  - Outcome
    - Both beneficial and adverse

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