These notes are copies of the overhead transparencies and material worked on the board in lectures, and are intended as a guide to this course.
1. handout today

- Computing Practical 2.
  - Randomizing, generating randomization lists,
  - R scripts, functions

Last time: showed patient effects average out under randomization.
In summary: randomization

- protects against confounding variables and avoids bias (inc. selection bias)
- provides basis for formal inference
- facilitates blinding
- use of control group

See handout ‘Why randomize’ for reasons against non-random assignment
  e.g. systematic allocation
  e.g. historical controls
systematic allocation:

e.g. odd birthday → A
     even "     → B

Invites selection bias.

Historical controls:

e.g. current patients get treatment
     use pre-trial patients as control

Problems? Don't know that any differences observed are due to treatments.
Chapter 2: Clinical trials

Key references:
See 'Notes for students' Encyclopedia article Chandol

2.1 Phases of trials

Within the pharmaceutical industry, clinical trials are classified as

Phase I: exploratory, concerned with clinical pharmacology and toxicity.
20-80 healthy volunteers.

Phase II: pilot studies, initial clinical investigation.
100-300 diseased patients. Concern efficacy & safety.
Phase III: definitive, full-scale evaluation of new treatment. Patients randomized to tr. or current standard (or placebo). Often > 1000 patients. Often last 3 - 5 years, or longer.

Phase IV: further testing and monitoring of experience with new treatment after it has been approved for general use. Referred to as ‘post-marketing surveillance.’
Notes:

Categories not strict: purpose of a trial can overlap boundaries, esp. II and III.

Terminology now used more widely, esp. disease prevention trials.

Ethical debate: when to randomize, and for how long. Practical approach: start early, continue as long as uncertainty exists.
2.2 Key aspects of design

"Design" encompasses all structural aspects of the trial.

- Study population (eligible patients)
- Treatments to be evaluated
- Choice of control group
- Sample size (how many patients?) based on power
- Method of randomization
- Procedures for blinding
- Type of trial
  - Parallel group
  - Crossover
  - Equivalence
  - Sequential

\( \begin{align*}
  p_1: & \ A \to B \\
  p_2: & \ B \to A
\end{align*} \)
- outcome measures
  - disease incidence
  - death rate
  - survival time
  - symptom alleviation
  - ...

A trial will have
  - operations manual
  - study protocol.

The Data Safety Monitoring Board plays a key role.

See Piantodosi (199...