1.4 Some Important Study Designs in Medical Research

I. **OBSERVATIONAL** (no intervention)

A. **LONGITUDINAL** (over some period of time)

1. Retrospective (backward-looking)

   ➢ **Case-Control Study**: Identifies present disease with past exposure to risk factors.

   
   "PAST" \hspace{1cm} "TIME" \hspace{1cm} "PRESENT"

   Investigate: Association with $E^+$ and $E^-$  
   Given: Cases ($D^+$) and Controls ($D^-$)

2. Prospective (forward-looking)

   ➢ **Cohort Study**: Classically, follows a cohort of subjects forward in time.

   "PRESENT" \hspace{1cm} "TIME" \hspace{1cm} "FUTURE"

   Given: Exposed ($E^+$) and Unexposed ($E^-$)  
   Investigate: Association with $D^+$ and $D^-$

   Example: Framingham Heart Study to identify CVD risk factors, ongoing since 1948.

B. **CROSS-SECTIONAL** (at some fixed time)

   ➢ **Survey**: Acquires self-reported information from a group of participants.

   ➢ **Prevalence Study**: Determines the proportion of a specific disease in a given population.

II. **EXPERIMENTAL** (intervention)

   ➢ **Randomized Clinical Trial (RCT)**: Randomly assigns patients to either a treatment group (e.g., new drug) or control group (e.g., standard drug or placebo), and follows each through time.
Phases of a Clinical Trial

- *In vitro* biochemical and pharmacological research, including any computer simulations.

- Pre-clinical testing of *in vivo* animal models to determine safety and potential to fight a specific disease. Typically takes 3-4 years. Successful pass rate is only $\approx 0.01\%$, i.e., one in a thousand compounds.

- **PHASE I.** First stage of human testing, contingent upon FDA approval, including protocol evaluation by an International Review Board (IRB) ethics committee. Determines safety and side effects as dosage is incrementally increased to “maximum tolerated dose” (MTD) that can be administered without serious toxicity. Typically involves very few ($\approx 12$, but sometimes more) healthy volunteers, lasting several months to a year. Phase I pass rate is approximately 70%.

- **PHASE II.** Determines possible effectiveness of treatment. Typically involves several ($\approx 14-30$, but sometimes more) afflicted patients who have either received previous treatment, or are untreated otherwise. Lasts from several months to two years. Only approximately 30% of all experimental drugs tested successfully pass both Phases I and II.

- **PHASE III.** Classical randomized clinical trial (although most Phase II are randomized as well) that compares patients randomly assigned to a new treatment versus those treated with a control (standard treatment or placebo). Large-scale experiment involving several hundred to several thousand patients, lasting several years. Seventy to 90 percent of drugs that enter Phase III studies successfully complete testing. FDA review and approval for public marketing can take from six months to two years.

- **PHASE IV.** Post-marketing monitoring. Randomized controlled studies often designed with several objectives: 1) to evaluate long term safety, efficacy and quality of life after the treatment is licensed or in common use, 2) to investigate special patient populations not previously studied (e.g., pediatric or geriatric), 3) to determine the cost-effectiveness of a drug therapy relative to other traditional and new therapies.

Total time from lab development to marketing: 10-15 years