Clinical Trial

A Clinical Trial is a type of study used to determine the safety and efficacy of an intervention, which is a change from already existing treatment. The object of study is usually a drug or a surgery. This course focuses on drugs.

The ideal clinical trial is randomized, double-blind (neither patient nor administrator of treatment knows which is treatment and which is control), and controlled (there is a "baseline" group receiving known treatment or placebo to compare to)

Phase I

1st human trial of a new drug, idea to determine the MTD (maximum tolerated dosage)

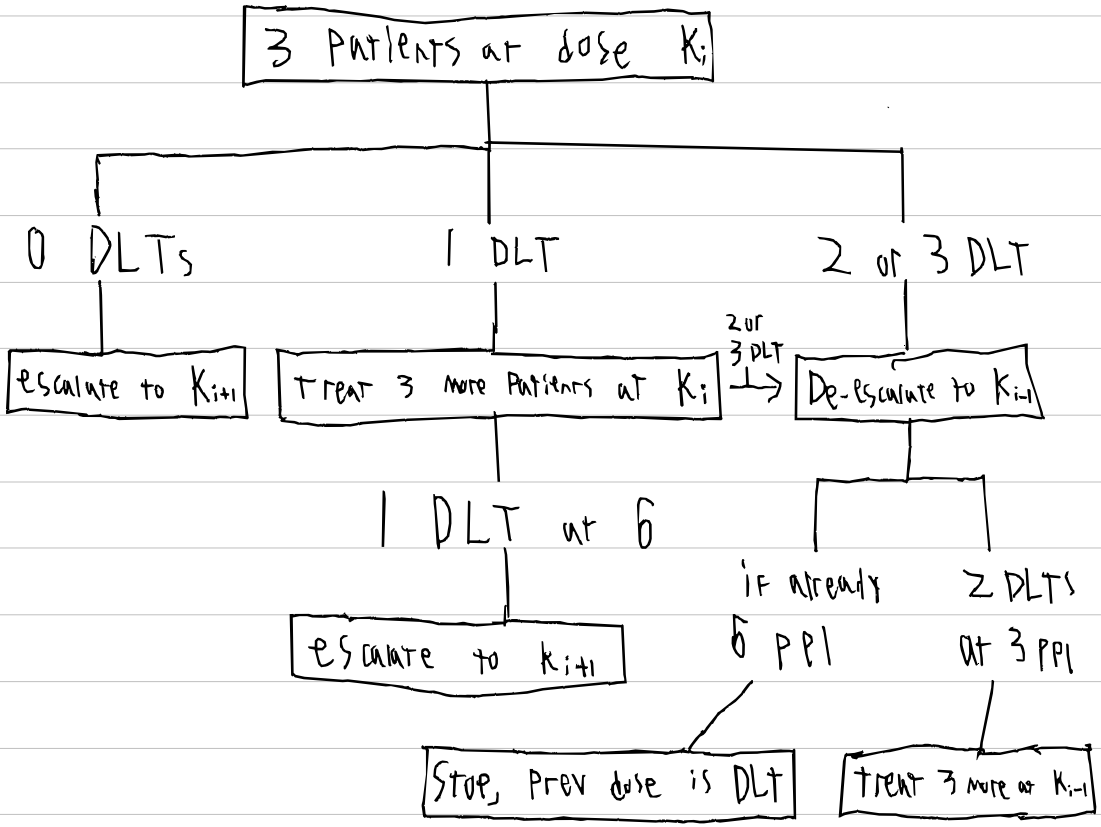
Adaptive designs, two common types of Phase I designs are "3+3" aka "up and down" and "CRM" (continual reassessment method)

Response (ie. person has toxic response) referred to as "DLT" event, Dose Limiting Toxicity

No randomization in Phase I

3 + 3 Design

Choose a fixed # of doses, 6 patients, start 3 subjects at lowest dosage, then follow chart e.g. $K_i \in$ 50mg, 100mg, ..., 1000mg, start from lowest K_i, K_1



Poor estimate of MTD

Better for "dose ranging" than dose finding

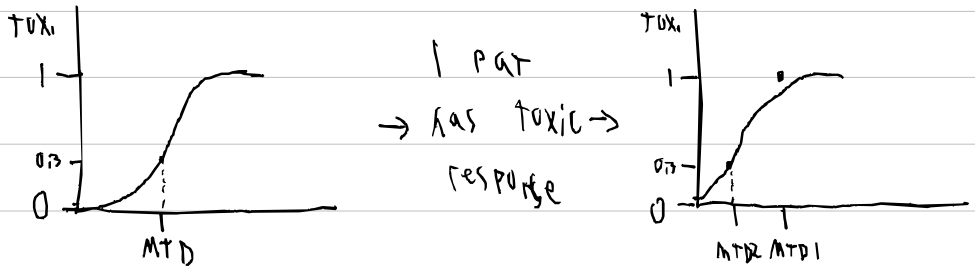
CRM

Continual reassessment method (CRM)

Assume stat. model of dose response relationship

Monotone (↑ dose ↑ prob toxic), start 1 patient on dose at estimated MTD

Update dose-response curve w/ Bayesian methods, use new curve to trx dose at new est. MTD



Can specify MTD, e.g. 0.3, 0.25, etc.

Sometimes CRM is adjusted to be more like 3+3

- Pre-define dosage levels
- Start at lowest dose instead of MTD
- Enroll 2-3 subj instead of 1 at a time
- These changes sacrifice efficiency for practical, safety reasons

Phase II

Build on the results of Phase I

Optimize dosage within safe range, determine interactions between drugs, evaluate drug efficacy, long-term safety

Enroll 30-200 subjects

1-12 month follow up, explore several dosages, perform in target population

Often called "Safety & Efficacy" Study

Outcomes measured in short term response, used to predict long-term response

Measure Biomarkers, want shorter Phase # at lower cost

Phase II Designs

Types of designs:
- Two Stage design
- Selection trials
- Randomized, Multiple (fixed) dosages
- Adaptive designs

Design should be tailored to goal of the study

Two Stage Designs: Treatment first given to a small number of subjects, if a small number of responses ($\leq r_1$) is seen, further consideration of the treatment is abandoned. Otherwise, more subjects enrolled.

If total # of responses in Stage I and II, r, is large enough the treatment is considered for further study. r depends on π_0 and π_1, the "acceptable" probabilities of response

Phase II Continued

Choice of r_1 and r also depends on α and β

α: probability of deciding to go further when true response rate is $< \pi_0$

β: probability of rejecting treatment when true response rate is $> \pi_1$

Another Design: Parallel groups

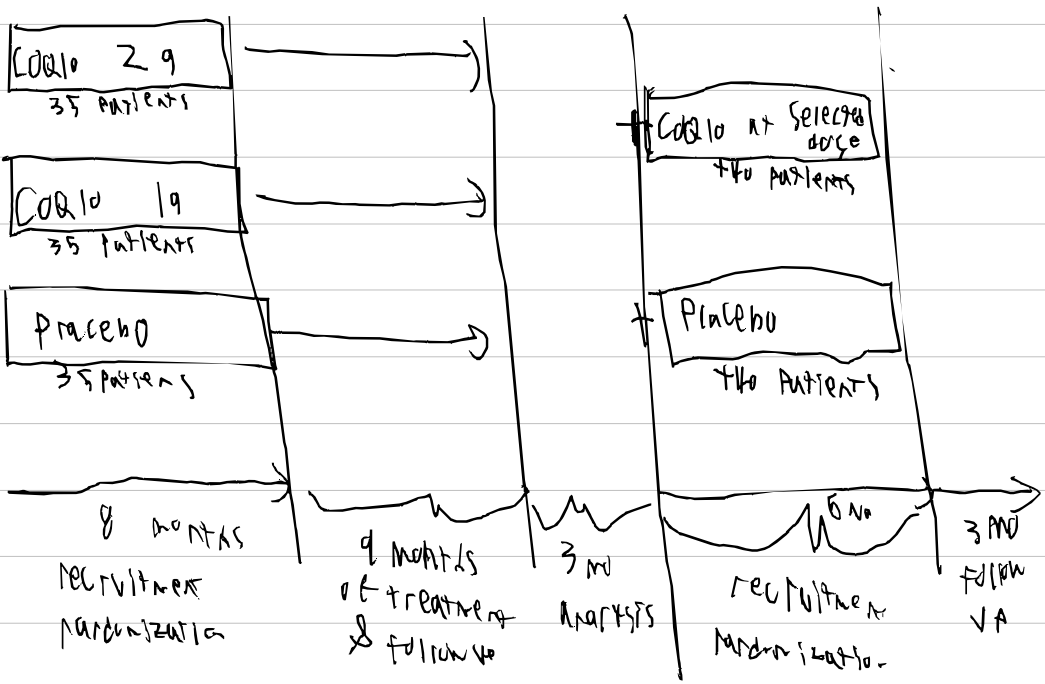
Phase II designs sometimes feature multiple dosages to determine optimum dose. Sometimes $\alpha = 0.1$ or $\alpha = 0.2$ is used, willing to accept higher FPR since confirmation required in phase III

Power should still be high (say 0.8), we don't want to abandon a working drug!

Selection

Phase II is also sometimes called a "selection trial", out of K potential treatments we want to find the one with the best response

Example Design ALS:



Total duration: 42 months

Phase III

If Phase II demonstrates the treatment is safe and may be effective, we move on to Phase III

Primary goal is to compare the efficacy of the new treatments with that of existing treatments / placebo

"Comparative treatment Efficiency" (CTE) is another name for a Phase III

Long term follow up, many patients

Explanatory & pragmatic Aims

Explanatory: Theoretical explanation for mechanism

Pragmatic: Create recommendations for clinicians

Phase IV

Long-Term Safety follow up Studies

- Phase IV often called "Extended Safety" studies (ES)
- Often difficult to attribute adverse events to treatment
- "Denominator" usually unknown (at-risk group)

Often, these types of trials are designed to achieve marketing objectives

Example: New indications to protect patents

Distinction among "phases" is often blurred, Adaptive Phase II/III designs becoming common

FDA recommends I, II, III structure in many diseases
ICH Guidelines (International conference on Harmonization)
Regulatory agencies of US., Europe, and Japan

Adaptive Designs

Development process, from drug synthesis to marketing, can take 10+ years

Methodological research & usage of adaptive designs is growing in Industry, Academia, and Government

Need for greater efficiency, e.g. Preventing low success rates in phase III studies (< 50% fail in phase III)

Traditional paradigm led to correct but inefficient inference, e.g. Adaptive dose finding finds the optimal dose way more often than 3+3

Accumulating data can be used to modify trial according to pre-specified Adaptive design plan

Adaptive Design

Important Considerations:

- Validity: Control type I and type II error
  Minimize bias

- Integrity: "Blind" interim analysis
  results (can't "adapt" in favor of
  what we want to happen)

Unplanned Adaptations are NOT adaptive design

Should only be made based on info external to the study

Adaptive Examples: Dose finding
Dropping/Adding Arms
Early stopping rules
Sample-size re-estimation
(Beck says always do this)

Adaptive Designs

possible Adaptations of the Adaptive design:

Hypothesis / Objective
e.g. Non-inferiority vs Superiority

Primary outcome variable
Variable, timing
Eligibility Criteria

Biomarker-related Adaptations

"Seamless" Phase II → III designs:
Phase II Patients started at eventual Phase III dosage are "carried through" and their data is used in Phase III data

Adaptive design Concerns: Control type I, Bias, Interpretation, Logistical Issues, Procedural Issues

Clinical Trials in Drug Dev

Dose finding in ordinary phase I: randomize to a few fixed dosages & placebo

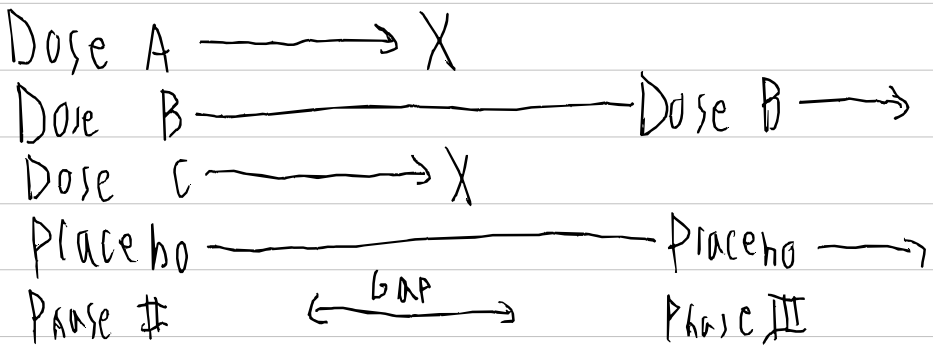
The disadvantage to this is there is a large "distance" between dosages, optimal dose may not be tried, motivates adaptive design

D- Optimal response adaptive design:
- Rich family of models for dose-response relationship chosen
- Randomize first cohort to several active dosages and placebo
- Estimate model parameters and dose response curve
- Maximize amount of info about dose-response curve by assignment of next cohort
- Penalty for assigning people to toxic dosages

Example: E max model

Phase II/III

The phase II/III seamless design diagrammed



Longer follow up time for "seamless" patients

Problem: for sponsors to pay for it, it's often risky because you don't get to see "how well" your treatment is doing before moving to phase III, you've already invested the resources for designing phase III before starting phase II.
A lot of planning & simulation study required.
Not taking advantage of availability of outcomes in short term relative to length of trial.
Time to event data best for adaptive design here, have "complete response" for all patients who have an event, use to adapt

Procedural Issues

- Need an unbiased party to review data and implement adaptations
- Must have personal expertise
- Need to create pre-specified decision plan

- Operational bias: Need adequate "firewall" between project personnel

Good Practices for Adaptive Clin. Trials

Adaptive	Non-Adaptive
Enroll 200 patients	$N=400$, $\alpha=0.05$, Power = 80%
if treat effect $\begin{cases} <0 & \text{stop study} \\ 0<<5 & \text{add 200 pts} \\ >5 & \text{add 100 pts} \end{cases}$	

In simulations, be sure to account for random patient drop out

Sometimes also account for contamination (meas. error)

Study Protocol

- Specifies the research plan of the trial before subject enrollment
- Deviations likely, protocol should require only those things that are essential for the scientific and ethical integrity of the study
- Should remain unchanged for minor problems
- Often accompanied by more detailed Operations Manual
- Periodic meeting of trial participants needed to promote strict adherence to protocol