

2.1 Phase I clinical trials (from Dr. Marie Davidian)

Broad definition: Phase I trials are the first studies in which a new drug is administered to human subjects.

- Previous studies in the laboratory (in vitro)
- Previous studies in animals, e.g. rats, dogs (in vivo)

Objectives: Before efficacy (activity of a drug on disease) of the drug may be established, first must

- Determine a “safe,” “tolerable” dose (through dose-escalation)
- Develop an appropriate schedule of administration
- Gain understanding of the *pharmacology* of the drug
- Need to examine interaction effects (drug-drug, drug-food, drug-alcohol) for safety profile and proper labeling.

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In addition: Do this in a timely manner, using a small number of subjects.

Features:

- Most are not comparative but rather are “informational”
- “Interaction studies” are comparative, but not aimed for efficacy, still “informational” (for safety).

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Types of studies:

- “Dose-finding” studies – determine the maximum dosage that can be given without serious “problems” – these studies are often themselves called “phase I studies” (especially for cancer studies)
- Clinical pharmacology studies – determine the *pharmacokinetics* of the drug to aid in setting dosage schedules, understanding how “problems” are related to amount of drug present
- Drug-drug interaction studies – determine how other commonly used drugs affect important *PK* parameters, using a cross-over or parallel design
- Drug-food interaction studies – determine how food affects important *PK* parameters, using a cross-over or parallel design
- Alcohol/benzo interaction studies – determine how alcohol/benzo affects *PD* parameters, using a cross-over or parallel design

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Pre-clinical Studies

Before administration to humans:

- *In vitro* studies – laboratory investigations using biological material but not actual organisms; look for biologic activity of the drug
- Dose-finding studies in rodents, large animal species (e.g. dogs)
- Pharmacology studies in rodents, dogs, etc
- Goal – “scale up” previous results to provide first idea of behavior in humans
- Advantage – Ethical issues involved in human experimentation circumvented (coming up)

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Phase I Dose-finding Studies

Paradox: Although results of "dose-finding" will be carried forward to be used in studies of efficacy (phase II) and later to comparative trials (phase III) and eventually to routine patient care

- Standard approaches to design and analysis have little statistical justification
- Many texts on clinical trials devote little or no discussion to dose-finding (or pharmacology) studies, e.g. Freedman et al. mention only on p. 3–4!

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Characterization: Often done on a standard, "graded" scale (especially for cancer research)

- Ordered categories increasing in severity – Grades I – IV or V
- Examples:

Abdominal	Mild	Moderate	Moderate	Severe	
Pain	(No trt)	(Trt)	(Hospital)		
Creatinine	60–75	50–59	35–49	> 35	
Clearance					(cc/min/1.73 m ²)
	I	II	III	IV	

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Toxicity: "Problems" that may arise in direct response to administration of the drug – side effects

- Nature depends on the drug
- E.g. change in organ function – a drug to treat cancer may induce irregular heartbeat
- May be life-threatening and irreversible
- May be life-threatening and reversible
- May be non-life-threatening

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Defining toxicity:

- Which toxicities are relevant depends on intervention, nature of likely subjects, clinical judgment – must be defined by the investigators
- What degree of toxicity is "acceptable" must be established

Terminology: *Dose Limiting Toxicity* (DLT)

- Serious or life-threatening but reversible

- Often used as the definition for dose-finding in cancer research

Assumption: Maximum benefit occurs at maximum doses

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Main objective: Determine the *Maximum Tolerated Dose* (MTD)

- The "highest possible while still tolerable" dose involves some level of toxicity we are willing to tolerate because of the drug's potential benefit
- E.g. "the dose that produces toxicity of grade III or worse in not more than one out of three patients" (often used for anticancer agents)
- **Statistically speaking:** Determine the dose at which the proportion of subjects in the population who would develop toxicity if given this dose is $1/3$
- I.e. the 33rd percentile of the distribution of toxicity in the population

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Subjects: Nature of subjects used depends on drug

- Healthy volunteers – used where toxicities unlikely to be severe, e.g. topical agents
- Patients with advanced disease – used where subjects have failed other therapies, toxicities likely. e.g. chemotherapy

Goal: Establish appropriate dose quickly while exposing as few subjects as possible to suboptimal doses that are likely not to be efficacious

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Ideal design:

- Select doses D_1, \dots, D_k for study such that one of these is (close to) the MTD
- Randomize subjects to each dose, n_i subjects at dose i
- Observe number r_i exhibiting DLT at each dose, and calculate proportions exhibiting DLT $p_i = r_i/n_i$
- Model dose-response (probability of toxicity) and fit to observed proportions at each dose
- Estimate MTD from fitted model

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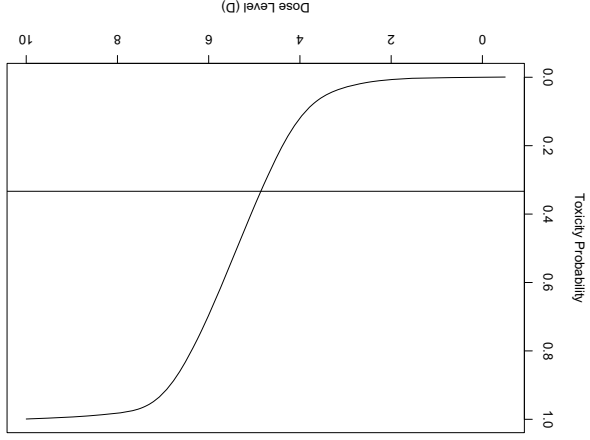


Illustration of MTD: a hypothetical example

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Models for dose-response:

- $Y = 1$ if toxicity observed for a subject at dose d
- $P(Y = 1|d) = f(d, \beta)$, f monotone in dose
- Dose d_0 associated with specified probability $p_0 = P(Y = 1|d_0)$ is $d_0 = f^{-1}(p_0, \beta)$
- E.g. If MTD is defined as dose where toxicity is 33%, $MTD = f^{-1}(0.33, \beta)$
- Estimate β from data and use to estimate MTD, i.e. $\widehat{MTD} = f^{-1}(0.33, \hat{\beta})$
- More generally
 - * May estimate dose associated with any probability
 - * May estimate probability associated with any fixed dose
- Standard approach for animal experiments

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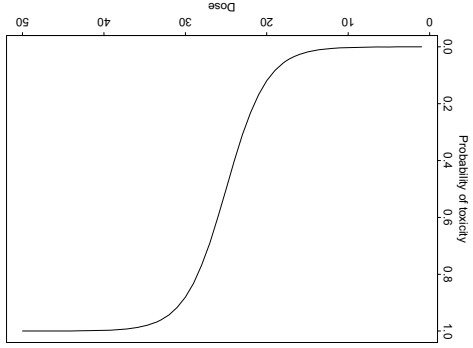
Problem: This approach not feasible in human subjects due to *ethical considerations*

- Because drug not previously used in humans, must test at lower doses first before feeling confident enough to move to higher doses
- Do not want to treat many subjects at dose that is too low to do good or too high (toxic)
- Result: cannot simply randomize subjects to different dose levels

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Logistic model:

$$P(Y = 1|d) = \frac{\exp(\beta_0 + \beta_1 d)}{\exp(\beta_0 + \beta_1 d) + 1}, \quad \beta = (\beta_0, \beta_1) = (-10, 0.4)$$



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Approach: "Adaptive" designs – *dose escalation*

- Try a dose in several subjects
 - If no toxicities, try a higher dose in several (new) subjects
 - Continue until dose is found that yields toxicity
 - Sometimes, may "de-escalate" from a dose that is not tolerated
 - Many variations on this idea
- Result:** Sample size is not specified in advance; rather, it is an outcome of the study
- Usually, sample size is small (~ 20)

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Standard design (to find MTD): Select a sequence of increasing doses. Start at lowest dose level and administer drug to 3 subjects

1. If no toxicity observed in any of the 3 subjects, escalate to the next dose and begin again
2. If toxicity observed in 2 or more of the 3 subjects, STOP
3. If toxicity observed in exactly 1 subject of the 3, treat 3 additional subjects at this dose. If none of the additional subjects exhibits toxicity, then escalate to the next dose and begin again; otherwise, STOP

MTD: Usually defined as one of

- Dose at which trial stops
- Next lowest dose in the sequence
- Some fraction of the last dose

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Determining the sequence: Want to select doses in a way that will reveal the "MTD" without requiring an excessive number of dose levels

- Common technique – "modified Fibonacci" sequence
- Usual Fibonacci sequence 1, 1, 2, 3, 5, 8, 13, 21, ...
- Ratio of successive terms $\rightarrow 1.618$ ($\approx 62\%$ increase)
- Modify to increase less rapidly with decreasing increments
- Alternative: equally-spaced doses on log scale over range

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Determining the initial dose: The starting dose of the sequence is chosen in a conservative way, e.g.

- From rodent studies, estimate of LD_{10} is available; LD_{10} = dose where percentage of rodents exhibiting mortality is 10%
- Use as starting dose 1/10 of the rodent LD_{10} given on a mg/kg basis (scaled from rodent to human size)
- OR from larger animal (e.g. dog) studies, determine the *toxic dose* low (TDL) = the lowest dose at which any toxicity seen
- Use as starting dose 1/3 of the dog TDL

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Example: Modified Fibonacci with D = initial dose

Step	Usual	Modified	% Increment
1	D	D	–
2	$2 \times D$	$2 \times D$	100
3	$3 \times D$	$3.3 \times D$	67
4	$5 \times D$	$5 \times D$	50
5	$8 \times D$	$7 \times D$	40
6	$13 \times D$	$9 \times D$	29
7	$21 \times D$	$12 \times D$	33
8	$34 \times D$	$16 \times D$	33

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Performance of the standard design: Example

Dose level Actual toxicity prob. (π_i) Prob (p_i) of stopping (unknown in practice) at this dose

1	0.15	0.186
2	0.20	0.237
3	0.25	0.231
4	0.30	0.178
5	0.33	0.096
6	0.50	

- Given the trial reaches level 2, the probability of stopping at dose level 2 can be calculated in the same way (replace π_1 by π_2), which is 0.2912.
- The probability of stopping at dose level 2 ($\pi_2 = 0.20$):

$$p_2 = 0.2912 \times (1 - p_1) = 0.237.$$
- Chance of ever reaching the 3rd percentile is only 16.8%

$$(1 - p_1 - p_2 - p_3 - p_4)$$
- Given the trial reaches the 3rd percentile (dose level 5), the chance of stopping there is only 57% (calculated similarly to p_1 by replacing π_1 with π_5)

- E.g. probability of stopping at dose level 1 ($\pi_1 = 0.15$):

$$\begin{aligned}
 p_1 &= P[(Z_1 > 1) \cup (Z_1 = 1, Z_2 < 0)] \approx \text{binomial}(3, \pi_1) \\
 &= P[Z_1 > 1] + P[Z_1 = 1, Z_2 < 0] \\
 &= P[Z_1 > 1] + P[Z_1 = 1]P[Z_2 < 0] \\
 &= 3\pi_1^2(1 - \pi_1) + \pi_1^3 + 3\pi_1(1 - \pi_1)^2(1 - \pi_1) = 0.186
 \end{aligned}$$

Remarks: Statistically speaking

- If the true MTD is defined as previously, not clear that the dose announced as MTD is a credible estimate of this quantity
- The design has no intrinsic property that makes it stop at the 3rd or any other percentile of the toxicity distribution
- The announced MTD can only be at or near one of the doses in the sequence used, none of which may be exactly equal to the 3rd percentile
- No basis for accounting for sampling error (standard errors?)
- No appeal to formal statistical model
- Likely to treat most subjects at low doses

- Attempts to improve upon the standard design and analysis: Two-stage designs (Storer, 1989):**
- Stage 1 – use very few patients to get to the dose region where the “action is” (close to MTD)
 - Stage 2 – use a version of the standard design and find the MTD
 - Allow dose de-escalation (go to lower dose) as well as escalation (“up and down” design)
 - Use a statistical model, MLE to estimate MTD formally

- Remarks:**
- The standard design with this method of declaring the MTD is widely used, despite statistical concerns
 - The method of MTD determination is favored by investigators (the declared MTD depends on individual patient outcomes)
 - The method of MTD determination is of concern to statisticians (sampling error is not taken into account)
 - Proposals in the statistical literature for more rigorous analysis and other designs have been made

- Two-stage designs (Storer, 1989):**
- Stage 1:
 - * Single subject at a dose
 - * If no toxicity, escalate dose for next subject
 - * If toxicity, de-escalate dose for next subject
 - * Begin second stage at first toxicity
 - Stage 2:
 - * 3 subjects at a dose
 - * If no toxicity escalate dose for next group
 - * If 1 toxicity, add 3 subjects at this dose
 - * If > 1 toxicity, de-escalate dose for next group
 - * # groups fixed in advance

- Formal approach to analysis of the standard design:**
- Assume a statistical model for probability of toxicity at dose d

$$P(Y = 1|d) = f(d, \beta)$$
 - For the i th group of 3 subjects, let $Z_i = \#$ of subjects experiencing toxicity, corresponding $X_i =$ dose level
 - It is possible to write out the likelihood for the data (Z_i, X_i) , $i = 1, \dots, n$, where n is the (random) sample size
 - The MTD as formally defined could then be estimated by maximizing likelihood in β and solving for MTD
 - Writing down the likelihood requires a recursive conditioning
 - **Important:** Properties of this are not as simple because sampling was not random

Stochastic approximation methods (Anbar, 1984):

- *Estimate* the next dose sequentially

Continual reassessment method (CRM, O'Quigley, Pepe, and Fisher, 1990):

- Bayesian approach – specify a prior distribution for the MTD and model for probability of toxicity

- First subject gets dose = prior value of the MTD

- After each subject, use Bayes' rule to update the posterior distribution of the MTD given the data so far

- Use the mode of this distribution (Bayesian "estimate") as dose for next subject

- Stop after a fixed number of subjects and do a Bayesian analysis to estimate the MTD

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Disadvantages: Both approaches

- Require analysis after each subject

- May be too aggressive

- Require doses that may be difficult to prepare

- Modifications have been suggested; are area of current research and investigation

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