testing on animals (in vivo)

* lab testing for biological activity (in vitro)

* to human subjects

Preclinical (drug discovery): experimentation before a drug is given

Phases of Clinical Trials:

Chapter 2: Phase I and Phase II Clinical Trials
morbidity/adverse effects.

Phase IV: (postmarketing) Observational study of

and toxicity.

the current standard of treatment; both with respect to efficacy to

Phase III: Comparison of new intervention (drug or therapy) to

toxicities (safety and tolerability).

therapeutic effects; dose finding and further assessment of

Phase II: Screening and feasibility by initial assessment for

Phase III-Phase II trials or First-in-human trials.

explore pharmacology of the drug and investigate its interaction

determine a tolerated dose for further experimentation. Also

Phase I: To explore possible toxic effects of drugs and

Clinical: •
drug-alcohol) for safety profile and proper labeling.

- Need to examine interaction effects (drug-drug, drug-food,

- Gain understanding of the pharmacology of the drug

- Develop an appropriate schedule of administration

- Determine a "safe," "tolerable" dose (through dose-escalation)

May be established, first must

Objectives: Before efficacy (activity of a drug on disease) of the drug

- Previous studies in animals, e.g.: rats, dogs (in vivo)

- Previous studies in the laboratory (in vitro)

- Drug is administered to human subjects.

Broad definition: Phase I trials are the first studies in which a new

Phase I clinical trials (from Dr. Marie Davidsen)
still "informational" (for safety).

"Interaction studies" are comparative, but not aimed for efficacy.

- Most are not comparative but rather are "informational"

Features:

Subjects.

In addition: Do this in a timely manner, using a small number of
Inhibitory parameters, using a cross-over or parallel design

PK parameters, using a cross-over or parallel design

Drug-food interaction studies – determine how food affects
design

PK parameters, using a cross-over or parallel design

Drug-drug interaction studies – determine how other commonly used
problems are related to amount of drug present

Clinical pharmacology studies – determine the pharmacokinetics of
themselves called "phase I" studies (especially for cancer studies)
be given without serious "problems" – these studies are often
"dosage-finding" studies – determine the maximum dosage that can

Types of studies:
Circumvented (coming up)

Advantages - Ethical Issues involed in human experimentation

- Humans

Goal – ”scale up” previous results to provide first idea of behavior in

Pharmacology studies in rodents, dogs, etc

Dose-finding studies in rodents, large animal species (e.g. dogs)

In vitro studies – Laboratory investigations using biological material

Before administration to humans:

Pre-clinicial Studies
mention only on p. 3-4!
dose-finding (or pharmacology) studies, e.g. Freedman et al.

Many texts on clinical trials devote little or no discussion to

Justification

Standard approaches to design and analyses have little statistical

Paradox: Although results of „dose-finding“ will be carried forward to

Phase I: Dose-finding Studies
May be non-life-threatening

May be life-threatening and reversible

May be life-threatening and irreversible

Irregular heartbeat

E.g. change in organ function – a drug to treat cancer may induce

Nature depends on the drug

administration of the drug – side effects

Toxicity: “Problems” that may arise in direct response to
<table>
<thead>
<tr>
<th>Grade</th>
<th>Pain</th>
<th>Abdominal Pain</th>
<th>Clearance</th>
<th>Creatinine</th>
<th>Creatinine (cc/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>IV</td>
<td>III</td>
<td>II</td>
<td>I</td>
<td></td>
</tr>
</tbody>
</table>

Examples: •

Ordered categories increasing in severity – Grades I – IV or V

(expecially for cancer research)

Characterization: Often done on a standard, "Graded" scale
Assumption: Maximum benefit occurs at maximum doses

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

Serious or life-threatening but reversible

Terminology: Dose Limiting Toxicity (DLT)

What degree of toxicity is acceptable must be established

Subjects, clinical judgment – must be defined by the investigators

Which toxicities are relevant depends on intervention, nature of likelihood

Defining toxicity:
population

- The 3rd percentile of the distribution of toxicity in the population
- The dose is \( \frac{1}{3} \)

of subjects in the population who would develop toxicity if \( \frac{1}{3} \) given this

Statistically speaking: Determine the dose at which the proportion

(agents)

more than one out of three patients" (often used for anticancer

E.g. the dose that produces toxicity of Grade III or worse in not

the drug's potential benefit

involves some level of toxicity we are willing to tolerate because of

The "highest possible while still tolerable" dose

Main objective: Determine the Maximum Tolerated Dose (MTD)
Illustration of MTD: a hypothetical example
as possible to suboptimal doses that are likely not to be efficacious

Goal: Establish appropriate dose quickly while exposing as few subjects

other therapies, toxicities likely, e.g.

chemotherapy

Patients with advanced disease – used where subjects have failed

topical agents

Healthy volunteers – used where toxicities unlikely to be severe, e.g.

Subjects: Nature of subjects used depends on drug
Estimate MTD from fitted model

- Proportions at each dose

Model dose-response (probability of toxicity) and fit to observed proportions exhibiting DLT

- \( \frac{n_i}{n} \cdot \frac{t_i}{p_i} \) for each dose, and calculate

Observe number of subjects exhibiting DLT at each dose, and calculate

- Randomize subjects to each dose, \( n_i \) subjects at dose \( i \)

- Select doses \( D_1, \ldots, D_k \) for study such that one of these is (close to) the MTD

Ideal design:
Standard approach for animal experiments

May estimate probabilistically associated with any fixed dose

May estimate dose associated with any probability

More generally

\[ (\mathcal{O}^{\text{MTD}}_{0.33})_{1-\gamma}^f = \text{MTD} \]

Estimate from data and use to estimate MTD, i.e.,

\[ (\mathcal{O}^{\text{MTD}}_{0.33})_{1-\gamma}^f = \text{MTD} \]

E.g., if MTD is defined as dose where toxicity is 33%

\[ (\mathcal{O}^{0})_{0}^f = 0^p \]

Dose associated with specified probability

\[ (\mathcal{O}^{0})_{0}^f = (p|1 = \lambda)_{d} \]

Dose monotonically increasing in dose

\[ (\mathcal{O}^{0})_{0}^f = (p|1 = \lambda)_{d} \]

For dose-response models
\( (\forall \cdot 0, 10^-) = (\int_0^1 g^D \, dx) = \int_0^1 \left( \frac{(p\int g^D + 0g^D) \, dx}{(p^D) + (0g^D) \, dx} \right) = (p|I = \lambda) \)
Result: cannot simply randomize subjects to different dose levels.

Good or too high (toxic)

Do not want to treat many subjects at dose that is too low to do
doses first before feeling confident enough to move to higher doses

Because drug not previously used in humans, must test at lower
considerations

Problem: This approach not feasible in human subjects due to ethical
Usually, sample size is small (n ~ 20).

Result: Sample size is not specified in advance; rather, it is an outcome of the study.

Many variations on this idea.

Sometimes, may ‘de-escalate’ from a dose that is not tolerated.

Continue until dose is found that yields toxicity.

If no toxicities, try a higher dose in several (new) subjects.

Try a dose in several subjects.

Some fraction of the last dose

Next lowest dose in the sequence

Dose at which trial stops

MTD: Usually defined as one of

STOP

toxicity, then escalate to the next dose and begin again; otherwise,
subjects at this dose. If none of the additional subjects exhibits

3. If toxicity observed in exactly 1 subject of the 3, treat 3 additional
dose and begin again

2. If toxicity observed in 2 or more of the 3 subjects, STOP

1. If no toxicity observed in any of the 3 subjects, escalate to the next

lowest dose level and administer drug to 3 subjects

Standard design: Select a increasing sequence of doses. Start at
Use as starting dose $1/3$ of the dog TDL

$\text{low (TDL)} = \text{the lowest dose at which any toxicity seen}$

OR

From larger animal (e.g. dog) studies, determine the toxic dose

(basis: scaled from rodent to human size)

$D_T I_{010} \text{ given on } a \text{ mg/Kg}$

Use as starting dose $1/10$ of the rodent dose

$\% \text{ where percentage of rodents exhibiting mortality is } 10\%$

From rodent studies, estimate of $D_T I_{010}$ is available; $D_T I_{010} = \text{ dose}$

chosen in a conservative way, e.g.:

Determining the initial dose: The starting dose of the sequence is
Alternative: equally-spaced doses on log scale over range

Modestly to increase less rapidly with decreasing increments

Ratio of successive terms \( \rightarrow 0.618 \)

Usual Fibonacci sequence 1, 2, 3, 5, 8, 13, 21, \ldots

Common technique – "modified Fibonacci" sequence

Determining the sequence: Want to select doses in a way that will

Dawen Zhang
<table>
<thead>
<tr>
<th>Step</th>
<th>% Increment</th>
<th>Modified Ideal</th>
<th>Modified Fibonacci with $D = \text{Initial dose} $</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>$a \times 16$</td>
<td>$a \times 34$</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>$a \times 12$</td>
<td>$a \times 21$</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>$a \times 9$</td>
<td>$a \times 13$</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>$a \times 7$</td>
<td>$a \times 8$</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>$a \times 5$</td>
<td>$a \times 5$</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>$a \times 3.3$</td>
<td>$a \times 3$</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>$a \times 2$</td>
<td>$a \times 2$</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>$a$</td>
<td>$a$</td>
</tr>
<tr>
<td>Dose Level</td>
<td>Actual toxicity prob. ($p_i$) of stopping</td>
<td>Proportion of the standard design: Example</td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>-----------------------------------------</td>
<td>------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>0.96</td>
<td>0.33</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>0.78</td>
<td>0.30</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>0.237</td>
<td>0.25</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>0.237</td>
<td>0.20</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>0.186</td>
<td>0.15</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

*unknown in practice*
\[ 9186 = \left( \frac{1}{\mu} - 1 \right) \zeta \left( \frac{1}{\mu} - 1 \right) \frac{1}{\zeta} + \frac{1}{\mu} + \left( \frac{1}{\mu} - 1 \right) \frac{1}{\zeta} \frac{1}{\mu} \]
Replacing $\nu_1$ with $\nu_3$

of stopping there is only 57% (calculated similarly for $p_1$ by
Given the trial reaches the 33rd percentile (close level 5), the chance

\[
(\nu_1 d - 3\nu_1 d - 2\nu_1 d - 1\nu_1 d - 1)
\]

Chance of even reaching the 33rd percentile is only 16.8% •

\[
\nu_1 d = 0.2912 \times 0.237 = 0.2912
\]

The probability of stopping at close level 2 ($\nu_2 = 0.20$): •

is 0.2912.

Level 2 can be calculated in the same way (replace $\nu_1$ by $\nu_2$), which
Given the trial reaches level 2, the probability of stopping at close
Likely to treat most subjects at low doses

No appeal to formal statistical model

No basis for accounting for sampling error (standard error)

Percentile sequence used, none of which may be exactly equal to the 33rd percentile

The announced MTD is only be at or near one of the doses in or any other percentile of the toxicity distribution

The design has no intrinsic property that makes it stop at the 33rd percentile as MTD is a credible estimate of this quantity

If the true MTD is defined as previously, not clear that the dose

Remarks: Statistically speaking
other designs have been made.

Proposals in the statistical literature for more rigorous analyses and sampling error is not taken into account.

The method of MTD determination is of concern to statisticians.

The method of MTD depends on individual patient outcomes.

Declared MTD is favored by investigators (the method is used, despite statistical concerns).

The standard design with this method of declaring the MTD is

Remarks:
was not random

Important: Properties of this are not as simple because sampling

Writing down the likelihood requires a recursive conditioning

maximizing likelihood in and solving for MTD

The MTD as formally defined could then be estimated by

It is possible to write out the likelihood for the data

\((?X, ?Z)\)

toxicity, corresponding dose level

For the ith group of 3 subjects, let \(\# = ?Z\) of subjects experiencing

\(\text{if subject exhibits toxicity, otherwise} \)

\(\text{Assume a statistical model for probability of toxicity at dose } p\)

Formal approach to analysis of the standard design:
Use a statistical model, MLE to estimate MTD formally •

(“up and down” design)

Allow dose de-escalation (go to lower dose) as well as escalation

Stage 2 – use a version of the standard design and find the MTD •

Stage 1 – use very few patients to get to the dose region where the action is “close to MTD” •

Two-stage designs (Storer, 1989):

Attempts to improve upon the standard design and analysis:
Groups fixed in advance

1. If toxicity, de-escalate dose for next group
2. If I toxicity, add 3 subjects at this dose
3. If no toxicity escalate dose for next group
4. 3 subjects at a dose

Stage 2:

Begin second stage at first toxicity

1. If toxicity, de-escalate dose for next subject
2. If no toxicity, escalate dose for next subject
3. Single subject at a dose

Stage 1:

Two-stage designs (Storer, 1989):
Estimate the MTD

- Stop after a fixed number of subjects and do a Bayesian analysis to next subject

Use the mode of this distribution (Bayesian “estimate”) as dose for distribution of the MTD given the data so far

- After each subject, use Bayes’ rule to update the posterior

First subject gets dose = prior value of the MTD

- Model for probability of toxicity

Bayesian approach – specify a prior distribution for the MTD and and Piseker, 1990):
Continual reassessment method (CRM, O’Quigley, Pepe, and Piseker, 1990):

Estimate the next dose sequentially

- Stochastic approximation methods (Anbar, 1984):
Disadvantages: Both approaches have been suggested; an area of current research and investigations require doses that may be difficult to prepare. May be too aggressive. Require analysis after each subject.

Investigation
Pharmacology: Understand the processes that allow these objectives to be achieved

- Maximize therapeutic effect
  - Minimize difficulty of administration, optimize dose regimen
- Minimize toxicity
- Achieve therapeutic objective (cure disease, mitigate symptoms)

Goals of Drug Therapy:

Phase I Pharmacokinetic Studies
drug in humans

first time, it is sensible to begin to understand the pharmacology of a

Result: In Phase I trials, where the drug is given to humans, for the

How long?

How often?

How much?

In what form?

To whom?

Which drug?

Implementation of Drug Therapy:

Dawei Zhang
Monitor concentration at site by concentration in blood/plasma

Drug concentration can be measured in blood/plasma

Drug concentration at site cannot be measured directly

Metabolized, eliminated, and then moved:

Drug can not be placed directly at site of action, but must be absorbed and then moved.

Magnitudes of desired response, toxicity are functions of drug concentration at site of action

There is a "site(s) of action" where drug produces effect(s)

Basic principles:
Drug plasma concentration following oral administration (single dose) at $t = 0$
Motion of drug in the body over time

Understanding of the kinetics of these processes

Elimination

Metabolism

Distribution

Absorption

Knowledge of mechanisms of ADME

Result: Optimal administration of drugs requires
Response

Relationship between drug concentration and pharmacologic

Pharmacodynamics: "What the drug does to the body"

Kinetcis of absorption, distribution, elimination

Relationship between concentration and time/dose

Drug concentration in blood/plasma used to monitor concentration at site of action over time

Pharmacokinetics: "What the body does to the drug"
Therapeutic Window

Min Effective Conc

Therapeutic Window

Max Tolerated Conc

\( C(t) \)
Width of therapeutic window

Absorption, elimination, distribution, metabolism - kinetics

Governed by:

Achieve steady-state: amount gained = amount lost

Route, frequency of administration, amount

Maintenance dose: dose at discrete time intervals

Concentration within therapeutic window

Replace drug eliminated by sustaining doses to maintain

Load initial dose to achieve concentration within therapeutic window

Optimal dosage regimen:
The first studies are conducted in Phase I with a small number of subjects. Use PK data from several subjects to infer population behavior (mean, variability). Use concentration/time data to learn about subject-specific PK. Collect blood samples over time on each subject following dose. **Pharmacokinetic studies:**
Result: concentration as a nonlinear function of time/dose

Compartmental models: represent body as system of

Compartmental solutions, solution of differential equations

Elimination

Parameters of function pertaining to absorption, distribution

Describe concentration as a function of time/dose

Subject within mathematical framework

Formalize notions of absorption, distribution, elimination for each

Pharmacokinetic models:

Dawen Zhang
\[
\exp (-\lambda t) = C(0) = C(t) - \lambda t \\
\Rightarrow \log C(t) = \log C(0) - \lambda t
\]

Suggests

- No absorption required
- Dose of drug given in rapid (instantaneous) bolus

Example: Pharmacokinetics following IV administration
\[ \Lambda/lC = \exp (\Lambda/lA) = (t)C \]
\[ \Lambda/lA = (0)C, \quad (t)C^{\alpha} - \frac{MP}{(t)Cp} \]

Diagram:

\[ ^\alpha \Lambda \quad (t)C \quad D \]

I. One compartment open model: Intravenous dose \( D \)
Aparent (volume of distribution) \( \Lambda \) 

Not a real physiological

time unit

\[
\frac{(\text{mg/L}) (t)}{\text{Drug elimination rate (mg/hr)}} = \Lambda
\]

Volume of plasma that would be cleared of drug in one

Clearance – rate of elimination relative to concentration:

\[
\frac{\Lambda}{(t)D} = (t)C
\]

Amount of drug in the body

Drug elimination rate

\[
\left| \frac{PP}{(t)DP} \right|
\]

Drug elimination rate

\[
\frac{(t)D}{(t-1)\text{Drug elimination rate}} = \kappa_e
\]

Elimination rate constant – Fractional rate of removal:

PK parameters:
parameters then can be used to make inference of interest.

These estimated PK parameters can be used to estimate the PK parameters. The maximum likelihood method (assumptions distribution for the data) subject-specific. Given individual’s concentration data, least squares

Note: The above PK parameters' $\frac{t_1}{T} = \frac{\log(t_e)}{\log(2)}$ (hr)

$\frac{t_1}{T} = \frac{\log(t_e)}{\log(2)}$ (hr)

Elimination half-life – Time for concentration to fall by half

Drug in body volume, but fluid volume that would be required to account for all
\[
\Lambda / J_C = \frac{r_Y}{(t)^D} \left\{ \left( t^D y - \int r y \, dx \right) \right\} \frac{\frac{r y}{(t)^D} - \frac{r y}{(t)^D}}{\Lambda} = (t)^D \\
\text{fraction available} = (t)^D \\
\text{oral dose} = D
\]

\[
A D = (0)^D, (t)^D y - \frac{\mathcal{P}}{(t)^D} D^p
\]

\[
0 = (0)^D, (t)^D y - (t)^D D^p = \frac{\mathcal{P}}{(t)^D} D^p
\]

\[
\frac{\Lambda}{(t)^D} = (t)^C
\]
\( C_{\text{max}} \) is then given by \( \mathcal{C}(t_{\text{max}}) \).

\[
\frac{e^{-\gamma} - p}{(e^{-\gamma}) \log \left( \frac{p}{e^{-\gamma}} \right)} = t_{\text{max}}
\]

It can be shown that \( \mathcal{C} \) reaches its max at \( t \).

Here the PK parameters include \( K_e, t_{1/2}, C_{\text{max}} \) and \( A \).

\( K_d < K_e \). Otherwise, there will be no drug in the body.

Note:

\[
\left\{ \left( e^{\frac{\gamma}{p}} - \exp \right) - \left( e^{\frac{\gamma}{p}} - \exp \right) \frac{e^{-\gamma} - p}{p} \right\} A = (t) \mathcal{C}
\]
\[
0 = (0)^{s_{12}} \mathcal{A}^\varepsilon \mathcal{A}_{12} - (\mathcal{A})^{s_{12}} \mathcal{A}_{12} = \frac{\mathcal{M}}{(\mathcal{A})^{s_{12}} \mathcal{A}_{12}}
\]

\[
\mathcal{A} = (0) \mathcal{A}^\varepsilon \mathcal{A}_{12} - (\mathcal{A})^{s_{12}} \mathcal{A}_{12} - (\mathcal{A})^{s_{12}} \mathcal{A}_{12} = \frac{\mathcal{M}}{(\mathcal{A})^{s_{12}} \mathcal{A}_{12}}
\]

Second compartment is required to explain distribution of drug to various tissue groups after administration.
\[ \Lambda/\overline{\mathcal{Z}} = \overline{\mathcal{Z}} \] and \[ \Lambda/\overline{\mathcal{I}} = \overline{\mathcal{I}} \]

\[ \left( \mathcal{Z}/\overline{\mathcal{C}} \right) \left( \mathbf{\overline{\mathcal{C}}}/\mathcal{A} \right) \] \[ = \mathcal{Z} \]

\[ \left( \mathcal{I}/\overline{\mathcal{C}} \right) \left( \mathbf{\overline{\mathcal{C}}}/\mathcal{A} \right) \] \[ = \mathcal{I} \]

\[ \mathcal{A}/\mathbf{\overline{\mathcal{C}}} + \mathcal{A}/\mathbf{\overline{\mathcal{C}}} + \mathcal{A}/\mathbf{\overline{\mathcal{C}}};\quad \text{Obviously, } \mathcal{Z}/\overline{\mathcal{C}} \]

\[ \left( \mathcal{Z}/\overline{\mathcal{C}} \right) \left( \mathbf{\overline{\mathcal{C}}}/\mathcal{A} \right) \] \[ = \mathcal{Z} \]

\[ \left( \mathcal{I}/\overline{\mathcal{C}} \right) \left( \mathbf{\overline{\mathcal{C}}}/\mathcal{A} \right) \] \[ = \mathcal{I} \]

\[ \mathcal{A}/\mathbf{\overline{\mathcal{C}}} + \mathcal{A}/\mathbf{\overline{\mathcal{C}}} + \mathcal{A}/\mathbf{\overline{\mathcal{C}}};\quad \text{Hence, } \]

\[ \left( \mathcal{Z}/\overline{\mathcal{C}} \right) \left( \mathbf{\overline{\mathcal{C}}}/\mathcal{A} \right) \] \[ = \mathcal{Z} \]

\[ \left( \mathcal{I}/\overline{\mathcal{C}} \right) \left( \mathbf{\overline{\mathcal{C}}}/\mathcal{A} \right) \] \[ = \mathcal{I} \]

\[ \mathcal{A}/\mathbf{\overline{\mathcal{C}}} + \mathcal{A}/\mathbf{\overline{\mathcal{C}}} + \mathcal{A}/\mathbf{\overline{\mathcal{C}}};\quad \text{where} \]

\[ \mathcal{Z}/\overline{\mathcal{C}} < \mathcal{A}/\overline{\mathcal{C}} \quad \left( \mathcal{Z}/\overline{\mathcal{C}} \right) \left( \mathbf{\overline{\mathcal{C}}}/\mathcal{A} \right) \] \[ = \mathcal{Z} \]

\[ \left( \mathcal{I}/\overline{\mathcal{C}} \right) \left( \mathbf{\overline{\mathcal{C}}}/\mathcal{A} \right) \] \[ = \mathcal{I} \]

\[ \mathcal{A}/\mathbf{\overline{\mathcal{C}}} + \mathcal{A}/\mathbf{\overline{\mathcal{C}}} + \mathcal{A}/\mathbf{\overline{\mathcal{C}}};\quad \text{(bi-exponential)} \]

Solving the above system leads to (bi-exponential)
Graphical representation:

1. **Drug Concentration**
   - Y-axis: Drug Concentration
   - X-axis: Time in Hours
   - The graph shows the concentration over time, with a smooth curve indicating an increase.

2. **Log–Drug Concentration**
   - Y-axis: Log–Drug Concentration
   - X-axis: Time in Hours
   - The graph shows the log-transformed concentration over time, with a linear trend indicating a consistent increase.

The graphs illustrate the relationship between drug concentration and time, with the log–Drug Concentration graph providing a clearer view of the trend due to the nature of logarithmic transformation.
and exposure following dose ($AUC_{0-\infty}$ or $AUC_{0-T}$).

Area Under the Curve $AUC$; Reflects extent of drug availability.
variables

Explore association between PK parameters and toxicity and other

Estimate typical values of PK parameters in model for each subject

Estimate values of PK parameters in model for each subject

Estimate values of PK parameters in model for each subject

Kinetcs of drug absorption and disposition

Use measurements of drug concentrations on subjects to elucidate

Pharmacokinetic analysis:
Nonlinear mixed effects models

Use estimates from m subjects to estimate mean and variance in population

\[ \hat{\theta} \quad \text{(constant CV)} \]

\[ \text{Errors with } \text{var}(\epsilon_i) \]

\[ m \quad \text{parameters for subject } i = 1, \ldots, m \]

\[ \hat{\epsilon}_i + (\hat{\theta}_i \text{D}_i(t)) \text{E} = \text{y}_i \]

With \( y_i \) concentration on subject \( i \) at time \( t_i \), following dose \( D_i \)

Weighted nonlinear regression techniques - fit the PK model to concentration-time data for each subject

Implemantation
Sample size calculation is usually based on precision.

Linear mixed model for formal statistical inference.

Given \( \mathcal{A} \) and then \( \mathcal{A} + \mathcal{B} \). Compare \( \mathcal{PK} \) parameters of \( \mathcal{A} \) and then to \( \mathcal{A} + \mathcal{B} \) and then to \( \mathcal{A} \); other subjects are randomly assigned to \( \mathcal{A} + \mathcal{B} \) and then to \( \mathcal{A} \). Some study subjects are in each of the 4 treatment groups. When wash-out is possible.

Cross-over design

Drug-drug interaction: Investigate the effect of a commonly used drug on some important \( \mathcal{PK} \) parameters of the new drug.

Interaction Studies
Design and analysis are similar to the drug-drug interaction study.

- Parameters of the new drug.

Food effect: Investigate the food effect on some important PK parameters.

- Sample size calculation is usually based on precision.
- Two-sample t-test can be used for formal statistical inference.
- Parameters of A under $A + B$ to the PK parameters under $A$.
- Compare important PK parameters of $A + B$ or $A$.
- Parallel design (when wash-out is hard to achieve): Study subjects

Fall 2006
Multivariate mixed models for multiple endpoints

Mixed models for each endpoint

Longitudinal data for each endpoint

Cross-over design or parallel design

Body balanced, etc.

parameters such as reaction time, short-term memory, ability to keep alcohol/benzo taken alone or some important pharmacodynamic (PD)

administered together with alcohol/penzo over the effect of

Alcohol interaction: Investigate the effect of the new drug