CT 31: 第一期臨床試驗
Phase I Design

林建甫

台北大學 統計系

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Phase o I

- Translational
- Sub-therapeutic dose levels administered to humans
- Look at
  - pharmacokinetics (how agent is absorbed, metabolized, excreted)
  - pharmacodynamics (how agent impacts patient)
- Measure biomarkers

Phase o II

- Not dose finding
- Proof-of-principle
  - Give small dose not expected to be therapeutic
  - Test that target is modified
  - Small n (10-15?)

Phase o III

- Short term: one dose
- Requires pre and post subject sampling.
- Provides useful info for phase I

  (or if you should simply abandon agent).

Phase I (DF)

- Dose-finding (DF): maximum tolerated dose (MTD)
- Determine safe dosage range & identify AE
- Small group $\leq$ 30 subjects
- Safety trial
- Main outcome is toxicity
- Sometimes:
  - First-in-human study of agent (FIHS)
  - Study of agent for new indication
  - Study of novel combination of approved agents

Phase II (SE, SA)

- Safety and Efficacy Studies (SE)
- Safety-Activity (SA)
- Larger Size (20∼100)
- Carry forward recommended dose from phase I
- Seeking to establish evidence of activity
- Not comparative (II, IIa) vs. comparative (IIb)
- Sometimes controlled
- Several months to 2 years
- Practice for phase 3

Phase I Trials Overview I

- Typically first study of drug (treatment) focused on clinical outcomes, specifically safety
- Passed pre-clinical hurdles.
- Drug mechanism works in cell lines, animals.
- e.g., Targeted therapy
  has been shown to inhibit genetic pathway has been inhibited.

Phase I Trials Overview II

- Assumption is that toxicity (and potential for efficacy) increases with dose level
- Goal is to identify maximum tolerated dose (MTD): greatest dose level that induces an acceptable level of toxicity

Phase I can mean different things

- Common elements: focus on safety
- Points of divergence: Multiple dose levels?
- What are expected side effects of drug?
- For whom is it intended?

目錄

Preclinical Toxicology Studies for Drugs

- Determine in Appropriate Animal Models
- Animal Study: Lethal Dose LD_{50}
- Maximum Tolerated Dose (MTD)
- Dose Limiting Toxicities (DLT)
- Schedule-Dependent Toxicity
- Reversibility of Adverse Effects
- A Safe Clinical Starting Dose

Lethal Dose LD_{50}

- the dose which kills 50% of the animals
- replaced with single dose administration
- increasing dose tolerance studies

Adverse Events and Toxicity

- An Adverse Event is any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease temporally associated with the use of a treatment or procedure regardless of whether it is related to the treatment or procedure.
- The term “toxicity” has no regulatory definition.
- Use “adverse event” instead.

Three Categories of Adverse Events

- serious adverse events
- general adverse events
- adverse events of special interest.

Serious Adverse Events (SAE)

- Defined by the U.S. FDA
  - (a) life threatening
  - (b) result in initial or prolonged hospitalization
  - (c) cause irreversible, persistent or significant disability
  - (d) are a congenital anomaly/birth defect
  - (e) require intervention to prevent harm
  - (f) have other medically serious consequences

Classification of Adverse Events

- Common Terminology
  - Medical Dictionary for Regulatory Activities (MedDRA)
  - Common toxicity Criteria (CTC)
  - All are graded 0-5:
    - 0 = none
    - 1 = mild
    - 2 = moderate
    - 3 = severe
    - 4 = life threatening
    - 5 = death

Dose Limiting Toxicity (DLT) I

- No consensus on the definition of DLT in phase I trials
- Hematologic Toxicity
- Non-Hematologic Toxicity

Dose Limiting Toxicity (DLT) II

- Usually defined as:
- Any irreversible grade 2+ AE
- Reversible grade 4 AE (except for Heme)
- Non-hematologic grade 3-4 AE
- Hematologic AE is considered DLT if any one
  - Grade 4 thrombocytopenia > 1 wk
  - Neutropenia with WBC < 1000 for > 2 wks
  - Neutropenic fever > 1 wk
- DLT may vary according to disease under study

Maximum Tolerable Dose (MTD)

- Dose with fewer than X% subjects demonstrating DLT
- X: usually approximate 33%
- Dose associated with serious

  but reversible side effects in a sizeable proportion of subjects
- Dose that offers best chance of therapeutic benefit
- MTD determination is the primary objective of phase I trials
- MTD exhibits acceptable and predictable toxicity
- MTD will be recommended as the starting dose for phase II

目錄

Phase I Designs

► Design driven by type, severity of expected toxicities, particularly dose-limiting toxicities (DLTs)

- When DLTs are not terrible, subjects are healthy volunteers. Designs more closely resemble true experiments.
- When they are terrible, e.g. cytotoxic drugs, subjects are patients. Designs focus on ethical treatment of enrolled patients

Phase I trials in Healthy Volunteers

- Often randomized, placebo-controlled, cross-over design
- Randomize patients to (i) placebo or (ii) one of several dose levels
- Monitor patients for DLTs, e.g. headache, rash, cold symptoms.
- Typically minor and reversible.
- MTD could be largest dose level in which estimated rate of DLT is less than X%

Ethical Considerations (for Healthy Volunteers)

- What is definition of healthy?
- Is it safe to extrapolate from healthy to diseased?
- How much should volunteers be paid?
- Does financial compensation account for risks?

Ethical Considerations for Patients with Cancer, HIV/AIDS

- Not randomized. No placebo
- Typically dose-escalation study:
  - Start at very low, conservative dose.
  - Monitor for DLTs,

    e.g. hematologic, renal or hepatic function, cardiac, neurotoxicity
  - Escalate dose level in next patient(s) if warranted
  - Stop when toxicity is too large.
- MTD is largest dose level in which

  estimated rate of DLT is less than X%

Ethical Considerations for Patients

- Acceptable to purposefully induce serious or life-threatening toxicity?
- Is truly informed consent possible?

Phase I Design Constraints

- Enrolling sick/terminally-ill patients means:
  - Small study population
    $\rightarrow$ few patients
    $\rightarrow$ low precision, no adjustment for confounding
  - Heterogenous patients
    $\rightarrow$ complicated disease and many prior therapies
    $\rightarrow$ limited extrapolation, high false-positive rate
  - Toxicities occur over time
    $\rightarrow$ irreversible toxicities (i.e. death) may occur

Phase I Initial Steps I

- Key assumption of phase I designs:
  risk of toxicity (and therefore efficacy/response)
  monotonically increases with dose
- How should first dose (d_1) be chosen?
  - Too low risks being sub-therapeutic
  - Too high may be too toxic
- d_1 is often = 0.1 $\times$ MELD10
  = 1/10th of dose that kills 10% of mice

Phase I Initial Steps II

- How should subsequent dose levels $(d_2, \ldots, d_k)$ be selected?
- Subsequent dose levels are fractional increases of d_1

Fibonacci Sequence for Subsequent Dose

- Starting with 0 and 1
- The next number = adding up the two numbers before it
- 0, 1, 1, 2, 3, 5, 8, 13, 21, 34, 55, 89, 144, . . .
- The ratios of the successive numbers in the Fibonacci series quickly converge on Phi = 1.6180339887498 95...

Modified Fibonacci Sequencee I

- Starting numbers other than 0 and 1
- i.e., starting with 1 and 3
- 1, 3, 4, 7, 11, 18, 29, 47, 76, 123, 199, 322, 521, 843, 1364, 2207, . . .

Modified Fibonacci Sequencee II

- Assuming the d_1 is the starting dose for the first cohort, according to the modified Fabonacci series, the next dose cohort will be

  $d_2 = 2 \times d_1$,

  $d_3 = 1.67 \times d_2$,

  $d_4 = 1.5 \times d_3, \ldots$

Modified Fibonacci Sequencee III

- If the start dose is 5 mg and a study with 5 cohorts, the dose schema will be:
  Cohort 1 (5 mg) $\Rightarrow$ Cohort 2 (10 mg) $\Rightarrow$ Cohort 3 (15 mg) $\Rightarrow$ Cohort 4 (25 mg) $\Rightarrow$ Cohort 5 (40 mg)

Fibonacci Ratio

$$\frac{2}{1}, \frac{3}{2}, \frac{5}{3}, \frac{8}{5}, \frac{13}{8}, \ldots \tag{2.1}$$

$$d_2 = 2.00 \times d_1, \tag{2.2}$$

$$d_3 = 1.50 \times d_2 \tag{2.3}$$

$$d_4 = 1.67 \times d_3, \tag{2.4}$$

$$d_5 = 1.60 \times d_4, \tag{2.5}$$

$$d_6 = 1.63 \times d_5. \tag{2.6}$$

Modified Fibonacci Ratio

$$d_2 = 2.00 \times d_1, \tag{2.7}$$

$$d_3 = 1.50 \times d_2 \tag{2.8}$$

$$d_4 = 1.67 \times d_3, \tag{2.9}$$

$$d_5 = 1.50 \times d_4, \tag{2.10}$$

$$d_6 = 1.33 \times d_5. \tag{2.11}$$

Constant growth

$$d_2 = c \times d_1, \tag{2.12}$$

$$d_3 = c \times d_2 \tag{2.13}$$

$$d_4 = c \times d_3, \tag{2.14}$$

$$d_5 = c \times d_4, \tag{2.15}$$

$$d_6 = c \times d_5. \tag{2.16}$$

- equivalent to equal-spaced log-dose levels

Penel and Kramar (2012)

- BMC Medical Research Methodology 2012, 12:103
- Review total 198 phase I oncology trials.
- 81 (41%) are based on modified-Fibonacci series.
- Actual incremental ratios varied from 0.80 to 2.08.
- The median of actual increments was about

  2.00, 1.50, 1.33, 1.33, 1.33, 1.33, 1.30, 1.35 . . .
- The “modified Fibonacci-sequence” gathers heterogeneous variation of the genuine sequence.
- Does not tend to a constant number at higher dose-levels.
- This confusing term should be avoided.

Remaining Questions

- how to escalate?
- how many patients to enroll?
- what is MTD?
- tied to choice of design

Two Classes of Phase I Designs

- Algorithmic = Rule-Based
- Model-based

目錄

Le Tourneau, Lee and Siu (2009)

- J Natl Cancer Inst 2009; 101: 708–720

世代 (Cohort)

- Group of patients treated at a dose level
- 接受相同劑量治療的一組受試者

起始劑量 (Starting Dose)

- The dose chosen to treat the first cohort of patients
- 第一期臨床試驗第一組世代受試者所接受的藥物劑量

劑量增量, 劑量減量

(dose increment or decrement)

- The percent increase (or decrease) between dose levels
- 劑量增量或減量的百分比或實質量

劑量限制性毒性 (Dose Limiting Toxicity, DLT)

- Toxic effects that are presumably related to the drugs that are considered unacceptable
- 指藥物所造成無法接受的嚴重毒性

劑量–藥效曲線 (Dose Efficacy Curve)

- 描述劑量與療效的關係
- 一般是定義成羅吉斯函數 (logistic function)
- reflects the relationship between dose and probability of efficacy
- A logistic function is commonly assumed
- θ: parameter = slope
  - small θ: probability of efficacy increases very slowly
  - large θ: a sharp increase in efficacy

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毒性目標 (Target Toxicity Level)

- 可以接受 DLT 的最大機率值, 一般介於 20%～33% 之間
- The maximum probability of DLT that is considered acceptable

最大耐受劑量 (Maximum Tolerated Dose, MTD)

- US: $\leq$ 33% 的病人產生 DLT 的最高劑量
- EU/Japan: $\geq$ 33% 的病人產生 DLT 的最低劑量
- the highest dose level at which $\leq$ 33% of pts experience DLT.
- EU/Japan: the lowest dose level at which $\geq$ 33% of pts experience DLT (a misnomer in the sense that the MTD is actually not a tolerable dose).

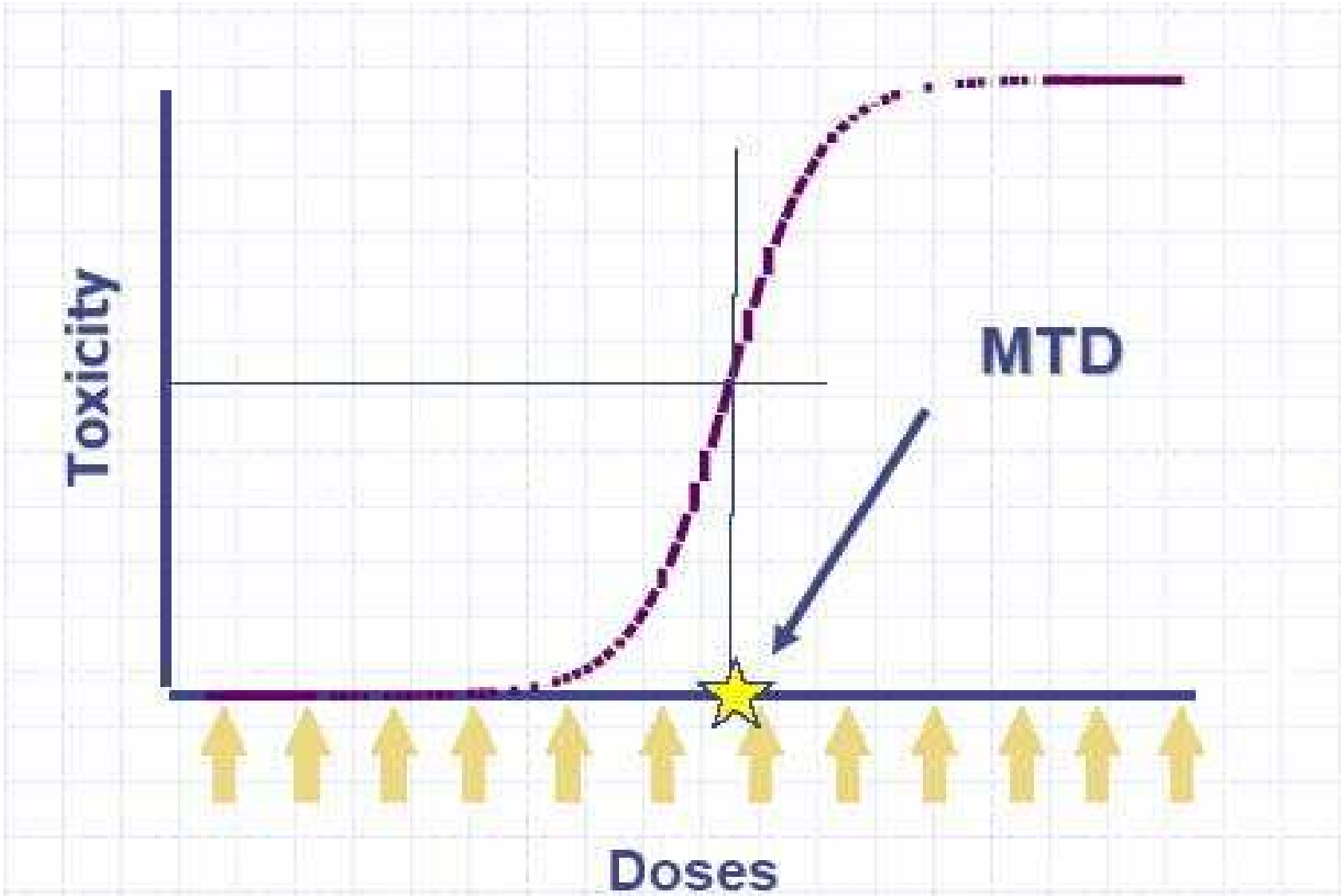


圖 1: Dose Toxicity Curve and MTD

建議的第二期試驗劑量
(Recommended Phase II Dose)

- RP2D = P2RD
- 取代 MTD (US and EU/Japan)
- US: 以 MTD 為第二期試驗的建議劑量
- EU: 以 MTD 的次一個安全劑量作為第二期試驗的建議劑量

最佳生物性劑量 (Optimal Biological Dose)

- 細胞毒性藥物 (cytotoxic agentc)
- small molecular, chemical product
- 分子標靶藥物 (molecular target agent, MTA)
- 細胞製劑 (cellular product)
- 生物製劑 (biological product), large molecular
- 藥效評估之用
- 生物製劑的劑量–藥效曲線和一般的細胞毒性藥物並不同
- 利用生物性標記 (biomarker) 的反應, 決定最佳生物性劑量
- Dose associated with a prespecified most desirable effect on a biomarker among all doses studied

藥物動力學 (Pharmacokinetics)

- 研究藥物的 吸收 (absorption), 分布 (distribution), 代謝 (metabolism), 排泄 (excretion)
- Pharmacologic effects of the body on the drug

藥物效力學 (Pharmacodynamics)

- 研究藥對身體的影響 血球性毒性 (hematological toxicity),
  非血球性毒性 (nonhematological toxicity),
  腫瘤影像評估, 分子影響評估 (molecular correlate)
- Pharmacologic effects of the drug on the body

治療性指標 (Therapeutic Index)

- 特定劑量或劑量範圍所造成的毒性與藥效之比值
- The dosage or range of dosages of a drug that produce toxicity divided by efficacy

目錄

Algorithmic Design = Rule-Based Design

- Traditional 3+3 Design = Storer's Design A
- Variations of the Traditional Escalation Rule
- Best of 5 Rule
- Up and Down Designs
- Storer's Design B, C, D (Storer, Biometrics, 1989)
- Accelerated Titration Designs (Simon, et al., JNCI, 1997)
- Biased Coin Designs
- Pharmacologically Guided Dose Escalation (PGDE)
- Rolling Six Design (Pediatrics)

Traditional 3+3 Design = Storer's Design A (Storer, 1989) I

- 最常使用的第一期臨床試驗
- 從最低劑量 d_1 開始收納一組世代 3 位受試者
- 每個劑量至多收納 6 位受試者
- 一組世代 3 位受試者接受 d_j:
  - 若 0 位發生 DLT, 則劑量增加 1 個水準為 d_{j+1}
  - 若 2 位發生 DLT 則停止試驗
  - 若 1 位發生 DLT, 則使用同一劑量 d_j, 增加 3 位受試者
  - 若 ≥ 2 位發生 DLT 則停止試驗

Traditional 3+3 Design = Storer's Design A (Storer, 1989) II

- 若最低劑量 3 位中 $\geq$ 2 位 DLT, MTD 不存在.
- 若最高劑量 3 位受試者中皆無 DLT, 則可以再收 3 位確認此劑量.

Traditional 3+3 Design = Storer's Design A (Storer, 1989) III

- MTD 定義為最多 6 位受試者中有 1 位或 0 位經歷 DLT 之最高劑量.
- MTD is dose below largest dose having > 1/3 or > 1/6

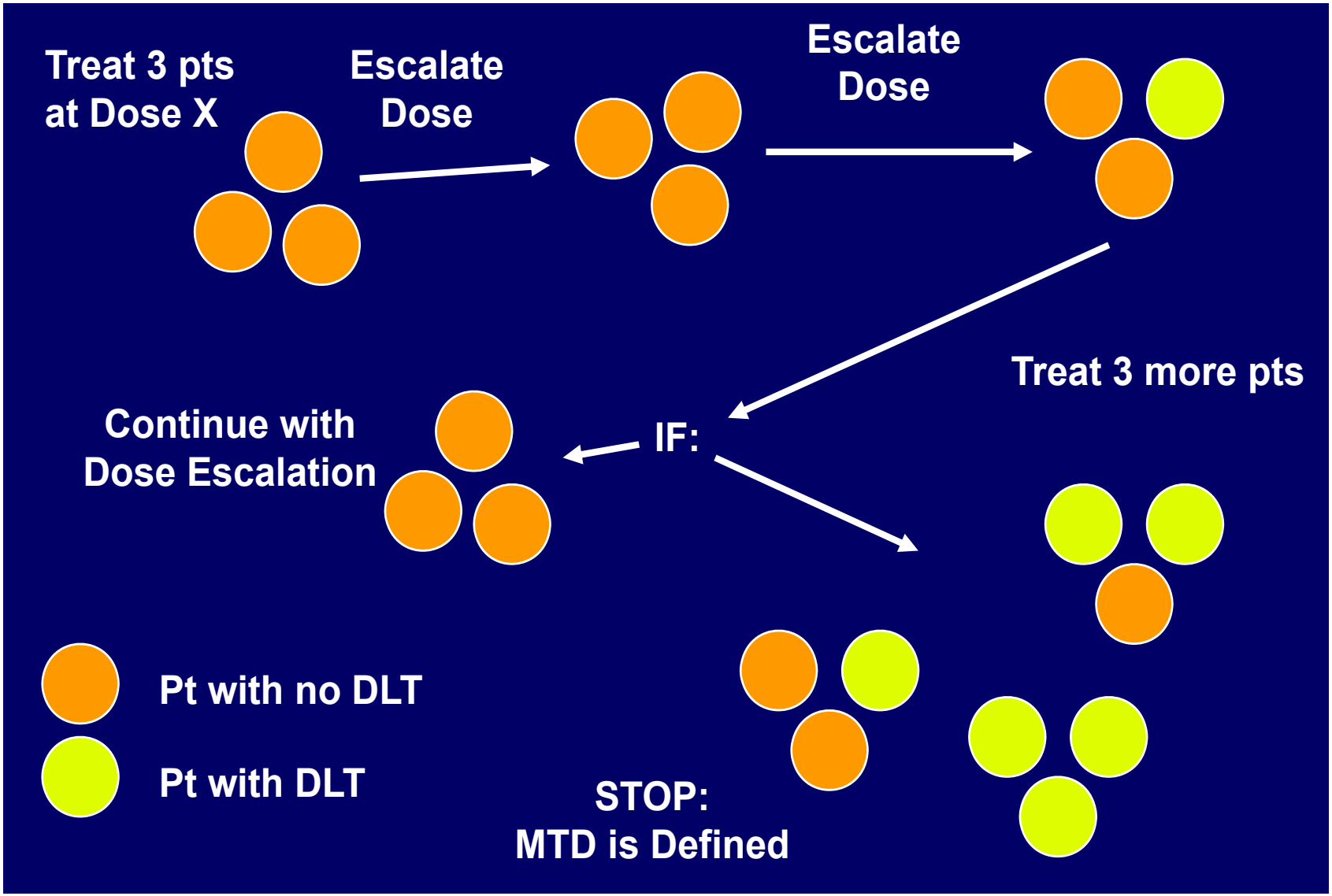


圖 2: 第一期臨床試驗: 傳統 3+3 設計

測驗 1

A 3+3 trial is studying 4 dose levels. At the end of the trial, the results are, respectively, 0/3, 1/6, 0/3, and 2/3. What is the estimated MTD? 1, 2, 3, 4?

Traditional 3+3 Design: Advantages

- Will always pick dose with 0/3 or 1/6 toxicities
- No need for statisticians or software

Traditional 3+3 Design: Disadvantages I

- No de-escalation
- As few as 3 patients enrolled
- What is interpretation of MTD?

Traditional 3+3 Design: Disadvantages II

- (1) 估計 MTD 並不精確.
  - 每個劑量最多僅有 6 位, 信賴區間寬, 變異程度大.
- (2) 找到的 MTD 多低於真正的 MTD.
  - 會讓大部分受試者接受無效的劑量 (ineffective dose level).
  - 若受試者為嚴重疾病族群, 則更耽誤到受試者治療時程.
- (3) 僅利用最近的世代 (cohort) 結果來決定 MTD.

Traditional 3+3 Design: Disadvantages III

表 1: Significant degree of uncertainty

X = # DLT	n = # Subjects	95% CI
0	3	(0.000, 0.707)
0	6	(0.000, 0.459)
1	6	(0.004, 0.641)
2	6	(0.043, 0.777)
3	6	(0.118, 0.882)
4	6	(0.223, 0.957)
5	6	(0.359, 0.996)
6	6	(0.541, 1.000)

Traditional 3+3 Design: Disadvantages IV

表2: Four Trials with the Same MTD

Dose 1	Dose 2	Dose 3
0/3	0/3	1/3+1/1
1/3+0/3	1/3+0/3	1/3+1/1
1/3+0/3	0/3	1/3+1/3
0/3	1/3+0/3	1/3+1/2

Variations to Traditional 3+3 Design

- After escalation stops, fill out all lower levels until at least 6 subjects are treated at each level
- Treat subjects at a dose level between the level where escalation stopped and the next lower level
- Expand cohort

Best of 5 Rule

- Variations to Traditional 3+3 Design
- Cohort with 3 subjects
- First DLT occurs, enroll one-by-one
- $\leq$ 2/5 DLT, escalate one level
- $\geq$ 3/5 DLT, stop

Best of 5 Rule

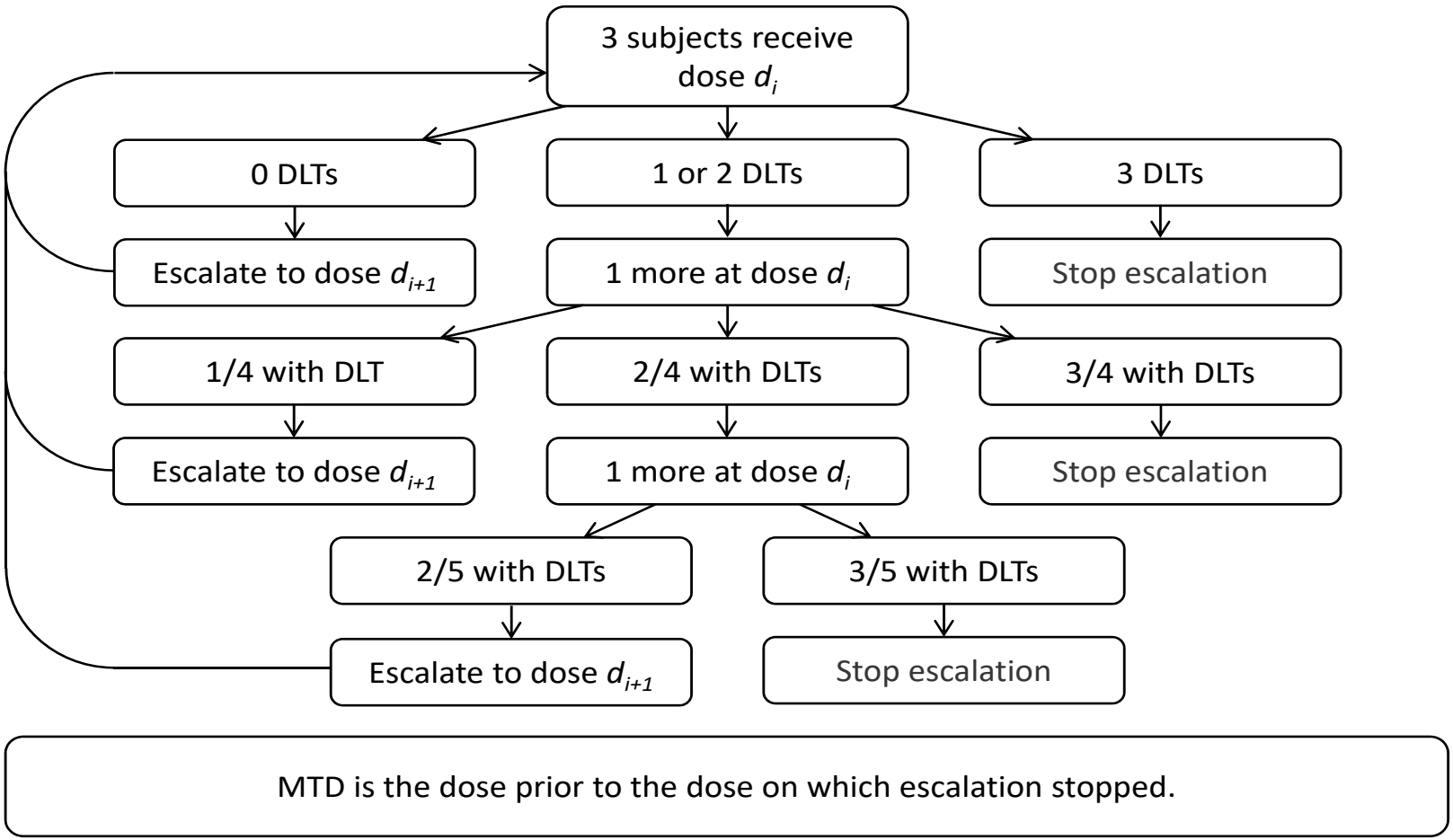


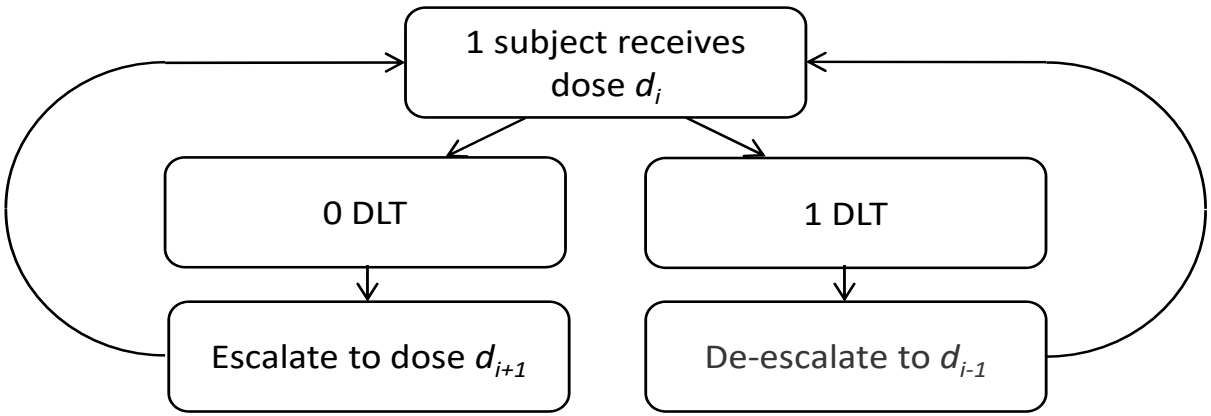
圖 3: 第一期臨床試驗: Best of 5 Rule

Up and Down Design I

- try to “speed up” the escalation process
  - 1 Up, 1 Down
    - observe single pt
    - no toxicity $\rightarrow$ increase dose
    - toxicity $\rightarrow$ decrease dose

Up and Down Design II

Up-and-Down Design (UaD)



Perform UaD for a pre-specified number of subjects (j).
MTD is the dose that would be assigned to the $j+1^{st}$ subject.

圖 4: 第一期臨床試驗: 1 Up and 1 Down Design

Up and Down Design III

Up and Down Design IV

- 2 Up, 1 Down
  - observe single pt
  - no toxicity in two consecutive $\rightarrow$ increase dose
  - toxicity $\rightarrow$ decrease dose

Up and Down Design V

- 2 Up, 2 Down
  - observe groups of 2 patients
  - no toxicity $\rightarrow$ increase dose
  - one toxicity $\rightarrow$ dose unchanged
  - both toxicities $\rightarrow$ decrease dose

Up and Down Design VI

- Whatever the modification:
  these don't use all the previous dose-toxicity info.

Storer's Two Stages Design B, C, D I

- try to "speed up" the escalation process
  - Storer's Design B, C, D
  - Two Stages

Storer's Two Stages Design B, C, D II

- Stage 1
  - Evaluate patients individually
  - Escalate after each DLT-free patient
  - After first DLT, go to stage 2

Storer's Two Stages Design B, C, D III

- Stage 2 (Storer's Design B)
  - De-escalate one dose level after first DLT
  - Escalate after one DLT-free patients
  - De-escalate after each DLT
  - Stop after fixed sample size

Storer's Two Stages Design B, C, D IV

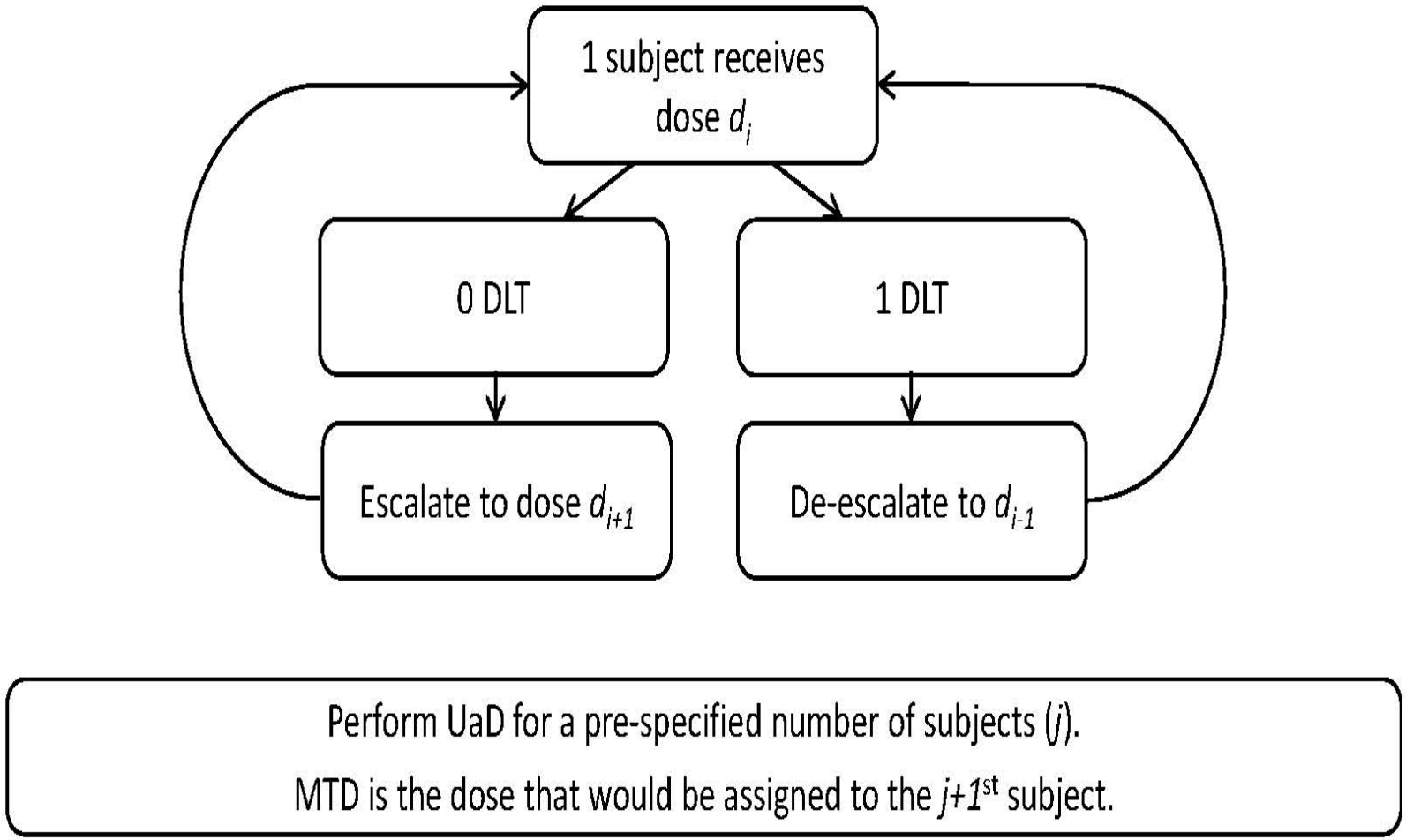


圖 5: 第一期臨床試驗: Storer's Design B

Storer's Two Stages Design B, C, D V

Storer's Two Stages Design B, C, D VI

- Stage 2 (Storer's Design C)
  - De-escalate one dose level after first DLT
  - Escalate after two consecutive DLT-free patients
  - De-escalate after each DLT
  - Stop after fixed sample size

Storer's Two Stages Design B, C, D VII

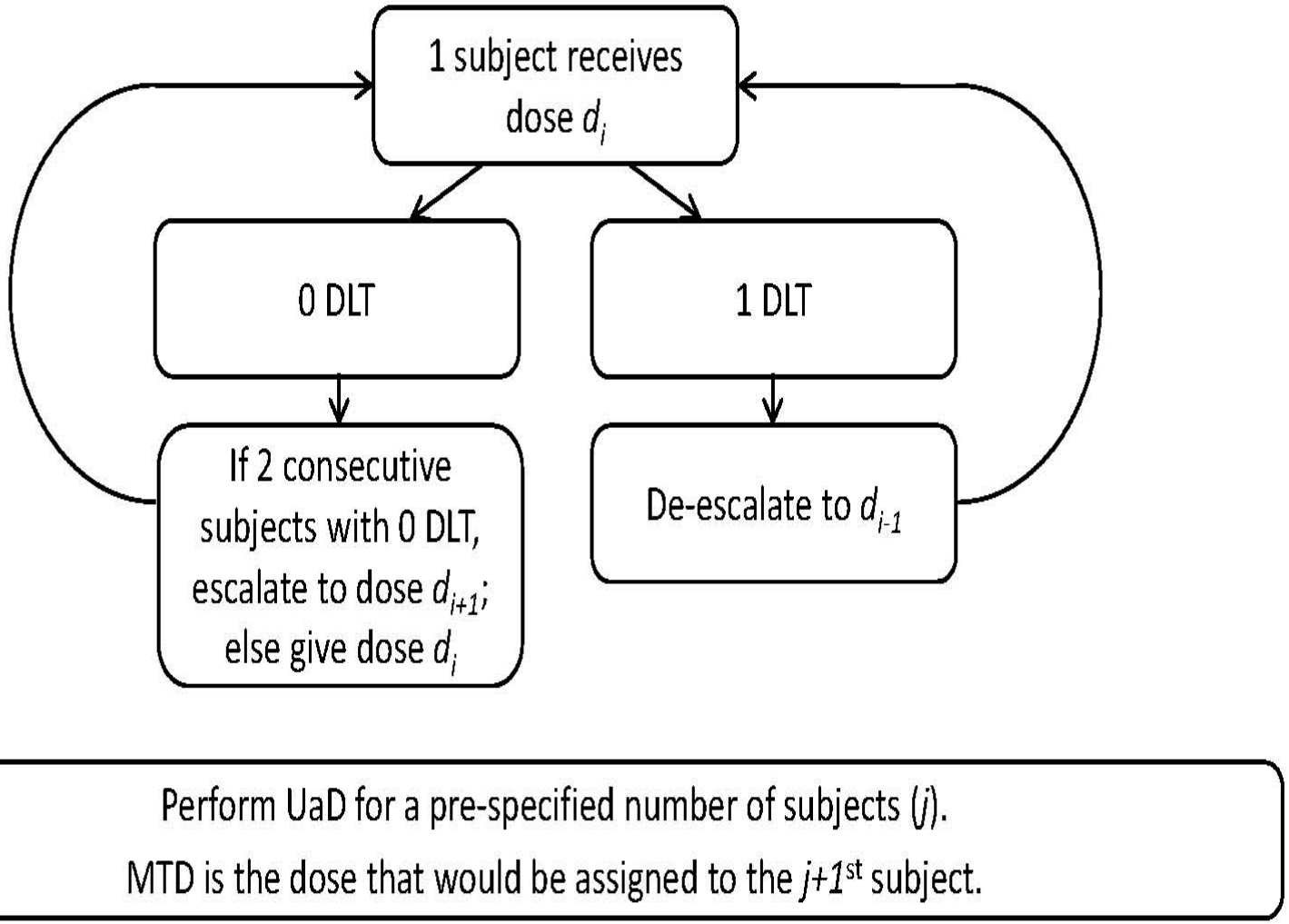


圖 6: 第一期臨床試驗: Storer's Design C

Storer's Two Stages Design B, C, D VIII

Storer's Two Stages Design B, C, D IX

- Stage 2 (Storer's Design D)
  - De-escalate one dose level after first DLT
  - Initiate traditional design (Storer's Design A)

Storer's Two Stages Design B, C, D X

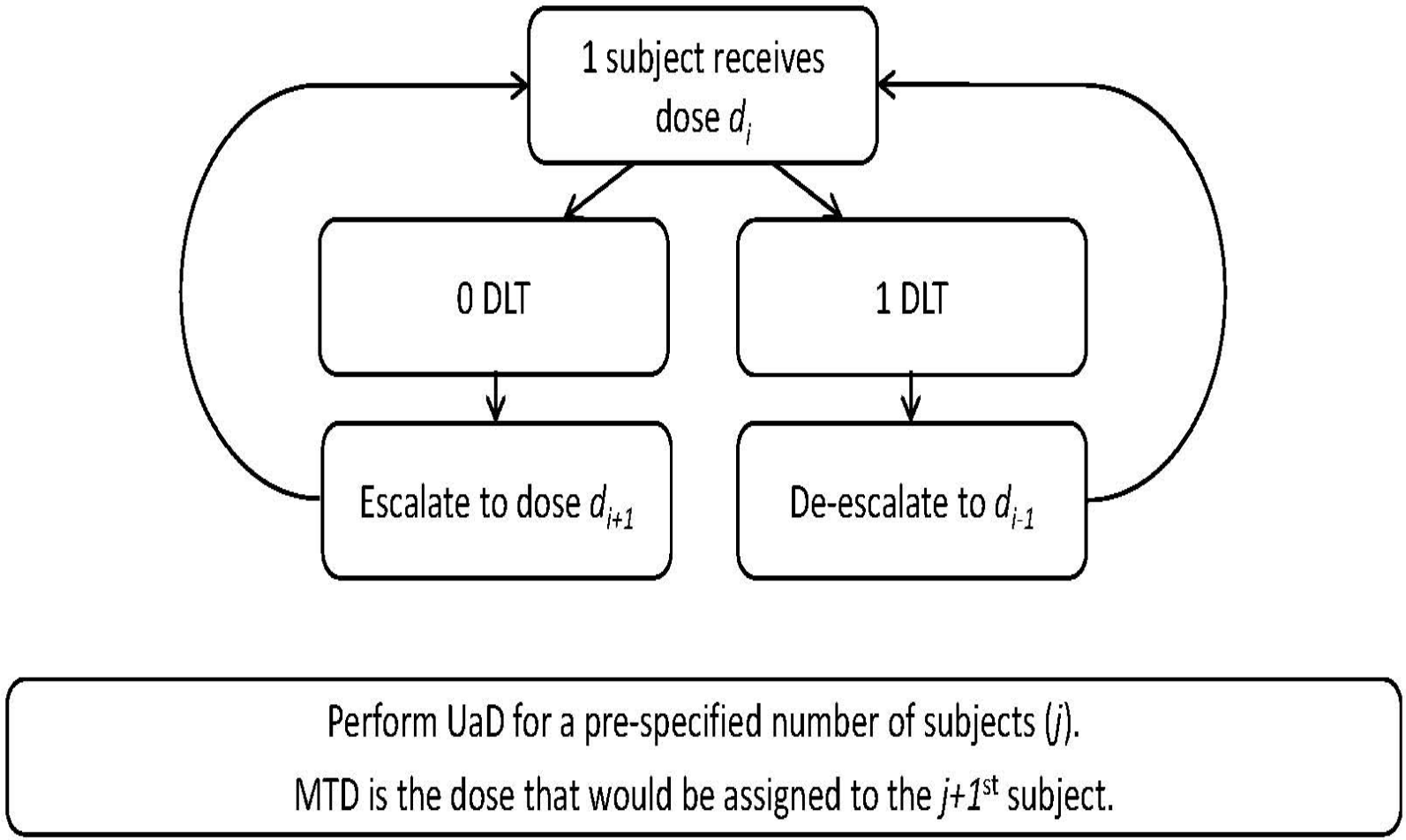


圖 7: 第一期臨床試驗: Storer's Design D

Storer's Two Stages Design B, C, D XI

Storer's Two Stages Design B, C, D XII

- Designs B through D are variations on "up and down" schemes described by Wetherill (1963) and Wetherill and Levitt (1965).
- They are implemented here with fixed sample sizes.

Storer's Two Stages Design B, C, D XIII

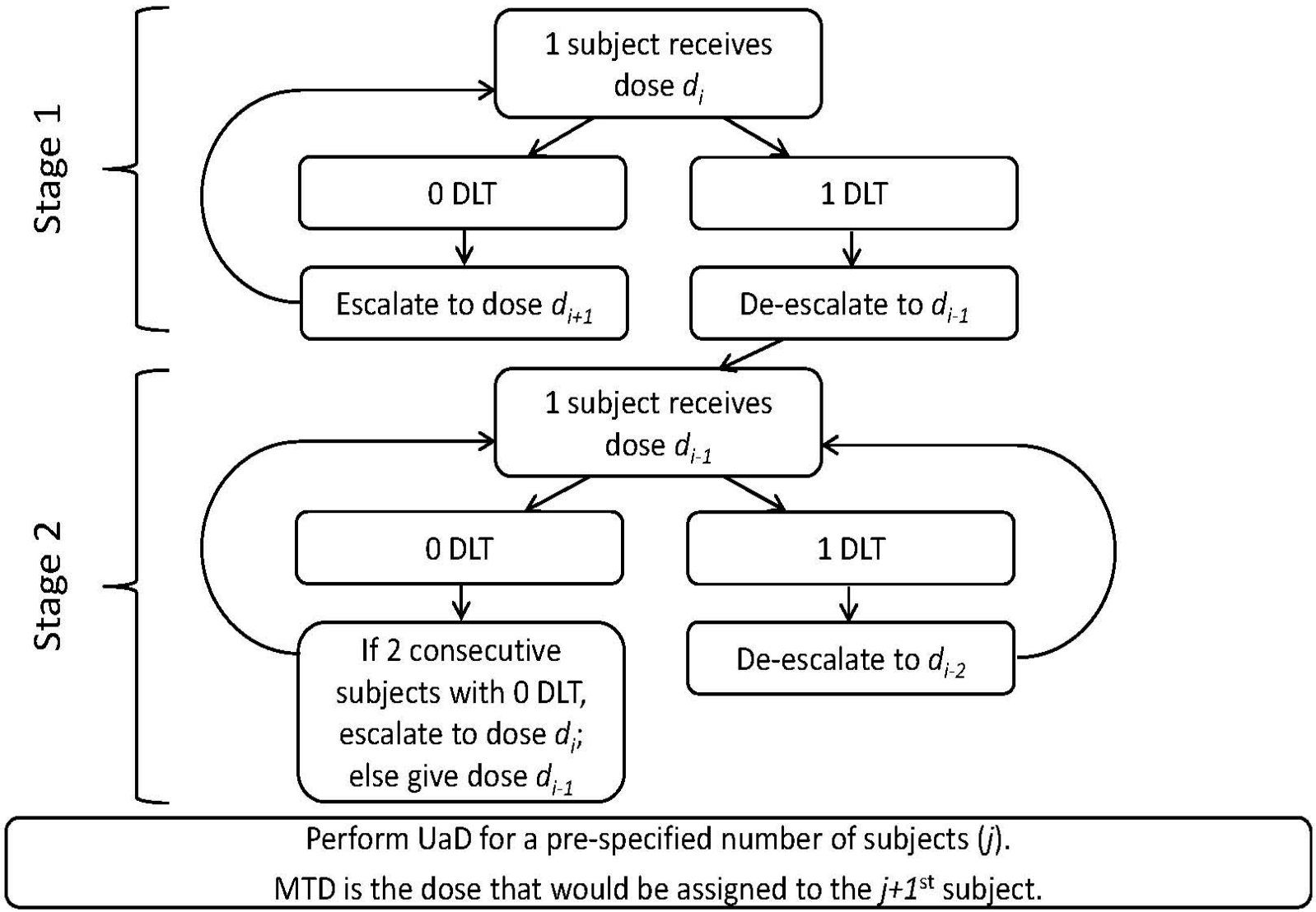


圖 8: 第一期臨床試驗: Storer's Two Stages Design

Storer's Two Stages Design B, C, D XIV

Storer's Two Stages Design B, C, D XV

- At end of study:
  - have observed k dose levels
  - n_j patients treated at dose level d_j
  - y_j toxicites at dose level d_j; $j = 1, 2, \ldots, k$
  - Assume logistic dose-toxicity model for true toxicity probabilities

Storer's Two Stages Design B, C, D XVI

- To estimate MTD, fit logistic regression.
- $\pi_j = P(\text{DLT at dose } d_j)$

$$\text{logit}(\pi_j) = \alpha + \beta d_j; \tag{4.1}$$

$$\Rightarrow \quad \text{logit}(\widehat{\pi}_j) = \widehat{\alpha} + \widehat{\beta} d_j. \tag{4.2}$$

- Yields estimated dose-toxicity curve.

Storer's Two Stages Design B, C, D XVII

- Estimated MTD

$$\text{MTD} = \frac{\text{logit}(\widehat{\pi}_{\text{target}}) - \widehat{\alpha}}{\widehat{\beta}}. \tag{4.3}$$

- π_{target}: targeted toxicity level, i.e., 33%
- Choose j that is closest to desired rate.

Storer's Two Stages Design B, C, D XVIII

- Difficult statistical issues:
- Does method produce finite estimates for α and β?
- Is $\widehat{\beta} > 0$?
- Technical statistical issues with estimates of this kind (inverse regression estimates).

Storer's Design B, C: Advantages

- Ability to go up and down
- Fast "climbing" of dose-toxicity curve
- Easy
- Fixed sample size

Storer's Design B, C: Disadvantages

- No guarantee that current pts are assigned to the best dose level
- Not using full patient information to make dose assignments

Accelerated Titration Designs (Simon, et al., JNCI, 1997) I

- try to “speed up” the escalation process
- Extension by Simon et al. (1997) of Storer’s work
  - Design 1 is as for 3 + 3 design
    - but with 40% dose increments

Accelerated Titration Designs (Simon, et al., JNCI, 1997) II

- Designs 2–4
  - Stage 1: Single subjects until first DLT or second grade 2 AE
  - Stage 2: traditional 3+3 Design

Accelerated Titration Designs (Simon, et al., JNCI, 1997) III

- Design 2 has single patient cohorts
  - Toxicities observed in first cycle only
  - one exhibits DLT or two exhibit grade 2 toxicity during their first course
    cohort expands and reverts to design 1.

Accelerated Titration Designs (Simon, et al., JNCI, 1997) IV

- Design 3 has single patient cohorts
  - with double-dose escalation steps (80% dose increments).
  - Toxicities observed in first cycle only
  - one exhibits DLT or two exhibit grade 2 toxicity

    during their first course

    cohort expands and reverts to design 1.

Accelerated Titration Designs (Simon, et al., JNCI, 1997) V

- Design 4 is the same as design 3
  - with double-dose escalation steps (80% dose increments).
  - Toxicities may be observed in any cycle
  - the first DLT or the second grade 2 toxicity
    is observed in any course of treatment
    trigger to revert to design 1.

Biased Coin Designs

- Also up-and-down
- Always de-escalate after DLT
- Escalate with probability q if no DLT, otherwise stay at current dose level.

Pharmacologically Guided Dose Escalation (PGDE) I

- Two Stages
- A pre-specified plasma exposure from preclinical data.
- Pharmacokinetic data are obtained for each patient in real time.
- Reach the pre-specified plasma exposure?
  - No, 100% dose increments
  - Yes, stop
- DLT occurs, stop.

Pharmacologically Guided Dose Escalation (PGDE) II

- 藥理引導藥物增量設計
- 先由臨床前期的藥理資料來決定要達到的血清濃度.
- 當開始給藥後, 則測量病人的血液藥物.
- 濃度是否有達到事先設定的要求:
  - 無, 則下一位受試者給予多一倍的劑量.
  - 有, 停止試驗.
  - DLT 發生, 停止試驗.

PGDE: Disadvantages

- 1) difficulties in obtaining realtime pharmacokinetic results.
- 2) problems in extrapolating preclinical pharmacokinetic data to phase I studies with different treatment schedules.
- 3) risk of exposing the next patient to a highly toxic dose.

Rolling Six Design (Pediatrics)

- only after completion of adult phase I trials
- allows accrual of two to six patients concurrently

Thanks!