CT 34: 第一期臨床試驗
Phase I Design

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目錄

Time-To-Toxicity-Event Trials

- Suppose investigators are interested in toxicities over a span of (say) six months.
- For a study with 30 subjects, three-at-a-time designs require 5 years to complete, even with perfect accrual.
- Since sequential (one-at-a-time or three-at-a-time, etc.) methods take so long in such cases, other designs should be considered.

目錄

Prorated Designs I

- Cheung and Chappell, 2000, Biometrics
- Modification of traditional designs
- Instead of collecting a group of 5 subjects for 2 years each,
  collect data on more than 5 subjects
  for a total of 10 subject-years.
- One subject measured for one year counts
  (is “prorated” as) 1/2 of a subject.

Prorated Designs II

- Require more subjects than traditional designs, provide more information at study's conclusion.
- Is much quicker than traditional designs (commensurate with the number of extra subjects).
- May require some modification if subjects from earlier groups have toxicities after dose level is increased.

目錄

Time-to-Event CRM (TiTE-CRM) I

- Cheung and Chappell, 2000, Biometrics
- A Bayesian version
- Time-To-Event Continual Reassessment Method, TITE-CRM
- Require more patients than traditional designs.
- Provide more information at study's conclusion.
- Are much quicker than traditional designs (commensurate with the number of extra patients).

Time-to-Event CRM (TiTE-CRM) II

- Both prorated designs and TITE-CRM are much quicker than traditional designs.
- If 30 patients are recruited in ten groups of 3,
- Prorated & TITE-CRM (adding one group every 2 weeks) take 18 weeks + 6 months followup = 10 months.
- Traditional & CRM designs take 6 months / group x 10 groups = 5 years.

Time-to-Event CRM (TiTE-CRM) III

- Modifies CRM by allowing patient status to contribute to model before six months.
- No extra assumptions in final analysis beyond CRM.
- Extra assumptions invoked for early dose-escalation.
- Like CRM, it is model-based and thus very flexible.

Time-to-Event CRM (TiTE-CRM) IV

- Uses information from subjects accrued,
  even if they haven't finished observation period.
  - Subjects with DLT are given full weight
  - Subjects without DLT are given weight t/T.
- Allows subjects to be enrolled
  without waiting for prior cohorts to finish.
- Benefits studies with delayed toxicity (e.g. radiation studies)

Additional TITE-CRM Considerations I

- Choice of weight function
- Uniform toxicities may use a linear function
- Expecting late toxicities may use a convex function
- Expecting early toxicities may use a concave function
- Setting a Margin (i.e. upper limit) on toxicity
- If $\pi_{\text{target}} = 0.20$ and Margin = 0.05,
  dose for next subject will be dose closest to 0.20
  and not greater than 0.25.
- Determine cumulative time exposure (B)
  before allowing escalation (e.g. B = 2)

CRM Extension 1: Time-to-Event

- Occurrence of DLT usually not instantaneous
- What to do if next patient enrolls?
- Calculate next dose assignment excluding patients with incomplete follow-up (wastes information)
- OR assume no DLT ($y_j = 0$) and calculate next dose assignment (DLT may still occur)
- OR wait until observation window is complete (refuse treatment to patient; extend trial duration)
- OR?

Weighting Incomplete Observations I

- Record current status of all patients (DLT / no DLT yet)
- Calculate weights $wi \in (0, 1]$ for those with no DLT and are still being observed
- Use weighted binomial likelihood

$$L(y \mid \pi, d_j) = \prod_i^n \Big(\pi(d_j)\Big)^{y_i} Big\big(1 - w_i \pi(d_j)\big)^{1-y_i}. \quad (3.1)$$

$$\pi(d_j) = P(\text{DLT} \mid d_j). \quad (3.2)$$

Weighting Incomplete Observations II

- w_i is function of time, increases to 1 as follow-up completes
- Function form based on on expected timing of DLT
- If DLT is early onset, then 90/100 days of completed follow-up should imply $w_i = 1$.
- Assume total follow-up time is t

$$w(t) = \begin{cases} u_i/T, & \text{no TLT, up time } u \leq T \text{ follow-up;} \\ 1, & \text{TLT occur.} \end{cases} \tag{3.3}$$

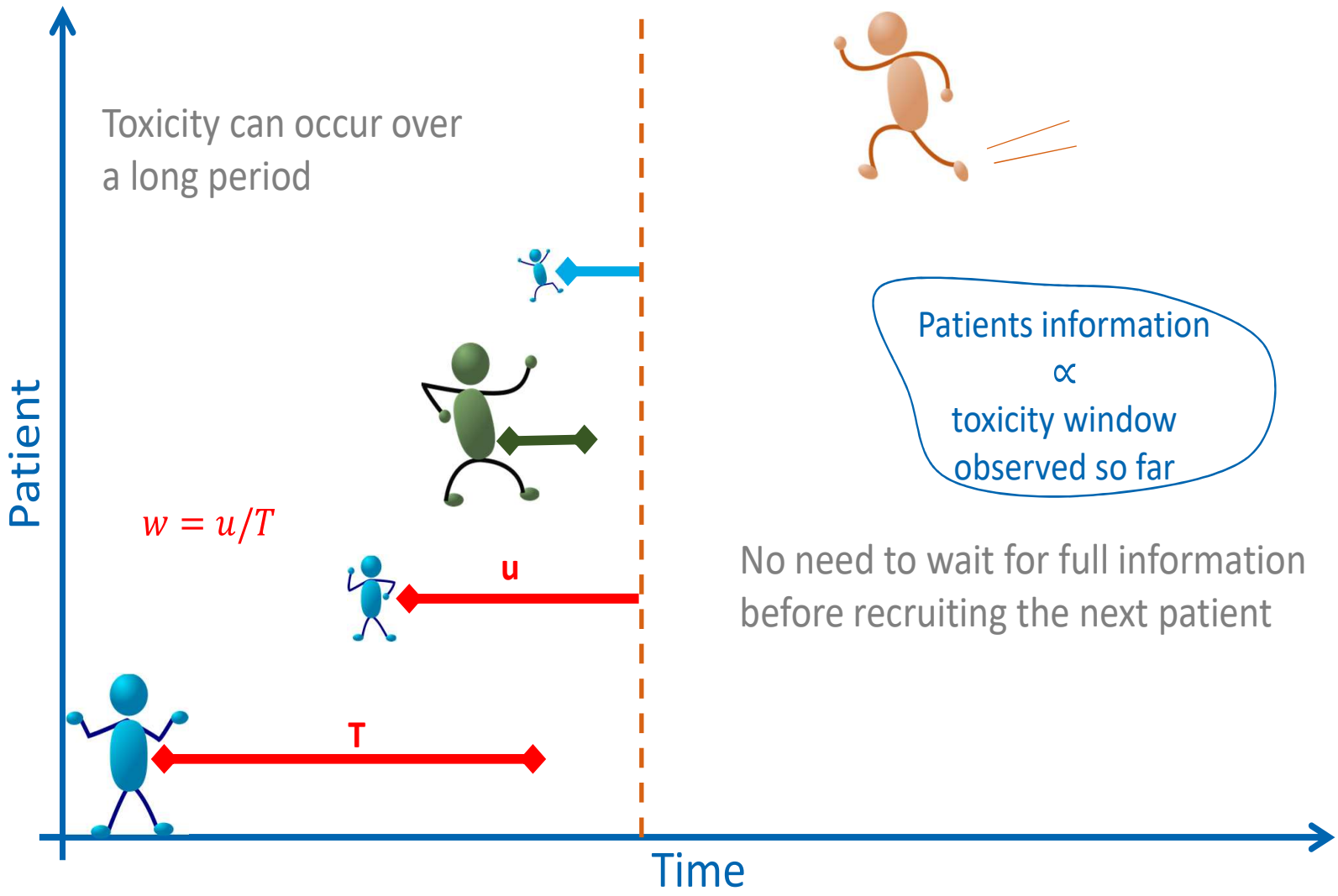

圖 1: 第一期臨床試驗: TiTE-CRM

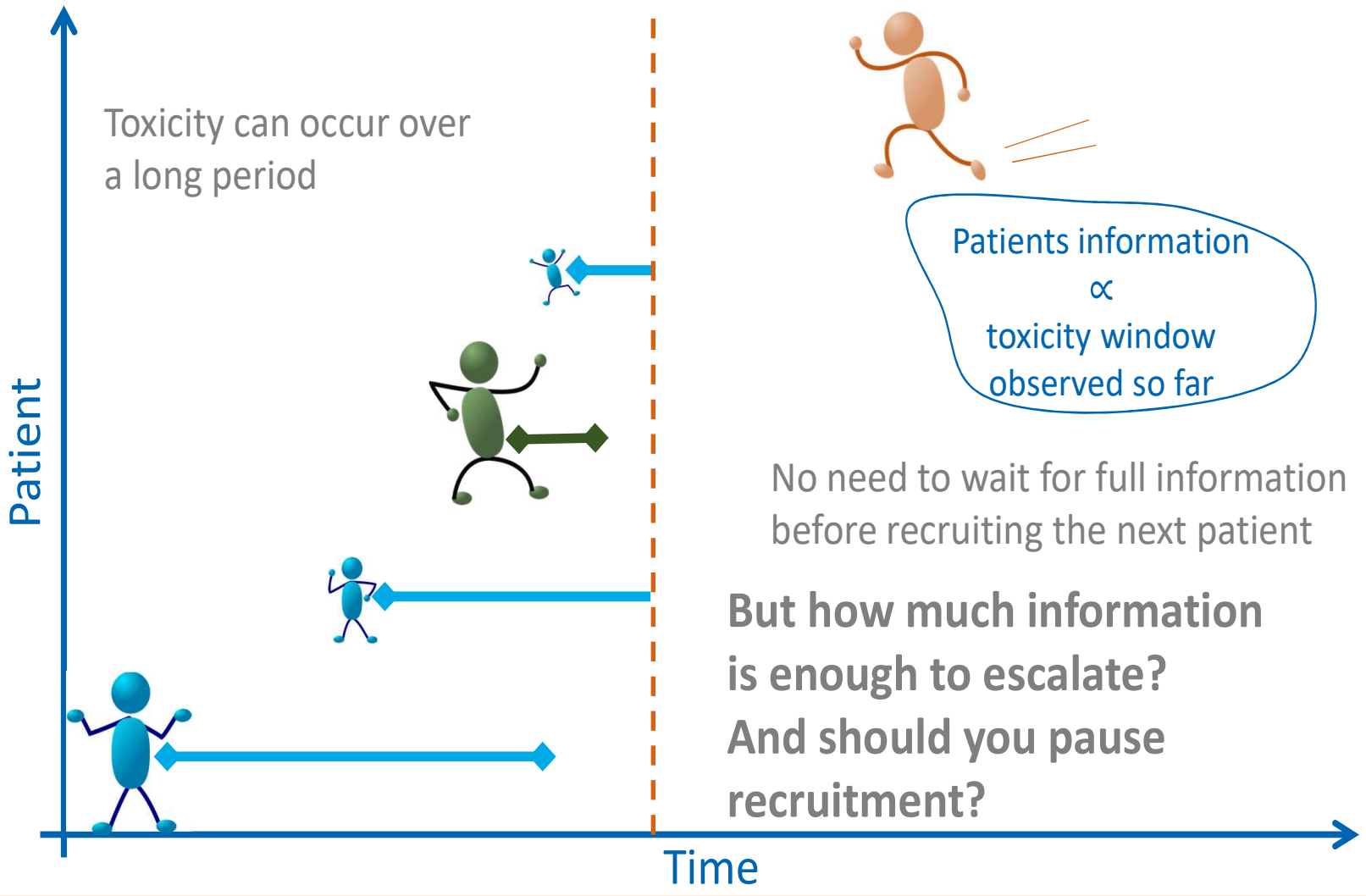

圖 2: 第一期臨床試驗: TiTE-CRM

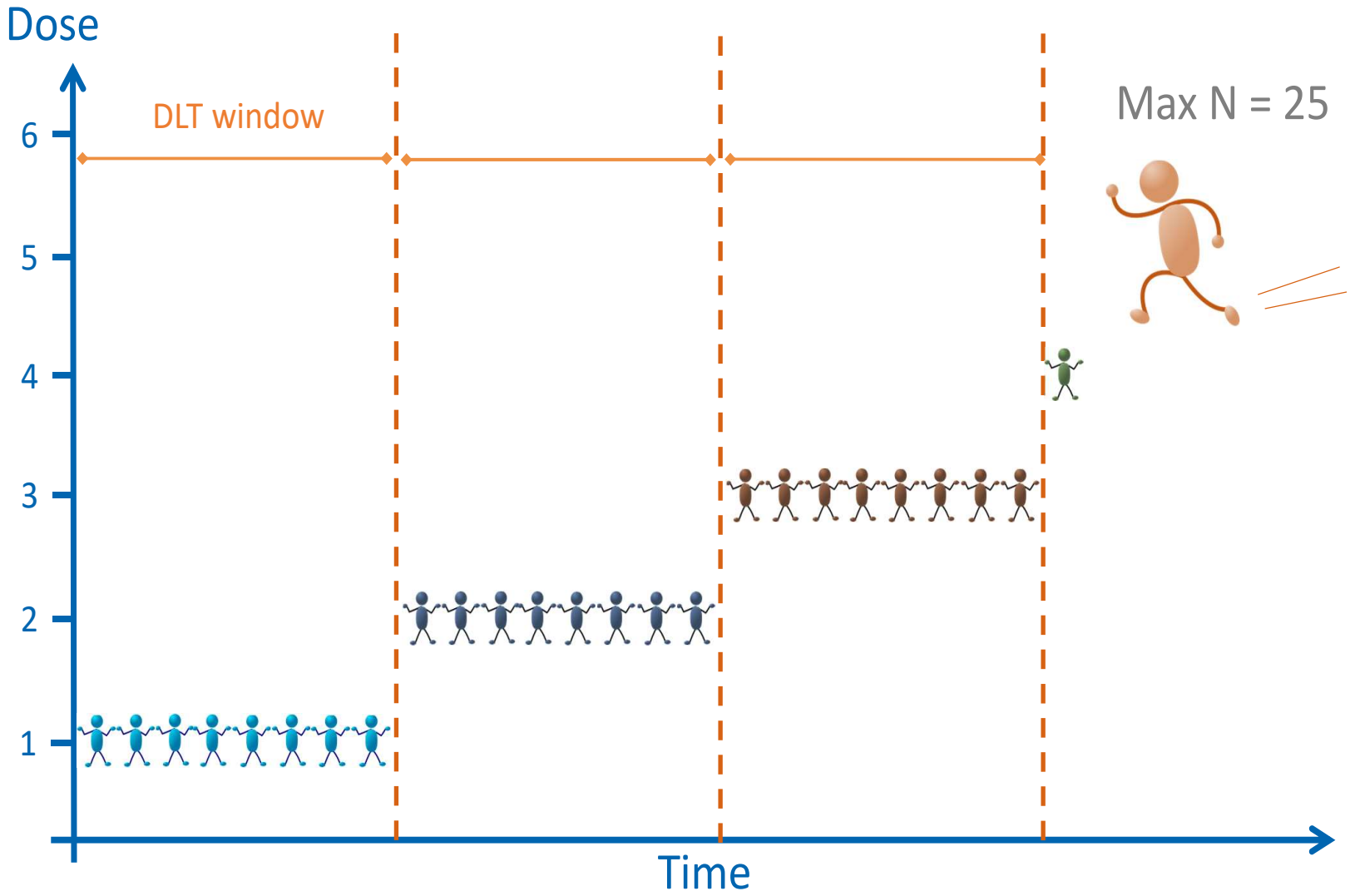

圖 3: 第一期臨床試驗: TiTE-CRM

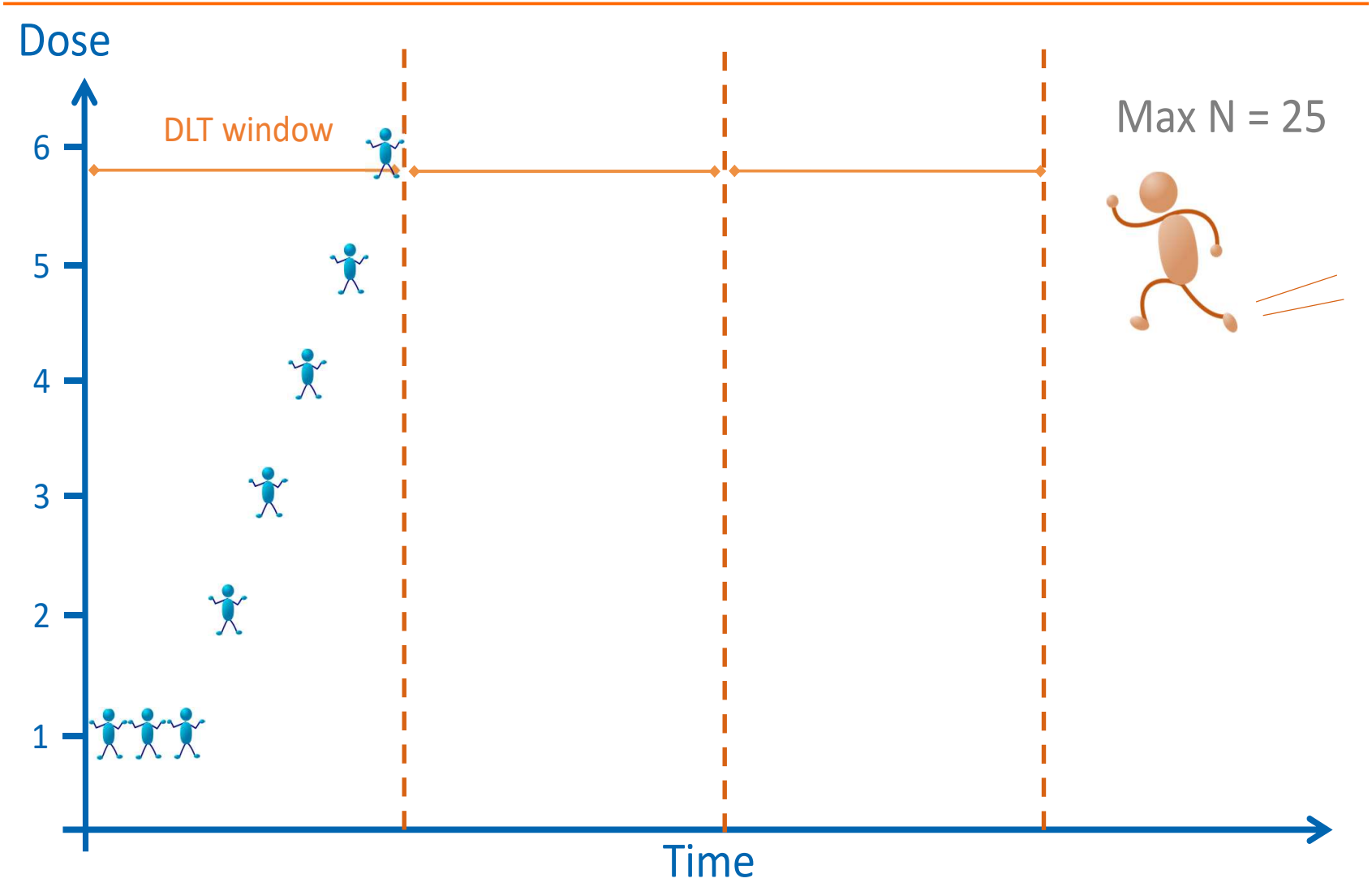

圖 4: 第一期臨床試驗: TiTE-CRM

測驗 1

Under which of the following scenarios is the “TITE” of the “TITE-CRM” more critical?

1. When the typical inter-subject enrollment time is substantially longer than the DLT period.
2. When the typical inter-subject enrollment time is comparable or shorter than the DLT period.

測驗 2

Some chemotherapies have late-onset DLTs, meaning that toxicities are frequently not observed until the end of the cycle. Assume the DLT observation window spans 28 days. Which of these options would be the best choice of the weight function $w(t)$, where t is time in days, under such a late-onset setting?

1. $w(t) = \frac{t}{28}$
2. $w(t) = \left(\frac{t}{28}\right)^2$
3. $w(t) = \left(\frac{t}{28}\right)^4$

CRM Extension 2: Overdose Control

- Posterior probability of Overdose
- Calculate posterior probability that dose *j* constitutes an "overdose", given data on first *i* patients:

$$\gamma_j = P(\pi_j > \pi_{\text{target}} \,|\, \boldsymbol{y}) \tag{3.4}$$

- Let γ_{target} be a pre-specified acceptable overdose probability.
- At each patient, identify [smallest / largest] *j* such that $\gamma_j [\geq, \leq] \gamma_{\text{target}}$, i.e. *j* such that probability of overdose is tolerable.

測驗 3

γ_{target} close to zero implies that tolerance for overdose is

1. low
2. high

目錄

Escalation with Overdose Control (EWOC)

- Replaces $\text{argmin}_j \left| \widehat{\pi}_j - \pi_{\text{target}} \right|$ (from original CRM) with $\text{argmax}_j \{ \widehat{\gamma}_j < \gamma_{\text{target}} \}$
  (Babb, Rogatko and Zacks, 1998)
- Reminiscent of MTPI overdose control
- What are differences?
- Implemented in `bcrm` package
  (Sweeting, Mander and Sabin, 2013)
  (requires additional Bayesian software packages)

Phase I Design: Considerations

- How do the designs compare?
  - Sample size
  - Conduct
  - Adaptability / extensibility
  - Ethics

測驗 4

Suppose the most recent patient was assigned to dose level *j*. The data from previous patients who were assigned dose level *j*-1, statistically impact the next dose assignment:

1. MTPI only
2. CRM only
3. Both
4. Neither

測驗 5

A model-based probability of DLT at dose level j-1 will always be less than or equal to the model-based probability of DLT at dose level j

1. MTPI only
2. CRM only
3. Both
4. Neither

測驗 6

You could also use the integer values of the dose labels $(1, 2, 3, \ldots, k)$ as the skeleton of a CRM

- Yes
- No

R Package

- Package `dfcrm`
  - function `titecrm()`: one dose assignment
  - function `titesim()`: operating characteristics, trial duration
  - function `getprior()`: skeleton so that OC are met
  - function `cohere()`: coherence status of 2 stage CRM
  - function `crmsens()`: model sensitivity via indifference intervals
- Package `CRM`
  - function `crmsiminc()`: OC, trial duration

測驗 7

- Use the `titesim` function do design a simple trial.
- Choose a model (options are empiric or logistic).
- Targeting DLT rate of 0.30.
- Determine number of subjects needed to

  identify true MTD with probability at least 0.70 under either truth
- Investigate sensitivity to prior scale
- What design elements did you choose?
- How many subjects do you need?

Thanks!