CENTRE for STATISTICS in MEDICINE

NDORMS
NUFFIELD DEPARTMENT OF ORTHOPAEDICS, RHEUMATOLOGY AND MUSCULOSKELETAL SCIENCES

UNIVERSITY OF OXFORD

Time-To-Toxicity-Event Trials

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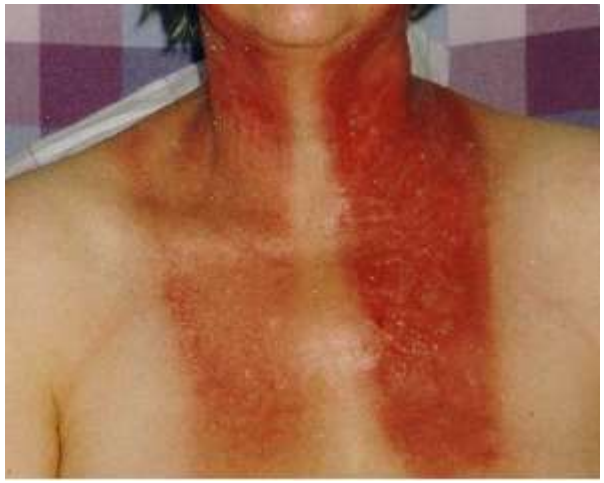
CRM

- CRM uses all enrolled patients to estimate the best dose to give the next patient
  - Assumes DLTs occur soon after administering treatment

- QUESTION: What happens in a radiotherapy trial where toxicities may occur a long time after treatment has finished?

Radiation toxicities

- There are some really long term toxicities, e.g. heart toxicity, that we don't know about for many years
- By late onset radiation toxicity we mean
  - toxicities that occur whilst the radiotherapy is still working but whilst you are not actually having treatment
- Patients are told to expect toxicity for the same time after treatment as the treatment takes
  - E.g. 6 weeks radiotherapy means 6 weeks of toxicity after the treatment before it stops getting worse/starts to get better



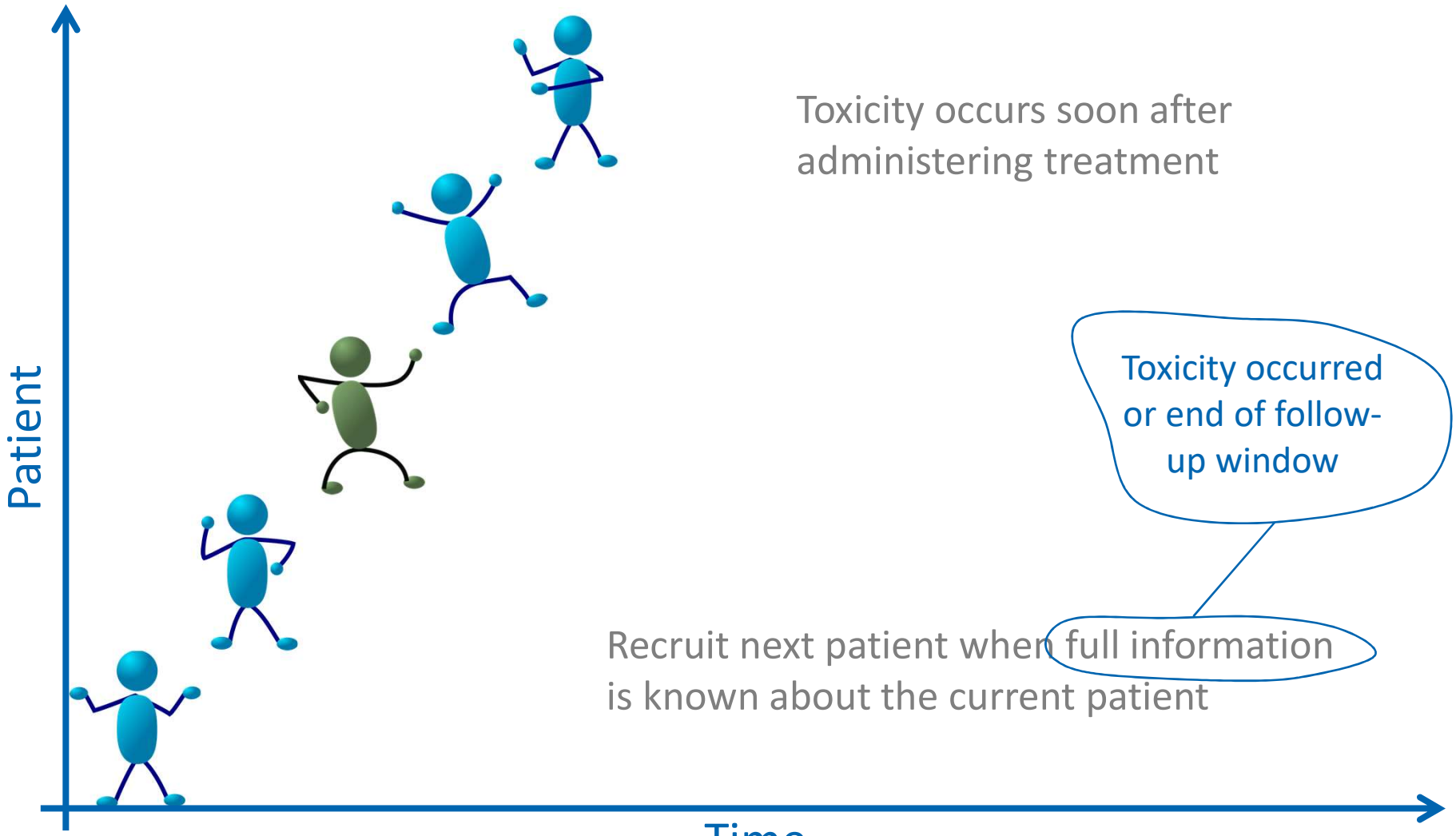
http://www.fashion-era.com/Radiotherapy_3.htm

TiTE-CRM

- TiTE CRM - Time To Event CRM – uses all enrolled patients to estimate the best dose to give the next patient
  - Accommodates DLTs that occur a long time after administering treatment
  - No need to wait until the end of the follow-up window before recruiting the next patient
  - Accounts for partial information via weighting
    - Weight each subject according to how much information they provide
    - DLT → full information, weight = 1
    - No DLT → partial information, weight = proportion of DLT window observed so far

Cheung YJ and Chappell R (2000). Sequential Designs for Phase I Clinical Trials with Late-Onset Toxicities. Biometrics, 56, 1177-1182

CRM – immediate toxicity

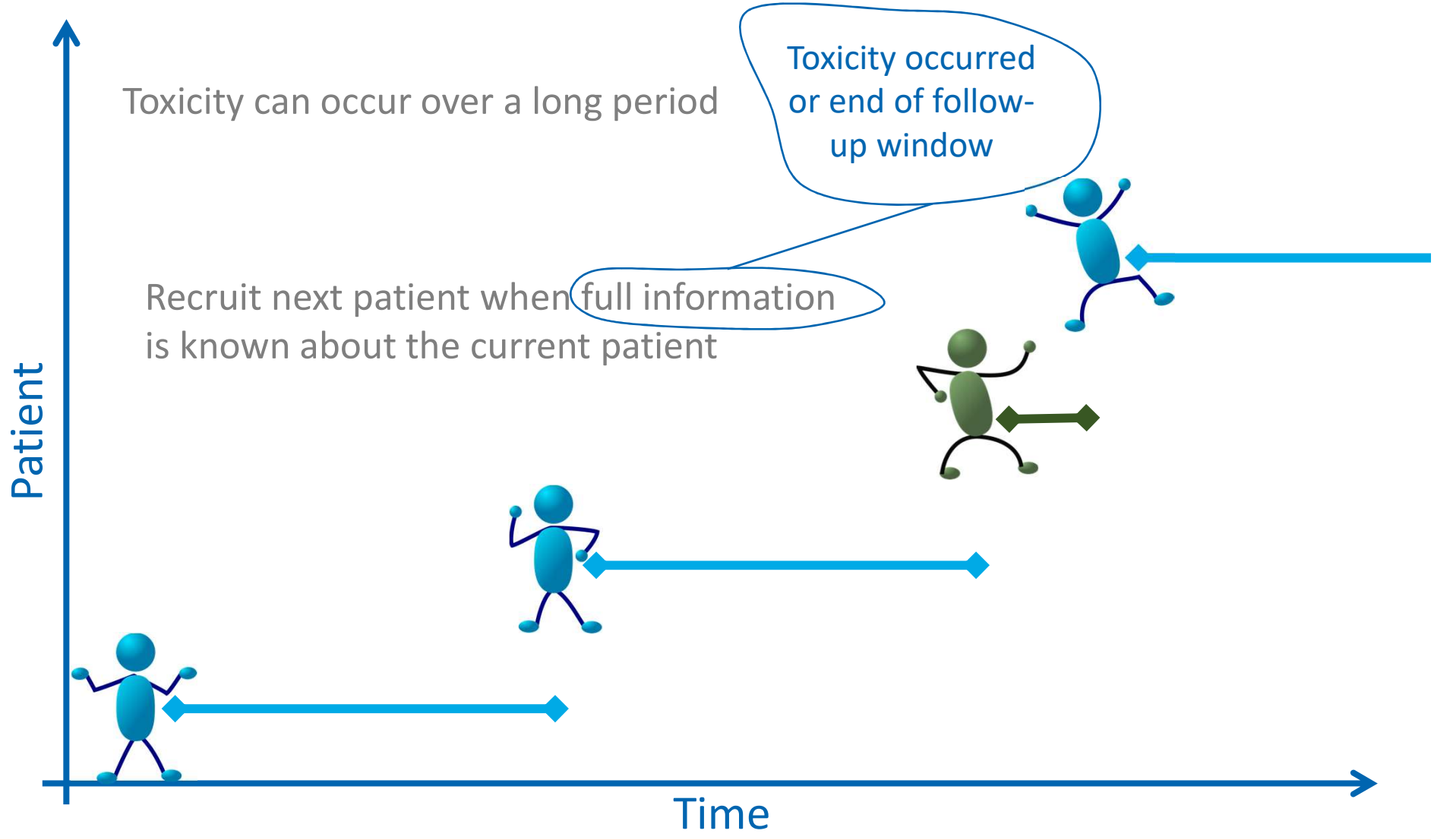


Toxicity occurs soon after administering treatment

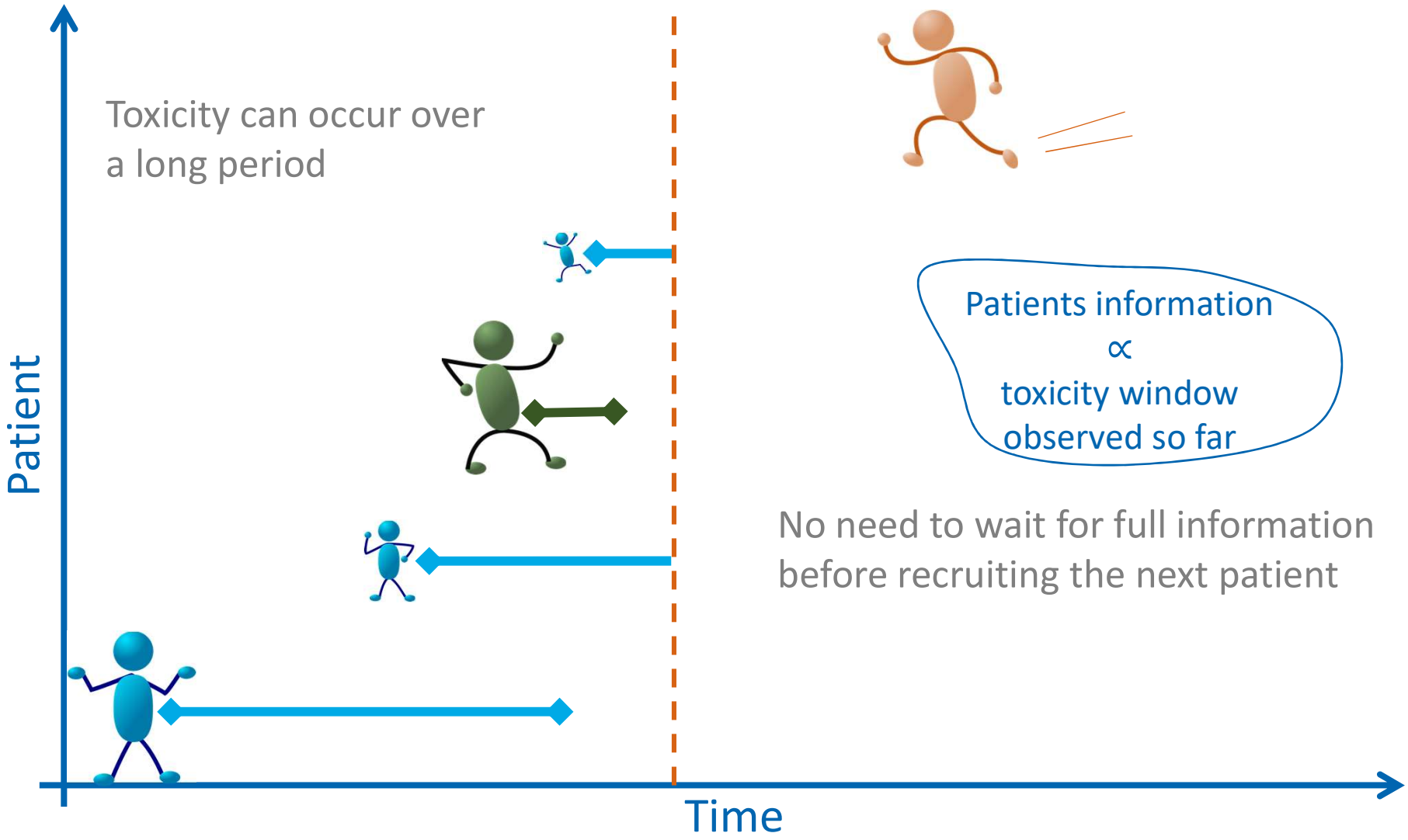
Toxicity occurred or end of follow-up window

Recruit next patient when full information is known about the current patient

CRM – long toxicity window



TiTE-CRM – long toxicity window



Using equations

- y_i = toxicity response $(0/1)$ for subject i at dose x_j
- $\pi_j = \mathrm{f}(x_j,\alpha)$ = probability of a toxic response at dose x_j
  $= E\left(y \middle| \text{dose} = x_j, \alpha\right)$

The likelihood function is given by

CRM

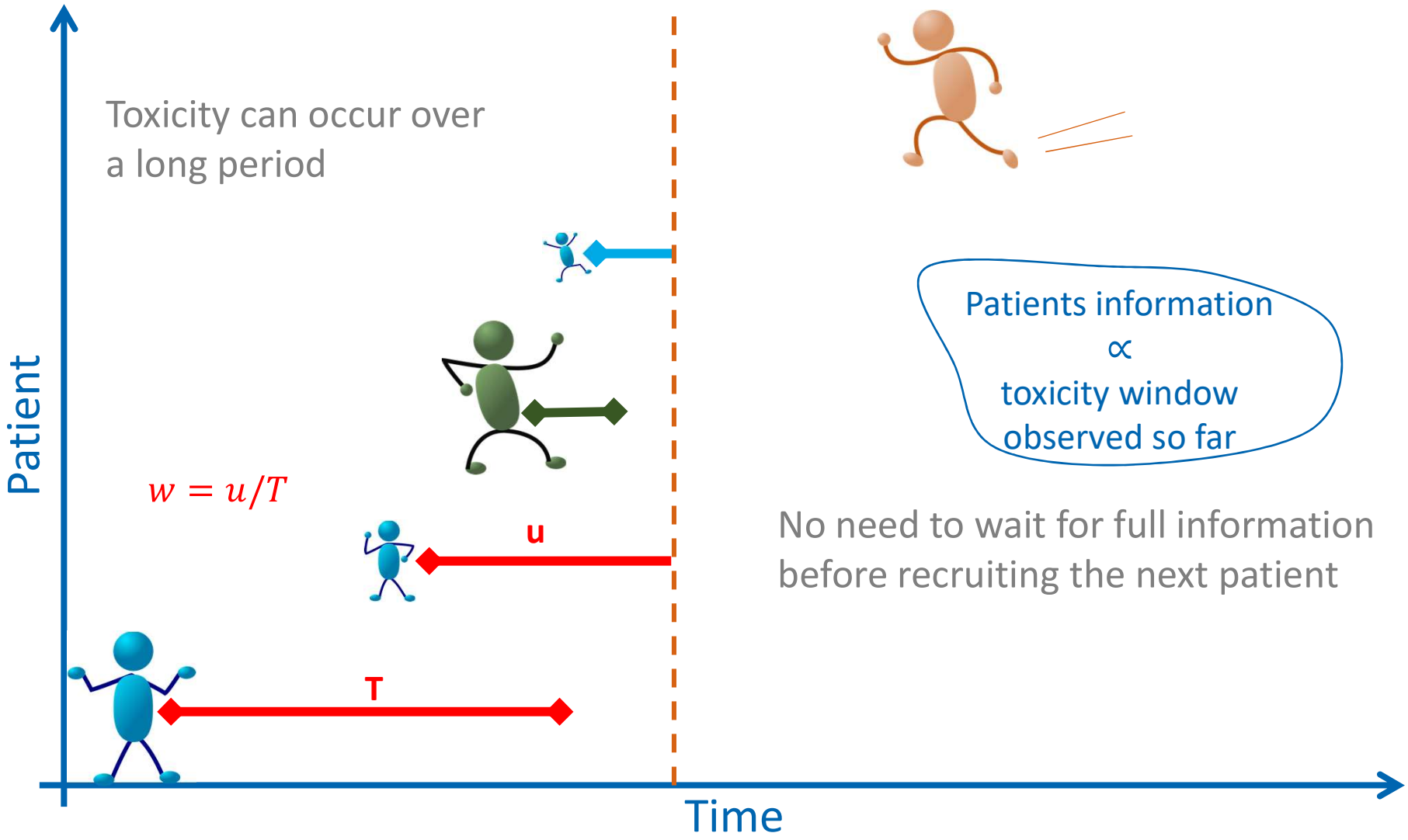
$$L(\alpha) = \prod_{i=1}^{n} \left[\pi_j(\alpha)\right]^{y_i} \left[1 - \pi_j(\alpha)\right]^{1-y_i}$$

TiTE-CRM

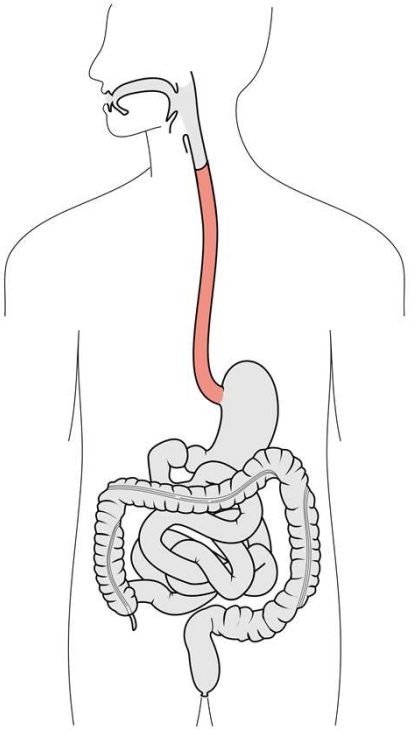
$$L(\alpha) = \prod_{i=1}^{n} \left[w_i \pi_j(\alpha)\right]^{y_i} \left[1 - w_i \pi_j(\alpha)\right]^{1-y_i}$$

$$w_i = \begin{cases} \mathrm{u_i/T}, & \text{if patient } i \text{ still in follow-up without a DLT} \\ 1, & \text{if patient } i \text{ has a DLT or has been followed for } T \text{ without a DLT} \end{cases}$$

TiTE-CRM – long toxicity window



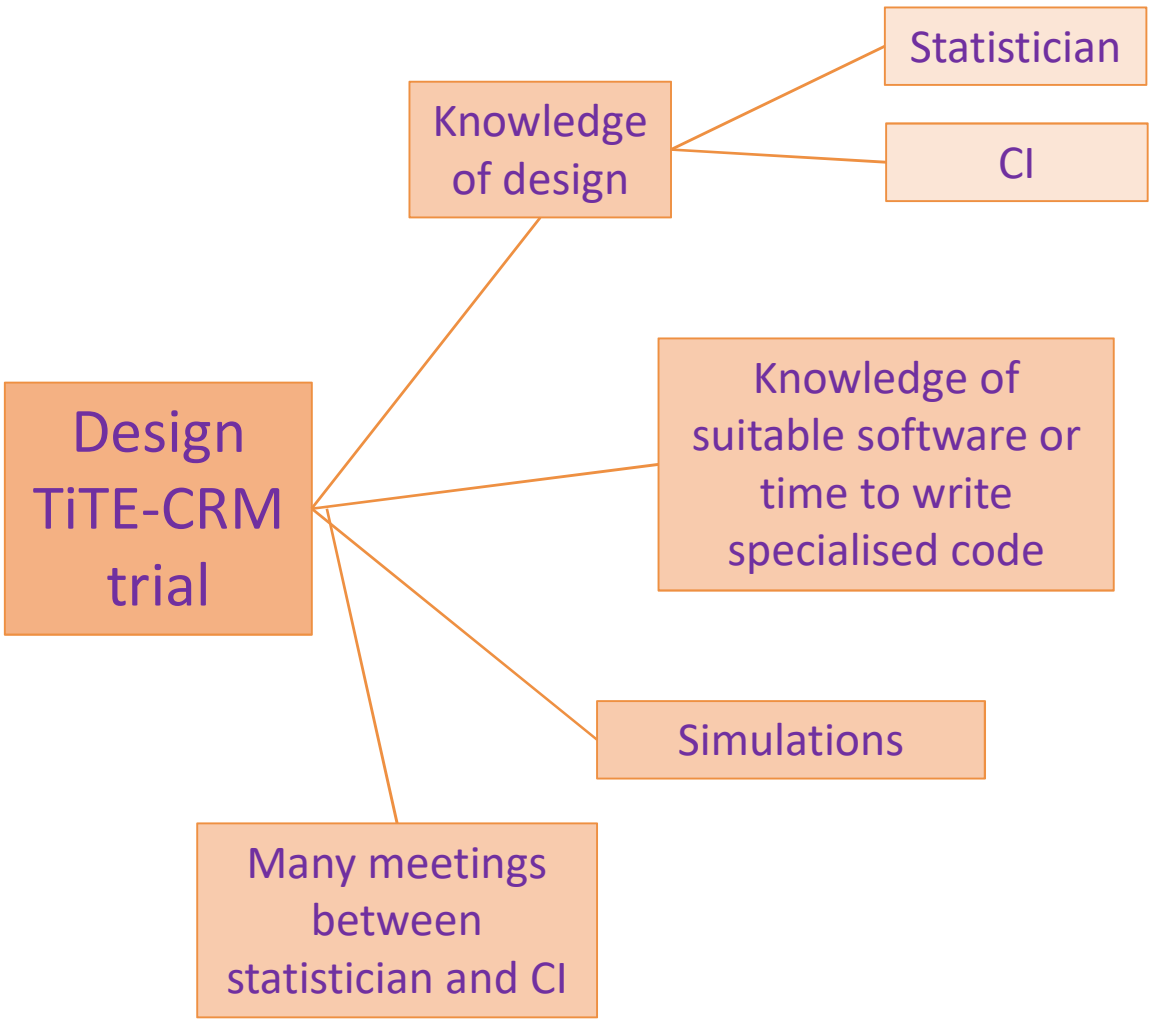
Phase I, single arm, open-label, multicentre, 2 stage trial in oesophageal cancer



CHARIOT

STAGE A1	STAGE A2	STAGE B
Oesophageal tumours	Metastatic or advanced inoperable solid tumours	Oesophageal tumours
M6620 and palliative radiotherapy	M6620 and palliative chemotherapy	M6620, chemotherapy and definitive radiotherapy
Treatment duration: 3 weeks	Treatment duration: 18 weeks	Treatment duration: 11 weeks
DLT window: 9 weeks	DLT window: 4 weeks	DLT window: 24 weeks
2 doses, 3 schedules	2 doses, 2 schedules	1 dose, 6 schedules
TTL: 0.25	TTL: 0.30	TTL: 0.45

Design a TiTE-CRM trial



But how much of this do you need completed for the grant application?

And how do you fund what does need to go in?

What did we do?

- Decided as a unit we didn't want to do 3+3 any more
  - Invested time in learning about CRM before we had our first trial to design
- Had many meetings with CI convincing her of the merits of the design
- Spent lots of time writing code and running simulations
- Put all details in the grant application.
- Grant was successful, we were ready to go

Fortunately we managed to find some local money to do this.

We funded the upfront time internally before grant submission

Now we are more prepared for the next one – or so we thought

Another approach

- Another potential trial came our way, but this one needed to include efficacy as well as toxicity in the dose-escalation – dual endpoint
- We weren't quite so prepared as we thought we were then
- This time we wrote in the grant application that we wanted time during trial set-up to finalise the design, and kept the details in the application as brief as possible
- Grant was successful. Now was time to research the relevant methods and design the trial

BUT

- Now the clock is ticking. The trial team has 1 year to recruit a patient after hearing about the grant. They want the design now, they don't want to wait while we work out the best thing to do

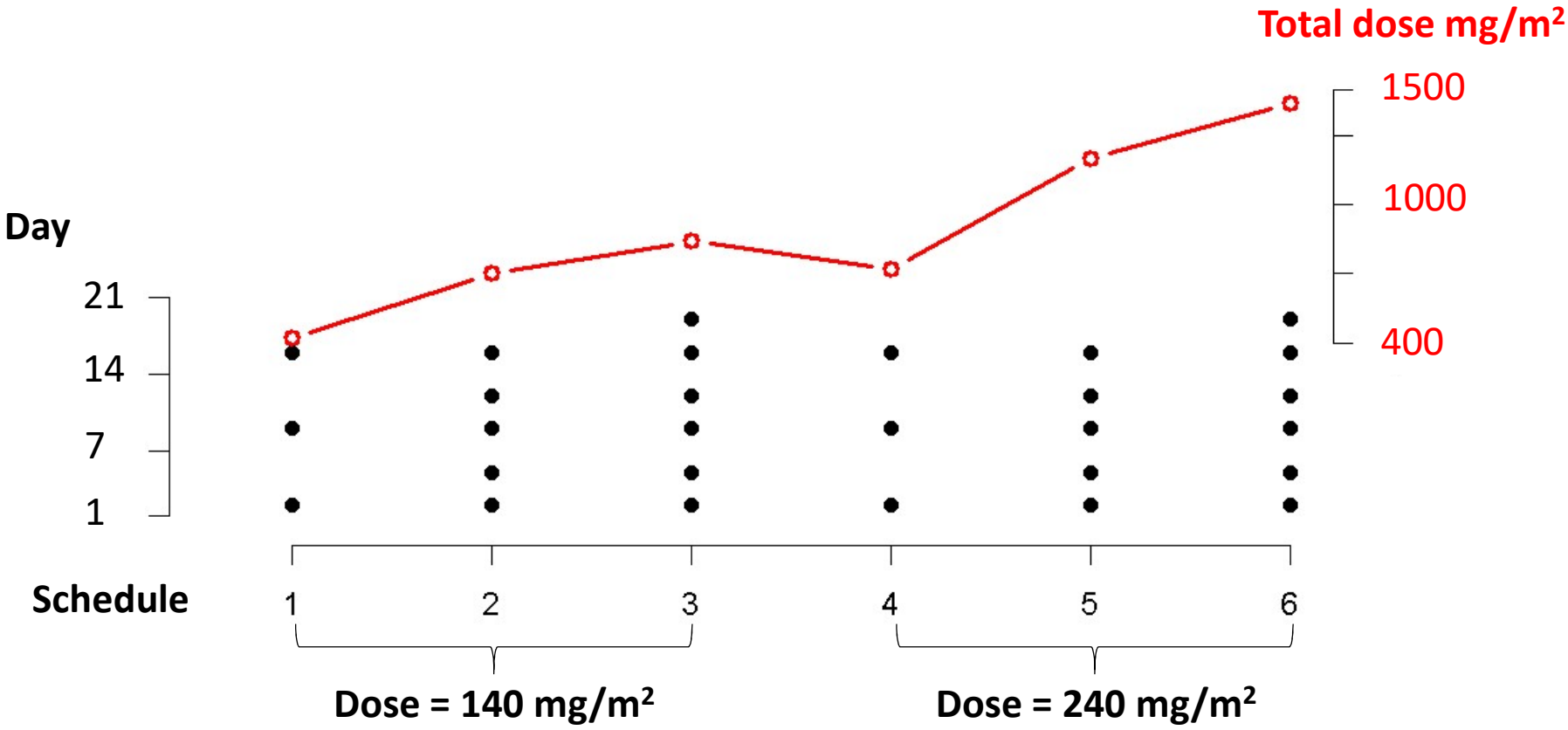
So what are the options?

- Upskill workforce in preparation
- Design the trial for free during grant application
- Fund internally during grant application and hope you get the grant
- Write in the grant that you will work up the design when the grant starts
- Apply for a grant to design the trial before the trial grant application goes in. Trial development and planning grants are offered by
  - UK Joint Global Health Trials scheme
  - US NIH

- Quicker but still risky option
  - Give scant details in the grant application
  - Ask for money in the grant to work out what to do
  - Start work on the design as soon as the grant application is complete

Schedules and doses, Stage A1

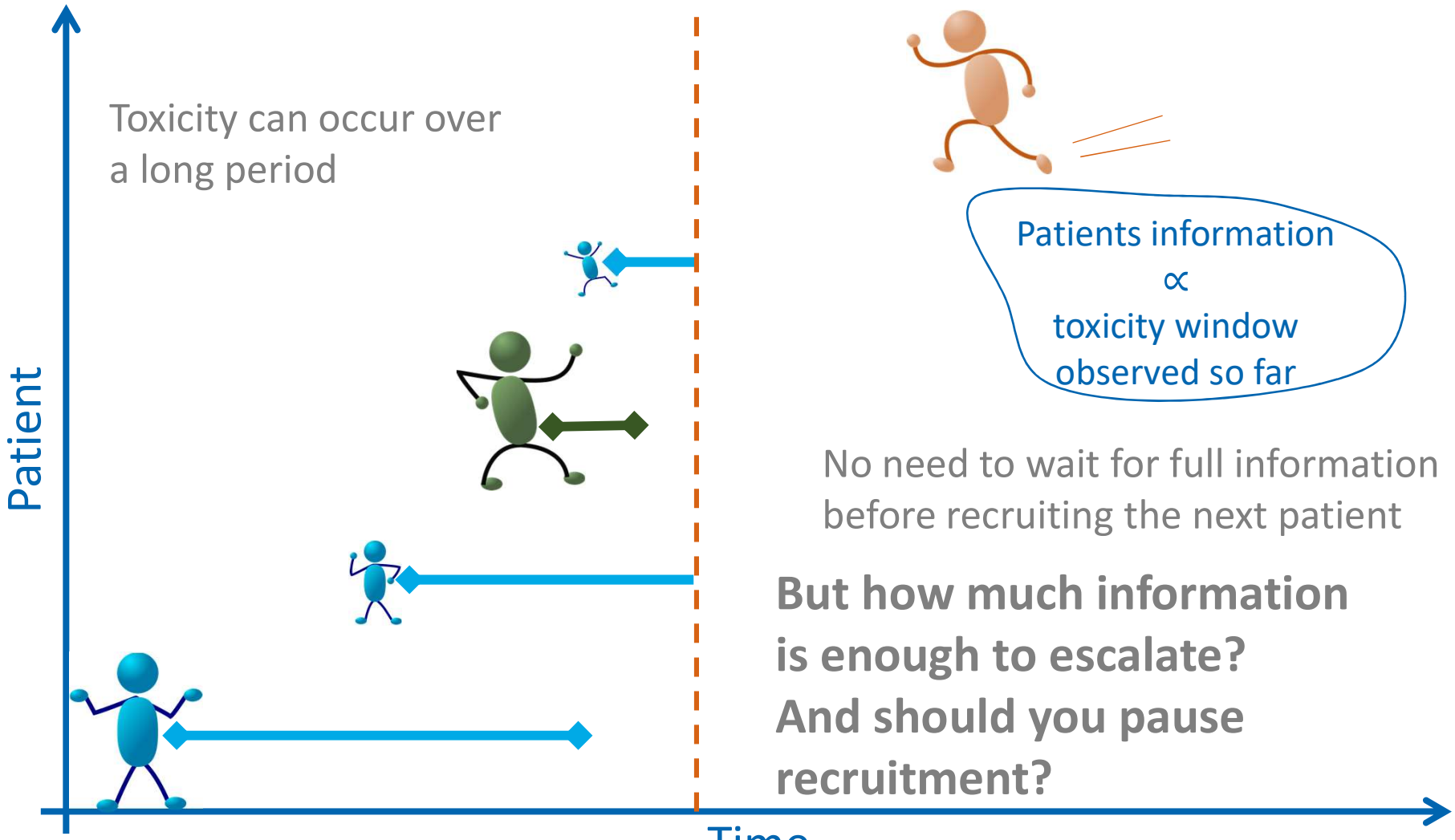
Monotonic in toxicity?



What are the options?

- Methods that model dose and schedule
  - Assume nested schedules, i.e. schedule 2 is schedule 1 repeated, etc.
- Partial ordering methods for dose combinations
  - Adapt to schedules for one drug?
- Talk to clinical experts about their toxicity beliefs

When to recruit patients and when to dose-escalate

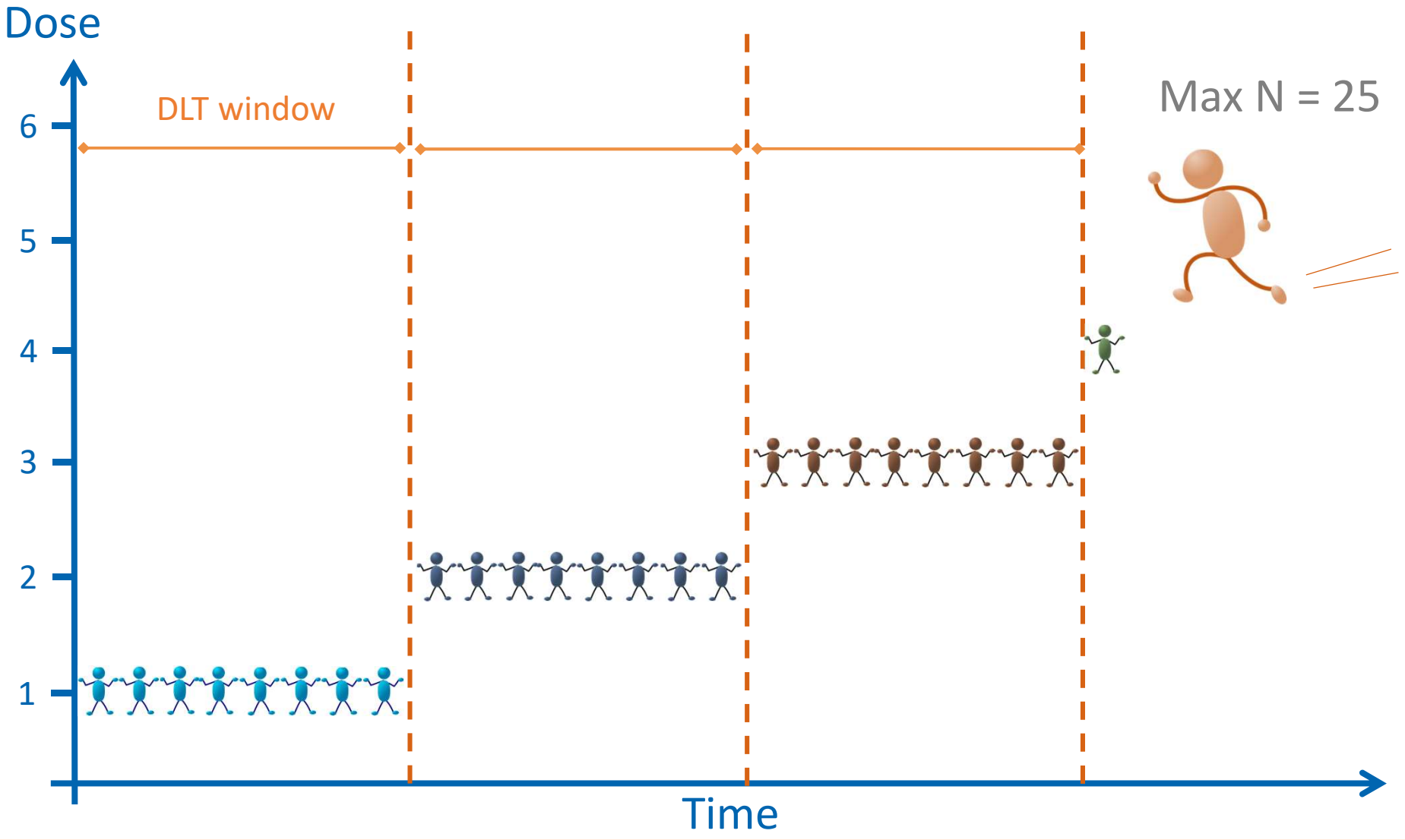


Patients information
$\propto$
toxicity window
observed so far

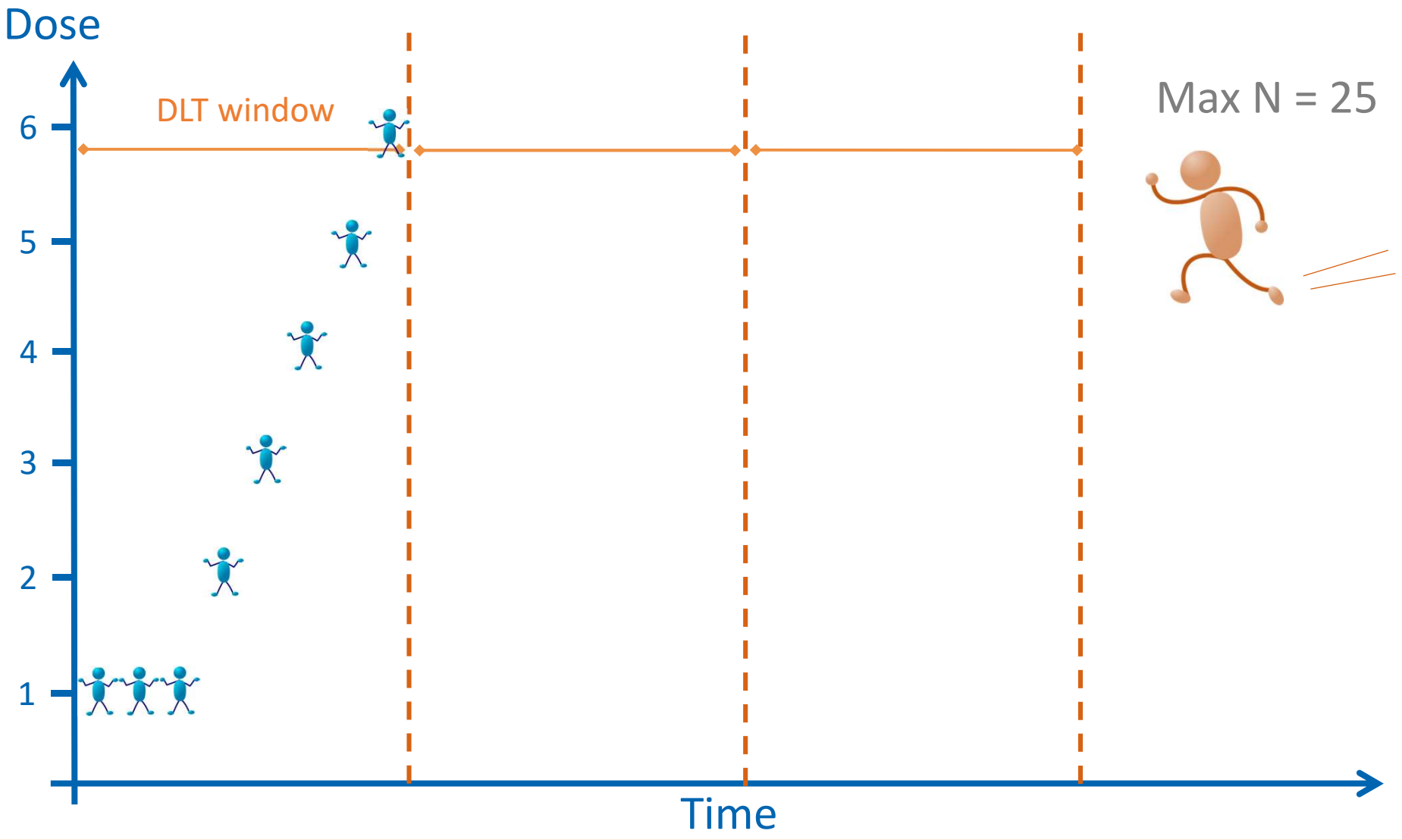
No need to wait for full information
before recruiting the next patient

But how much information is enough to escalate? And should you pause recruitment?

When to recruit patients and when to dose-escalate



When to recruit patients and when to dose-escalate



What did we do?

- TiTE-CRM – dose-escalation accounting for late-onset toxicity with continual patient accrual
  - BUT is this still valid with limited patients, fast accrual and long DLT observation window?

- Our solution for CHARIOT
  - No rules on how much information is needed before escalating, but no dose-skipping of untried treatment schedules
  - Control rate of recruitment using slots
  - Accept different recruitment rates at different points in the trial

- How do we guide someone through the decision process of when to escalate or pause recruitment for a while

Summary

- TiTE-CRM is essential for radiotherapy trials (and other trials with long follow-up)
- Still some issues that aren't straightforward to apply in practice
- Literature exploring some of these issues may be needed

Collaborators

Challenges in implementing model-based phase I designs in a grant-funded clinical trials unit.

Fangou E, Holmes J, Love S, McGregor N, Hawkins M

Trials (2017), 18:620-27