How to design a dose-finding study using the Continual Reassessment Method

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Outline

- The continual reassessment method
- Designing a trial
- What does our paper provide?

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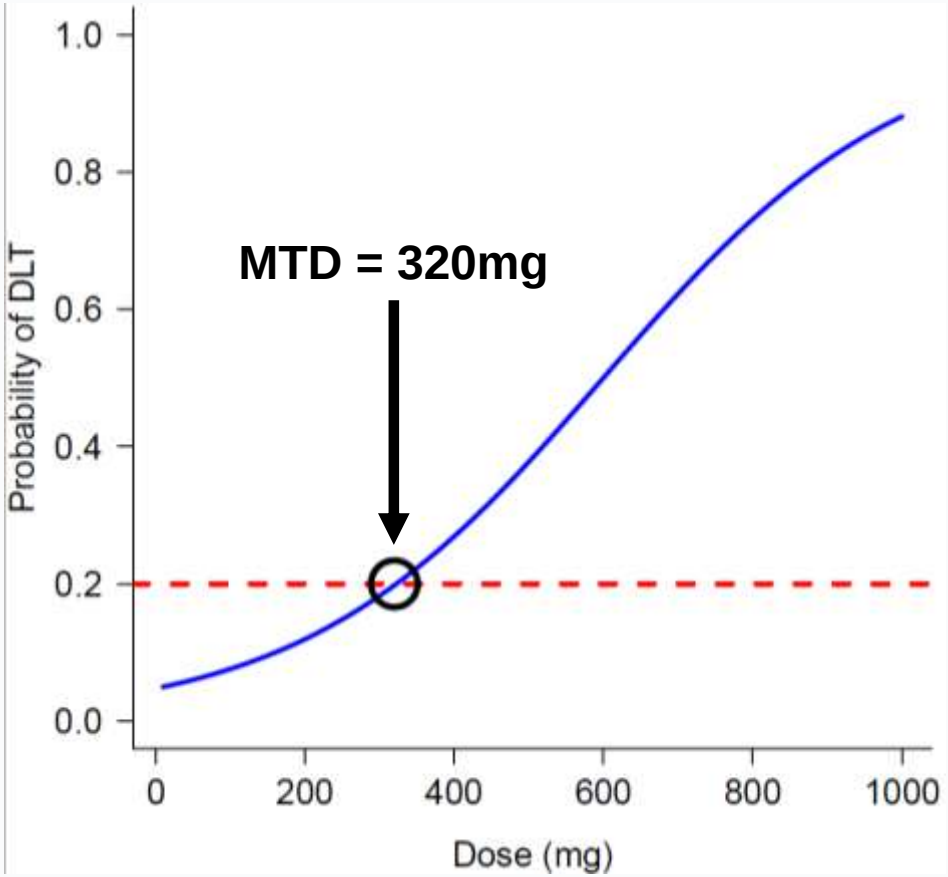
Aim: Find the maximum tolerated dose (MTD) of a drug

The dose expected to produce some degree of unacceptable, dose-limiting toxicity (DLT) in a specified proportion of patients



Target Toxicity Level (TTL)

TTL = 20%

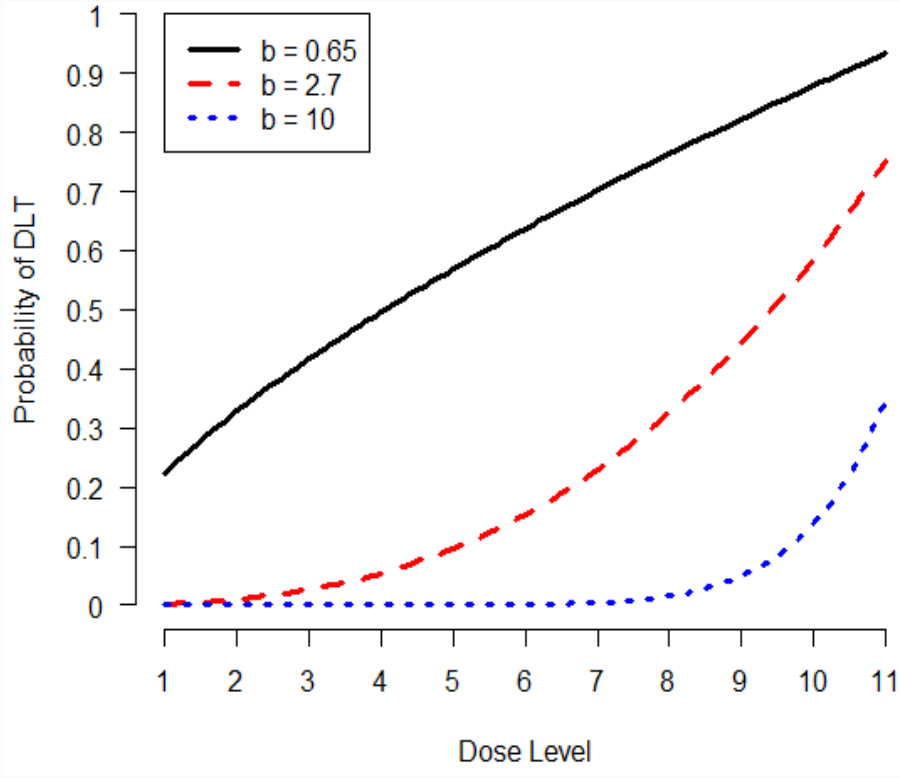
The main steps of the CRM

1. Choose a TTL
2. Estimate the risk of DLT for each dose
3. Choose a model to describe the relationship between dose levels and risk of DLT
4. Update the model using all available data and calculate the best estimate of the MTD
5. Allocate the next patient(s) using the MTD estimate as a guide

Two possible models for the CRM

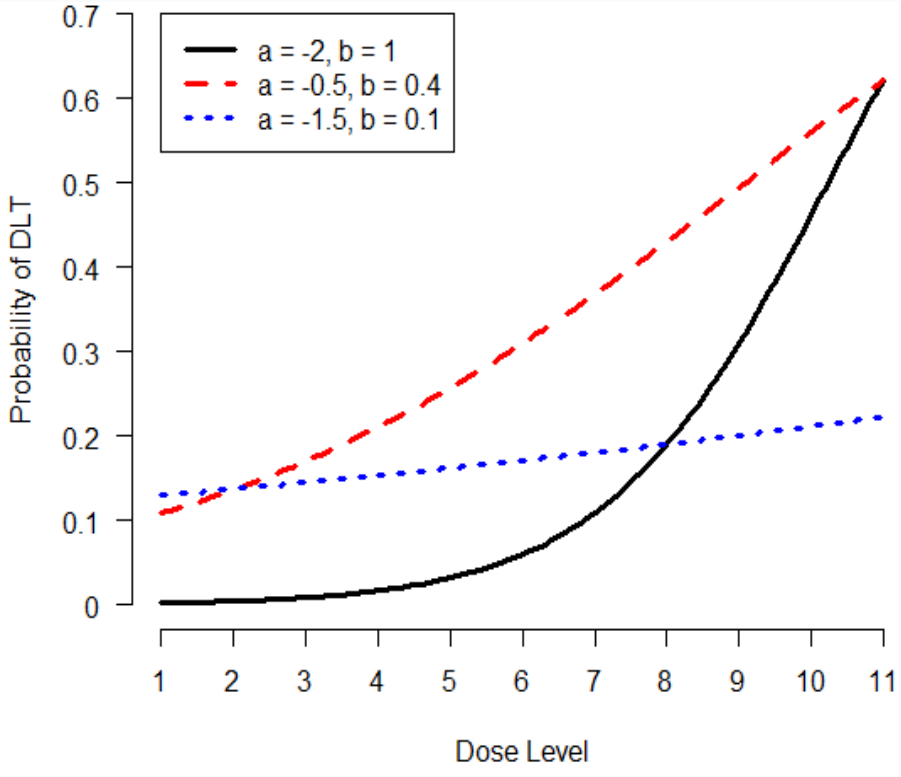
Power/Empiric Model
(1-parameter)

$$DLT\ risk = dose^{b}$$



Logistic Model
(1- or 2-parameter)

$$DLT\ risk = \frac{\exp(a + b\ \times dose)}{1 + \exp(a + b\ \times dose)}$$



Estimate risks of DLT (skeleton)

Need to specify a *skeleton* (prior DLT risks)

a) Use previous trial data and clinical judgement

b) Have a prior belief on what the MTD is, but not DLT risks of other doses?

   – Can use code provided in paper to generate a skeleton!

- Can then use skeleton to compute *dose labels*, to ensure model exactly fits prior DLT risks

Notes on models and skeletons

- Model and skeleton choice are not unique
  - Different setups can give identical recommendations
  - But skeleton choice is not arbitrary

- 1 vs. 2 parameter debate

- For 1 parameter models, guaranteed to (eventually) find the MTD

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You decide (1) – Bayesian or Likelihood?

How do you want to estimate DLT risks in your trial?

Bayesian	Likelihood
Specify a prior distribution on model parameter(s) = uncertainty around DLT risk at each dose	Estimate parameter (and DLT risks) using trial data only
Use prior and observed data to update model parameter(s) = update distribution of DLT risk per dose	Requires both at least one DLT and non-DLT response before estimates can be obtained
Priors can be as precise (based on other data) or vague as you wish – can be calibrated	Use a two-stage design – have a rule-based escalation until 1st DLT observed
Need to asses how different priors affect trial conduct	

You decide (2) – Decision rules

- Does next patient get
  - Largest dose with DLT risk no larger than TTL?
  - Dose with DLT risk closest to TTL?

- What is your starting dose?

- Will you allow skipping of untested doses?

You decide (3) – Sample size & Cohort size

- Sample size often based on practical constraints
  - Recruitment, budgets, available sites, number of doses
- Formula proposed for a lower bound to give the "correct" MTD x% of the time (on average)
- Proposal: specify both a lower bound (investigate in simulations) and a practical upper bound
- Cohort size: often 1-3 patients

You decide (4) – Stopping rules

- May want to stop trial early if
  - Dosing more patients won't help you learn anything new
  - The lowest dose available is too toxic

Stop trial if

- "*m* consecutive patients have received one dose"
- "probability that next *m* patients will be given same dose > 90%"
- "width of confidence/credible interval reaches a specific level"
- "> 90% chance that DLT risk at lowest dose is above TTL"

… or any combination of the above

Simulations

What's the chance each dose is chosen as the MTD? Average sample size? Risk of overdose?

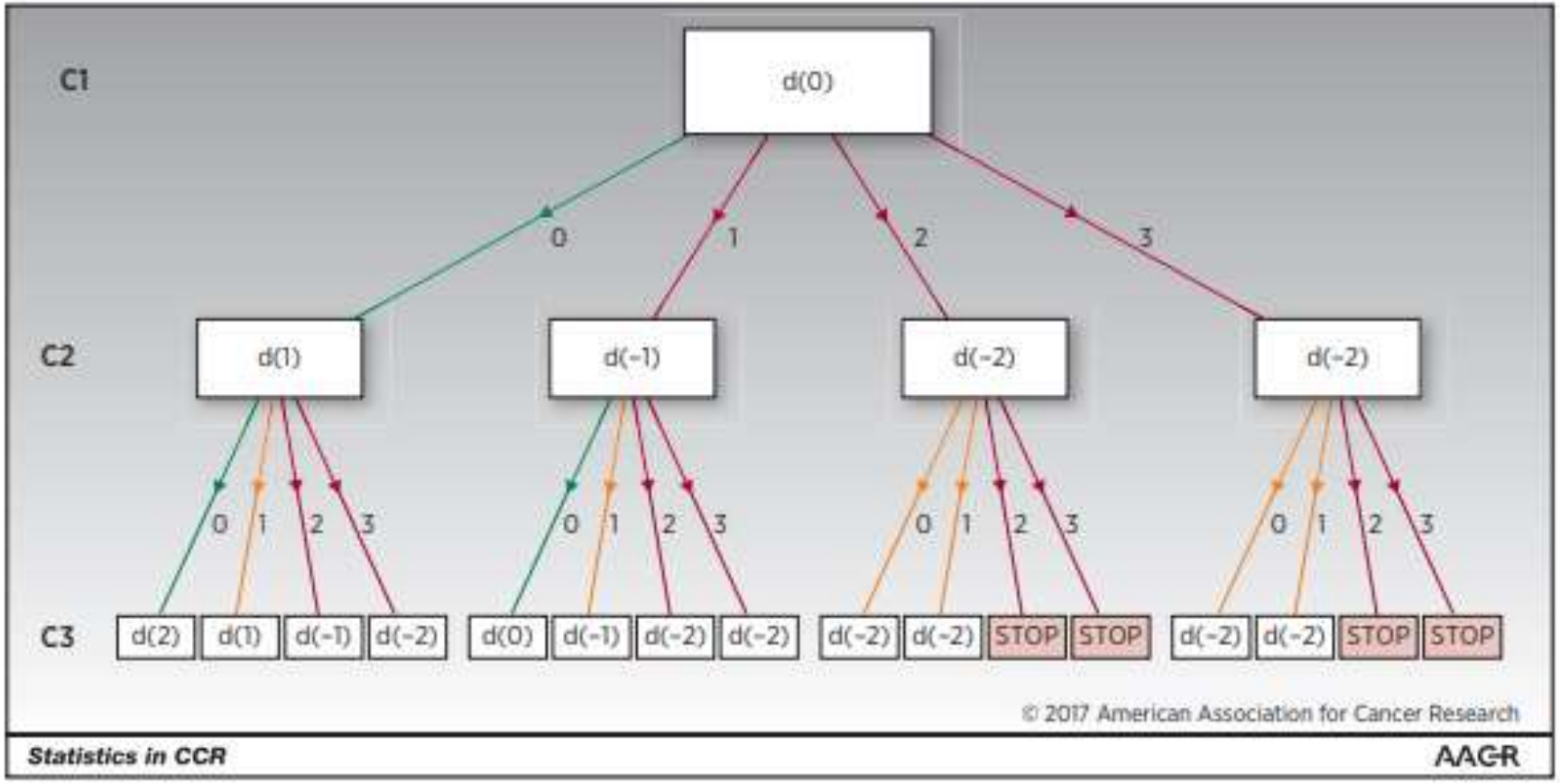
- Simulate design over several dose-toxicity curves

Allows you to compare to other designs (including 3+3 and theoretical benchmark), and assess whether you need to make changes to any choices

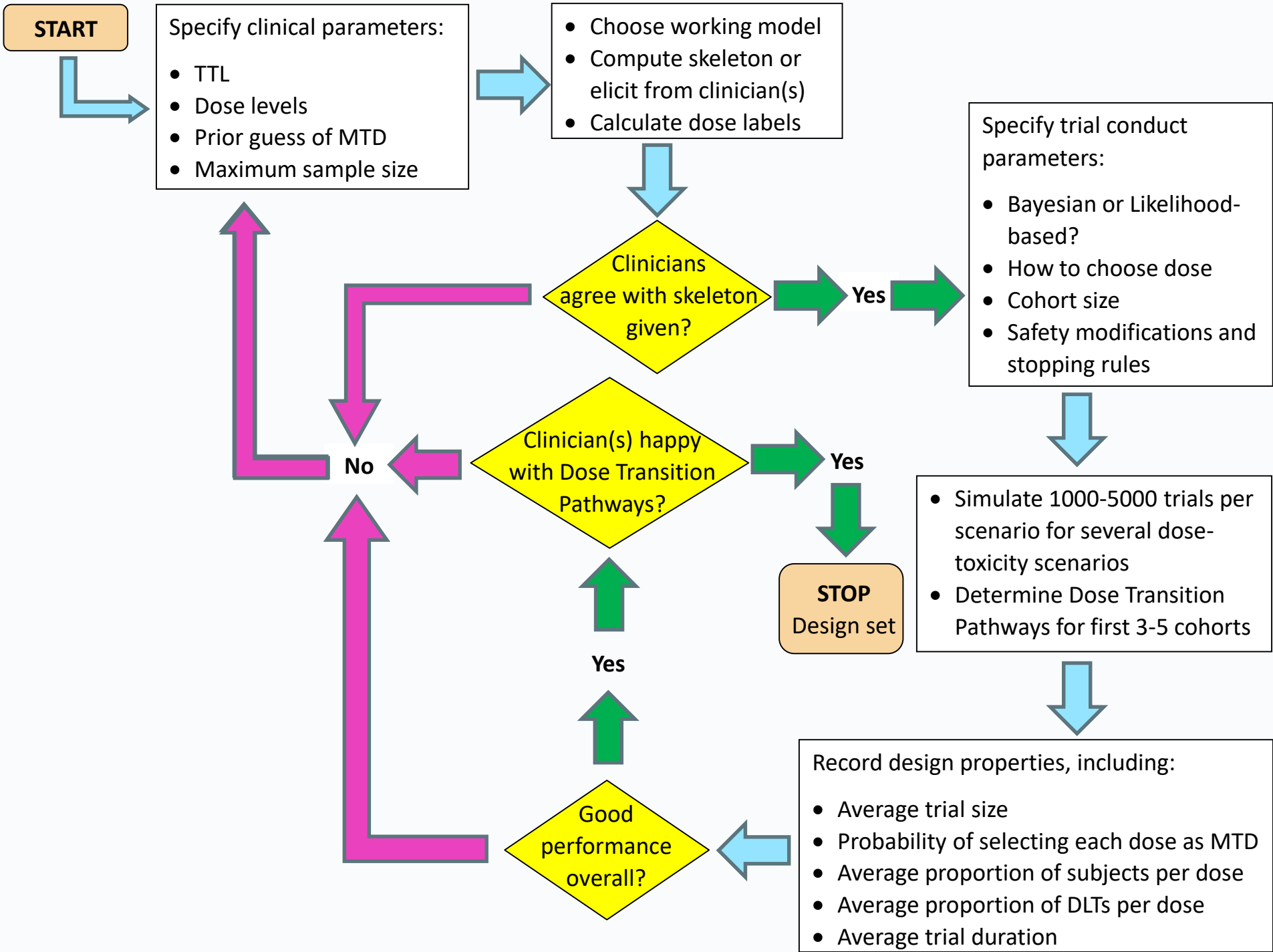
Also is good evidence for grant applications and trial protocols

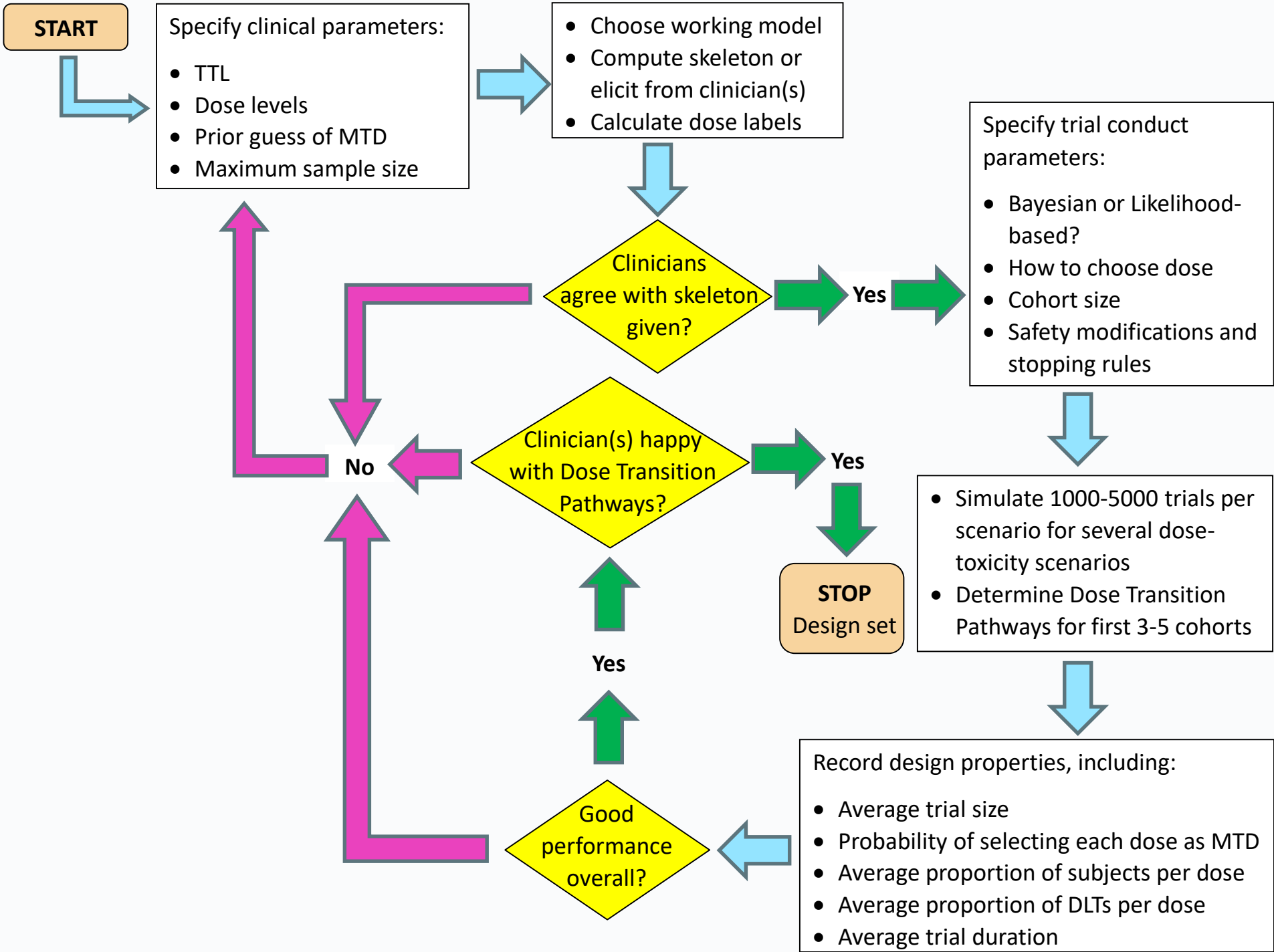
Dose Transition Pathways

Can look at first few cohorts to see what would be recommended by design? If not happy, change design



Yap et al (2017) *Clin Cancer Res.* DOI: 10.1158/1078-0432.CCR-17-0582


START
Specify clinical parameters:
TTL
Dose levels
Prior guess of MTD
Maximum sample size
Choose working model
Compute skeleton or elicit from clinician(s)
Calculate dose labels
Clinicians agree with skeleton given?
Yes
No
Specify trial conduct parameters:
Bayesian or Likelihood-based?
How to choose dose
Cohort size
Safety modifications and stopping rules
Clinician(s) happy with Dose Transition Pathways?
Yes
No
STOP
Design set
Simulate 1000-5000 trials per scenario for several dose-toxicity scenarios
Determine Dose Transition Pathways for first 3-5 cohorts
Record design properties, including:
Average trial size
Probability of selecting each dose as MTD
Average proportion of subjects per dose
Average proportion of DLTs per dose
Average trial duration
Good performance overall?
Yes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Recommendations

- Talk to a statistician!

- Allow plenty of time for designing the trial (and simulating/re-simulating designs)

- Model: power or logistic
- No. doses: 3-8 (sample size, pre-clinical, past trials?)
- Cohort size: 1-3 (≤ max sample size ÷ No. doses)
- Bayesian/Likelihood?
  - Bayesian (if you have some relevant data/insight, use it)
- Decision rules: no skipping, start dose = low but sensible

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Resources

- Design flowchart
- Recommendations for design parameters
- Good practice guidelines for conducting simulation studies
- Software suggestions
- Example trials (Bayesian and likelihood-based)
- *Example code for generating the skeleton and dose labels*
- *Suggested text for a trial protocol*

Summary

- Designing a CRM trial requires more planning than a 3+3 design, but is worth it in the end!

- We describe step-by-step how to design a CRM trial, with recommendations given along the way

- We provide resources to aid the design and conduct of a trial, citing other helpful research and example studies

Graham M. Wheeler · Adrian P. Mander · Alun Bedding · Kristian Brock
Victoria Cornelius · Andrew P. Grieve · Thomas Jaki · Sharon B. Love
Lang'o Odondi · Christopher J. Weir · Christina Yap · Simon J. Bond

The story so far…

27/06/17: Submitted to British Journal of Cancer
29/06/17: Rejected
06/07/17: Appeal submitted
10/07/17: Rejected

18/09/17: Submitted to BMC Medicine
26/09/17: Rejected

04/10/17: Submitted to BMC Medical Research Methodology
05/02/18: “Reviews received” …