Life Journey of a Continual Reassessment Method Trial: Design, Conduct and Reporting

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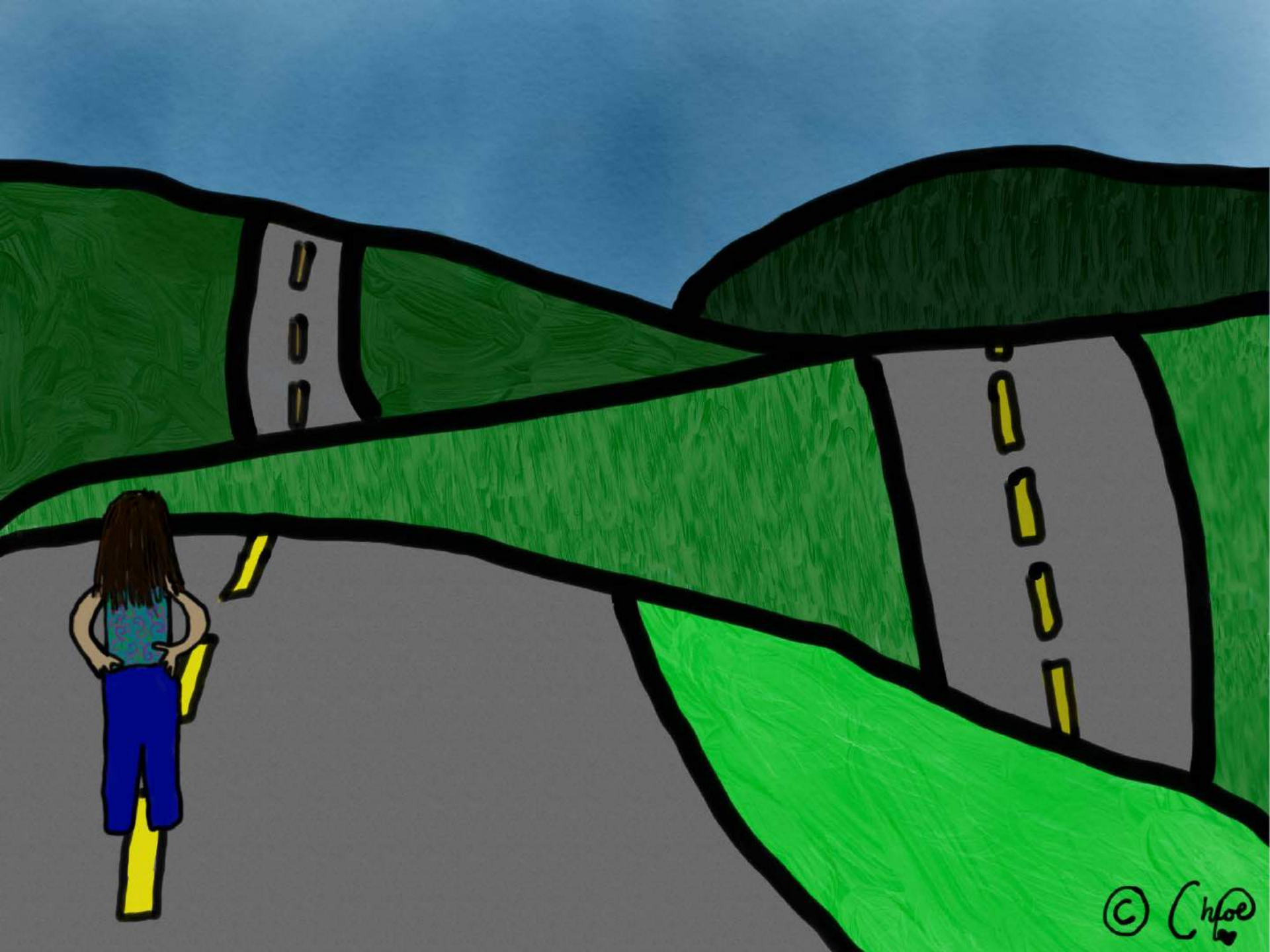
NIHR Statistics Early Phase Clinical Trials Meeting

28th February 2019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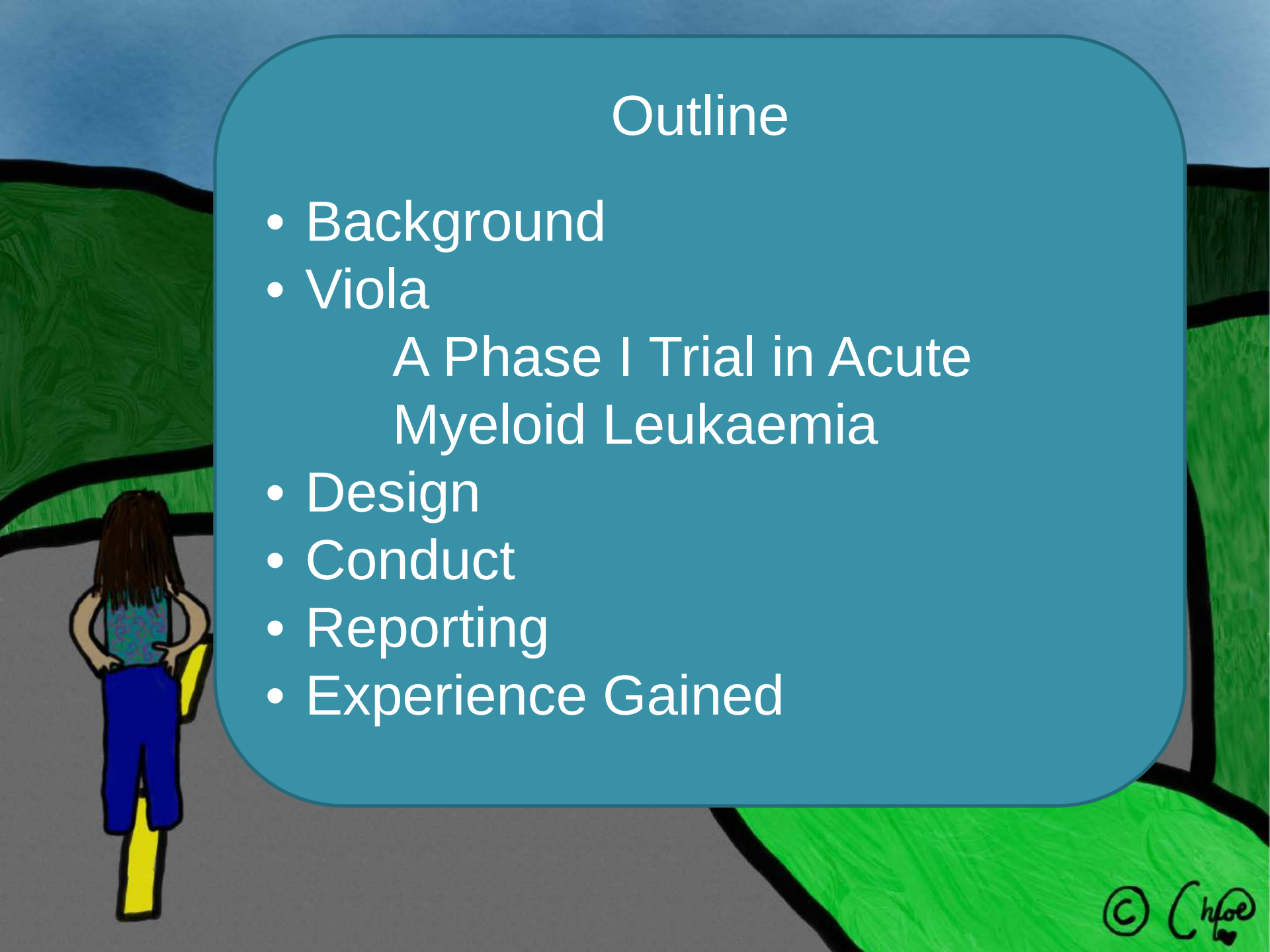
Outline

- Background
- Viola
  - A Phase I Trial in Acute Myeloid Leukaemia
- Design
- Conduct
- Reporting
- Experience Gained



Background

- It is *well established* that *model-based designs* are *superior* to rule-based designs in identifying the recommended phase II dose
- However, several commonly faced practical and methodological challenges remain and have limited their widespread use.
  - Review of 1,235 phase I oncology trials published 1991- 2006, only 1.6% used model-based approaches (Rogatko *et al*, 2007), increasing to only 6.4% by 2012–2014 (van Brummelen *et al*, 2016)

Viola: Phase I Acute Myeloid Leukaemia (AML) Trial

Patient Population:

- Patients with AML who relapse after Allogeneic Stem Cell Transplantation

Primary Objective:

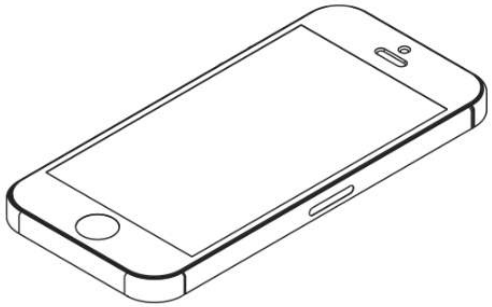
- ***Maximum Tolerated Dose (MTD)*** of combined Lenalidomide and Azacitidine with a target Dose Limiting Toxicity (DLT) probability of 20%

Trial Design: Modified Continual Reassessment Method (CRM)

Voting Time

Viola: How long do you think it took from initial conception to final publication?

Go to **www.menti.com** and use the code **49 10 0**

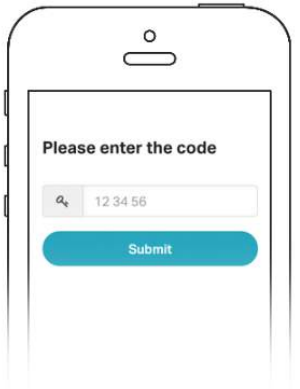


1

Grab your phone

2

Go to www.menti.com



3

Enter the code 49 10 0 and vote!

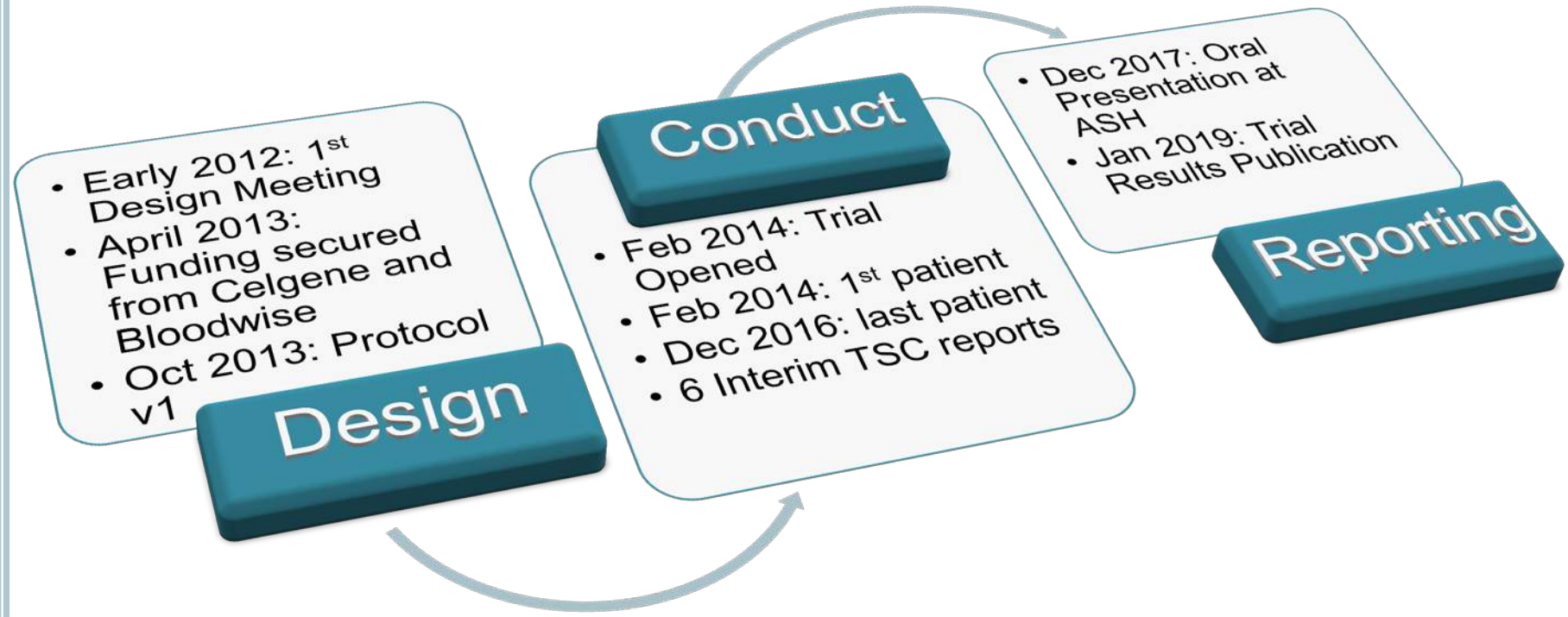
Cancer Research UK Clinical Trials Unit @CRCTU

CANCER RESEARCH UK

UNIVERSITY OF BIRMINGHAM

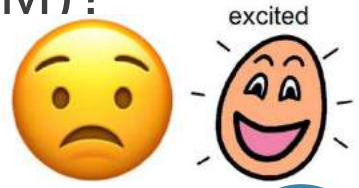
Viola: Initial Conception to Publication

Answer: 6 – 7 years

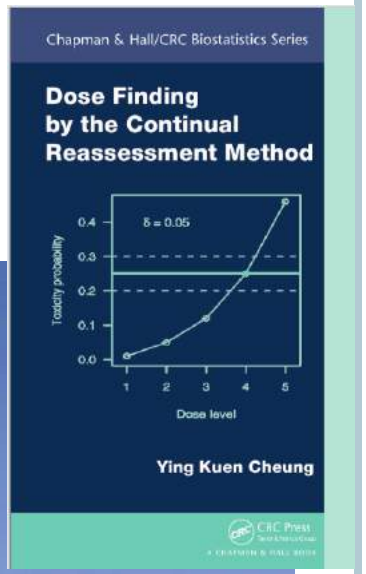


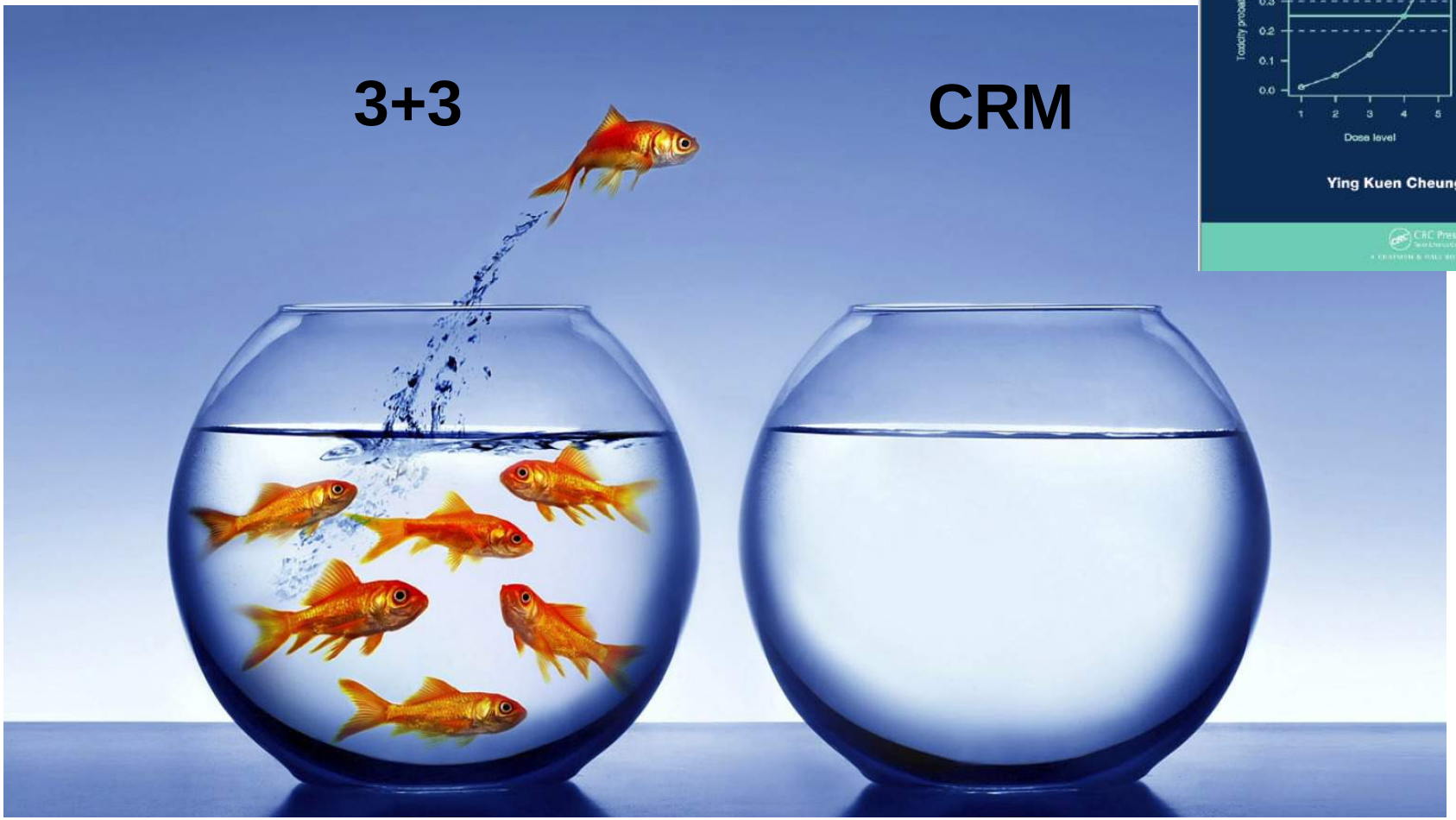
303 days from grant award to trial opening

- At the point of designing Viola in 2012, < 7% trials have used such designs globally (van Brummelen *et al*, 2016)
- Viola - First UK academic-sponsored Phase I trial to use a Continual Reassessment Method (CRM)?



R dfcrm package





Barriers in Implementing Model-Based Designs

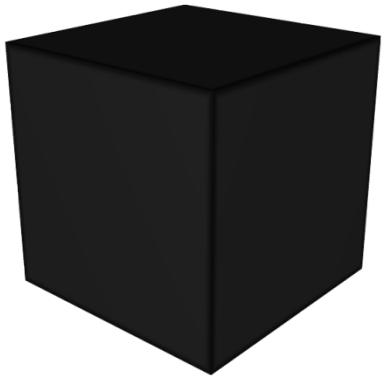
(Yap et al 2013, Yap et al 2017, Love et al 2017)

Lack of knowledge

Lack of familiarity

Experience

Lack of training / expertise



Black Box

Viola: Clinical Parameters (Yap et al 2017)

1. 7 dose levels (Aza fixed)
2. Target DLT rate for MTD: 20%
3. Sample size: 27 (with possible extension of 3 patients)
4. Cohort size: 3
5. Initial guesses of toxicity rates (clinical/model specification*)

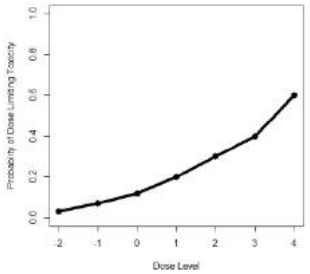
3+3 Design?

Starting dose **Prior MTD**

Dose Level	d(-2)	d(-1)	d(0)	d(1)	d(2)	d(3)	d(4)
Lenalidomide (mg)	0	2.5	5	10	15	25	35
Prior DLT rates (skeleton)	0.03	0.07	0.12	**0.2**	0.3	0.4	0.52

* getprior from dfcrm

Viola: Model Specification (Yap et al 2017)



1. Dose Toxicity Curve, DTC:
   Empiric Model, P(DLT at dose d_j) = $p_j^{\exp(\beta)}$
2. Estimation Approach: Bayesian (One-Stage)
3. Normal Prior for β with mean 0 and variance of 0.75

Starting dose **Prior MTD**

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Prior DLT rates (skeleton), p_j	0.03	0.07	0.12	**0.2**	0.3	0.4	0.52

Viola: Practical Considerations

- No skipping of untried doses in escalation
- Allow skipping of untried doses in de-escalation
- ***How do you determine when to stop early, particularly when there is excessive toxicity?***

Viola: Practical Considerations

- No skipping of untried doses in escalation
- Allow skipping of untried doses in de-escalation
- Stopping Early Criteria
  - If there are 12 patients at the most recent MTD
  - If there is a high probability that the lowest dose is too toxic

Bayesian safety stopping early criterion

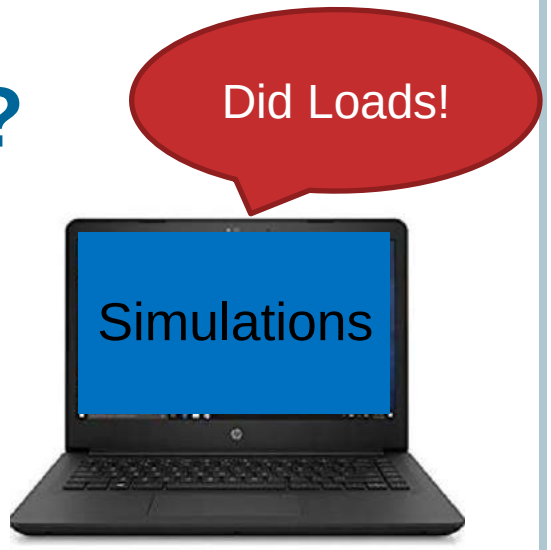
P(true DLT rate at lowest dose > target DLT rate + x% | current observed data and prior information) > y

Stop early if Pr(DLT rate at lowest dose > 30% | data) > 0.72

where **x = 10%** and **y = 0.72**

Re-thinking on What is an “optimal” design?

Is it one with the ***best statistical properties*** demonstrated via simulations across several clinically relevant scenarios?



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What is an “optimal” design?

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How do you know if your chosen design is suitable, acceptable and will be adopted in the **actual trial**?

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What is an “optimal” design?

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How do you know if your chosen design is suitable, acceptable and will be adopted in the **actual trial**?

“If I were to do this,
I need to do it right…”

Overcoming Barriers in Practical Implementation

Statistics in CCR

Clinical Cancer Research

Dose Transition Pathways: The Missing Link Between Complex Dose-Finding Designs and Simple Decision-Making

Christina Yap[1], Lucinda J. Billingham[1], Ying Kuen Cheung[2], Charlie Craddock[3], and John O'Quigley[4]

Check for updates

Design Tool

Operational Tool

Complex Models

Simple Decision Making

Overcoming

- ✓ **Challenges in Investigators' buy-in**
- ✓ **Operational Challenges**
- ✓ **Methodological Challenges**

Statistics in CCR

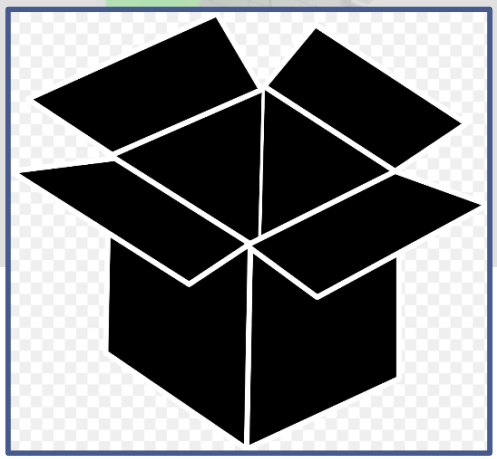
Clinical Cancer Research

Dose Transition Pathways: The Missing Link Between Complex Dose-Finding Designs and Simple Decision-Making

Christina Yap[1], Lucinda J. Billi

DTP **projects in advance** the doses recommended by a model-based design for subsequent patients (**stay**, **escalate**, **de-escalate**, or **stop early**), using all the accumulated information.

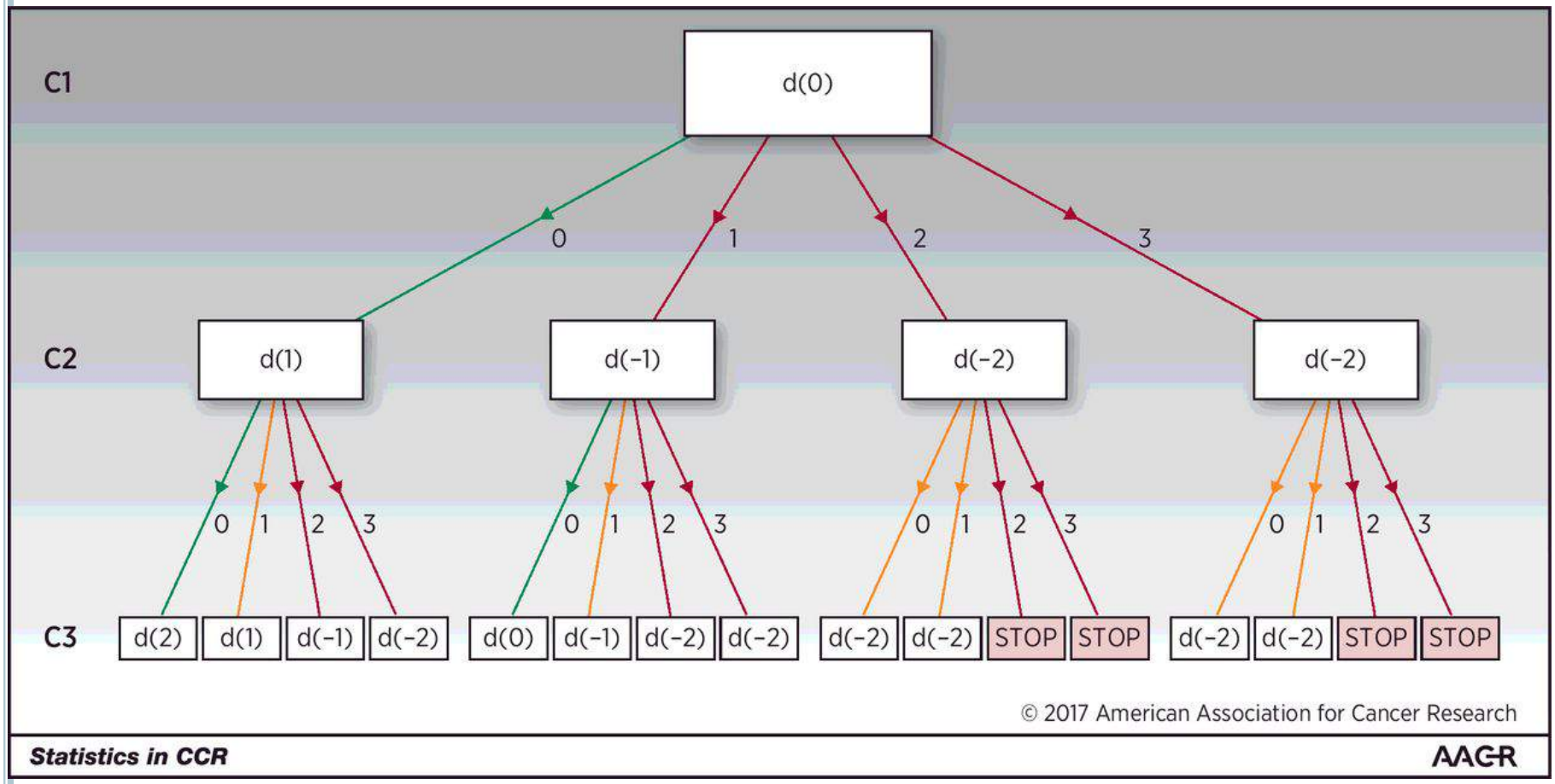
Complex Models



Viola: Initial Dose Transition Pathways

(Cohorts of 3)

(Yap et al, CCR 2017)



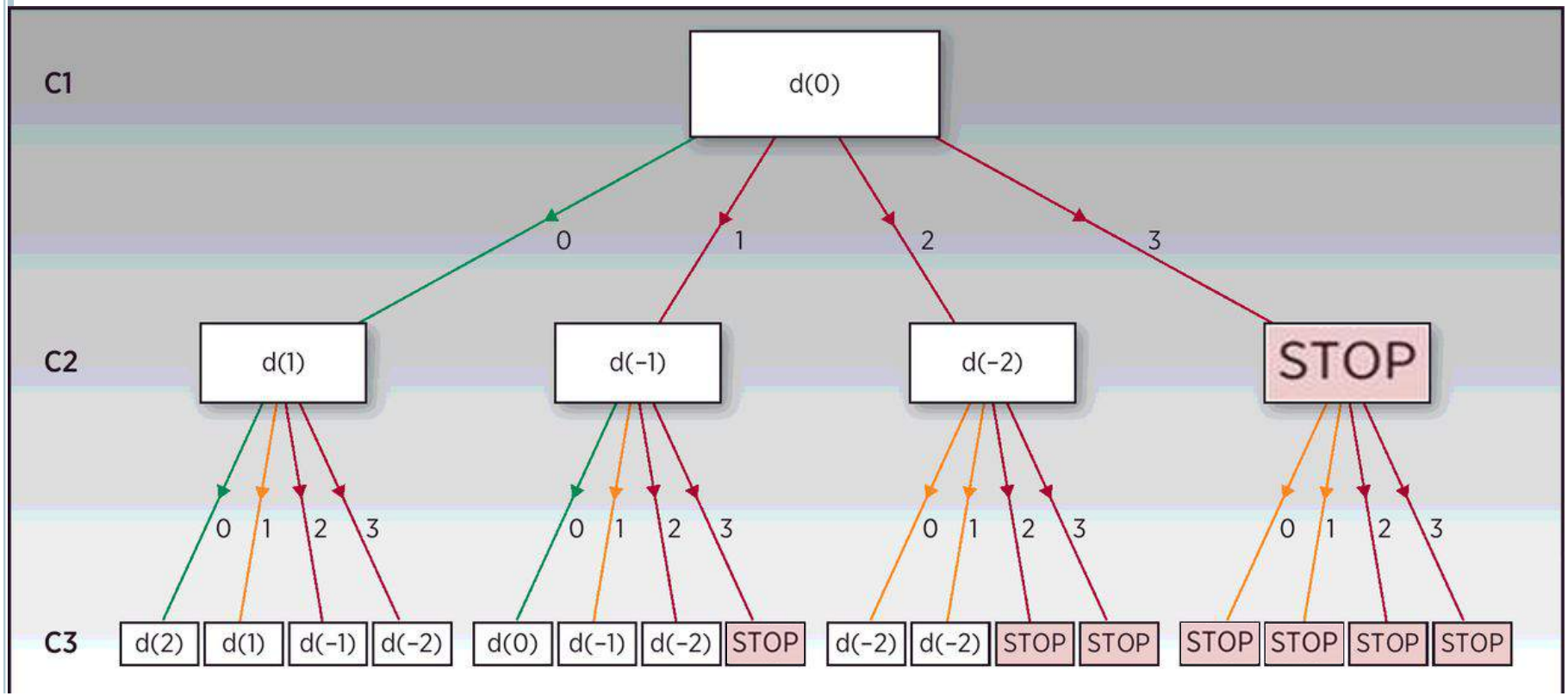
Stop early criteria for excessive toxicity:

if Pr(DLT rate at lowest dose > 30% | data) > 0.72

Viola: Initial Dose Transition Pathways

(Cohorts of 3)

(Yap et al, CCR 2017)

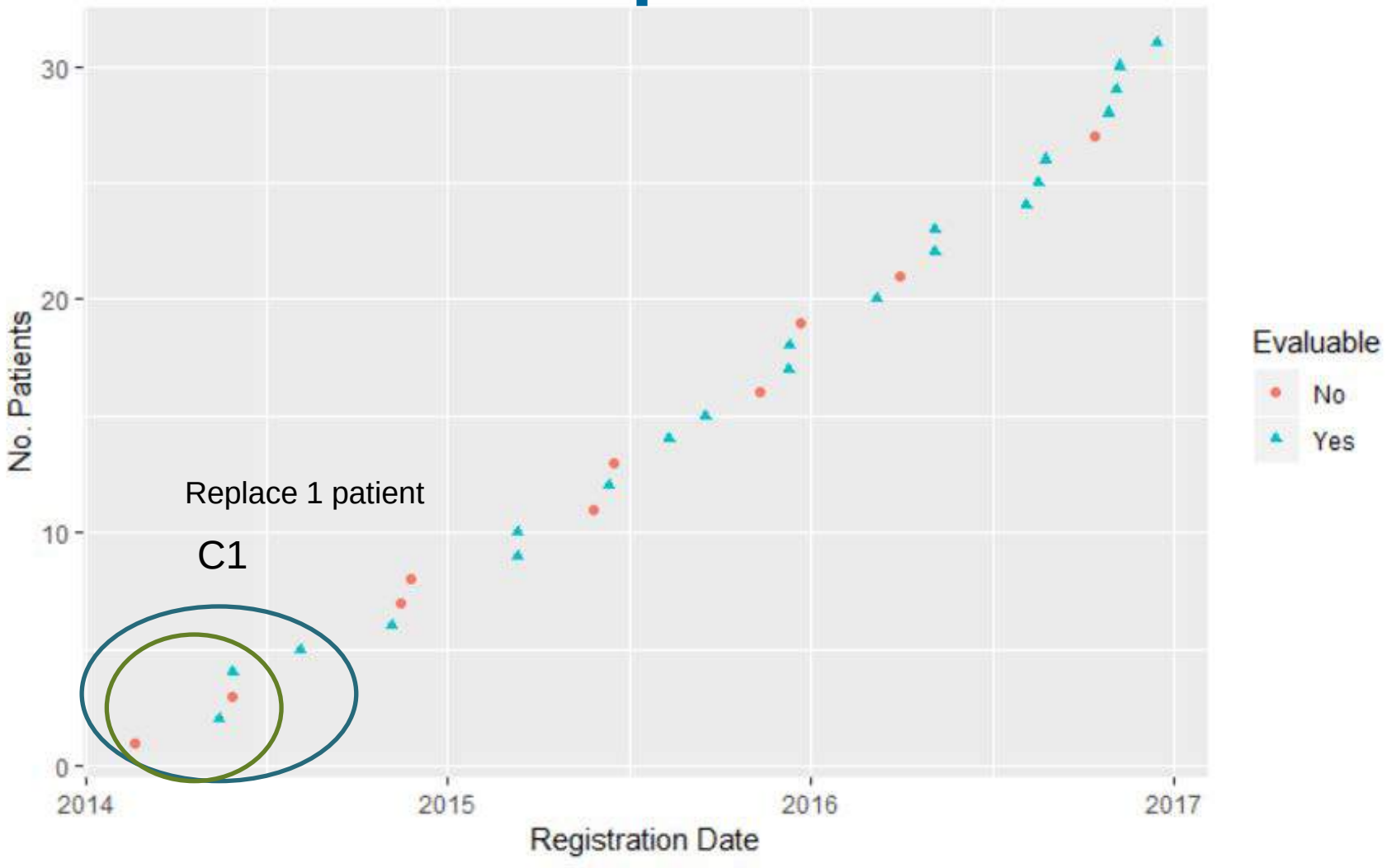


Stop early criteria for excessive toxicity:

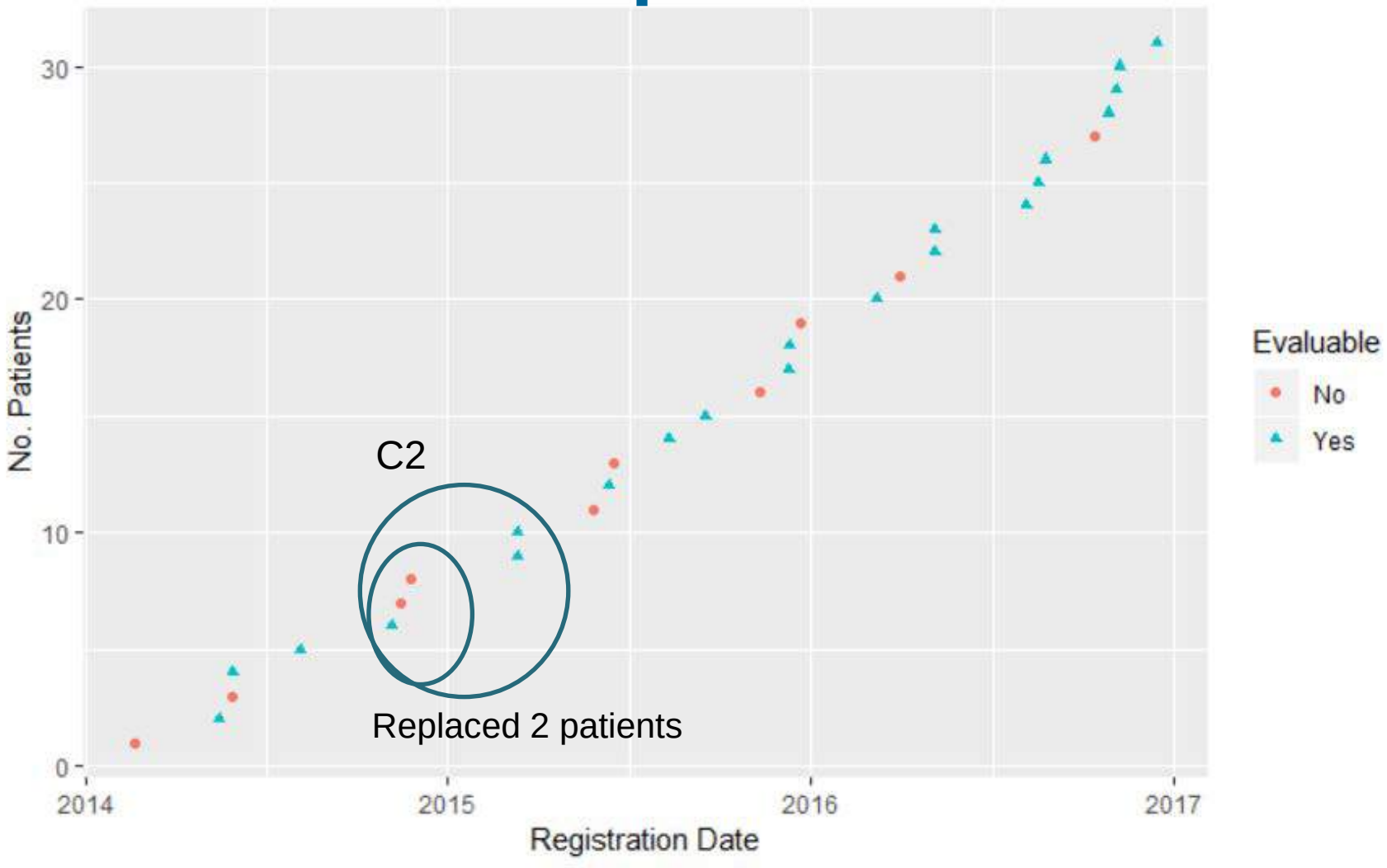
if Pr(DLT rate at lowest dose > 30% | data) > 0.6


Conduct

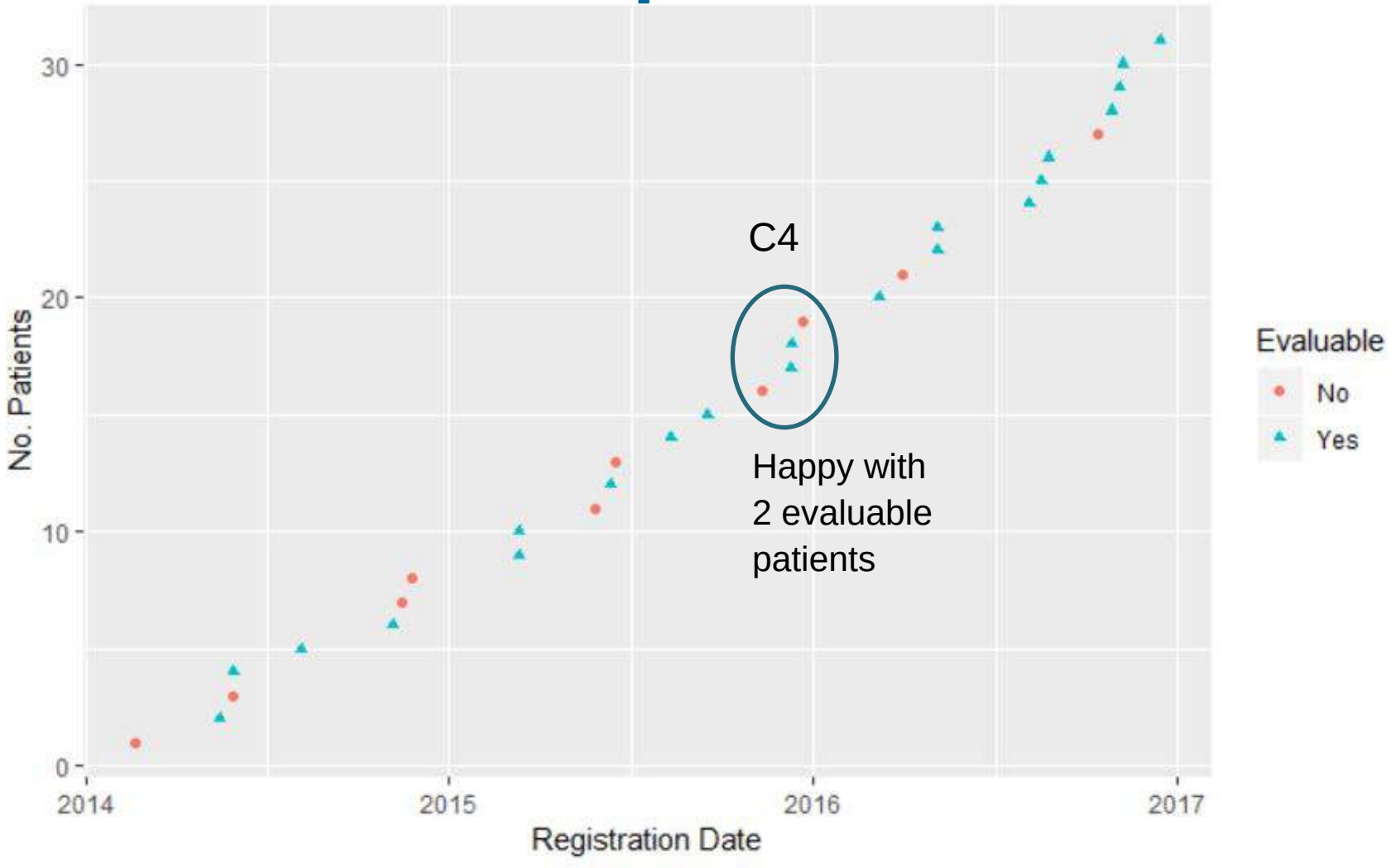
Recruitment Graph



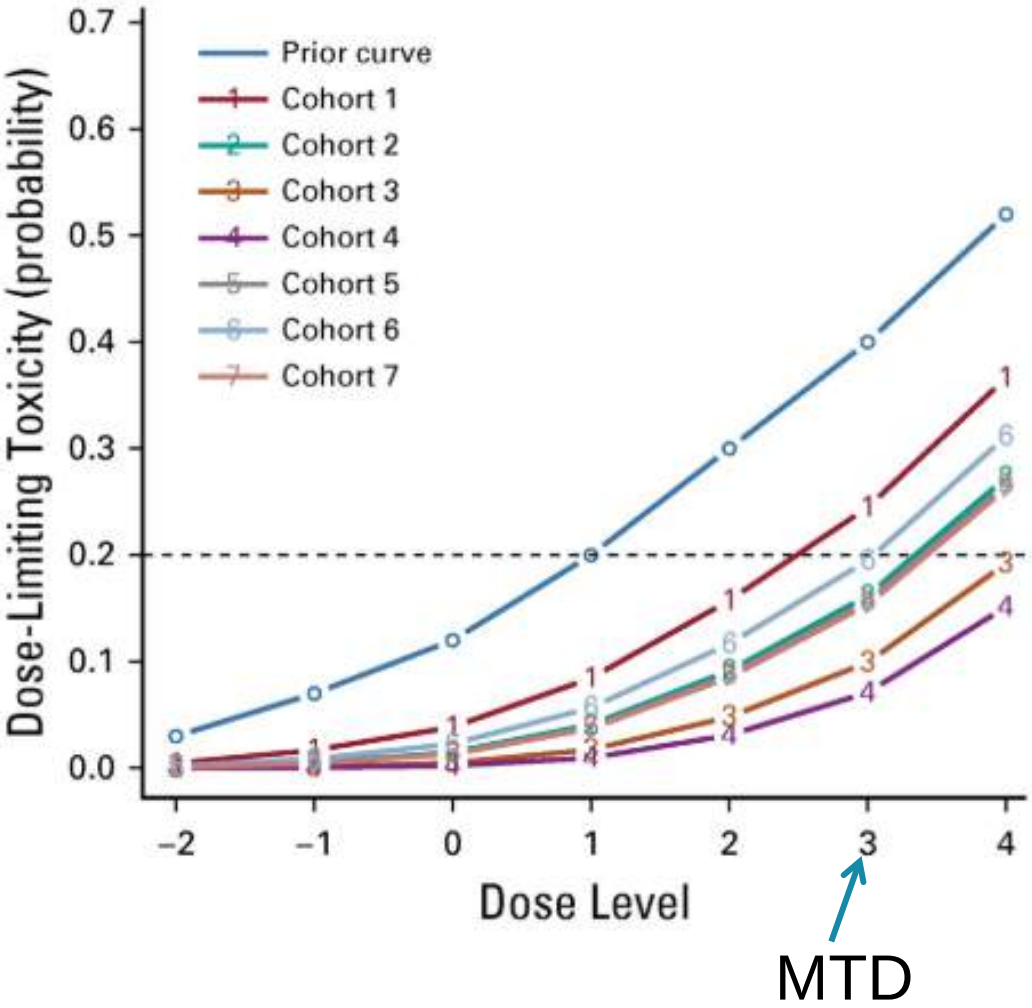
Recruitment Graph



Recruitment Graph



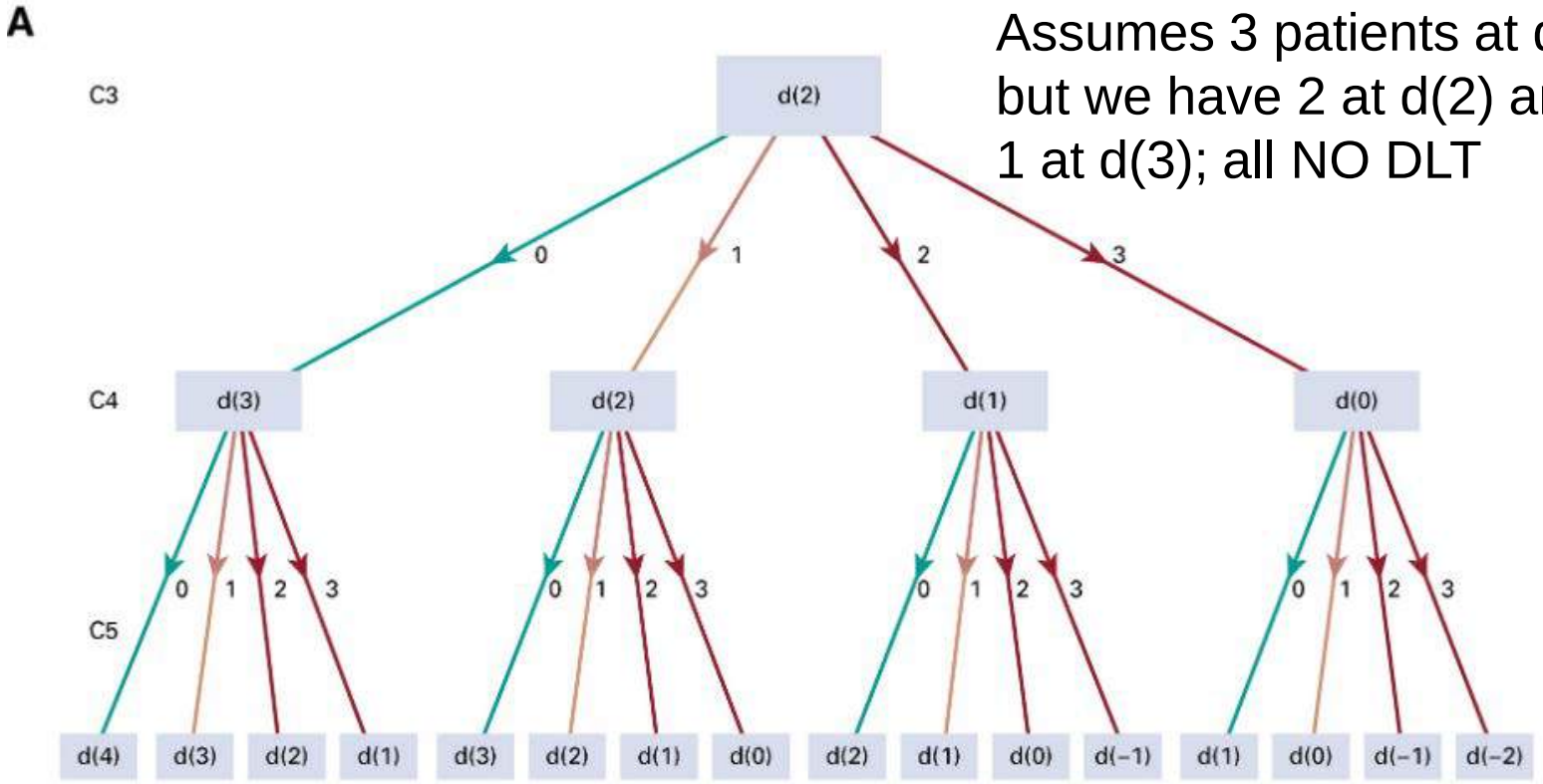
Updated Dose Toxicity Curves



Cohort	Dose	#DLT/#patients
1	0	0/3
2	1	0/3
3	2	0/**2**
	3	0/**1**
4	3	0/**2**
5	3	1/3
6	3	1/3
7	3	0/**4**

DTP for Cohorts 3 to 5

After 0/3 DLT for both d(0) and d(1)



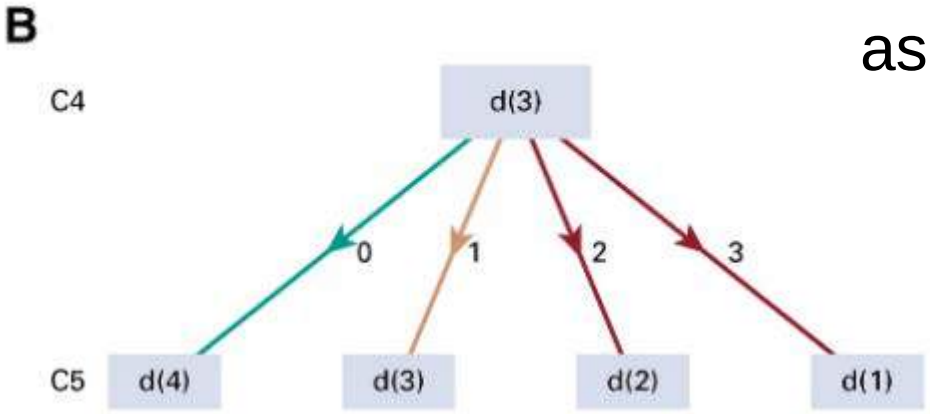
Assumes 3 patients at d(2), but we have 2 at d(2) and 1 at d(3); all NO DLT

d(2): dose 2

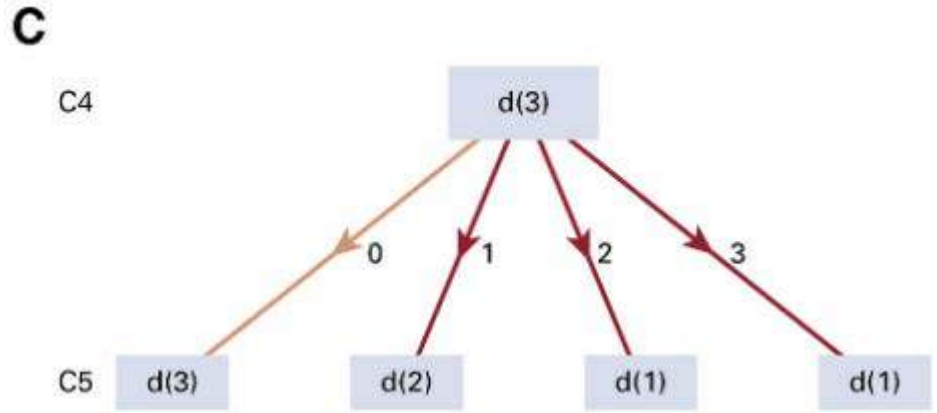
C3: Cohort 3

Update DTP with accumulated information

DTP is the same as previous



If patient at d(3) has a DLT,



original report

Combination Lenalidomide and Azacitidine: A Novel Salvage Therapy in Patients Who Relapse After Allogeneic Stem-Cell Transplantation for Acute Myeloid Leukemia

Charles Craddock, MD[1,2]; Daniel Slade, MSc[2]; Carmela De Santo, PhD[2]; Rachel Wheat, MSc[2]; Paul Ferguson, MD[3]; Andrea Hodgkinson, PhD[2]; Kristian Brock, MSc[2]; Jamie Cavenagh, MD[4]; Wendy Ingram, MD[5]; Mike Dennis, MD[6]; Ram Malladi, MD[1]; Shamyla Siddique, MPhil[2]; Francis Mussai, MD[2]; and Christina Yap, PhD[2]

Dose levels and Estimated DLT rates

(Craddock et al JCO 2019)

TABLE 1. Dose Levels and Prior and Posterior Probabilities of DLTs for Each Dose Level With Associated 90% Probability Intervals (based on the CRM dose-toxicity model)

Combination Dose of LEN With 75 mg/m² AZA	Prior DLT Rate	No. of Evaluable Patients	No. of DLTs	Posterior DLT Rate (90% probability interval)
Dose −2 (AZA only)	0.03	0*	0*	0.001 (0-0.012)
Dose −1 (2.5 mg LEN)	0.07	0*	0*	0.004 (0-0.035)
Dose 0 (5 mg LEN)	0.12	3	0	0.013 (0.001-0.068)
Dose 1 (10 mg LEN)	0.20	3	0	0.037 (0.005-0.131)
Dose 2 (15 mg LEN)	0.30	2	0	0.085 (0.019-0.218)
Dose 3 (25 mg LEN)	0.40	13	2	0.153 (0.048-0.314)
Dose 4 (35 mg LEN)	0.52	0*	0*	0.263 (0.115-0.437)

Abbreviations: AZA, azacitidine; CRM, continuous reassessment method; DLT, dose-limiting toxicity; LEN, lenalidomide.
*Untested doses.

Recommended MTD is **25 mg LEN**
(Posterior DLT rate of 15.3% is closest to target of 20%)

What Benefits Have We Seen?

(Yap et al CCR 2017, Craddock et al JCO 2019)

Use of CRM coupled with DTP

At the Design Stage

- Better engagement, communication and understanding
- Provides greater confidence on a desirable design that is suitable & ***applicable*** in practice
- **Simulations** assess the **overall performance** and **DTP** help to **fine-tune** it

  → ***acceptable in practice***

What Benefits Have We Seen? (cont…)

- **At the Trial Conduct Stage**

➢ Ease of use of DTP by trial managers and Trial Steering Committee (TSC)

➢ Not a black-box; does not need to have a statistician to be “on call” at all times

- **At the Analysis Stage**

➢ pre-analyse

➢ Allowed the flexibility to decide in advance with TSC that if no DLT occurred, dose could be escalated as projected by DTP without a formal meeting.

What Benefits Have We Seen? (cont...)

(Craddock et al JCO 2019)

Expected Benefits

- Majority of patients treated at the MTD (62%, 13/21)
- Higher accuracy in determining the MTD.

Unexpected Challenges

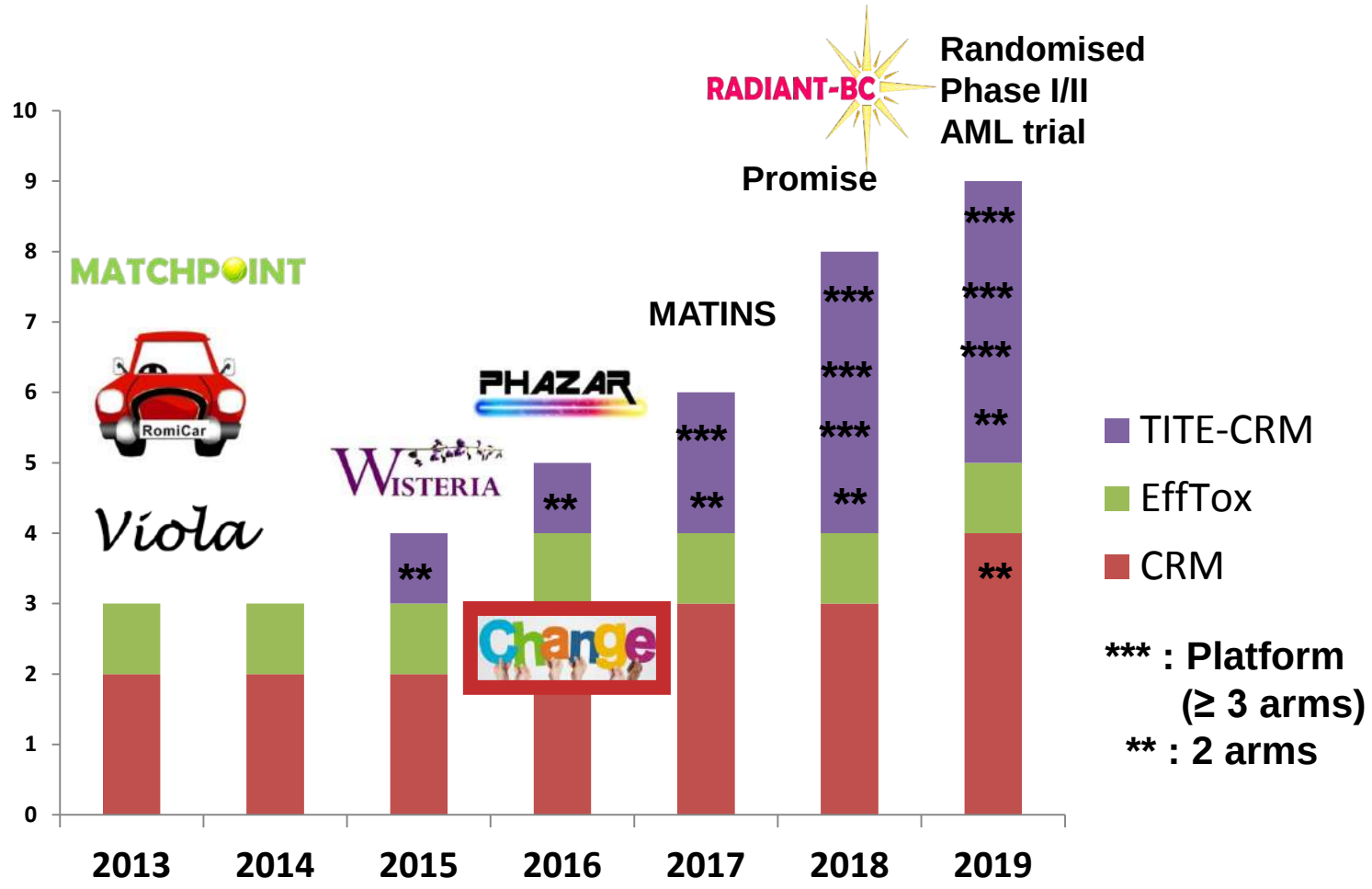
- Dosing error
- Cohort size variation due to early patient drop out

The CRM design coped effectively with the unexpected challenges and provided the flexibility of not having to replace inevaluable patient(s) in a cohort → saving time and resources

Would I do it again?

One of the greatest rewards as a statistical methodologist and trialist is to witness how one's "masterpiece" benefits the actual trial and ultimately the patients!

My Journey with Model-Based Dose-Finding Trials in Cancer…

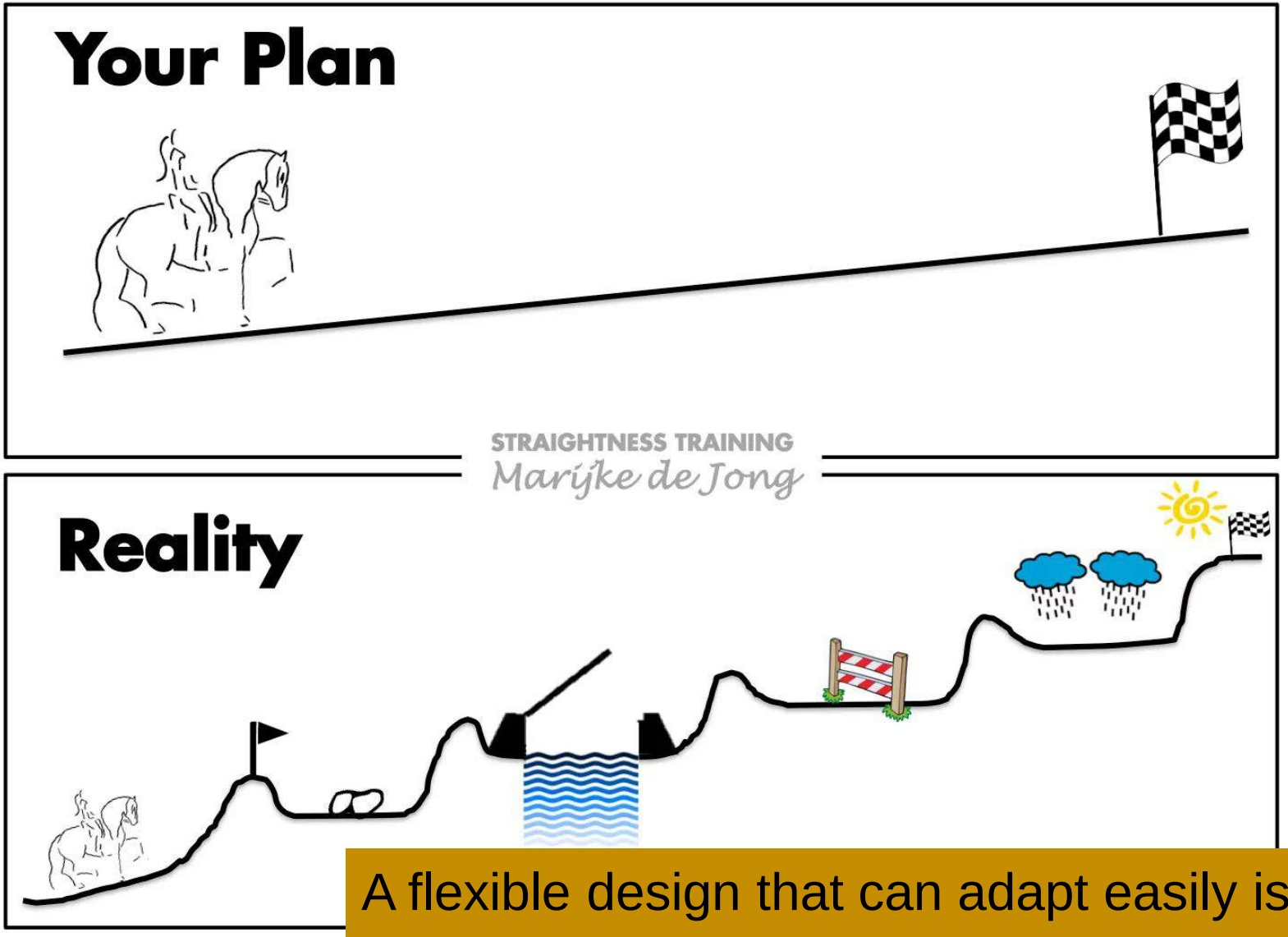


Experience gained…

ENGAGEMENT

↑ confidence will ↑ uptake

- The **“optimal”** adaptive design to be implemented might not necessary be one with the best statistical properties
- **Close interaction** with clinical investigators and trial managers to produce a suitable, ***acceptable*** design tailored to the needs of the trial is crucial
  - Incorporate clinical judgements
  - Take into account operational aspects



A flexible design that can adapt easily is even more attractive here!

Final Comments

- **DTP** can serve as a valuable ***design***, ***operational*** and ***analysis*** tool
- Advocate use of DTP as an ***integral*** procedure in the co-development and successful implementation of practical model-based designs by statisticians and investigators
- R package and shiny app (to be released soon)

Acknowledgements

Co-authors of Viola Trial Paper: C Craddock, D Slade, CD Santo, R Wheat; P Ferguson, A Hodgkinson, K Brock, J Cavenagh; W Ingram; M Dennis; R Malladi; S Siddique, F Mussai

Viola Trial Steering Committee: U Platzbecker; J Wason, R Kavita

Co-authors of DTP paper: L Billingham, K Cheung, C Craddock, J O'Quigley

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M Drummond, A Mead,
C Palmeri & A Kong),
Trial Statisticians (D Slade, A Kirkham,
K Brock, A Jackson, R Boucher,
I Ahmed, SM Vicente & J Khan) and
Patients and Families

A Team Effort

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Thank You

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