Flexible Early Phase Adaptive Designs: Better than a Robot Vacuum

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Why I love my Robot Vacuum?

- **Quality** - Does a good job in cleaning the house
- **Automatic** – set programmes at specific times
- **Efficient** – Quick and covers all areas
- **Smart** – Knows how to manoeuvre around
- **Saves me time and energy!** Allows me to spend more time with my lovely family

Why it may not be “perfect”?

Hmm.. It is smart… but…..

Flexible

Early Phase Adaptive Designs

- Shares similar features to a robot vacuum… but even better?

Flexible

Early Phase Adaptive Designs

- Shares similar features to a robot vacuum… but even better?
- Favourable properties
  - flexible
  - cope with unexpected circumstances
  - tailored to a trial's specific requirements, taking into account clinical, operational and patients' perspectives.

Viola: Phase I Acute Myeloid Leukaemia (AML) Trial

(CI: Charlie Craddock)

Primary Objective:

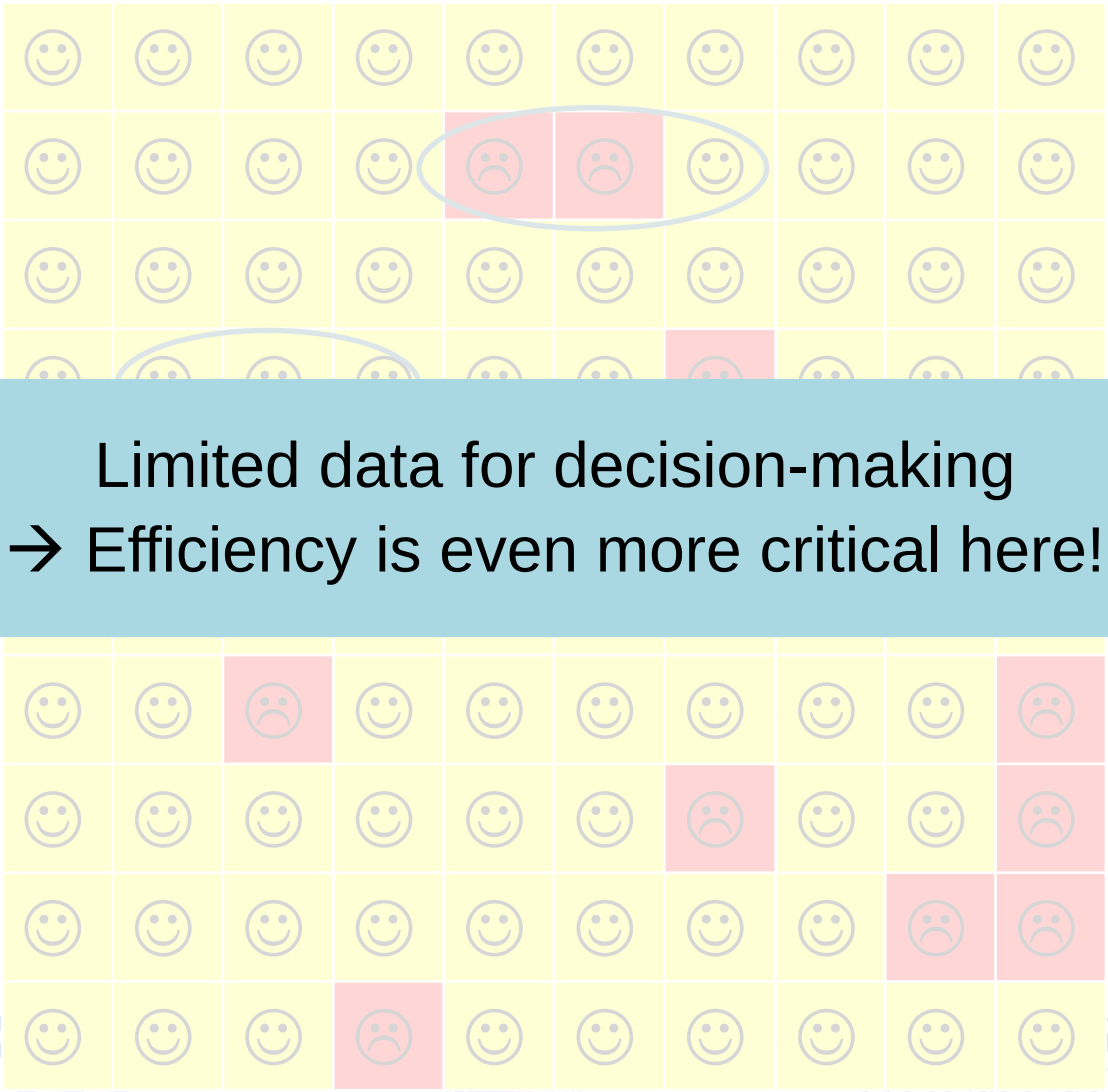
Maximum Tolerated Dose (MTD) of combined Lenalidomide and Azacitidine with a target Dose Limiting Toxicity (DLT) probability of 20%

Trial Design:

Classic 3+3 or

Modified Continual Reassessment Method (CRM)?

Dose level where *true* DLT rate = 10%



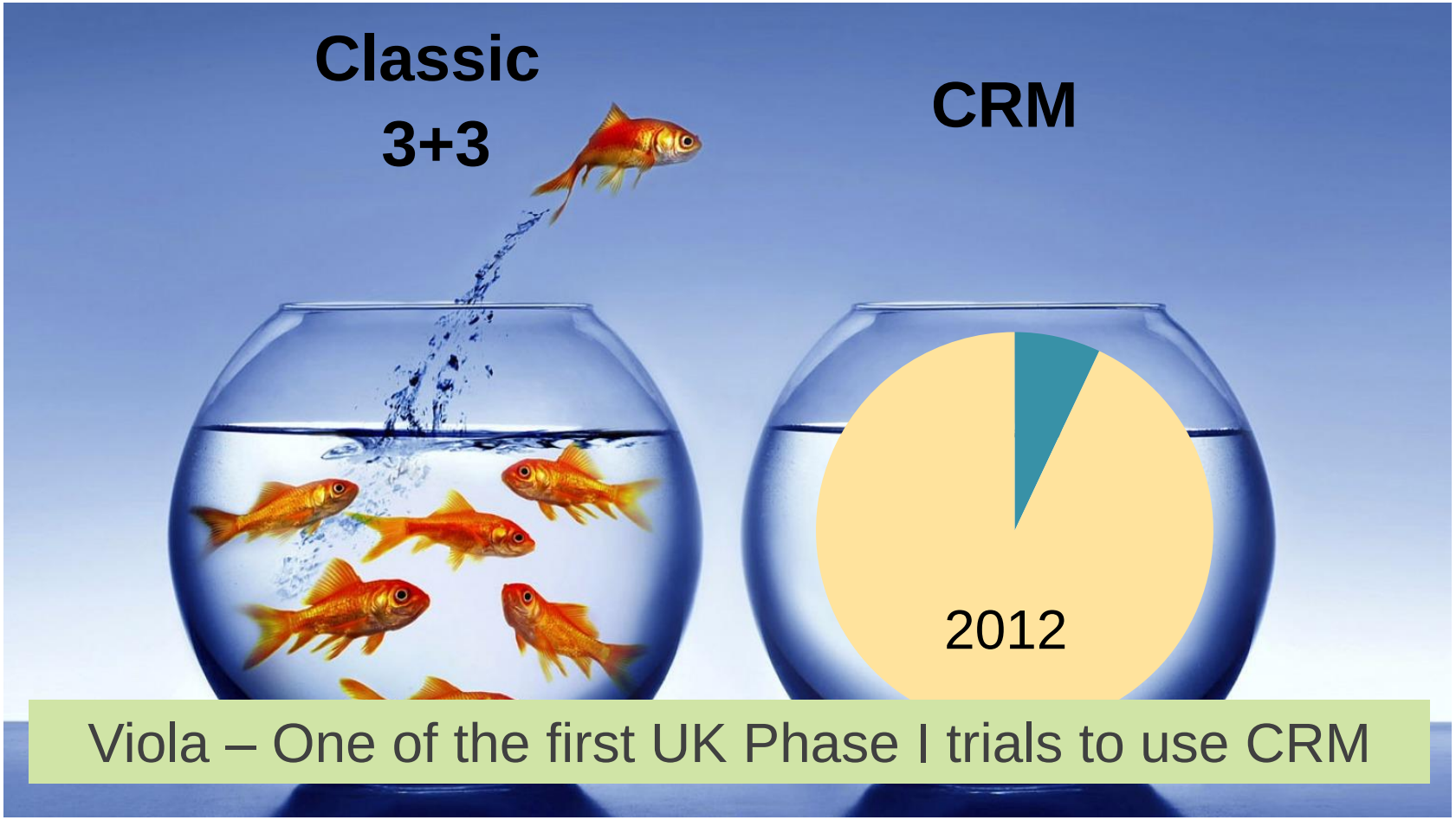
☺ : No DLT

☹ : DLT

Limited data for decision-making

→ Efficiency is even more critical here!


Classic
3+3
CRM



Viola – One of the first UK Phase I trials to use CRM

Barriers in Implementing Model-Based Designs

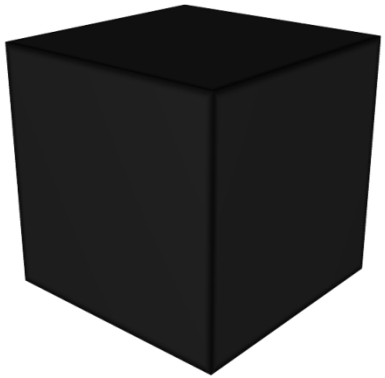
(Yap et al 2013, Yap et al 2017, Love et al 2017)

Lack of knowledge

Lack of familiarity

Experience

Lack of training / expertise



Black Box

Overcoming Barriers in Practical Implementation

Statistics in CCR

Clinical Cancer Research

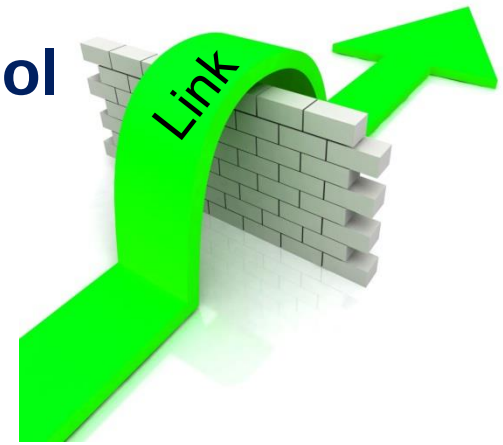
Dose Transition Pathways: The Missing Link Between Complex Dose-Finding Designs and Simple Decision-Making

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

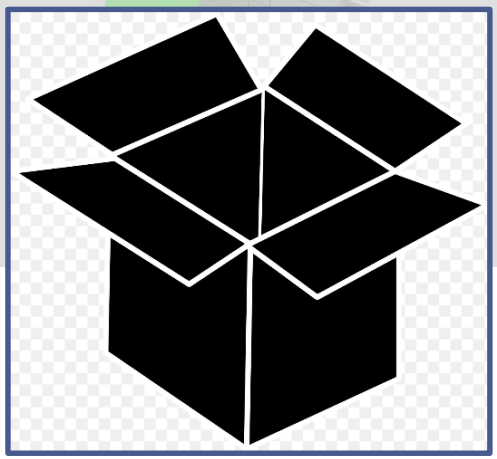
Clinical Cancer Research

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.

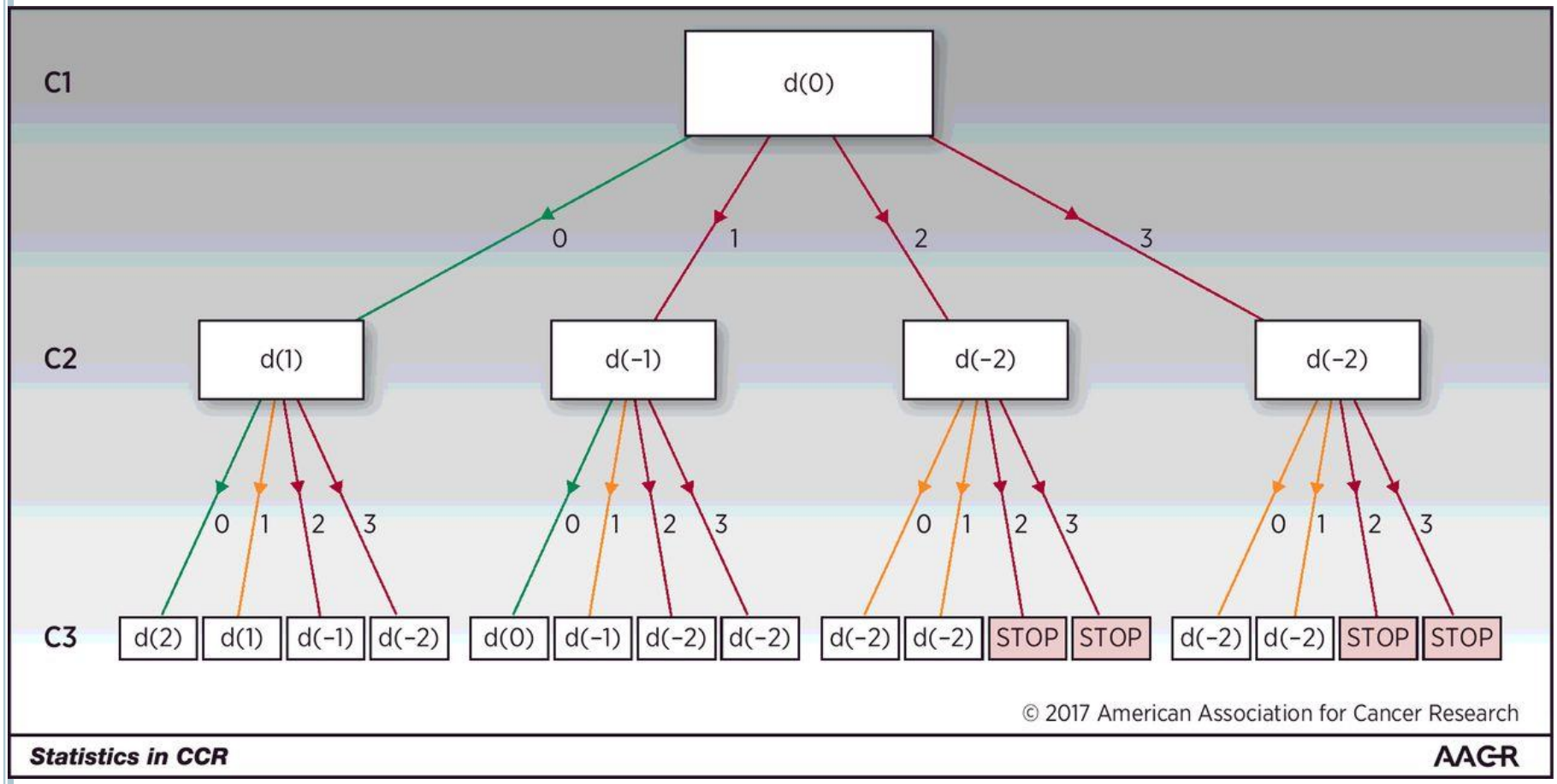
Complex Models



Viola: Initial Dose Transition Pathways

(Cohorts of 3)

(Yap et al, CCR 2017)



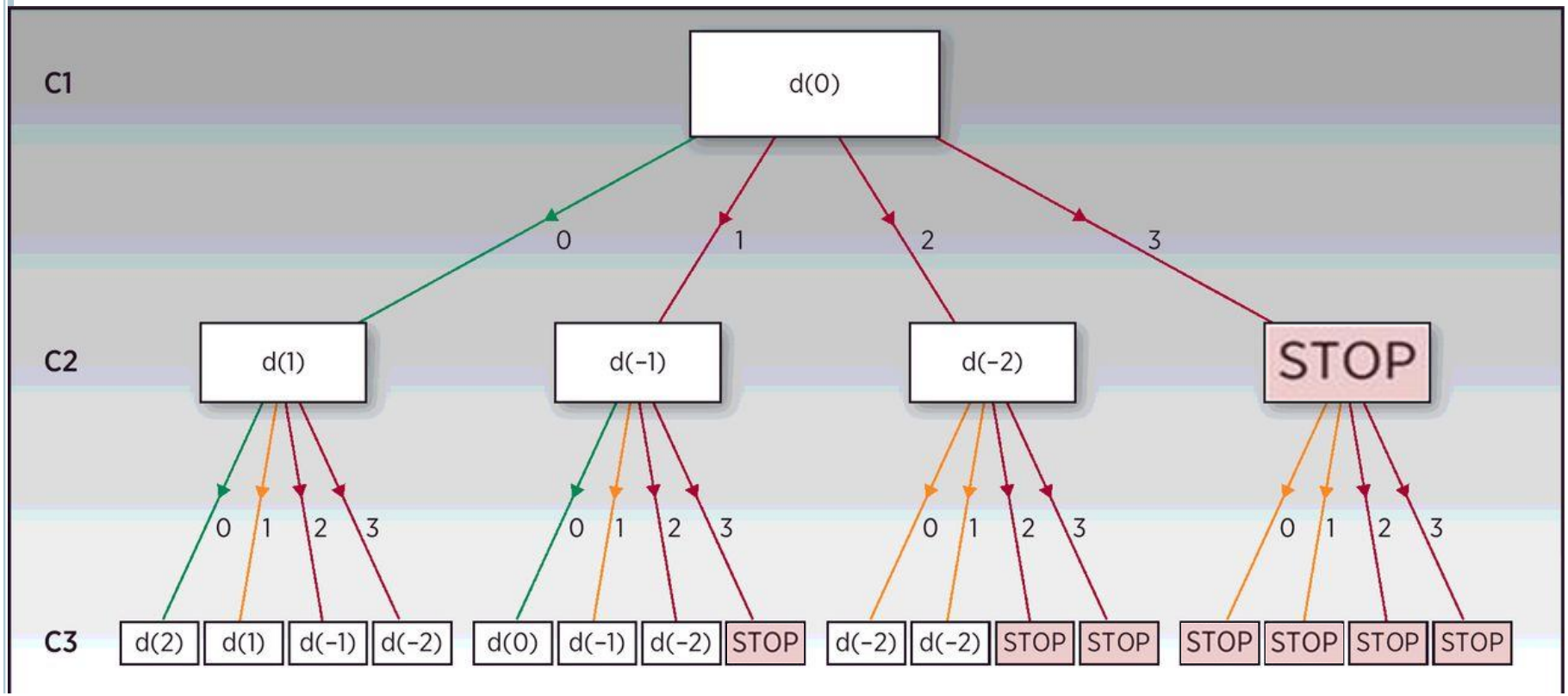
Stop early criteria for excessive toxicity:

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

Viola: Initial Dose Transition Pathways

(Cohorts of 3)

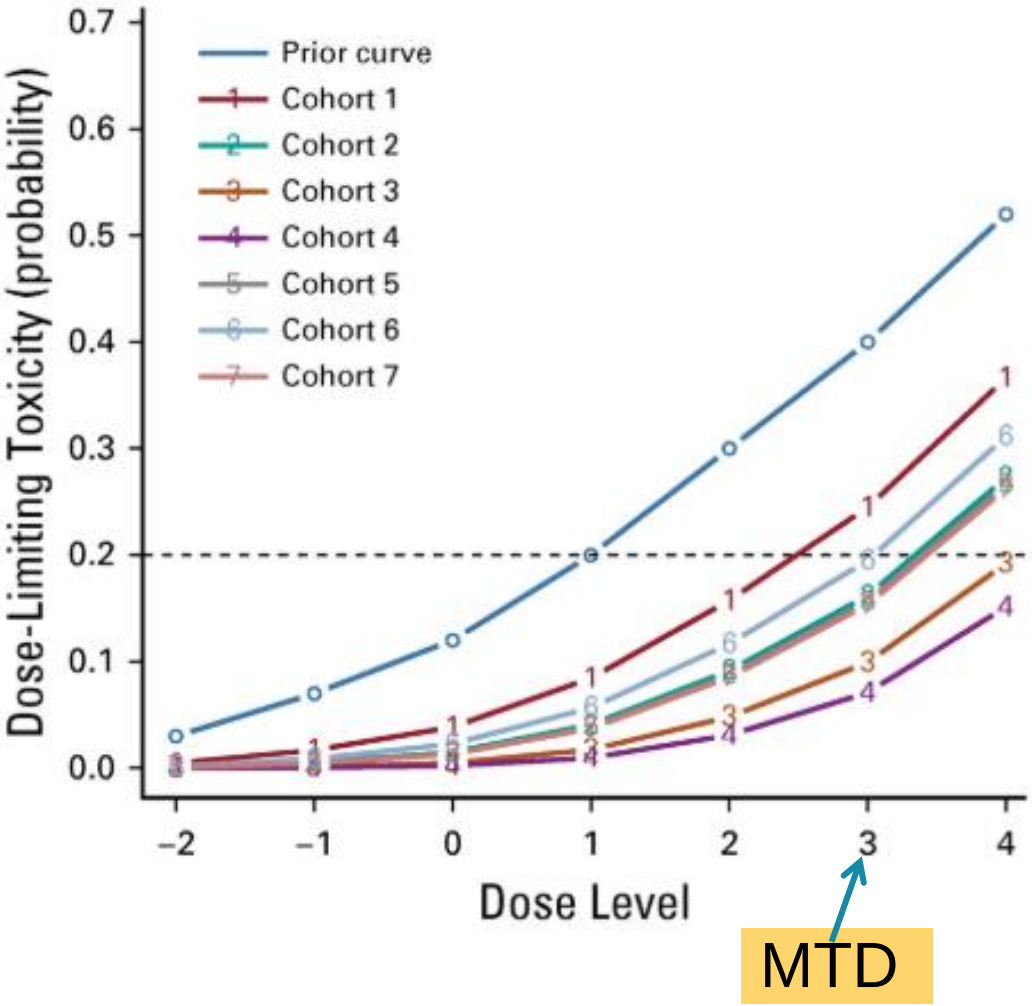
(Yap et al, CCR 2017)



Stop early criteria for excessive toxicity:

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

Updated Dose Toxicity Curves (Craddock et al JCO 2019)



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**

What Benefits Have We Seen?

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

Use of CRM coupled with DTP

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…)

Trial Conduct and Analysis Stage

- Ease of use of DTP by Trial Team and Trial Steering Committee
- Provides the flexibility to look ahead and decide in advance, e.g. if no DLT occurs, escalate as projected 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.

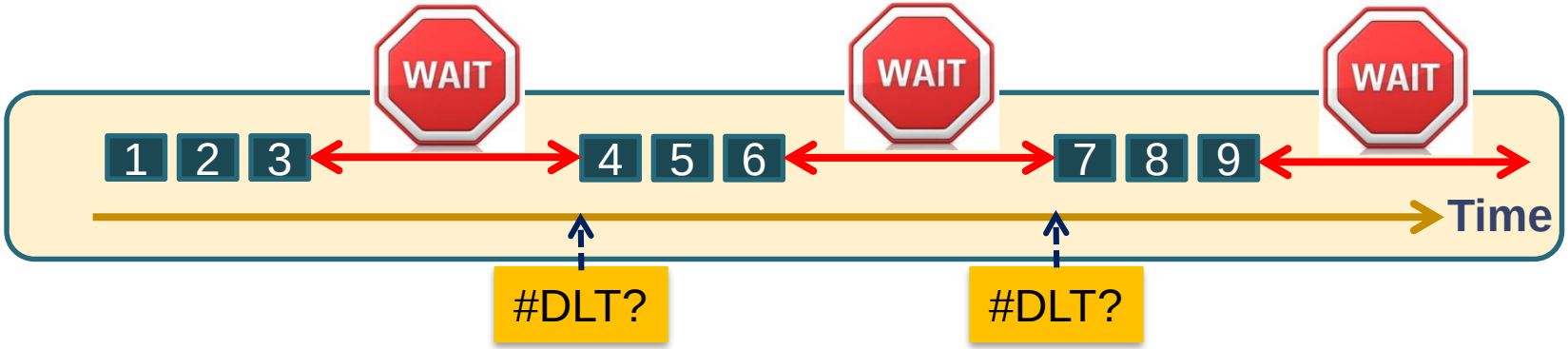
Unexpected Challenges

- 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***

What if ….?

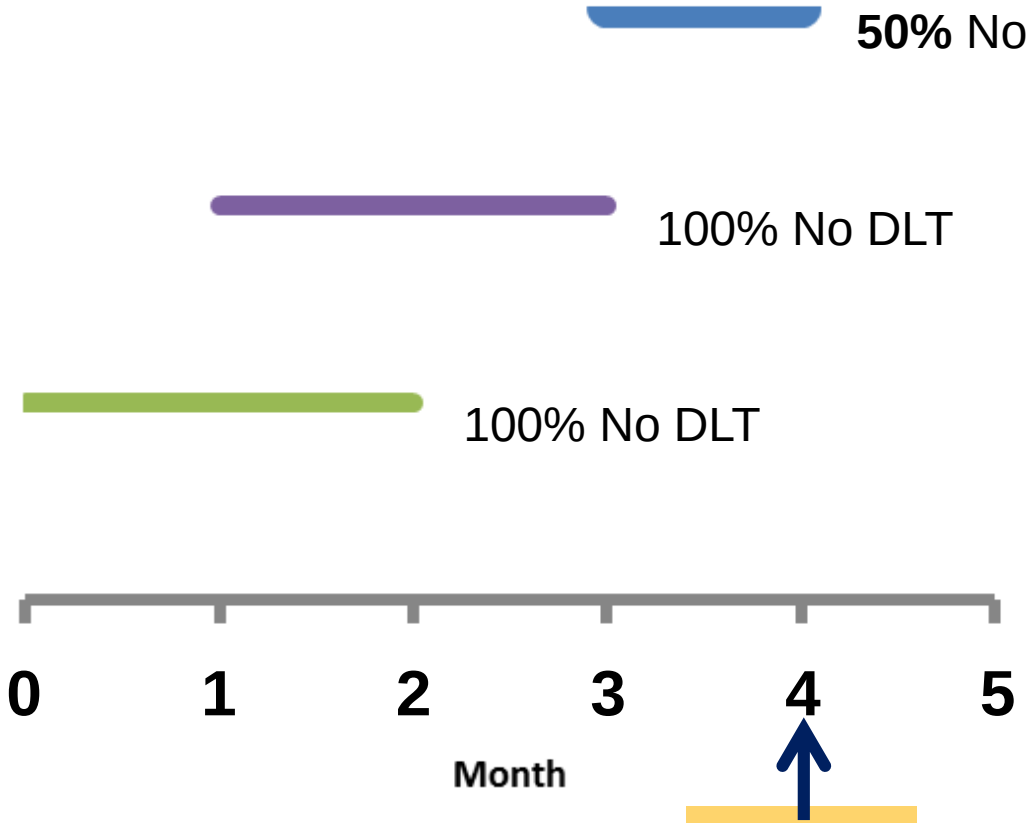
- Treatment might give late onset toxicities, e.g. radiotherapy, some molecular targeted agents
- DLT observation period might have to be longer
  - Extended trial suspensions
  - Long trial duration



Extension of CRM: TITE-CRM (Cheung & Chappell 2000)

Time to event CRM (event = toxicity)

DLT observation period = months



Options

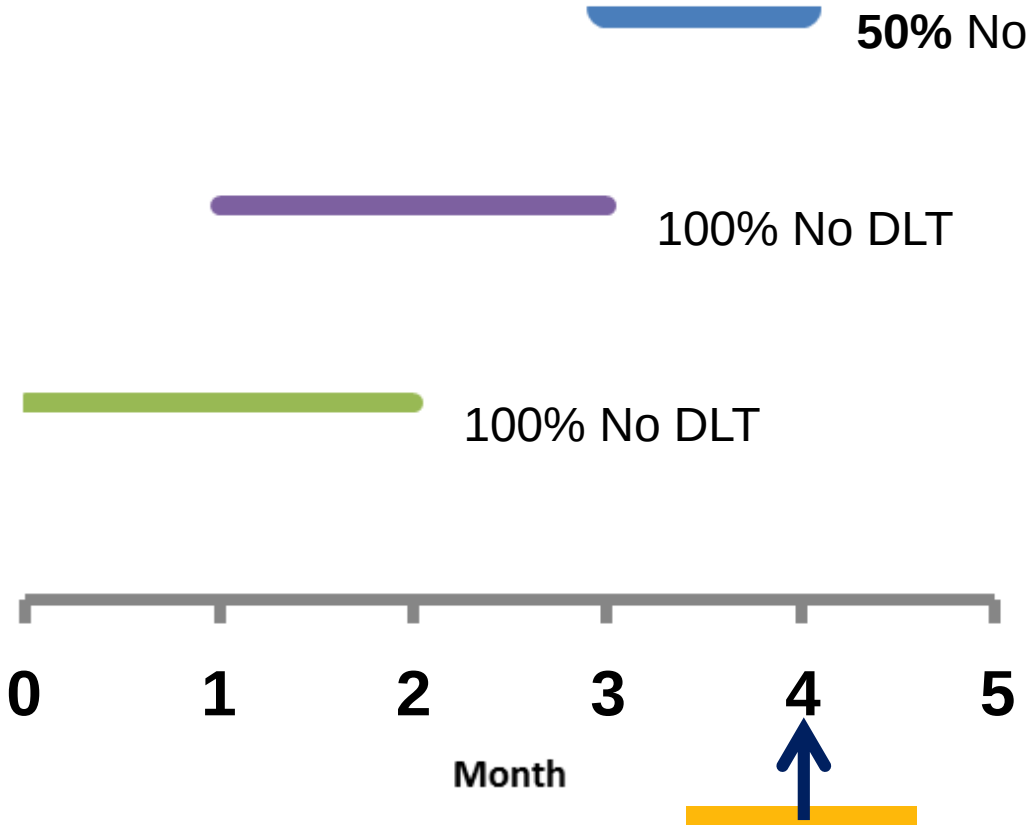
(1) Wait for another 1 month

(2) Use all available information and place fractional weights proportional to the length of follow-up period for patients who have not experienced DLT

Extension of CRM: TITE-CRM (Cheung & Chappell 2000)

Time to event CRM (event = toxicity)

DLT observation period = months



Cons: Might have a slight increase in risk of overdosing compared to CRM; ↑ resources

Pros: Overall duration of trial can be *drastically* reduced

Extension of CRM: Time-to-event CRM

CI: Hisham Mehanna

A Phase I trial in Patients with Head and Neck Cancer

Trial Design: Time-to-event CRM

Uses both partial and complete DLT information of all accumulated patients and dose information to inform dose recommendation

Initial DLT: 8 weeks
Final DLT: 12 weeks

An Early Phase MAMS Platform Trial

[Joint-Lead: Carlo Palmeri (Liverpool) & Anthony Kong (Birmingham)]

PATIENT POPULATION

- Breast cancer patients with (without) brain metastases

TRIAL DESIGN

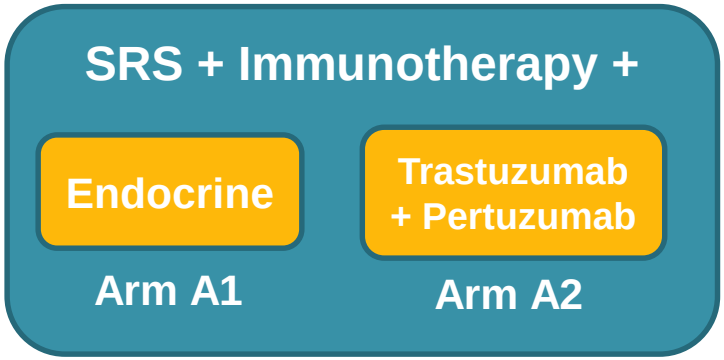
- Multi-arm multi-stage (currently 10-arms)
- Non-randomised (some with dose-finding)
- Patient is allocated to a treatment arm based on physician's choice of their 'real world' systemic therapy (standard of care).
- Primary Aims: Safety and preliminary activity

Funded by CRUK and pharma; in set-up

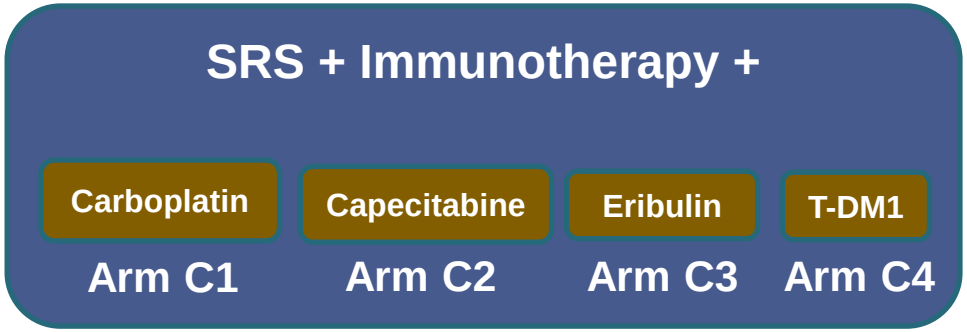
RADIANT-BC

Little evidence that
SRS + Immunotherapy + chemo
is safe

Group A: Brain Mets
Non-chemotherapy based



Group C: Brain Mets
Chemotherapy based



SRS: Stereotactic Radiosurgery
(non-surgical radiation surgery)

Cancer Research UK Clinical Trials Unit @CRCTU

CANCER RESEARCH UK

UNIVERSITY OF BIRMINGHAM

Group A: Brain Mets
Non-chemotherapy based

SRS + Immunotherapy +

Endocrine — Arm A1

Trastuzumab + Pertuzumab — Arm A2

Bayesian Adaptive

Group B: Non-Brain Mets
Chemotherapy based

CRM

Immunotherapy +

Carboplatin — Arm B1

Capecitabine — Arm B2

Eribulin — Arm B3

T-DM1 — Arm B4

Group C: Brain Mets
Chemotherapy based

TITE-CRM

SRS + Immunotherapy +

Carboplatin — Arm C1

Capecitabine — Arm C2

Eribulin — Arm C3

T-DM1 — Arm C4

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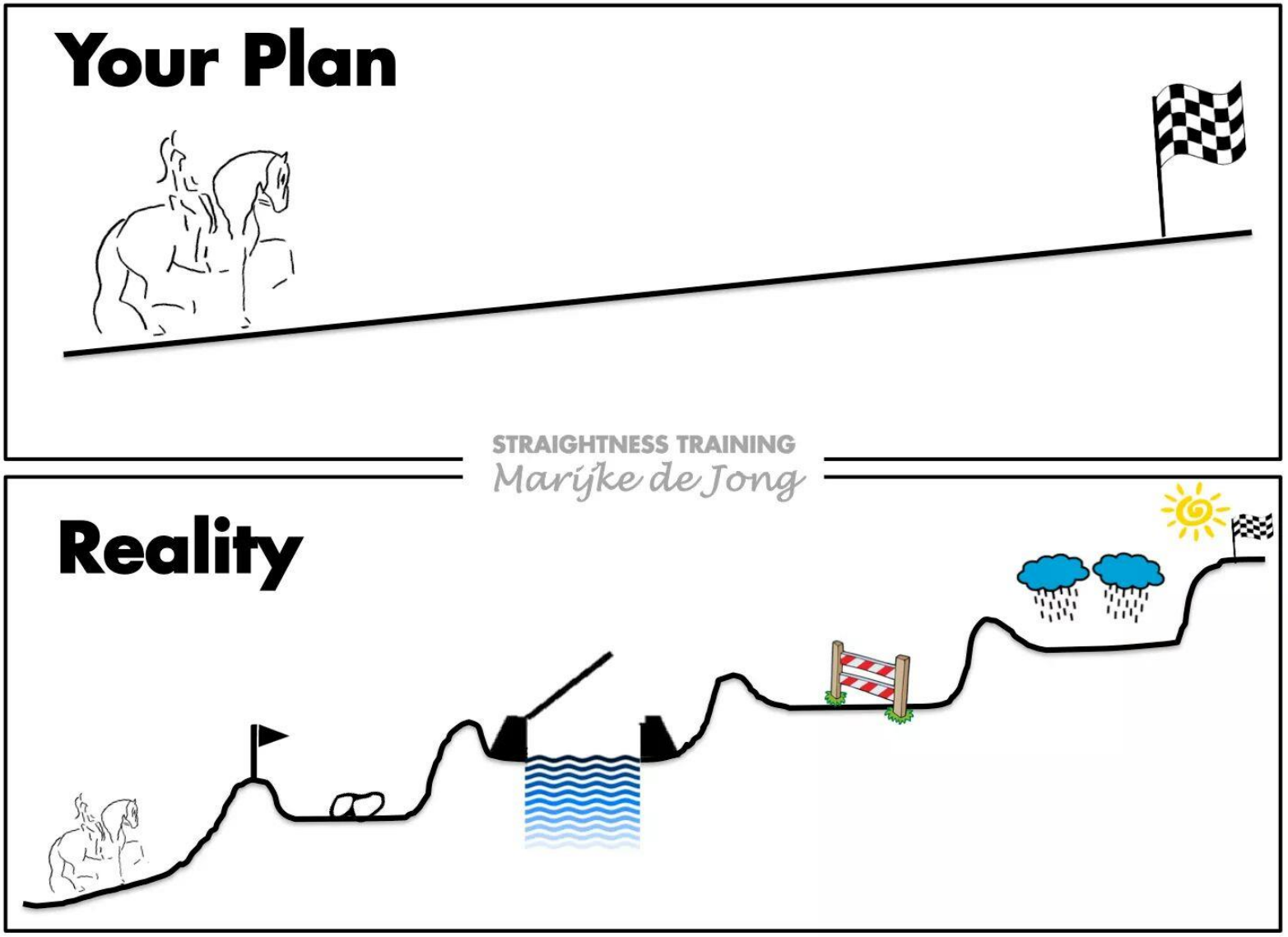
Experience gained…

ENGAGEMENT

↑ confidence will ↑ uptake

- **Close interaction** with clinical investigators and trial managers to co-develop a suitable, ***acceptable*** design tailored to the needs of the trial is crucial
  - Incorporate clinical judgements
  - Take into account operational aspects
- User friendly tools play an important role



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

Clinicians' Perspectives…

"**Very positive**. But ***needs time from CIs to invest*** to understand It's capabilities"

Prof Hisham Mehanna, **Wisteria** CI

"I like the fact..

- ***more dynamic*** than 3+3 design, ***making use of all the available data…***
- model will really enable the trial to proceed ***much faster (+ safe for patients)***…
- ***early and late DLT periods…*** can proceed to next level if early DLT period is acceptable to enable delivery of trial in time but subsequently can move back to lower level if late DLT period shows more toxicities"

Dr Anthony Kong & Prof Carlo Palmeri, **Radiant-BC** Joint CIs

Clinicians' Perspectives…

"VIOLA is a compelling example both of the importance of **innovation in trial design** driven through a **creative interaction** between statisticians and clinicians as well as the **pivotal role** of [**UK Trials Acceleration Programme**] - particularly in rare or complex cancer"

Prof Charlie Craddock, **VIOLA** CI

"… really exciting, but … difficult to get the companies to buy into these novel designs – they still seem to prefer the standard 3+3 approach.

In the future, with increasingly ***personalised medicine…*** much more common to use these novel designs."

Prof Mhairi Copland, **MATCHPOINT** & **MUSICAL** CI

"Problem… Recruitment….Could the CRM come to our ***rescue***?"

"I am a ***happy PI*** thanks to CRM."

Dr Graham Collins, **RomiCAR** CI

Features of a good adaptive design

- **Quality**
- **Automatic – pre-planned adaptations**
- **Efficient**
- **Smart**

Well-planned

Flexible

Copes with the unexpected

What makes a good adaptive design?

- **Quality**
- **Automatic – pre-planned adaptations**
- **Beneficial to patients**

Why Are We Not Doing More?

Well-planned

Flexible

Copes with the unexpected

Acknowledgements

For all listed trials:
All involved including
Trial Management Groups, Independent Safety Committees,
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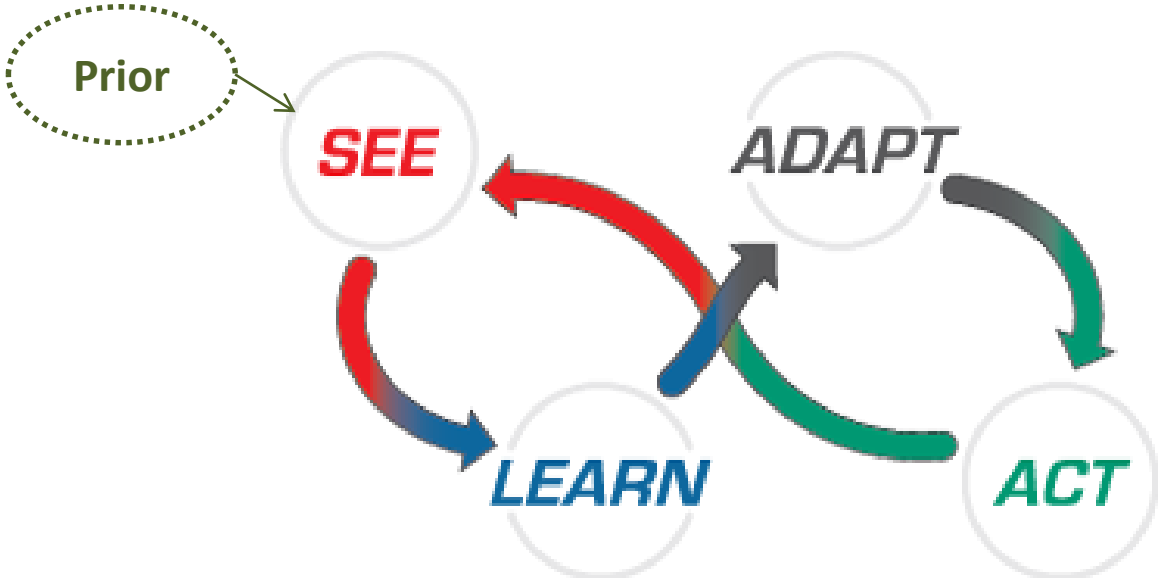
Patients and Families

Funders: CRUK, ECMC, Bloodwise
(Trials Acceleration Programme) and Pharma

Co-authors of Viola Trial paper and DTP paper

A Team Effort

Thank You



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