Clinical Trials Research Unit
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Designing phase I trials with backfilling to mitigate screening and treatment delays

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UK MYELOMA RESEARCH ALLIANCE

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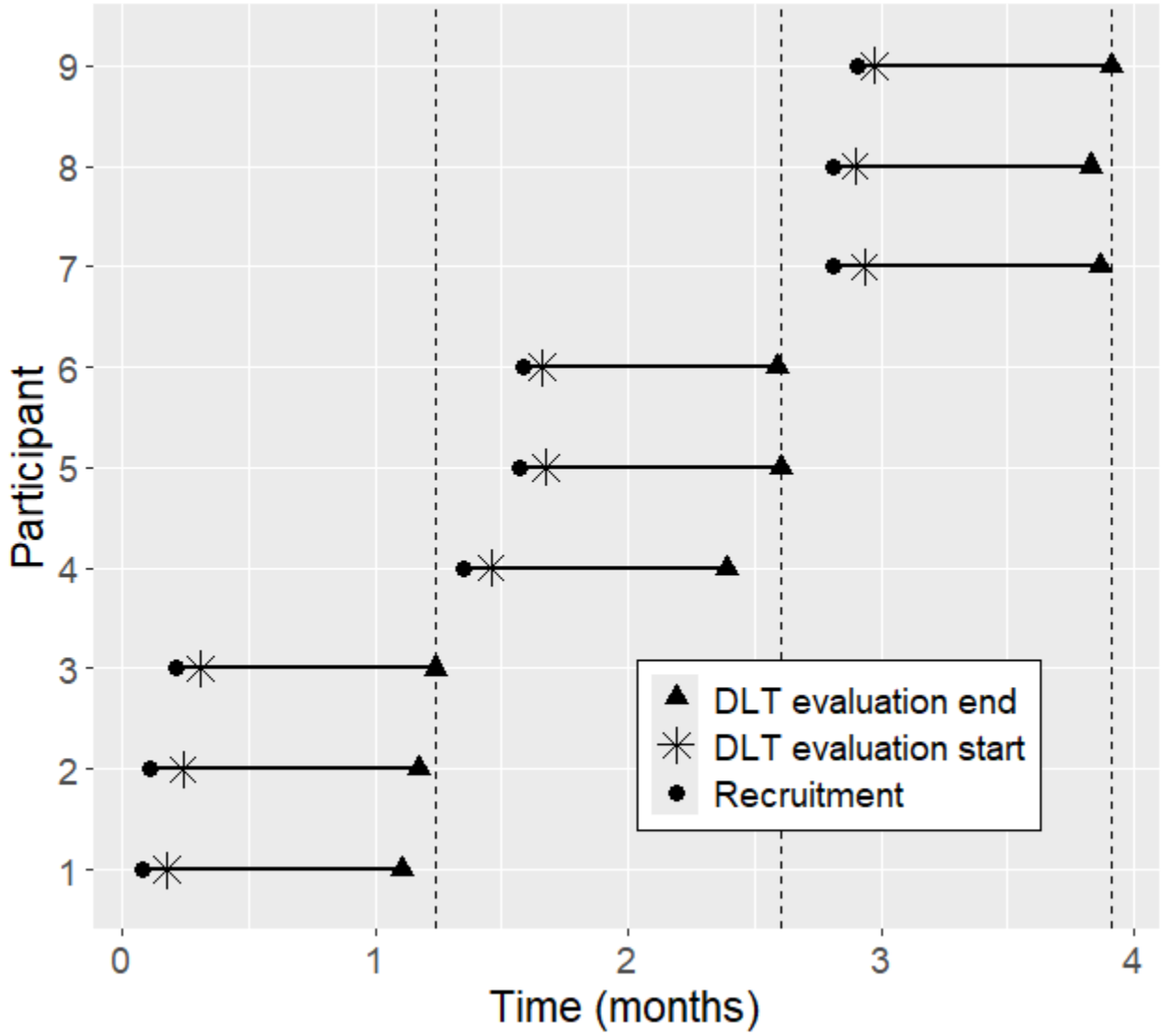
Timing for sequential oncology phase I trials

- Cohorts treated sequentially
- Short delay: recruitment → Dose limiting toxicity (DLT) assessment
- Dose decisions made after each cohort by safety review committee (SRC)



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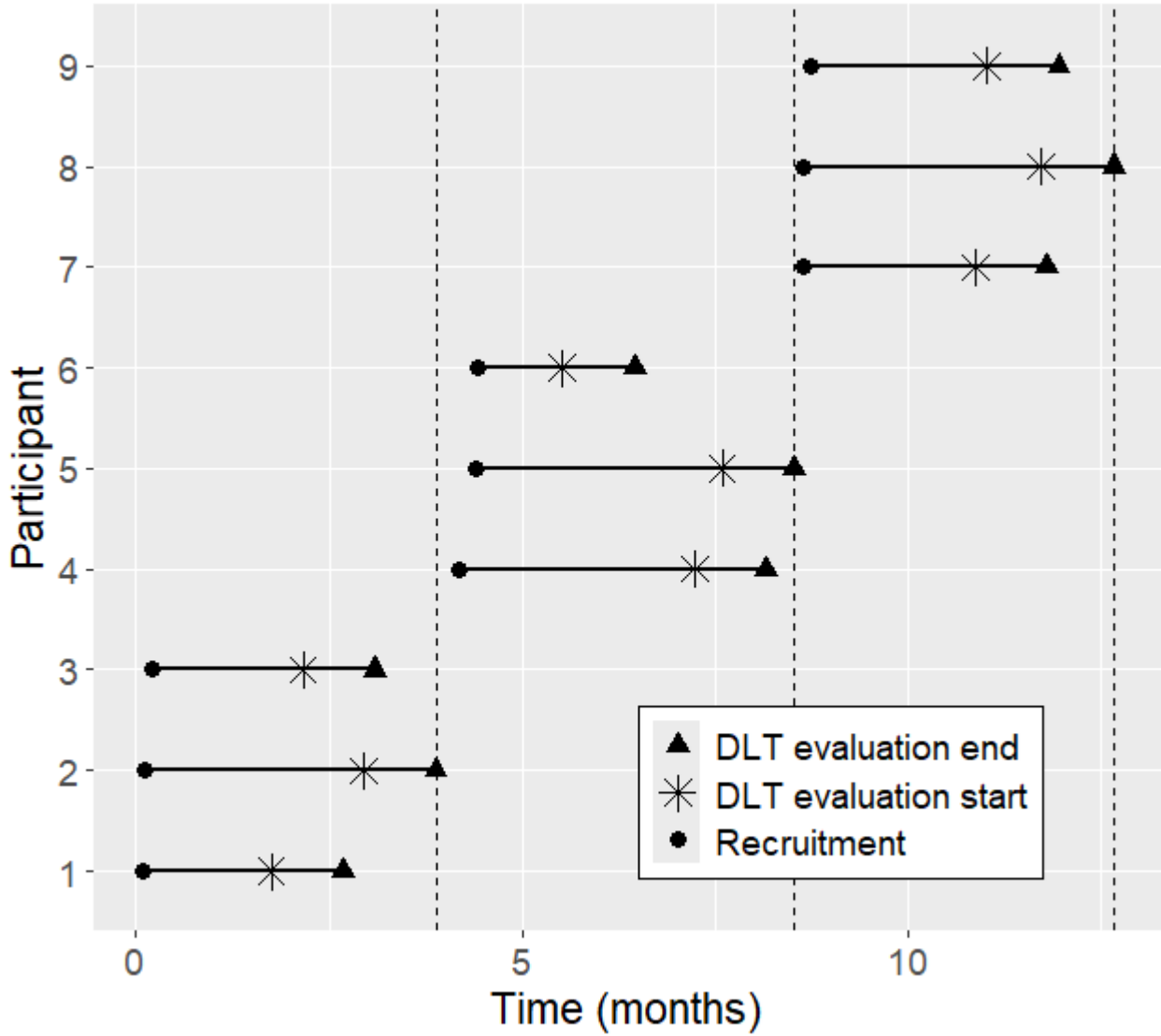
Treatment or screening prior to DLT evaluability period

Problem

- Delay between recruitment and allocation
- Timing is variable and unpredictable
- Standard designs → long trial duration

Constraint

- Patients already treated → ideally allocate
- Must maintain safety



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K-IMPACT: Phase I trial in Multiple Myeloma

- Multiple Myeloma is a cancer of plasma cells in the bone marrow
- Academic partnership with a small biotech company
  - Providing drug and distribution
  - Grant funding from a charity
- First in human pan-cancer trial in follow-up
  - Shown to be safe and well tolerated

Primary objective

- Determine an MTD of Drug-K maintenance therapy for relapsed myeloma after sASCT

K-IMPACT participant Flow

- Long delay between entry and dose allocation (≈4–6 months)
- Timing to eligibility varies across patients
  →Asynchronous arrivals at dose allocation
- Patients often undergo intensive therapy to access trial treatment
  →strong obligation to treat
- Limited trial capacity and high resource use
  →need efficient allocation

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K-IMPACT dose decisions

- 4 dose levels under consideration
- The DLT window is short, so partial follow-up methods are unnecessary
- Bayesian logistic regression model
  →Using information across all dose levels
  →Target toxicity [0.2-0.34]
- Dose determined continuously from the model
  →updated as data accrues
- No skipping in escalation (starting at dose level 2)

  Trial stops:
  →Safety concerns (all doses toxic)
  →9 participants have been treated at the current recommended dose
  →Total N=18

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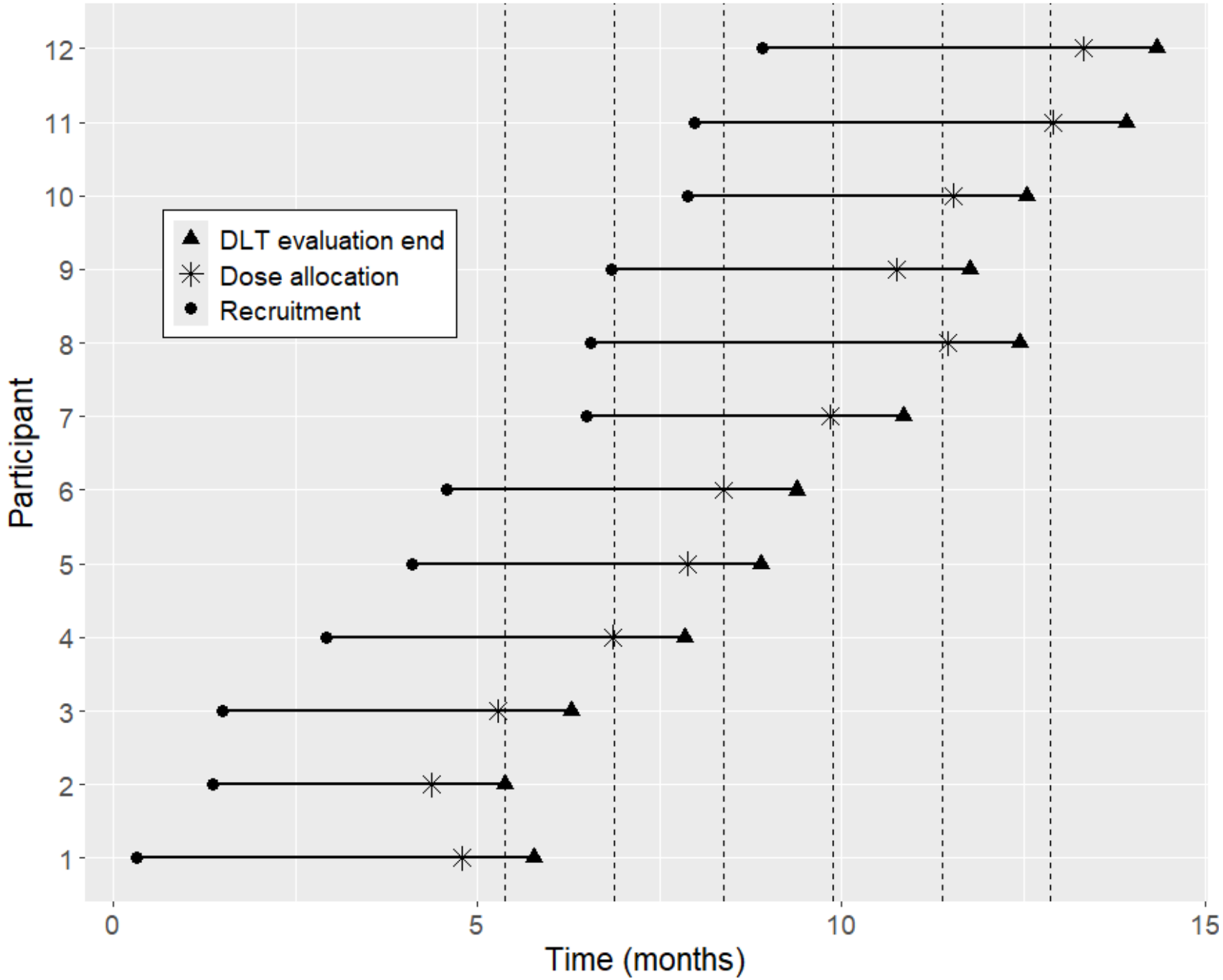
Participant flow

- Continuous recruitment (actively managed)
- Fixed regular SRC reviews (dashed lines)
- Dose under evaluation is aligned with available evaluable data and SRC review timing



K-IMPACT design

Backfilling allows for additional allocation at any one time

- Maximum 3 participants at the dose under evaluation
- Maximum 3 participants at the dose level below
- Escalation allowed after ≥1 DLT-evaluable participant

Allocation and flow control

- Participants allocated as close as possible to start of evaluable period (following ASCT and recovery)
- Allocation may be briefly delayed if no slots available

Recruitment constraints

- Recruitment is controlled at study entry to manage flow
- Maximum of 3 participants within a rolling 4 week time window

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Role of Safety Review Committee (SRC)

- Responsible for determining the optimal dose and patient safety (unchanged)
- Regular 4-weekly SRC meetings
  - (additional ad hoc reviews if needed)
- Model is re-evaluated at each SRC using available complete data
- Uncertainty driven by participant flow
  - Ongoing monitoring is essential
  - Inspecting how decisions evolve when looking ahead (dose transition pathways)

Simulation study

- Simulation reflects the full pathway and how data availability aligns with SRC review and allocation decisions
- **Key question:** How does recruitment under operational constraints impact dose-finding performance (across dose scenarios)

Recruitment scenarios

- Expected rate: ~42 weeks total recruitment
- Rapid rate: ~22 weeks total recruitment
- Sequential design: theoretical benchmark (~7 years)

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Simulation Results: All doses too toxic

Scenario	Percentage Selection (av. number participants)					N**	Delay***
	1	2	3	4	NDS*		
All doses too toxic							
True probs	0.45	0.55	0.65	0.75			
Expected	19.5 (4.9)	2.8 (2.9)	0.5 (1.4)	0.0 (0.2)	77.1	9.3	0.3 (1.6)
Rapid	19.2 (5.1)	2.8 (3.0)	0.4 (1.4)	0.0 (0.2)	77.5	9.7	0.6 (1.7)
Sequential	17.2 (4.0)	3.3 (2.4)	0.2 (1.0)	0.0 (0.3)	79.2	7.6	

- *percent no dose selected,
- ** overall expected sample size,
- *** average number of participants delayed (average delay in weeks for those delayed).Note: Delays are not possible in sequential design.

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Simulation Results: All doses well tolerated

Scenario	Percentage Selection (av. number participants)					N**	Delay***
	1	2	3	4	NDS*		
All doses not too toxic and true toxicity is below interval (0.2,0.34]							
True probs	0.05	0.1	0.15	0.2			
Expected	0.6 (0.8)	5.1 (3.1)	16.2 (5.1)	77.3 (7.4)	0.8	16.4	0.0 (1.8)
Rapid	0.4 (0.8)	5.3 (3.5)	17.6 (5.7)	75.9 (7.0)	0.8	17	0.1 (1.5)
Sequential	0.4 (0.5)	4.4 (2.2)	16.8 (3.6)	77.5 (7.3)	0.8	13.6	

- *percent no dose selected,
- ** overall expected sample size,
- *** average number of participants delayed (average delay in weeks for those delayed). Note: Delays are not possible in sequential design.

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Simulation Results: Dose level 3

Scenario	Percentage Selection (av. number participants)					N**	Delay***
	1	2	3	4	NDS*		
Dose level 3 within toxicity interval (0.2,0.34]							
True probs	0.07	0.17	0.27	0.37			
Expected	3.6 (1.8)	25.2 (5.0)	37.2 (5.9)	31.4 (4.1)	2.6	16.7	0.1 (1.8)
Rapid	3.2 (1.9)	24.0 (5.2)	39.6 (6.0)	30.2 (3.8)	2.9	17	0.2 (1.6)
Sequential	4.2 (1.4)	25.1 (4.3)	37.5 (5.3)	30.6 (4.1)	2.5	15.1	

- percent no dose selected,
- ** overall expected sample size,
- *** average number of participants delayed (average delay in weeks for those delayed). Note: Delays are not possible in sequential design.

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Summary

- Conventional sequential phase I designs are not viable in settings with long and variable pre-treatment delays (e.g. transplant pathways)
- The proposed approach safely decouples recruitment from dose allocation using
  - Near-continuous recruitment with flow constraints
  - Backfilling
  - Scheduled decision reviews
- Simulations show a substantial reduction in trial duration versus sequential designs, with no material loss in safety or dose-selection performance
- The main advantage is operational, enabling efficient and ethical use of patients in complex treatment pathways
- The framework is transferable to other early-phase trials with delayed eligibility and constrained capacity

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Questions?

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