Application of a Bayesian approach to treatment selection in a rare disease sub-population

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High risk multiple myeloma (HRMM)

- Multiple myeloma (MM) is a cancer that develops from cells in the bone marrow
  - ~ 4500 new cases each year in the UK
- High risk = certain genetic factors associated with poor outcomes
  - 20-30% of MM
  - Rare sub-population
- Standard treatment in newly diagnosed MM varies by practice
- Large phase III trial (Myeloma XI+) is currently evaluating treatment strategies
- Limited data available for HRMM sub-population

Designing the trial – challenges

Aim: assess whether we can improve outcomes for HRMM patients by selecting the optimum treatment strategy to take to phase III

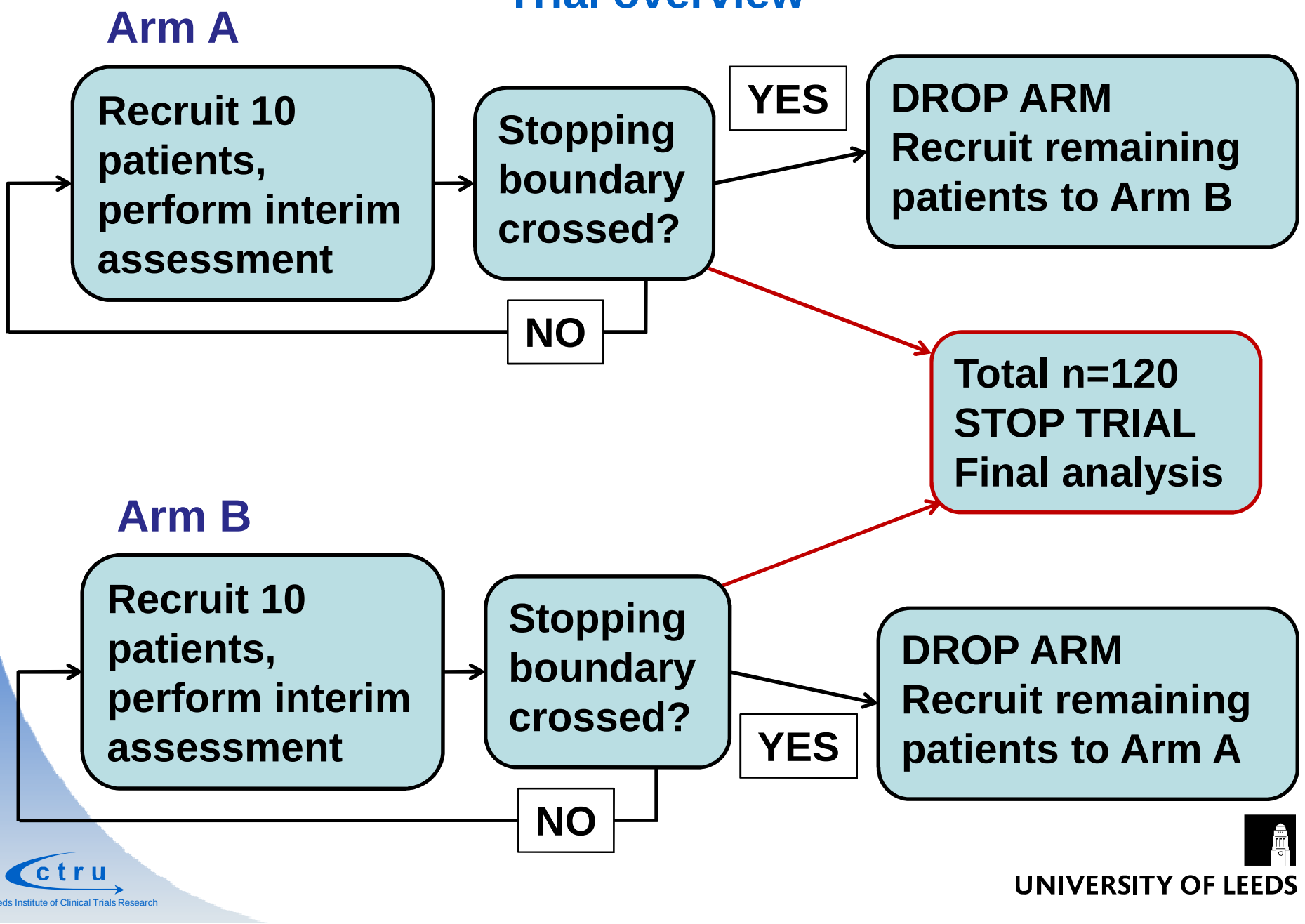
- Rare patient population
  - 3 arm phase II: n~450 HRMM (~2500 MM)
- Variable standard treatment
- Differing treatment approaches requiring multiple endpoint evaluation
  - Deliverability of treatment also important due to intense treatment in one arm

Designing the trial – overcoming the challenges

- Bayesian strategy, methodology of Thall, Simon and Estey (1995,1996), extended by Thall and Sung (1998)
- Treatment selection based on multiple outcomes and multiple interim assessments for futility
- Using data from Myeloma IX/XI+ to provide almost concurrent control data

Challenge	Overcome?
Rare patient population	✓ Efficient in terms of sample size (n=120)
Variable standard treatment	✓ 'Standard' control arm as up to date as possible
Differing treatment approaches requiring multiple endpoint evaluation	✓Can incorporate multiple endpoints

Trial overview



Endpoints

Interim analyses for futility
After every 10 patients reach 12 months post-rand

- Progression-free survival @ 12m post-rand
- Deliverability of treatment
- Minimal residual disease (MRD)
    - The small number of cancer cells remaining
    - Known to cause relapse

Final analysis
Compare each treatment arm to control prior
Compare two experimental treatment arms

- Progression-free survival at 18 months post-rand

Implementing the design

		Progression-free at 12m			Prog / died by 12m
		MRD +ve	MRD –ve	MRD unknown	
Deliverable	**y**	A1 + A9	A2 + A10	A3 + A11	A7
	n	A4 + A12	A5 + A13	A6 + A14	A8

A7, …, A14 = progressed or died by 18m

- Count data modelled using Dirichlet priors
  - Control data from MyeIX (later to be updated to MyeXI+):

    Dir(14, 29, 30, 15, 0, 0, 10, 50, 15, 18, 19, 13, 0, 0)

  - Experimental priors:

    $a_1 + \ldots + a_{14} = 14$, following the “flat prior” method suggested by Thall and Sung

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- Data monitored according to endpoints
  - Compound events follow Beta distribution
  - Monitor via posterior probability

Stopping rules

Interim analyses:

- P(MRD –ve rate > control rate + 10%) <0.05
- P(Non-deliverability > control rate + 20%) >0.9
- P(Proportion progressed/died @ 12m post-rand > control rate) >0.9

Final analysis:

- P(Proportion alive and progression-free at 18 months post-registration > control rate) <0.85

Converted to stopping boundaries, e.g.

“At the first interim assessment, if the number of participants who are MRD negative is 1 or less (out of 10), stop for futility.”

Design performance

- Simulations performed to determine operating characteristics
- Check sample size large enough
- Assess probability of early stopping, π, under various scenarios
- Under null scenario (no change from control), 1-π is equivalent to α

    5.27% in MUK nine with n=120

Summary / final thoughts

- Flexible design
  - Multiple endpoints
  - Complex data structure / interaction between endpoints
  - Updating control prior when additional data available

- MUK nine design now changed to 1 experimental arm
  - Remove deliverability endpoint (removed intense arm)
  - Re-evaluate simulations
  - Flexibility allows us to incorporate a new arm at a later date (if the opportunity arises!)

- Software freely available
  - Not all of the above are incorporated
  - R package being developed

References

- Thall, PF, Simon, R, Estey, EH: Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. *Statistics in Medicine* 14:357-379, 1995
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