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

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Overview

- Disease background and study objectives
- Initial frequentist and a Bayesian approach
- Introduce the mathematics of the model and ideas around model calibration
- Questions and discussion

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High-Risk Multiple Myeloma

- Multiple myeloma is a cancer arising from plasma cells, a type of white blood cell which is made in the bone marrow
- Median age of diagnosis is 69, 37% < 65 with OS ~ 10 years
- A group of patients have poor prognosis with OS < 3years
- High risk disease defined by genetic lesions and gene expression profiles associated with poor outcome

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A Rare Population

- Myeloma represents 1.5% of all malignant diseases, and representing 4500 new cases each year in the UK
- High- risk multiple myeloma (HRMM) occurs in approximately 20-30% of MM patients
- <6/100,000 per year, representing a rare cancer or sub-population

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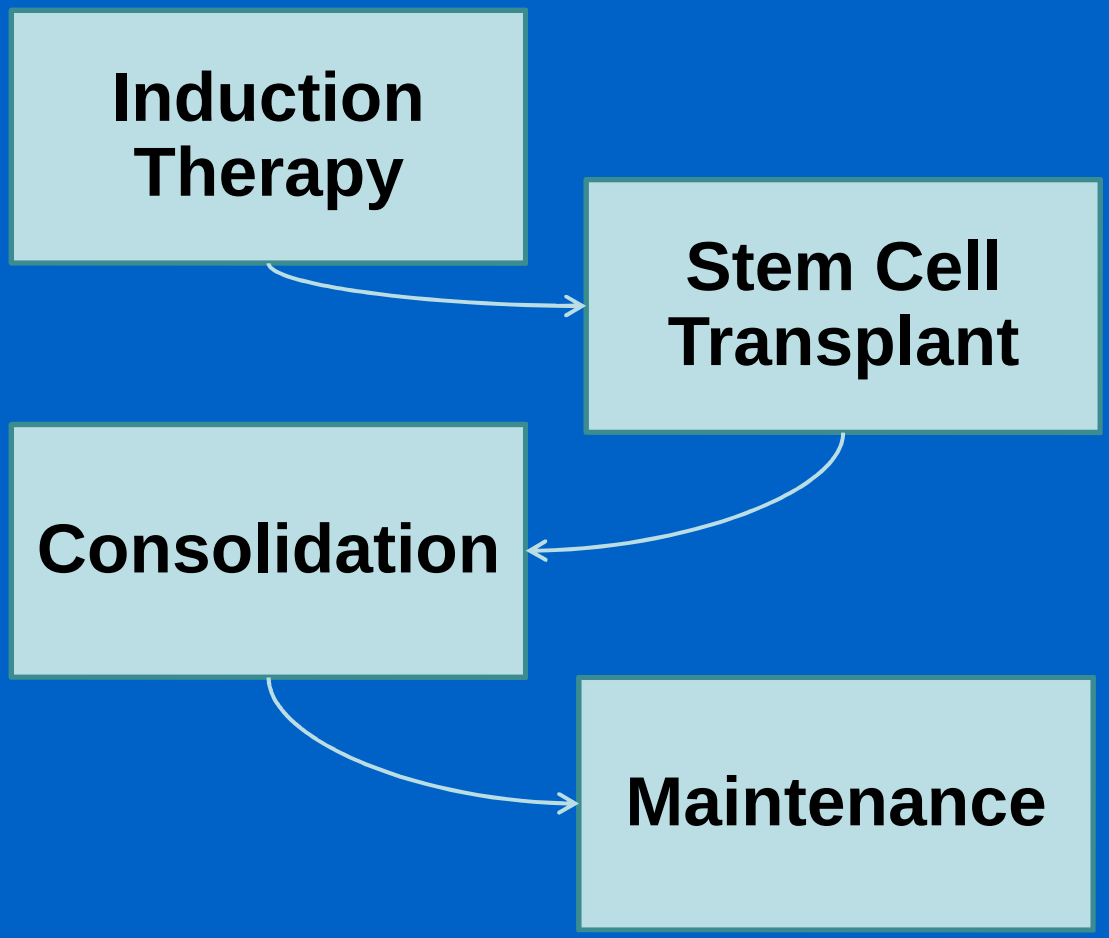
Treating newly diagnosed Myeloma



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Treating High-Risk disease

- Best practice currently unknown in UK, current therapy is ineffective
- Two approaches considered for induction therapy

High Intensity	Low Intensity

- Design a trial to assess whether we can improve outcomes for HR patients by selecting the optimum treatment strategy to take forward for further research

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Initial Approach to Trial Design

- A randomised controlled phase II trial selection trial was proposed (3 arms)
- Progression free survival primary endpoint

Problems

- Would result in sample sizes of up to 450 patients i.e. screening 2500 newly diagnosed patients
- Not comparing like for like –deliverability of treatment is important

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Bayesian Approach

- Reverse philosophy - How many patients can we recruit and whether this amount of data has sufficient value to justify the trial design
- Recruit 120 patients
- Thall and Sung (1998) Designs for single-arm clinical trials with multiple binary outcomes
- Chosen because allows multiple interims for futility

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A Control Arm?

- A ‘standard’ control arm for newly diagnosed MM patients is difficult to define, particularly while the Mye XI/XI+ trials are ongoing and results awaited.
- The data from Mye XI/XI+, would effectively provide almost concurrent control data
- Efficiencies in the overall sample size
- Only possible as CTRU conducting Mye XI/XI+

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Multiple endpoints

Final analysis

- Progression free survival at 18 months

Interim analyses – conducted after every 10 patients reach ASCT + 100 days

- Progression free survival, ASCT + 100 days
- Treatment deliverability
- Minimum residual disease

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Patient Pathways

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Patient Pathways

Group	Scenario				n
A1	Deliverable (ASCT) = YES	Progression-free at 100 days post-ASCT	Progression-free at 18 months post-randomisation	MRD +ve	14
A2				MRD –ve	29
A3				MRD unknown	30
A4			Progressed or died by 18 months post-randomisation	MRD +ve	15
A5				MRD –ve	18
A6				MRD unknown	19
A7		Progressed/died by 100 days post-ASCT			10
A8	Deliverable (ASCT) = NO	Progression-free at 100 days post-ASCT	Progression-free at 18 months post-randomisation	MRD +ve	15
A9				MRD –ve	0
A10				MRD unknown	0
A11			Progressed or died by 18 months post-randomisation	MRD +ve	13
A12				MRD –ve	0
A13				MRD unknown	0
A14		Progressed/died by 100 days post-ASCT			50

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The Model

- $A_1, \ldots, A_{14}$ possible pathways with probabilities $\theta_1, \ldots, \theta_{14}$ and outcomes
- Historic control data $\theta_S \sim Dir(a_S)$
- Prior for Experimental $\theta_E \sim Dir(a_E)$
- $X_n = (X_{n,1}, \ldots, X_{n,14})$ follows multinomial distribution in n (patients at analysis) and θ_E
- $\theta_E | X_n \sim Dir(a_{1E} + X_{n,1}, \ldots, a_{14E} + X_{n,14})$

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Compound events

- Objective is to monitor clinically important events
- $C = A_{j1} \cup \cdots \cup A_{jr}$ e.g. deliverability $(A_1 \cup \cdots \cup A_7)$
- Can be shown that Pr(C) $[\tau]$ follows a beta distribution
- $\tau_S \sim \text{Beta}(a_1 + \cdots + a_7, a_7 + \cdots + a_{14})$

Monitoring Criterion is posterior probability

$$\Pr[\tau_S + \delta < \tau_E | X_n]$$

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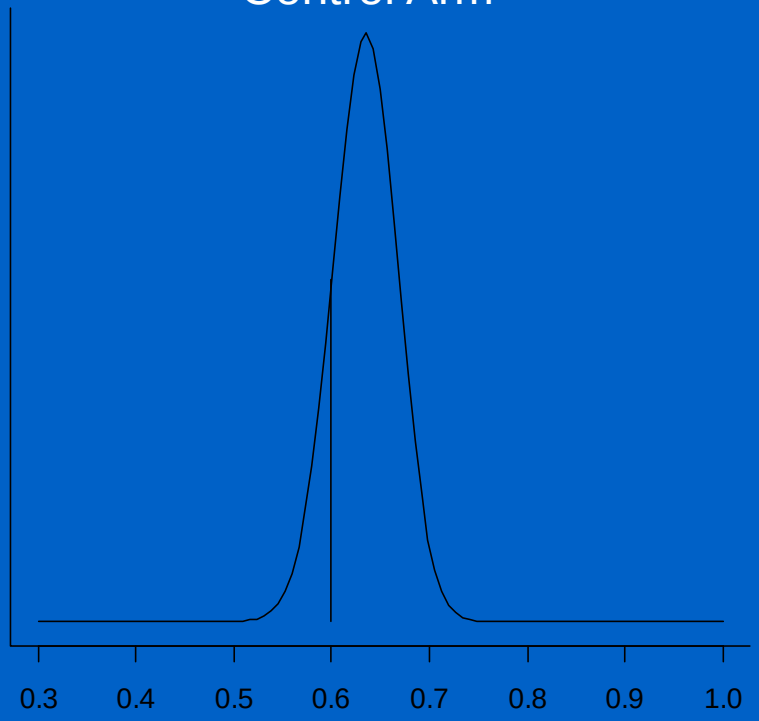
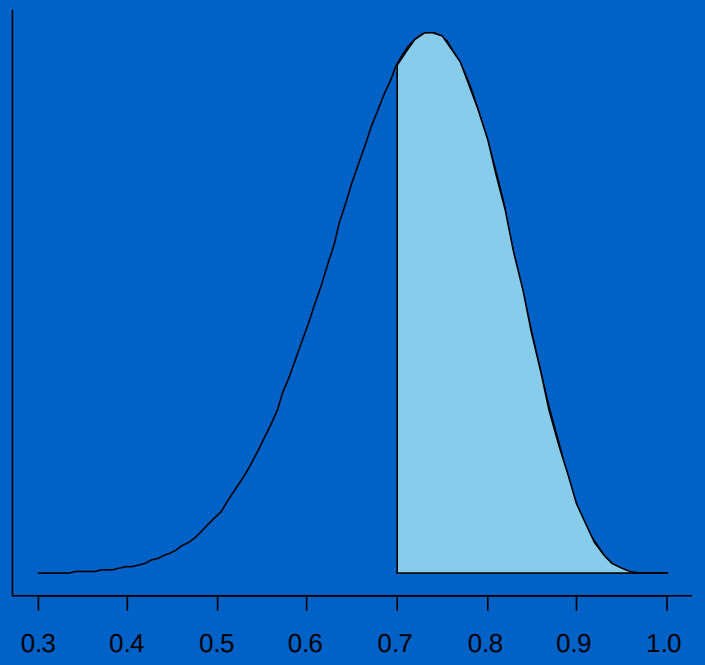
Monitoring criterion

$$\Pr[\tau_S + \delta < \tau_E | X_n]$$

Control Arm



Experimental Arm



$$\int_0^{1-\delta} \{1 - B_{\tau E}(p + \delta)\} b_{\tau S}(p)\, dp$$

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Stopping criteria - MUK9

Interim analyses

- P(Non-deliverability > control rate + 20%) >0.9
- P(Proportion progressed/died at 100 days post-ASCT > control rate) >0.9
- P(MRD –ve rate at 100 days post-ASCT > control rate + 10%) <0.05

Final analyses

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

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Simulations

- Simulations used to determine the operating characteristics of the design
- Assess the trials viability and tune the stopping boundaries
- Simulate at fixed value $\mu_S = \mu_E$ (null) and alternative to be some μ_E
- Assess the early stopping probability (π)
- Under null $1 - \pi$ considered type I error
- Under alternative π is type II error

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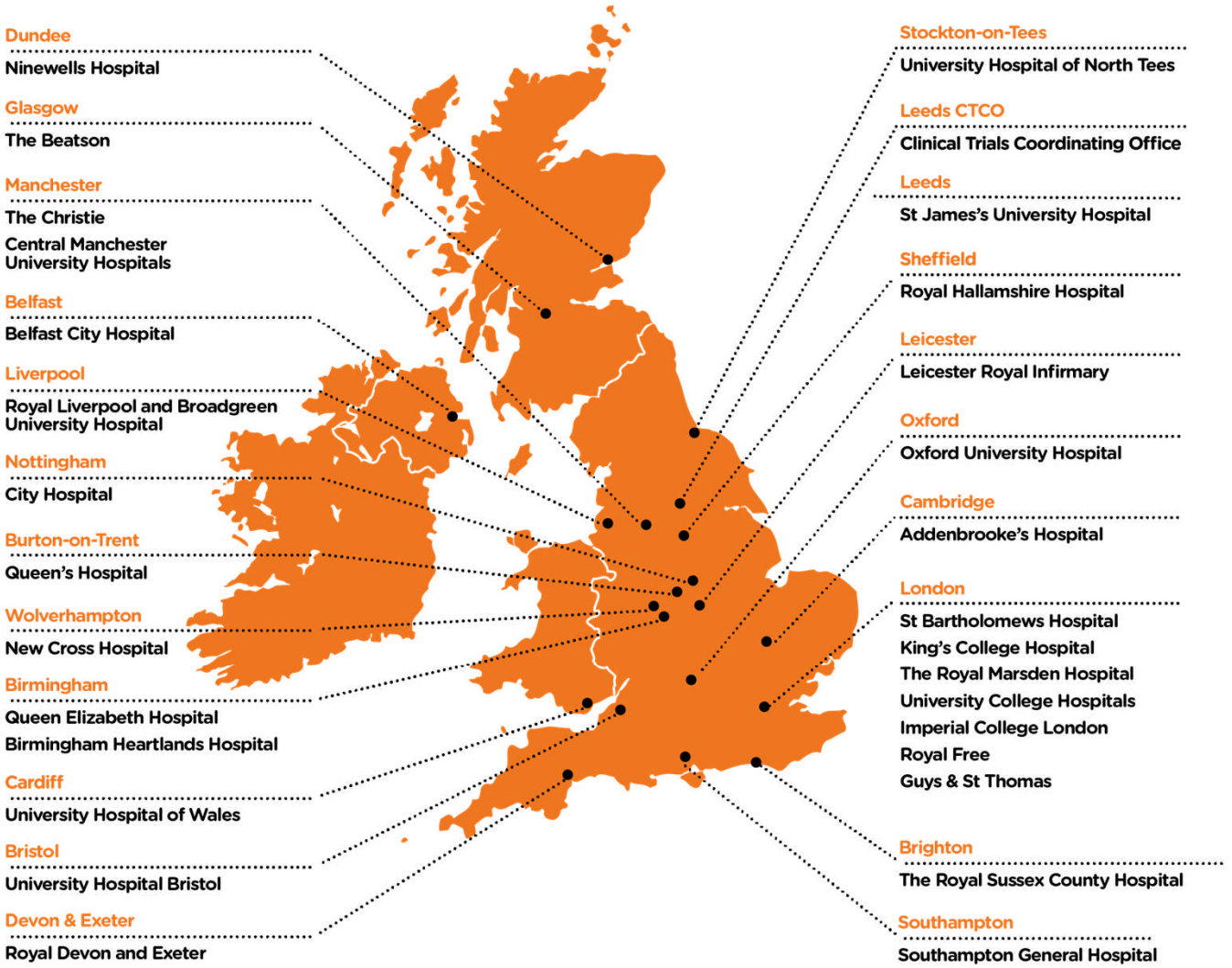
Myeloma UK Clinical Trial Network



Discussion Points

- Updating the control arm part way through recruitment
- How to define simulation scenarios to demonstrate good operating characteristics
- The use of a different progression time point at interim and final analyses
- 120 patients is fixed, patients will be enrolled to single arm if one arm is dropped
- Comparison of two arms at final analysis

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