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Choice of randomisation time-point in non-inferiority studies of reduced treatment duration: experience from the SCOT study

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SCOT Study

SCOT – Short Course Oncology Therapy – A Study of Adjuvant Chemotherapy in Colorectal Cancer

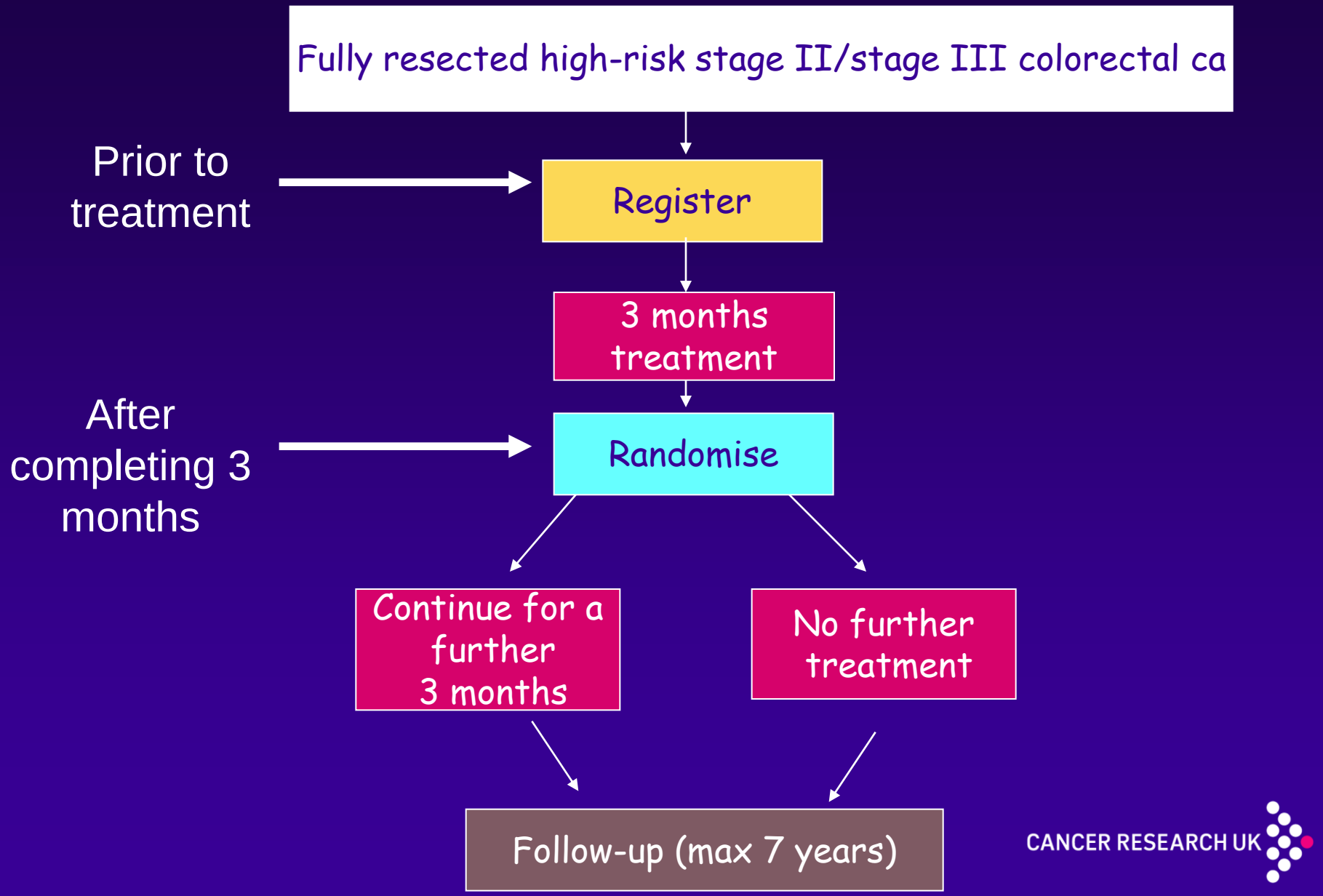
- Aim to show that 3 months of adjuvant chemotherapy is not inferior to the standard duration of 6 months

- Primary end-point: disease-free survival

- Introduction of new drugs has increased 3 year disease-free survival from 73% to 78% – wish to retain at least half this improvement

- Aim to exclude the possibility that 3 months of treatment reduces 3 years disease free survival by more than 2.5% compared to 6 months (aim to exclude hazard ratio >1.13)

Randomisation Time Point at 3 months (delayed randomisation)



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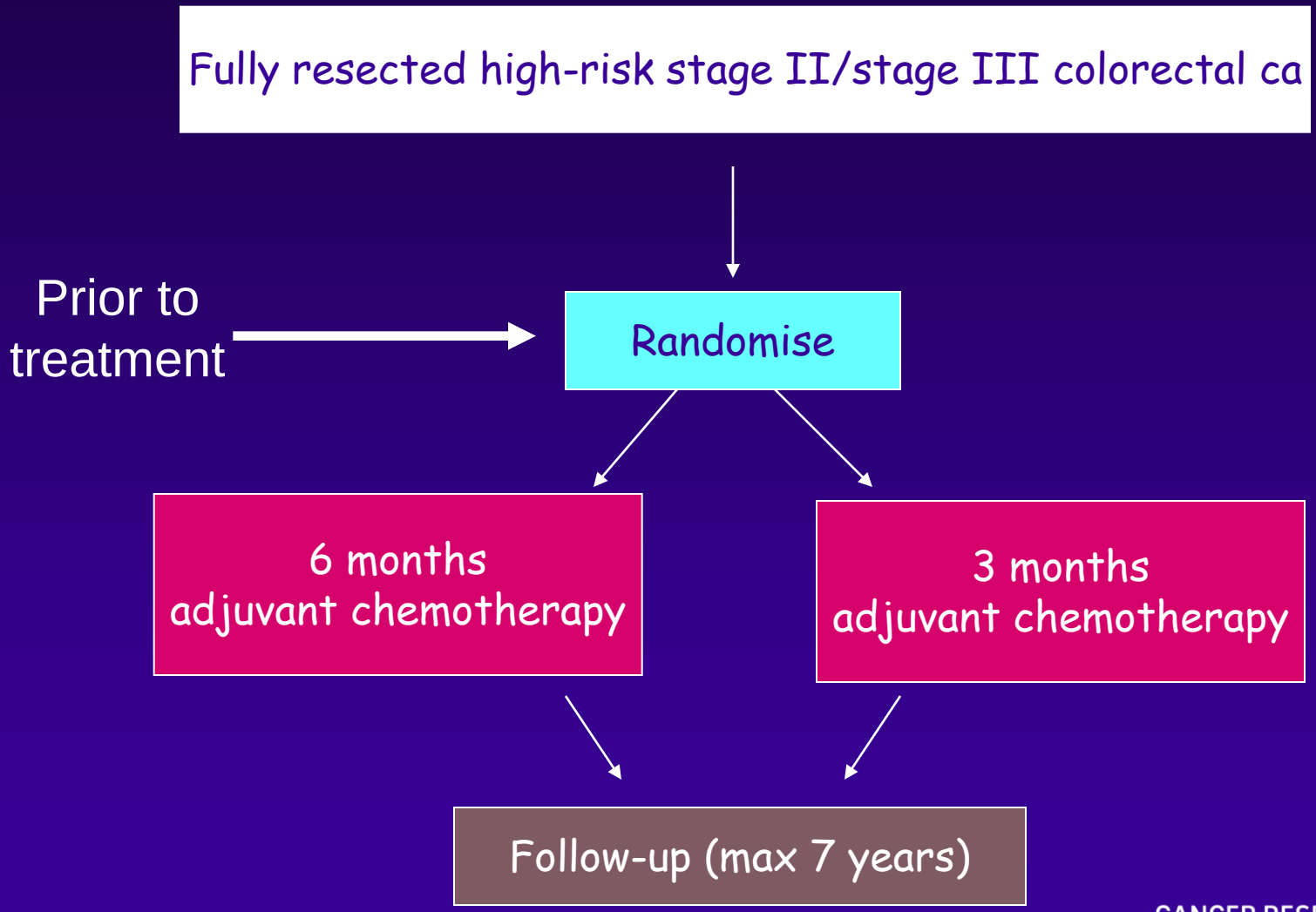
SCOT – Choice of Randomisation Time-Point

Randomise after patients have completed 3 months of treatment (delayed randomisation)

- Statistically optimum – only patients fit to receive at least 3 months included
- But potentially recruitment problems
- Smith IE et al Duration of chemotherapy in advanced non-small-cell lung cancer: a randomized trial of three versus 6 courses of Mitomycin, Vinblastine and Cisplatin. J Clin Oncol 2001 19: 1336-1343)
- Effect on representativeness of patients

Randomisation Time-Point
Pretreatment (Up-front randomisation)



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SCOT – Choice of Randomisation Time-Point

Randomise before any treatment starts (up-front randomisation)

- More acceptable to patient – can plan knowing length of treatment from outset
- Simpler for clinician
- Simpler for trials unit
- Improve recruitment
- More "realistic" in terms of clinician/patient behaviour

SCOT – Choice of Randomisation Time-Point

- To obtain objective evidence on the relative merits of these two approaches in the first year of the study centres were randomised to use one of these two randomisation time points

  - Random allocation was balanced for centre recruitment potential

  - Over the first 12 months 77 centres were randomised (41 centres to delayed randomisation and 36 to up-front randomisation)

SCOT – Choice of randomisation Time-Point

	At TSC review at 12 months
Up-front randomisation rate* *(patients/centre/year)*	6.1 (iqr: 3.1-7.9) *N=23*
Delayed randomisation rate*	4.1 (iqr: 0.4 – 7.8) *N=20*
Drop out rate on delayed randomisation (registered not randomised)	32% (95% ci 23-43%)
Percentage of patients dropping out before 3 months on up-front randomisation	7% (95% ci 2-26%)

P=.472

* Based on centres open at least 3 months

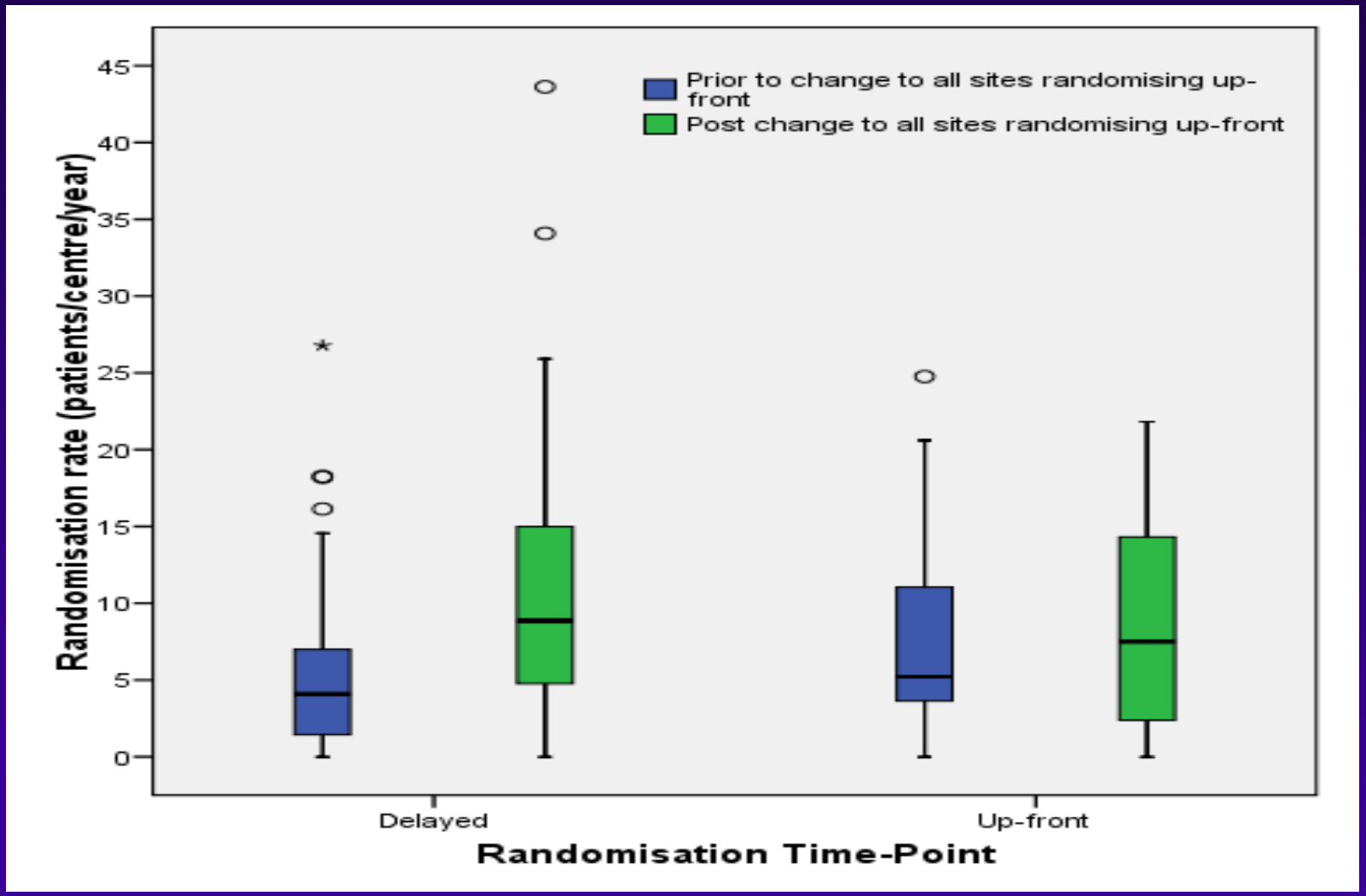
On the basis of this review all centres allocated to delayed randomisation were changed to up-front

SCOT Randomisation rate

	At TSC review at 12 months	Complete data (up to change over)
Up-front randomisation rate	6.1 (iqr: 3.1-7.9) *N=23*	5.2 (iqr: 3.6-11.6) *N=36*
Delayed randomisation rate	4.1 (iqr: 0.4 – 7.8) *N=20*	4.1 (iqr: 1.3-7.1) *N=41*
Drop out rate on delayed randomisation *(registered not randomised)*	32% (95% ci 23-43%)	26% (95% ci 21-32%)
Percentage of patients dropping out before 3 months on up-front randomisation	7% (95% ci 2-26%)	18% (95% ci 16-21%) *14% (95%ci 9-19%) based only on centres randomised to the randomisation time-points*

P=.091

Randomisation rate – Prior to and Post all sites Changing to Up-Front Randomisation

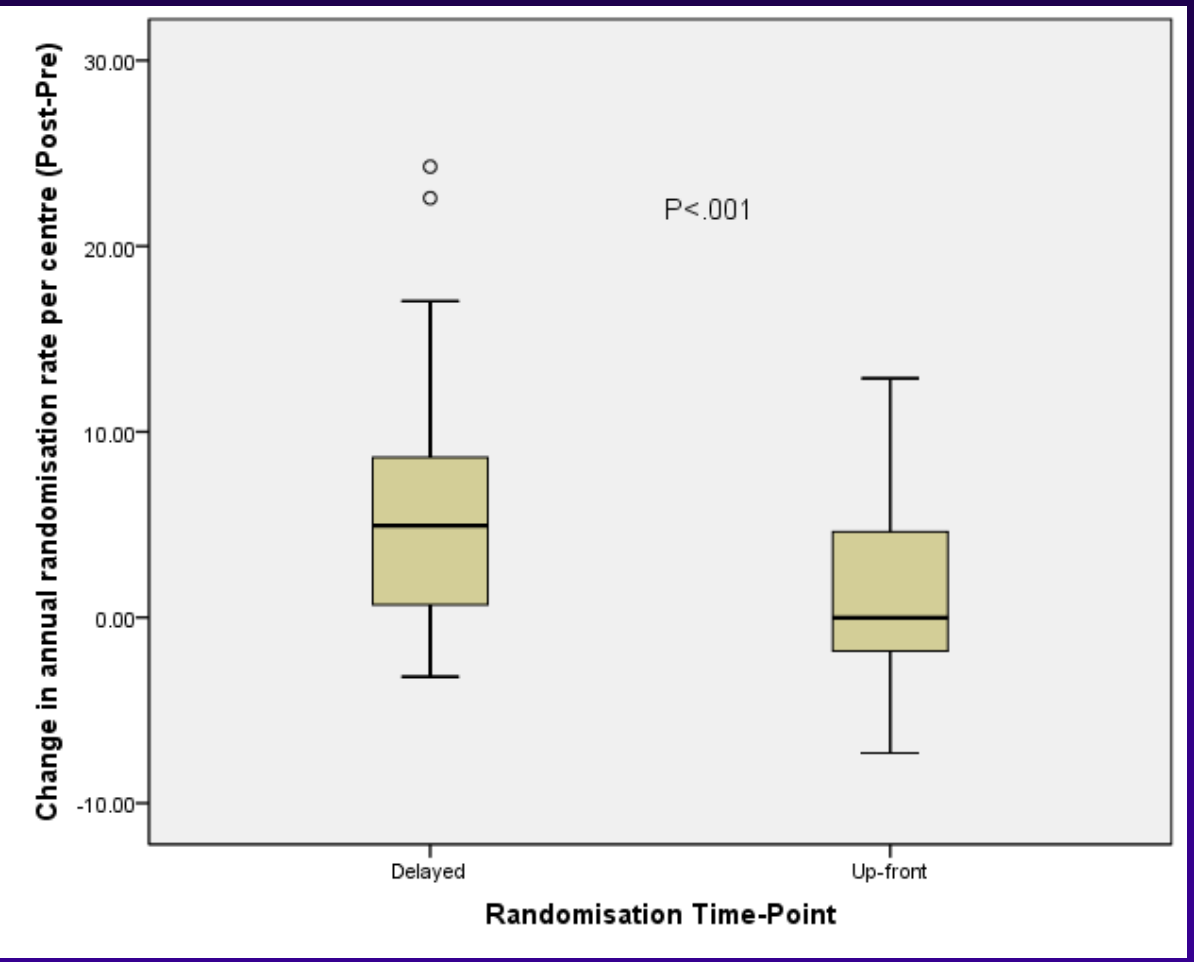


Randomisation rate – Prior to and Post all sites Changing to Up-Front Randomisation

Median Annual Randomisation Rates Per Centre

	Prior to change to up-front	**Post change to up-front**	**P-value**
Up-front randomisation	5.2 (iqr: 3.6-11.6) *N=36*	*7.5 (iqr: 2.2 -14.3) N=36*	*.121*
Delayed randomisation	4.1 (iqr: 1.3-7.1) *N=41*	*8.9 (iqr: 4.8-15.3) N=41*	*<.001*

Change in annual randomisation rate (Post-Pre)



Bootstrap estimate of relative randomisation rate (Up-front/delayed) ratio:-

1.74 (95% ci 1.34-2.28)

Potential Impact of Randomisation Time-Point on Study Duration

% Stopping before 3 months	Hazard ratio to be detected in patients in delayed randomisation*	%Reduction in required randomised sample size compared to up-front	Ratio of study recruitment duration (delayed/up-front)	
			Up-front radomisation rate 50% higher	*Up-front randomisation rate 75% higher*
5	1.14	13%	1.31	1.52
10	1.15	24%	1.14	1.33
15	1.16	32%	1.02	1.19
20	1.17	39%	0.92	1.07

* Gives an overall hazard ratio of 1.13 assuming a hazard ratio of 1 for patients stopping before 3 months

Conclusions

- In SCOT the randomisation rate is higher with up-front randomisation
- Higher drop-out rate prior to 3 months with delayed compared to up-front randomisation
- Up-front randomisation gives the patient more certainty to plan their life
- Up-front randomisation is easier to manage logistically

- Whether delayed randomisation is more efficient (in terms of study duration) depends on:-
  - The proportion of patients who stop treatment before the longer duration (<3 months in the case of SCOT)
  - The relative randomisation rate for up-front randomisation relative to delayed
  - Both these may be difficult to determine reliably in a particular situation

Thanks To

- The SCOT team in Glasgow and Oxford
- All the patients participating in SCOT