



TITRe2

The Great British NHS – delivering the evidence that the rest of the world fails to deliver:

TITRe2
Barney Reeves

Transfusion Indication Threshold Reduction



Prof Reeves has no competing interests.
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TITRe2: the research question

- **Population:** people having open heart surgery
- **Intervention:** transfuse red blood cells (RBC) after operation only when ‘substantially’ anaemic (restrictive threshold – Hb <7.5 g/dL)
- **Comparator:** transfuse red blood cells (RBC) after operation when ‘moderately’ anaemic (liberal threshold – Hb <9.0 g/dL)
- **Outcome:** serious post-operative complications, e.g. heart attack, stroke, renal failure, wound infection
- **Sample size:** 2,000 randomised (3,000 consented)

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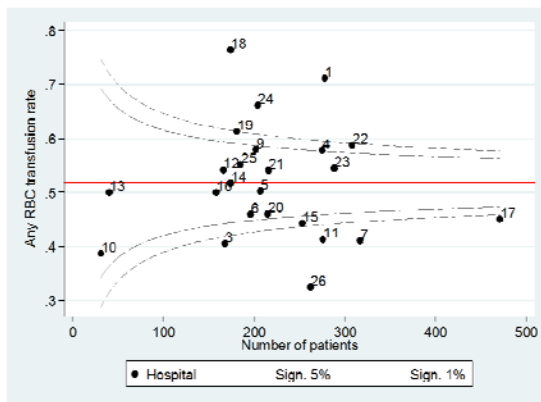
The “cast”: TITRe2 Investigators

Mr Augustine Tang, Dr P Saravanan, Charlotte Waterhouse; Dr Robert Kong, Nicola Skipper; Prof Gavin Murphy / Prof Gianni Angelini, Emma Hopkins, Penny Lambert; Mr Sunil K Bhudia, Denise Gocher; Dr Sean Bennett, Neil Smith, Adam Walker; Dr Mark Bennett, Mr M Dalrymple-Hay, Maxine Pearse; Professor Andrew J Ritchie, Emily Redman, Amanda Solesbury; Mr Vipin Zamvar; Dr Geoff Lockwood, Dr F Fiorentino, Ms A. Rahman; Dr Gudrun Kunst, Georgina Parsons, Fiona Wade-Smith; Dr MH Cross, Stuart Elliot, Zoe Beardow; Professor Tom Sypt, Martina Williams; Mr Brian Fabri/ Mr Mark Field, Ian Kemp, Andrea Young; Dr Nick Stratford, Heather Robinson; Mr Stephen Clark, Sarah Rowling, Hazel Forsyth; Dr Ravi Gill, Beverley Wadhams, Kim de Courcy-Golder; Dr Ian Morgan, Research team, Emma Greatbach, Alex Ng; Dr Chris A Rogers, Dr Rachel CM Brierley, Dr Alice Miles, Wendy Underwood, Dr Lucy A Culliford, Katie Pike, Rachel Nash, David Hutton, Emma Hopkins, Penny Lambert, Kate Rajakaruna, Kim Wright, Jenny Wilcox and Rachel Wyatt; Dr Sarah Wordsworth, Elizabeth A Stokes; Dr Tom W Johnson, Dr Sally Tomkins, Mr Jon Anderson; Dr Edwin Massey, Ian Millar; Prof Gordon Murray, Prof Tim Walsh, Mr Domenico Pagano; Mr Patrick Magee (deceased), Prof John Pepper, Dr Duncan Young, Dr Edwin Massey, Dr Gordon Taylor, Karin Smyth.

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Background

RBC Transfusion by UK Centre 2010



- Uncertainty about “safe” restrictive red cell transfusion threshold in cardiac surgery
- Reflected in wide variation in clinical practice

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Headline results

Liberal or Restrictive Transfusion after Cardiac Surgery

Gavin J. Murphy, F.R.C.S., Katie Pike, M.Sc., Chris A. Rogers, Ph.D., Sarah Wordsworth, Ph.D., Elizabeth A. Stokes, M.Sc., Gianni D. Angelini, F.R.C.S., and Barnaby C. Reeves, D.Phil., for the TITRe2 Investigators*

Transfusion rates after randomization were 53.4% and 92.2% in the two groups, respectively. The primary outcome occurred in 35.1% of the patients in the restrictive-threshold group and 33.0% of the patients in the liberal-threshold group (odds ratio, 1.11; 95% confidence interval [CI], 0.91 to 1.34; $P=0.30$); there was no indication of heterogeneity according to subgroup. There were more deaths in the restrictive-threshold group than in the liberal-threshold group (4.2% vs. 2.6%; hazard ratio, 1.64; 95% CI, 1.00 to 2.67; $P=0.045$).

Murphy et al., 2015 NEJM

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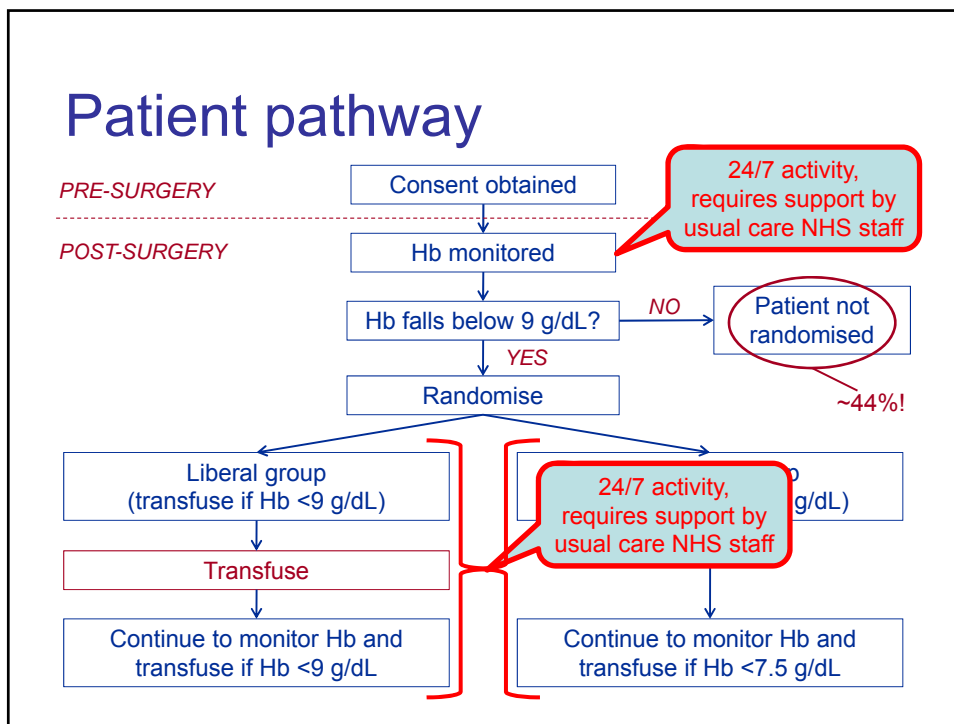
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Challenges in the TITRe2 trial

- Recruitment

- Adherence to the allocated transfusion protocol

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Challenges in the TITRe2 trial

ADHERENCE TO PROTOCOL

Local innovation to promote adherence

- Extra “TITRe2” wristband – to alert doctor when RBC transfusion being considered

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 National Institute for Health Research

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Challenges in the TITRe2 trial

ADHERENCE TO PROTOCOL

Local innovation
to promote
adherence

- All research notes
coloured differently



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NHS
National Institute for
Health Research

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Challenges in the TITRe2 trial

ADHERENCE TO PROTOCOL

Local innovation
to promote
adherence

- Ensure explicit
hand-over of
research
responsibilities
among CICU
nurses



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Challenges in the TITRe2 trial

ADHERENCE TO PROTOCOL

Local innovation to promote adherence

- Late night / weekend telephone call to CICU / ward to speak to nurse looking after TITRe2 participant





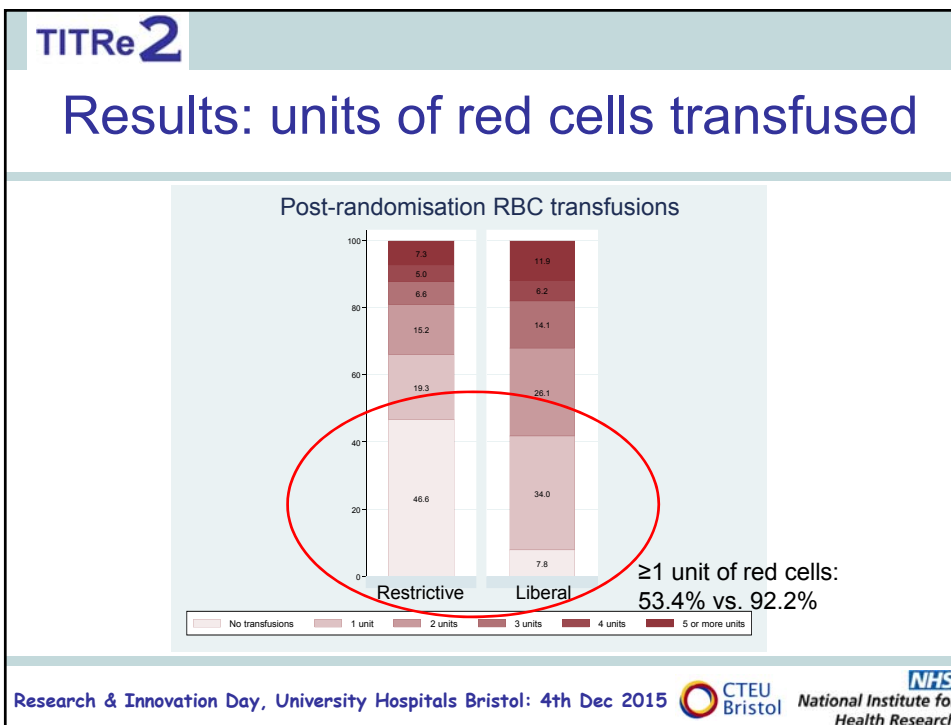
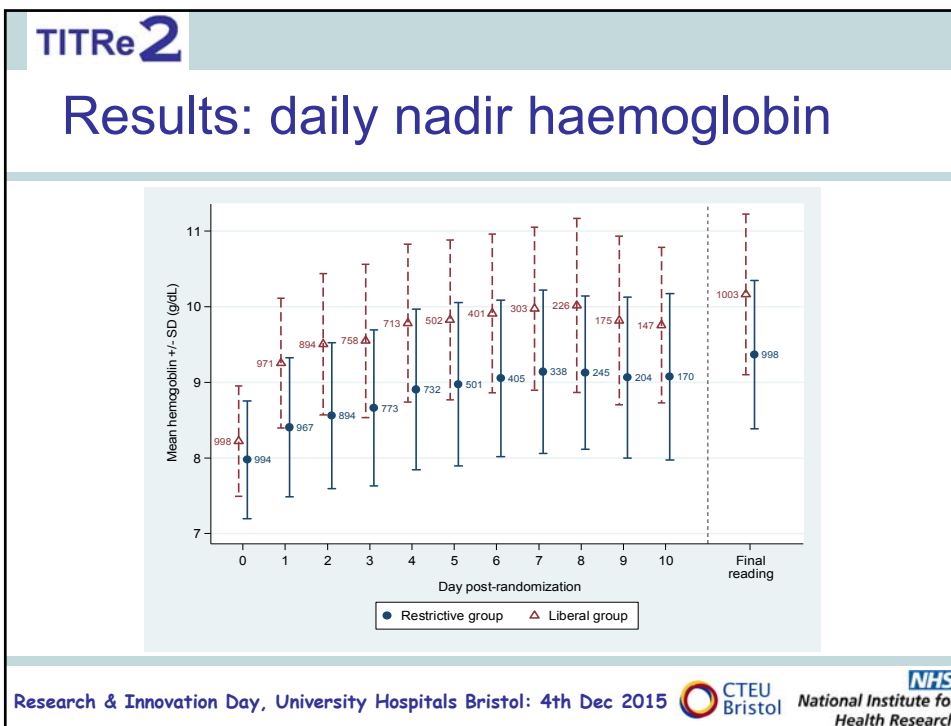
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TITRe2 compared to other trials

Study	Shehata et al. 2011		Murphy et al. 2015		Fergusson et al. 2011	
	Restr.	Liberal	Restr.	Liberal	Restr.	Liberal
Extra transfusions	11/375 2.9%	2/282 0.7%	273/1000 27.3%	107/1003 10.7%	-	-
Withheld transfusions	8/37 21.6%	86/161 53.4%	55/1000 5.5%	390/1003 39.0%	-	-
Missed randomizations	-	-	176/3565 4.9%		-	-

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Conclusions

- NHS provides an exceptional infrastructure for large pragmatic RCTs
- Changes in NIHR funding have created incentives for NHS Trusts to recruit to portfolio studies
- CRN can provide discrete help to resolve challenges experienced in portfolio studies

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Thank you!

Questions?