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

Prof Reeves has no competing interests.
The TITRe2 trial was funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (project number 06/02/094) and will be published in Health Technology Assessment. The views and opinions expressed are those of the authors and do not necessarily reflect those of the HTA programme, NIHR, the UK National Health Service or the Department of Health.

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)
TITRe2

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 Beadlow; 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 Courcey-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.

Background

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

Challenges in the TITRe2 trial

• Recruitment

• Adherence to the allocated transfusion protocol
**TITRe2**

**TITRe2 compared to other trials**

<table>
<thead>
<tr>
<th>Study</th>
<th>Shehata et al. 2011</th>
<th>Murphy et al. 2015</th>
<th>Fergusson et al. 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cardiac surgery</td>
<td>5,757</td>
<td>≈60,000</td>
<td>&gt;125,000?</td>
</tr>
<tr>
<td>Sites</td>
<td>1</td>
<td>17</td>
<td>43</td>
</tr>
<tr>
<td>Consented</td>
<td>50 (1%)</td>
<td>3,565 (6%)</td>
<td>3,592 (≈1,700 1%)</td>
</tr>
<tr>
<td>Randomized</td>
<td>50</td>
<td>2,007 (56%)</td>
<td>3,592 (≈1,700)</td>
</tr>
<tr>
<td>Analysed</td>
<td>50</td>
<td>1,978</td>
<td>3,592</td>
</tr>
<tr>
<td>Months rec’</td>
<td>42 months</td>
<td>43 months</td>
<td>48 (23)</td>
</tr>
<tr>
<td>Px/site/month</td>
<td>1.2</td>
<td>2.7 (4.9)</td>
<td>1.7 (1.7)</td>
</tr>
</tbody>
</table>

Total of 43 months
Patient pathway

PRE-SURGERY

Consent obtained

Hb monitored

POST-SURGERY

Hb falls below 9 g/dL?

YES

Randomise

Liberal group
(transfuse if Hb <9 g/dL)

Transfuse

Continue to monitor Hb and transfuse if Hb <9 g/dL

NO

Patient not randomised

Restrictive group
(transfuse if Hb <7.5 g/dL)

Continue to monitor Hb and transfuse if Hb <7.5 g/dL

TITRe2

Challenges in the TITRe2 trial

ADHERENCE TO PROTOCOL

Local innovation to promote adherence

• Extra “TITRe2” wristband – to alert doctor when RBC transfusion being considered
Challenges in the TITRe2 trial

ADHERENCE TO PROTOCOL

Local innovation to promote adherence

- All research notes coloured differently

- Ensure explicit hand-over of research responsibilities among CICU nurses
**TITRe2**

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**

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</thead>
<tbody>
<tr>
<td></td>
<td>Restr.     Liberal</td>
<td>Restr.   Liberal</td>
<td>Restr.    Liberal</td>
</tr>
<tr>
<td>Extra transfusions</td>
<td>11/375      2/282</td>
<td>273/1000 107/1003</td>
<td>-          -</td>
</tr>
<tr>
<td></td>
<td>2.9%        0.7%</td>
<td>27.3%     10.7%</td>
<td>-          -</td>
</tr>
<tr>
<td>Withheld transfusions</td>
<td>8/37        86/161</td>
<td>55/1000   390/1003</td>
<td>-          -</td>
</tr>
<tr>
<td></td>
<td>21.6%       53.4%</td>
<td>5.5%      39.0%</td>
<td>-          -</td>
</tr>
<tr>
<td>Missed randomizations</td>
<td>-           176/3565</td>
<td>-            4.9%</td>
<td>-          -</td>
</tr>
</tbody>
</table>
TITRe2

Results: daily nadir haemoglobin

![Graph showing daily nadir haemoglobin levels with mean hemoglobin values and standard deviations.](image)

Research & Innovation Day, University Hospitals Bristol: 4th Dec 2015

TITRe2

Results: units of red cells transfused

![Bar chart showing post-randomisation RBC transfusions with ≥1 unit of red cells.](image)

≥1 unit of red cells: 53.4% vs. 92.2%

Research & Innovation Day, University Hospitals Bristol: 4th Dec 2015
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

Thank you!

Questions?