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## Adherence to transfusion strategies in a randomized controlled trial: experiences from the TITRe2 trial

The Transfusion Indication Threshold Reduction (TITRe2) trial compared the effect of restrictive and liberal transfusion thresholds after cardiac surgery on post-operative morbidity. Seventeen UK centres randomized 2003 patients. Methods and primary results have been reported (Brierley *et al*, 2014; Murphy *et al*, 2015; Pike *et al*, 2015). The trial was pragmatic: clinicians could deviate from the allocated protocol but had to document why. Nevertheless, to be successful, the trial had to create groups with substantially different haemoglobin concentrations and red cell transfusion rates. Non-adherence attenuates these differences and reduces statistical power. Hence, monitoring adherence to the transfusion protocols was a key requirement.

Here, we report our methods for identifying, classifying and describing non-adherence and analyses to identify circumstances in which different types of non-adherence occurred. We also describe initiatives to minimize non-adherence.

We identified two types of non-adherence (not pre-specified in the protocol): ‘extra’ transfusions given when not indicated by the protocol and ‘withheld’ transfusions not given when indicated. Non-adherence was categorized as severe when it changed the overall transfusion rate and as mild or moderate when it only affected red cell units transfused (Pike *et al*, 2015). Figure S1 shows examples of non-adherent patient profiles.

**Table I.** Multiple logistic regression models to identify predictors of non-adherence

	Extra transfusions		Withheld transfusions	
	OR (95% CI)	P-value	OR (95% CI)	P-value
<b>Adherence characteristics</b>				
Time from operation end (days)	0.97 (0.95, 0.98)	<0.001	1.03 (1.01, 1.04)	<0.001
Weekend <i>versus</i> weekday	0.78 (0.63, 0.95)	0.013	1.79 (1.54, 2.09)	<0.001
ICU <i>versus</i> ward	4.68 (3.76, 5.83)	0.001	3.07 (2.55, 3.69)	<0.001
<b>Patient characteristics</b>				
Time between operation end and randomization (days)			1.15 (1.07, 1.25)	<0.001
Age (years)			0.99 (0.97, 1.00)	0.029
<b>Cardiac procedure</b>				
CABG only	Reference group	<0.001		
CABG + Valve	1.36 (1.01, 1.83)			
Valve only	1.75 (1.27, 2.40)			
Other	1.04 (0.66, 1.65)			
Transfused pre-randomization	1.49 (1.15, 1.93)	0.003		
<b>Centre characteristics</b>				
<b>Centre recruitment rate per month</b>				
≥6 patients/month	Reference group	<0.001	Reference group	0.022
4≤patients/month<6	1.04 (0.77, 1.39)		0.84 (0.61, 1.15)	
3≤patients/month<4	2.23 (1.62, 3.05)		1.39 (0.99, 1.96)	
<3 patients/month	1.54 (0.97, 2.44)		0.71 (0.41, 1.22)	

Shaded boxes represent that the characteristic was not a significant predictor of that type of non-adherence, and therefore was not included in the model.

CABG, coronary artery bypass graft, CI, confidence interval, ICU, intensive care unit, OR, odds ratio.

We investigated whether data characterizing the centre, patient and circumstances at the time predicted non-adherence. Circumstances included: haemoglobin concentration; intensive care unit (ICU) or ward care; normal versus outside normal working hours; weekdays versus weekends; the months August to October (when anaesthetic and surgical residencies start) versus other months. Patient characteristics were: time between operation and randomization, age, sex, EuroSCORE, operation type and pre-randomization transfusions. Centres were characterized by recruitment rate: we hypothesized that higher recruitment would reduce non-adherence.

Multivariate mixed-effects logistic regression models were fitted. Participant-days in hospital were analysed, with each day coded as adherent or not. Extra and withheld transfusions were analysed separately. Explanatory variables were modelled as fixed effects and included if significant ( $P < 0.05$ ), with patient identifier as a random effect. We did not include highly correlated terms in the same model.

One or more instances of non-adherence occurred in 37.6% (753/2003) of patients (Murphy *et al*, 2015), 30.0% and 45.2% in the restrictive and liberal groups, and at least one instance was severe for 7.9%, 9.7% and 6.2% of patients respectively. Approximately 80% of extra transfusions were

**Table II.** Methods implemented to monitor, feedback and/or provide training on adherence

Methods Implemented by the Trial Management Team Across All Centres:		
For centre research teams	For clinical staff	For clinical staff and centre research teams
Regular newsletters were sent to centres to try to motivate staff to improve adherence and maintain interest in study.	Regular teaching slots about the trial for new and existing staff, the timing of which was frequently aimed to coincide with the start of residents' rotations.	Colour-coded labels provided for research and clinical staff to add to patients' notes and charts (to clearly identify TITRe2 patients and allocated group).
Mid-study centre visits included analysis and discussion of non-adherence with local research teams to try to identify centre-specific barriers to adherence and potential solutions.	Nurses' manuals at nursing stations containing trial-specific information and summaries for treating the restrictive and liberal groups according to the trial protocol.	Daily haemoglobin transfusion checks by research nurses to monitor adherence with the protocol for randomization and treatment according to allocated group and to record non-adherence. Checks were usually done from Monday to Friday (due to research nurse working patterns). Checks provided useful additional information if trial-related queries arose and reinforced that the trial was ongoing to staff on the cardiac units.
Reports were fed back to centres, both at mid-study visits and thereafter on a quarterly basis, describing centre-specific non-adherence over time and non-adherence in relation to other centres. An example is shown in Figure S4.	A competition for clinical staff to promote adherence was attempted but this was difficult to implement. However, informal prizes were handed out at meetings of study investigators to commend centres that achieved good adherence.	Trial-branded stationery produced to remind clinical and research staff to check and react to haemoglobin concentrations.
Methods for avoiding non-adherence adopted by centres with better adherence were shared at meetings of study investigators. Research nurses were primary contributors at these meetings.	Study posters in staff rooms.	
Methods Implemented by Individual Centres:		
Careful 'handover' between nursing shifts, highlighting the need to monitor the haemoglobin of a patient carefully and to randomize/transfuse in the event of breaching the allocated threshold (Centre A).		
Additional plastic wrist band/tag identifying that the patient was taking part in the trial; this band was alongside another band with the participant's ID details, which doctors and nurses had to check when prescribing/administering a red cell transfusion (Centre E).		
Adding coloured covers to the patient's paper medical records highlighting that the patient was taking part in research (Centre C).		
Out of hours/weekend reminder calls to ICU/ward (for participants known to be at risk of breaching their allocated threshold) to ask whether a participant's haemoglobin had been checked.		

for clinical reasons, whereas most withheld transfusions (67%) were oversights/errors. Non-adherence differed between centres, although this was not strongly associated with the average rate of recruitment (see Table S1 and Figure S2 for details).

The odds of extra transfusions (Table I) reduced with increasing post-operative time, reduced at weekends, increased with incidence of either pre-randomization transfusions or valve procedures and increased at centres recruiting less than 4 patients/month. Conversely, the odds of withheld transfusions increased with increasing post-operative time, increased at weekends, increased with increasing post-operative time before randomization and reduced with increasing age.

Methods used to monitor adherence are described in Table II. At several centres, research nursing methods were amended to promote adherence: ensuring careful handover between nursing shifts, providing additional wrist bands identifying trial patients, adding coloured covers to paper medical records and reminding colleagues to check haemoglobin levels out-of-hours. Despite these initiatives, adherence did not improve over the course of the study (Figure S3).

These findings provide insights about the TITRe2 trial. Despite investing in time-consuming data collection, non-adherence was prevalent. However, severe non-adherence occurred for only a small proportion of patients, consistent with the assumptions made when calculating the target sample size (Pike *et al*, 2015), and good separation in average haemoglobin was maintained between groups (Murphy *et al*, 2015).

The impact of non-adherence on the trial findings is difficult to quantify. Centre-specific effect estimates for the primary outcome did not vary by the frequency of severe non-adherence (Murphy *et al*, 2015). However, non-adherence did not occur at random; patients who had extra transfusions differed from those who had withheld transfusions. A sensitivity analysis excluding non-adherent patients was not performed because it would be biased. Nevertheless, overall non-adherence must have attenuated the relative treatment effect, i.e. biased the estimate towards unity.

We attempted to identify sources of non-adherence. Withheld transfusions most commonly occurred due to oversight and might have reduced by more careful monitoring; extra transfusions were more likely to be given sooner after surgery for clinical reasons. Centres with higher recruitment rates tended to be more adherent, consistent with greater familiarity with trial procedures. A few centres were simply excellent, typically because research staff innovated to promote adherence or senior staff reported non-adherence as clinical incidents.

Non-adherence persisted despite feedback and training. We do not know whether some initiatives were successful and adherence would have declined otherwise. We believe

that adherence did not improve because inadequate research staffing was not addressed. This finding might cause future researchers to question whether monitoring non-adherence in such detail is warranted, especially given the intensity of data collection required. Our answer is, unequivocally, yes. Information about non-adherence is vital, e.g. to monitor its frequency against assumptions when calculating the target sample size. In terms of adherence to local transfusion guidance, monitoring might be expected to improve adherence. However, in TITRe2 everyone was acutely aware they were being monitored, and adherence did not improve.

Non-adherence documented in TITRe2 is not directly comparable to non-adherence reported in several previous trials of different transfusion strategies (Johnson *et al*, 1992; Bracey *et al*, 1999; Murphy *et al*, 2007; Hajjar *et al*, 2010). Such studies reported only extra or withheld transfusions, had different trial designs or defined non-adherence differently. Two more recent studies, which defined non-adherence in a comparable way (Carson *et al*, 2011; Shehata *et al*, 2012), had broadly consistent rates.

We believe this is the first attempt to identify and classify non-adherence to a transfusion strategy in this level of detail. Non-adherence remains a key issue in trials comparing transfusion strategies and our findings provide insight about when and why they occur. Enhancing vigilance and providing reminders appear to be the most successful ways to prevent non-adherence, selecting centres with high projected recruitment and established research infrastructure.

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## Authorship Contributions

Reeves (Chief Investigator) and Murphy (lead clinical investigator) conceived the trial. Reeves, Murphy and Rogers wrote the application for funding (with others) and designed the trial. Brierley, Reeves, Rogers and Murphy managed the conduct of the trial. Pike and Maishman managed the data during the trial and Pike carried out the statistical analyses, under the supervision of Rogers. Pike, Reeves and Murphy drafted the report. All authors reviewed the report for important intellectual content and approved the final version.

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## Declaration of Interests

None declared.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Characteristics of instances of non-adherence to transfusion protocol by group.

**Fig S1.** Example Hb concentration and RBC transfusion profiles that result in non-adherence with the transfusion protocol.

**Fig S2.** Non-adherence rates by centre.

**Fig S3.** Change over time in proportions of non-adherent patients.

**Fig S4.** Adherence section of quality feedback report to sites (example for site H).

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