NKR9 PICO 5 Transfusion for haematological malignancies

Characteristics of studies

Characteristics of included studies

De Zern 2016

Methods	Type of Study: Open-labelled single-centre parallel-arm randomised controlled trial Full Setting and country: USA Number of centres: single Recruitment dates (start and end): April 15, 2014 to July 23 2015 Median follow-up duration: 5.9 weeks restrictive 6.1 weeks liberal
Participants	Inclusion criteria: acute leukaemia patients (AML, ALL, APL, high grade MDS) admitted with plans for inpatient myelosuppressive chemotherapy (with standard of care or protocol regimens) Exclusion criteria: • aged less than 18 years • acute coronary syndrome as defined by active chest pain, dynamic ECG changes, troponin greater than 2.5 • active blood loss • receiving erythropoietin stimulating agents prior to admission • chronic renal failure on renal replacement therapy • documented wish against transfusion for personal or religious beliefs Number screened: 162 eligible, only 112 approached due to resource limitations, 22 declined to participate Number recruited: 90 (1 participant withdrew prior to any transfusion) Age: restrictive: median 56 years (IQR 45.5 to 67): liberal: median 62.5 years (IQR 55. 2 to 67.8) Gender: Male 49 (restrictive 33; liberal 16); Female 40 (restrictive 26; liberal 14) Ethnicity: not reported Diagnosis: AML (excluding APL) 73 (restrictive 50; liberal 23); APL 2 (restrictive 2; liberal 0); ALL 7 (restrictive 7; liberal 7) Stage of disease: not reported Baseline haemoglobin level: restrictive: median 83 g/L (IQR 75 to 89), liberal: median 89 g/L (IQR 81 to 92) Treatment: all received induction chemotherapy Number analysed for primary outcome: 89 participants (59 restrictive transfusion policy and 30 liberal transfusion policy) Were participants with active bleeding explicitly excluded? Yes Were participants with a history of myocardial ischaemia/infarction explicitly excluded? No, only participants with acute coronary syndrome where excluded
Interventions	Restrictive RBC transfusion group: participants will receive blood transfusion with transfusion threshold of 70 g/L Hb Liberal RBC transfusion group: participants will receive blood transfusion with threshold of 80 g/L Hb Off-protocol transfusions: There were two protocol deviations, one per arm, where patients were transfused before reaching their preset trigger accidentally Red cell component: Standard leucocyte-reduced and irradiate red-cell units irradiated and prepared in additive solutions Duration of red cell storage: Not reported
Outcomes	Primary Outcome: Safety of a restrictive transfusion threshold of 70 g/L compared to a standard transfusion threshold of 80 g/L at 60 days Seondary Outcomes: • Transfusion requirements (the number of red cells and platelets transfused per participant at 60 days) • The number of participants with neutropenic infections at 60 days • Grade 3 and 4 bleeding at 60 days • The length of hospital stay • Treatrment-related mortality at 60 days • End organ dysfunction at 60 days • Number of participants with Easten Cooperative Oncology Group (ECOG) performance status Bleeding was graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 “The patients were assessed for bleeding and fatigue daily by the treating providers and documented in the daily progress notes. This was prospectively planned at the start of the trial and is the standard protocol for these patients at our institution. The bedside nurses as well as the physicians are required to document bleeding and fatigue daily. There were no adjudicators.” Fatigue was assessed by the National Cancer Institue Fatigue Scale (Mendoza 1999). It is a rapid assessment of the fatigue severity in people with cancer. It is a numeric 10-point scale, with a score of 0 indicating no fatigue, a score of 5 interpreting as moderate fatigue and the maximum score of 10 is an indicate of the worst possible fatigue.This numeric scale was reported by the participants in the trial and the scoring form was completed by the clinical staff
Notes	Trial Register ID: National Institute of Health, Clinicaltrials.gov registry NCT02086773 Supported by: Sidney Kimmel Comprehensive Cancer Center Conflicts-of-interest statement: No conflict of interest was disclosed

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“The random-number sequence was generated using computer software (JMP Version 9.0, SAS Institute). Treatment assignment was done with a 2: 1 ratio, for the LOW:HIGH Hb trigger groups, respectively. Blocking was used to specify a 2:1 ratio of treatment groups for each group of 18 consecutive patients.”
Allocation concealment (selection bias)	Low risk	“Sealed opaque sequentially numbered envelopes were opened upon determination of inclusion for each patient in the trial. The randomization sequence and creation and numbering of the envelopes was performed by an investigator who did not enroll or consent patients for the trial.”
Blinding of participants and personnel (performance bias)	High risk	“...the study, by its nature, was not blinded and both the patients and their providers were aware of the treatment assignment groups.” “There was initial inherent bias among nurses and physicians who were concerned about withholding transfusions from patients who need them, which may have increased the incidence of crossovers from the LOW to the HIGH group.”
Blinding of outcome assessment (detection bias)	High risk	“Lack of blinding could theoretically have influenced some outcome measures. For example, the fatigue scores may have been falsely low in the LOW group, resulting in an overestimation of fatigue difference between groups”
Incomplete outcome data (attrition bias)	Unclear risk	“One patient randomized to the LOW arm was not treated on study as the patient withdrew consent before any transfusions performed.All 89 patients randomly assigned and treated on the study protocol were included in the analysis. The patients who were approached and declined cited reasons for refusal as lack of willingness to participate in a clinical trial (seven patients), refusal for randomization (12 patients), and expressed concern of withholding of standard of care transfusion threshold (three patients).” “Both patient and clinician decisions to withdraw from study were slightly higher in the LOW arm: patient decision two of 59 (3.4%;

		95% CI, 0.41%-11.71%) versus zero of 30 (0%; 95% CI, NA-11.57%), and clinician decision five of 59 (8.5%; 95% CI, 2.81%-18.68%) versus one of 30 (3.3%; 95% CI, 0.08%-17.22%). The two patient reasons for withdrawal of consent were both noted as decreased performance status or fatigue that they believed would improve after transfusion to a higher Hb. Upon subsequent query, both patients believed that they did feel better off the trial. The clinician withdrawals of consent were an inpatient fall attributed to anemia resulting in a head laceration (one patient), sepsis and goal of improved perfusion with higher Hb (two patients), inability to follow trial trigger due to extensive alloantibodies and the requirement to transfusion only when blood was available (one patient) , and a decreased patient performance status or fatigue perceived by the provider as related to anemia (one patient).”
Selective reporting (reporting bias)	Unclear risk	Planned outcomes reported in the trial registration but not reported in the published paper were: • Treatment-related mortality [Time Frame: 60 days] • End organ dysfunction [Time Frame: 60 days] • Number of patients with Eastern Cooperative Oncology Group (ECOG) performance status
Other bias	Unclear risk	“Baseline Hb levels were somewhat lower in the LOW threshold group, a median of 8.3 g/dL compared to 8.9 g/dL in the HIGH group (Wilcoxon p = 0.03).” “When the mean number of RBC units transfused was compared between arms of the study, adjusting for baseline Hb, the LOW arm was transfused 8.0 (95% CI, 6. 9-9.1) units per patient while the HIGH arm patients received 11.7 (95% CI, 10. 1-13.2) units for an estimated difference (LOW minus HIGH) of 23.7 (95% CI, 25.6 to 21.7) units per patient, analysis of covariance p = 0.0003.” “The incidence of crossover was also similar in the two study arms: seven of 59 (11.9%; 95% CI, 4.91%-22.93%) in the LOW arm and two of 30 (6.7%; 95% CI, 0.82%-22. 07%) in the HIGH (chi-square, p = 0.44) .” “The primary objective was the feasibility of conducting a larger randomized trial, which was defined a priori as achieving the following four criteria: 1) more than 50% of the eligible patients consented, 2) more than 75% of the patients randomized to the 7 g/dL arm tolerated the transfusion trigger, 3) fewer than 15% of patients crossed over from the lower transfusion threshold arm to the higher transfusion threshold arm, and 4) no indications for the need to pause the study for safety concerns. ” All these criteria were met but the upper limit of the 95% CI was higher than the prespecified 15% limit for cross-over of participants

Rygard 2017

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Restrictive transfusion group ● *Age (median)*: 65 (56-71) Median, range ● *Gender (% male)*: ● *Cancer diagnosis*: Hematological malignancies ● *Baseline haemoglobin level (median, IQR)*: ● *No. patients recieving cancer treatment* : 36 Liberal transfusion group ● *Age (median)*: 66 (58-73) median, range ● *Gender (% male)*: ● *Cancer diagnosis*: Hematological malignancies ● *Baseline haemoglobin level (median, IQR)*: ● *No. patients recieving cancer treatment* : 39 Overall ● *Age (median)*: ● *Gender (% male)*: ● *Cancer diagnosis*: ● *Baseline haemoglobin level (median, IQR)*: ● *No. patients recieving cancer treatment* : **Included criteria:** All 998 patients from the intention-to-treatpopulation of the TRISS trial were included inour post hoc analyses. We dichotomized sub-groups based on the following pre-randomizationcharacteristics (1) chronic lung disease defined asany history of chronic obstructive pulmonary dis-ease (COPD), asthma or other chronic lung disease(yes/no); (2) haematological malignancy (yes/no);(3) metastatic cancer as proven by surgery, CT scanor any other method (yes/no); (4) elective or emer-gency surgery within index hospitalization butprior to randomization (yes/no); and (5) septicshock where shock was defined according to thenew definition: plasma lactate≥ 2mmol/l(within24 h before randomization) and the need for vaso-pressor treatment to maintain a mean arterial pres-sure (MAP)>65 mmHg at the time ofrandomization (yes/no).20 **Excluded criteria:** See original TRISS study **Pretreatment:** The baseline characteristics were mostly similarbetween the subgroups (Table 1); the highestSAPS II differed between the two interventiongroups in the subgroup of patients with nohaematological malignancy and in those with newdefinition of septic shock. There was some imbal-ance between the number of patients with addi-tional haematological malignancy in the subgroupof patients with metastatic cancer (Table 1).
Interventions	**Intervention Characteristics** Restrictive transfusion group ● *Transfusion trigger (g/L)*: 70g/l ● *Longest follow-up after randomization*: 90 day period Liberal transfusion group

	● *Transfusion trigger (g/L)*: 90g/l ● *Longest follow-up after randomization*: 90 day period
Outcomes	*Mortality, n* ● **Outcome type**: DichotomousOutcome ● **Direction**: Lower is better *Quality of life, ratio difference (CI)* ● **Outcome type**: DichotomousOutcome *Transfusion volume (Red blood cell units), median (IQR)* ● **Outcome type**: ContinuousOutcome *Transfusionrate, n* ● **Outcome type**: DichotomousOutcome
Notes	**Sponsorship source:** The trial was funded by the Danish StrategicResearch Council and supported by CopenhagenUniversity Hospital, Rigshospitalet, theScandinavian Society of Anaesthesiology andIntensive Care Medicine (the ACTA Foundation)and Ehrenreich's Foundation. The funders had norole in the design of the study, collection andanalyses of data or the writing of the report. TheTRISS trial was endorsed by the European ClinicalResearch Infrastructures Network (ECRIN) **Country:** Denmark **Setting:** Multi-centre **Comments:** This is a subgroup analysis from the original TRISS trial. Trials 2013, 14:150 **Authors name:** S.L Rygård **Institution:** Department of Intensive Care, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark **Email:** anders.perner@regionh.dk **Address:** A. Perner, Department of Intensive Care 4131,Rigshospitalet, Blegdamsvej 9, DK-2100Copenhagen, Denmark

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was stratified by site and the presence or absence of haematological malignancy." Judgement Comment: Taken from the original TRISS trial: randomization was performed uding a centralized computer generated assignment sequence
Allocation concealment (selection bias)	Low risk	Judgement Comment: Taken from the original TRISS trial: Patients were randomly assigned with the use of permuted blocks.
Blinding of participants and personnel (performance bias)	Unclear risk	Judgement Comment: Nothing mentioned
Blinding of outcome assessment (detection bias)	Low risk	Judgement Comment: Taken from the original TRISS trial: Treatment assignment was concealed from the investigators assessing mortality, the data and safety monitor commitee and the trial statistician.
Incomplete outcome data (attrition bias)	Low risk	Quote: "The primary analyses were done in the inten- tion-to-treat population of 998 patients" Quote: "Four patients who were on vasopressors had missing data on the highest plasma lactate level 24 h before randomization; they were excluded from the analyses of the subgroup with the new definition of septic shock. There were no missing data in any of the remaining subgroups."
Selective reporting (reporting bias)	Low risk	Judgement Comment: Matches study protocol
Other bias	Low risk	Judgement Comment: No other apparent sources of bias No other apparent sources of bias

Tay 2016

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Restrictive transfusion group ● *Age (median)*: ● *Gender (% male)*: ● *Cancer diagnosis*: hematologic malignancy ● *Baseline haemoglobin level (median, IQR)*: ● *No. patients recieving cancer treatment* : Liberal transfusion group ● *Age (median)*: ● *Gender (% male)*: ● *Cancer diagnosis*: hematologic malignancy ● *Baseline haemoglobin level (median, IQR)*: ● *No. patients recieving cancer treatment* : Overall ● *Age (median)*: ● *Gender (% male)*: ● *Cancer diagnosis*:

	● *Baseline haemoglobin level (median, IQR)*: ● *No. patients recieving cancer treatment* : **Included criteria:** We enrolled 300 patients (150 allogeneic and 150 autologous) undergoing HSCT between 28 Mar 2011 and 3 Feb 2016 at 4 Canadian adult HSCT centres. **Excluded criteria:** **Pretreatment:**
Interventions	**Intervention Characteristics** Restrictive transfusion group ● *Transfusion trigger (g/L)*: 70g/l ● *Longest follow-up after randomization*: 100 days Liberal transfusion group ● *Transfusion trigger (g/L)*: 90g/l ● *Longest follow-up after randomization*: 100 days
Outcomes	*Mortality, n* ● **Outcome type**: DichotomousOutcome *Quality of life, ratio difference (CI)* ● **Outcome type**: DichotomousOutcome ● **Reporting**: Fully reported ● **Scale**: FACT-BMT ● **Direction**: Higher is better *Transfusion volume (Red blood cell units), median (IQR)* ● **Outcome type**: ContinuousOutcome ● **Reporting**: Fully reported ● **Direction**: Lower is better *Transfusionrate, n* ● **Outcome type**: DichotomousOutcome
Notes	**Sponsorship source:** Xenocostas, Janssen Inc **Comments:** Only an abstract **Authors name:** Jason Tay, David **Institution:** University of Calgary

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement Comment: Only an abstract
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: Only an abstract
Blinding of participants and personnel (performance bias)	Unclear risk	Judgement Comment: Only an abstract
Blinding of outcome assessment (detection bias)	Unclear risk	Judgement Comment: Only an abstract
Incomplete outcome data (attrition bias)	Unclear risk	Judgement Comment: Only an abstract
Selective reporting (reporting bias)	Unclear risk	Judgement Comment: Only an abstract
Other bias	Unclear risk	Judgement Comment: Only an abstract

Webert 2008

Methods	Type of study: A multicentre, single-blinded pilot randomised-controlled trial Type of publication: Full paper Setting and country: Canada, North America Number of centres: 4 tertiary haematology centres Recruitment dates (start and end): 01/03/2003 to 31/10/2004 [20 months] Mean follow-up duration: 25.9 days (SD 8.4) in the restrictive group, 23.6 days (10. 0 SD) in the liberal group. 1482 days of observation. The study observation periods started on the day after randomisation and ended when one of the following criteria was met: Participant's platelet count was greater than 20 x 109 /L for 7 days without a platelet transfusion or when it was not possible to perform daily bleeding assessments or when participant's physician requested removal from the study or when death occurred Was a power calculation performed?: No
Participants	Inclusion criteria: adults (age >16 years) with acute leukaemia admitted for induction or re-induction chemotherapy or adult patients admitted to receive conditioning for HLA antigen-matched myeloablative allogeneic SCT for a haematologic malignancy Exclusion criteria: acute promyelocytic leukaemia (French-American BritishM3); aplastic anaemia; history of myocardial infarction or angina in the past 6 months; refusal to receive blood transfusions; history of inherited or acquired coagulation disorders; known haemolytic disease; international normalized ratio (INR) of greater than 1.5 (uncorrected by the administration of vitamin K); evidence of significant acute bleeding during the first 12 hours after admission to the hospital (defined as evidence of ongoing blood loss accompanied by a decrease in the Hb concentration of at least 30 g/L during the first 12 hours after admission or a requirement of at least 3 units of RBCs during the same period); presence of an alloantibody that could limit compatible blood supply; previous enrolment in this trial; and unwillingness or inability to give informed consent Number screened: 84 (9 ineligible; 15 declined to participate) Number recruited: 60 (all included in analyses) Age: mean 47.9 years (range 18 to 77 years) Gender: Male 32 (restrictive 18; liberal 14); Female 28 (restrictive 11; liberal 17) Ethnicity: not reported Diagnosis: AML 39 (restrictive 19; liberal 20); ALL 5 (restrictive 3; liberal 2); haematological malignancy (unspecified) 16 (restrictive 7; liberal 9) Stage of disease: newly diagnosed AML 30 (restrictive 15; liberal 15); relapsed AML 9 (restrictive 4; liberal 5); unknown 21 (restrictive 10; liberal 11) Treatment: chemotherapy 44 (restrictive 22; liberal 22); SCT 16 (restrictive 7; liberal 9) Baseline haemoglobin level: restrictive: 96.3 g/L, liberal: 96.5 g/L Number analysed for across outcomes: For bleeding 60 (29 restrictive and 31 liberal) , for platelets and RBC and Hb levels 57(29/28) Were participants with active bleeding explicitly excluded? Yes. Participants with acute bleeding during the first

	12 hours after admission were excluded Were participants with a history of myocardial ischaemia/infarction explicitly excluded? Yes, participants with a history of myocardial infarction or angina in the last 6 months
Interventions	Patients were randomised to one of the following transfusion strategies: i) Restrictive: two units of RBC transfused when Hb below 80 g/L ii) Liberal: two units of RBC transfused when Hb below 120 g/L Off-protocol transfusions: 36.4% of transfusions received in restrictive group when Hb > 80g/L; 29.8% of transfusions received when Hb > 120g/L in the liberal group Red cell component: leucocyte-reduced before storage by Canadian blood services. volume 240 mL to 340 mL per unit, suspended in AS-3, estimated haematocrit of 0.55 to 0.65 Duration of storage: not reported
Outcomes	Primary and secondary: All five outcomes reported in the study considered relevant to the study feasibility and no single primary outcome was selected The outcomes of the study included; 1) bleeding (the occurrence graded by the WHO score, the time to the first bleed and number of bleeding days); 2) proportion of days of thrombocytopenia where the Hb level was within the targeted range; 3) blood product utilisation (number of RBC and platelet units) and blood donor exposure; 4) the ability to document bleeding symptoms and bleeding severity; and 5) participant number enrolled Assessment of bleeding: Clinical assessment of bleeding was performed each morning and reported according to the WHO scale. Each morning Monday to Friday a trained blinded assessor performed the observation. Saturday and Sunday assessments were performed retrospectively by reviewing the participant's chart All bleeding episodes were independently reviewed by an adjudication committee who were blinded to the participants' treatment assignments and Hb levels. Bleeding categorised by the committee by severity: no bleeding, non-clinically significant bleeding, and clinical significant bleeding.
Notes	Trial registration: Unknown. Source(s) of funding: Canadian Blood Services & CIHR Canada Research Chair (Public source) Conflicts-of-interest statement: Unclear

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated "A computer-generated random treatment allocation schedule was developed with a variable blocking factor with the size of the blocks selected in a random fashion from a limited number of possibilities"
Allocation concealment (selection bias)	Low risk	Computer generated "patients were randomly assigned with an Internet-based randomisation web site"
Blinding of participants and personnel (performance bias)	High risk	Study participants and clinicians were not blinded
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors were blinded, a member of the study group would assess clinical records to check if any bleeding episodes were missed. Bleeding reviews at weekend performed on Monday through review of patient's chart (not all bleeding episodes may have been recorded). Other reported outcomes are "hard" and/or "utilisation" outcomes, which could be argued to less influenced by un-blinding
Incomplete outcome data (attrition bias)	Low risk	All participants were followed up until study completion.
Selective reporting (reporting bias)	Low risk	No missing data identified. The analysis is assumed be intention-to-treat but neither explicitly confirmed in the report
Other bias	Unclear risk	Number of study days after target Hb levels reached differed were variable between groups (467 days restrictive; 410 days liberal), as it took longer for liberal group to reach the Hb threshold. Due to the way that bleeding assessed some bleeding episodes might had been missed

Footnotes

Characteristics of excluded studies

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

Summary of findings tables

Additional tables

References to studies

Included studies

De Zern 2016

[Empty]

Rygard 2017

[Empty]

Tay 2016

[Empty]

Webert 2008

[Empty]

Excluded studies

Studies awaiting classification

Ongoing studies

Other references

Additional references

Other published versions of this review

Classification pending references

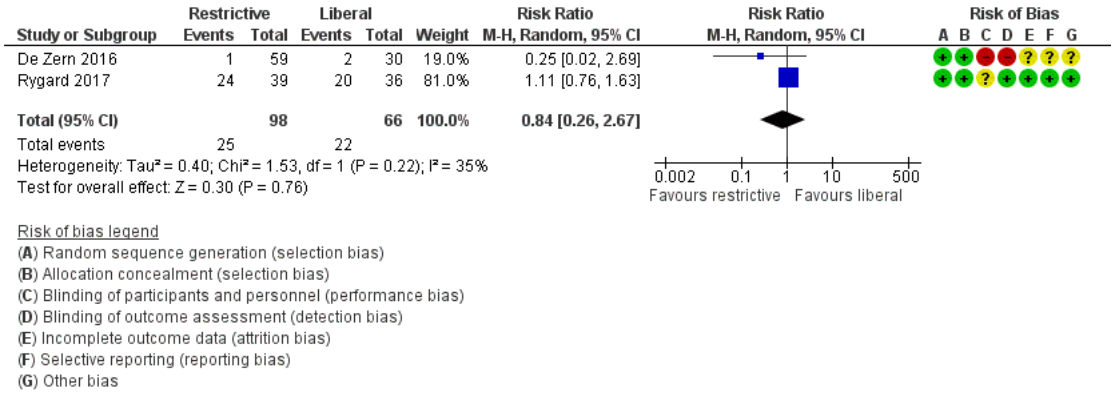
Data and analyses

1 Restrictive versus liberal red blood cell transfusion RCTs

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 All-cause mortality at 60 to 100 days	2	164	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.26, 2.67]
1.2 Quality of life. (National Cancer Institue Fatigue Scale) during entire study period	1	89	Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.15, 0.75]
1.5 Mean number of RBC (units) transfusions per participant. OBS! Rygard+ Tay Median!!	3	464	Mean Difference (IV, Random, 95% CI)	-2.14 [-2.77, -1.51]
1.6 Number of participants with RBC transfusion from study entry	3	224	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.70, 1.10]
1.10 Number of participants with serious infection episodes during entire study period	1	89	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.74, 2.04]
1.11 Severe or life-threatening bleeding events during entire study period (WHO bleeding scale??))	2	149	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.37, 6.28]

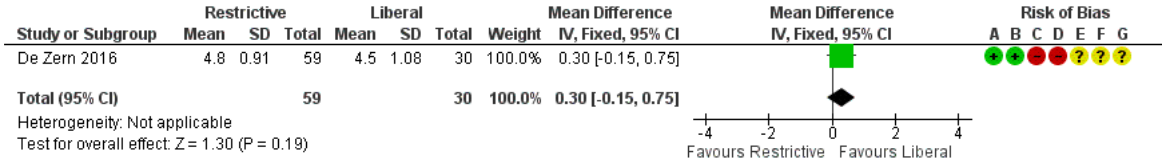
Figures

Figure 1 (Analysis 1.1)



Forest plot of comparison: 1 Restrictive versus liberal red blood cell transfusion RCTs, outcome: 1.1 All-cause mortality at 60 to 100 days.

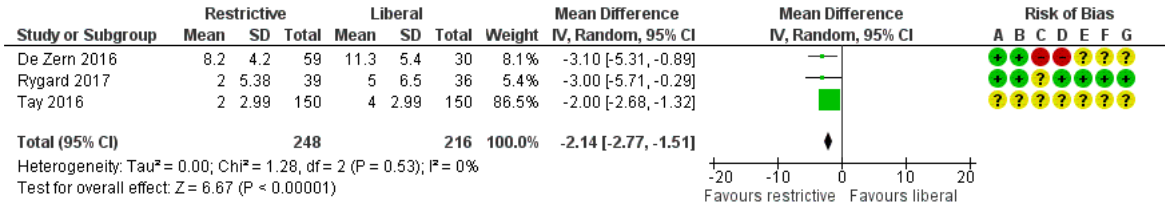
Figure 2 (Analysis 1.2)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: 1 Restrictive versus liberal red blood cell transfusion RCTs, outcome: 1.2 Quality of life. (National Cancer Institue Fatigue Scale) during entire study period.

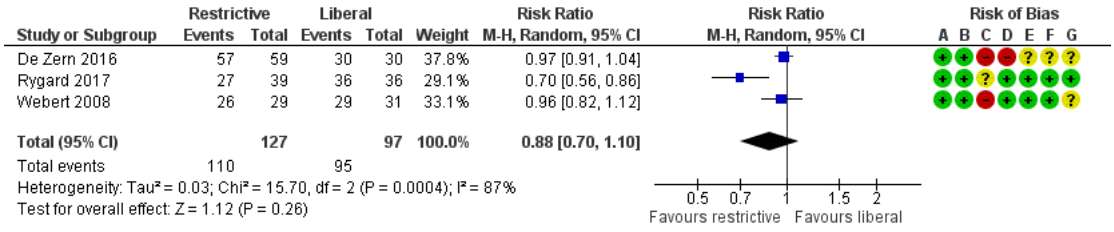
Figure 3 (Analysis 1.5)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: 1 Restrictive versus liberal red blood cell transfusion RCTs, outcome: 1.5 Mean number of RBC (units) transfusions per participant. OBS! Rygard+ Tay Median!!.

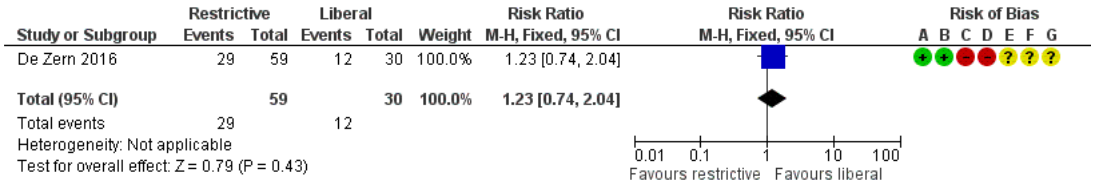
Figure 4 (Analysis 1.6)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: 1 Restrictive versus liberal red blood cell transfusion RCTs, outcome: 1.6 Number of participants with RBC transfusion from study entry.

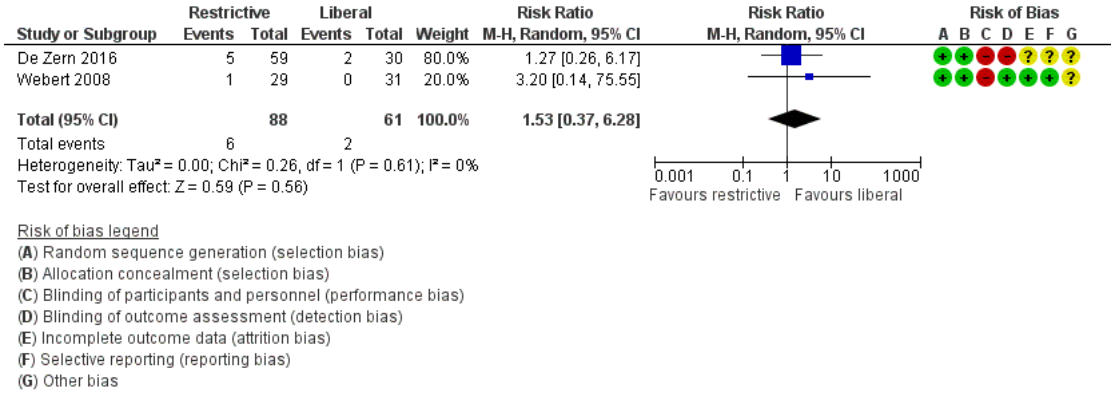
Figure 6 (Analysis 1.10)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: 1 Restrictive versus liberal red blood cell transfusion RCTs, outcome: 1.10 Number of participants with serious infection episodes during entire study period.

Figure 7 (Analysis 1.11)



Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Forest plot of comparison: 1 Restrictive versus liberal red blood cell transfusion RCTs, outcome: 1.11 Severe or life-threatening bleeding events during entire study period (WHO bleeding scale??)).