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Patient Blood Management
Recommendations From the 2018 Frankfurt Consensus Conference

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IMPORTANCE Blood transfusion is one of the most frequently used therapies worldwide and is associated with benefits, risks, and costs.

OBJECTIVE To develop a set of evidence-based recommendations for patient blood management (PBM) and for research.

EVIDENCE REVIEW The scientific committee developed 17 Population/Intervention/Comparison/Outcome (PICO) questions for red blood cell (RBC) transfusion in adult patients in 3 areas: preoperative anemia (3 questions), RBC transfusion thresholds (11 questions), and implementation of PBM programs (3 questions). These questions guided the literature search in 4 biomedical databases (MEDLINE, EMBASE, Cochrane Library, Transfusion Evidence Library), searched from inception to January 2018. Meta-analyses were conducted with the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) methodology and the Evidence-to-Decision framework by 3 panels including clinical and scientific experts, nurses, patient representatives, and methodologists, to develop clinical recommendations during a consensus conference in Frankfurt/Main, Germany, in April 2018.

FINDINGS From 17 607 literature citations associated with the 17 PICO questions, 145 studies, including 63 randomized clinical trials with 23 143 patients and 82 observational studies with more than 4 million patients, were analyzed. For preoperative anemia, 4 clinical and 3 research recommendations were developed, including the strong recommendation to detect and manage anemia sufficiently early before major elective surgery. For RBC transfusion thresholds, 4 clinical and 6 research recommendations were developed, including 2 strong clinical recommendations for critically ill but clinically stable intensive care patients with or without septic shock (recommended threshold for RBC transfusion, hemoglobin concentration <7 g/dL) as well as for patients undergoing cardiac surgery (recommended threshold for RBC transfusion, hemoglobin concentration <7.5 g/dL). For implementation of PBM programs, 2 clinical and 3 research recommendations were developed, including recommendations to implement comprehensive PBM programs and to use electronic decision support systems (both conditional recommendations) to improve appropriate RBC utilization.

CONCLUSIONS AND RELEVANCE The 2018 PBM International Consensus Conference defined the current status of the PBM evidence base for practice and research purposes and established 10 clinical recommendations and 12 research recommendations for preoperative anemia, RBC transfusion thresholds for adults, and implementation of PBM programs. The relative paucity of strong evidence to answer many of the PICO questions supports the need for additional research and an international consensus for accepted definitions and hemoglobin thresholds, as well as clinically meaningful end points for multicenter trials.

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Supplemental content

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Transfusion of blood components can save lives, but like all therapeutics, also carries risks and costs. Therefore, transfusion must be used judiciously.

The World Health Organization (WHO) defined patient blood management (PBM) as "a patient-focused, evidence-based and systematic approach to optimize the management of patients and transfusion of blood products for quality and effective patient care. It is designed to improve patient outcomes through the safe and rational use of blood and blood products and by minimizing unnecessary exposure to blood products...."[1] In the same 2011 article, WHO acknowledged that "blood transfusion is a life-saving intervention that has an essential role in patient management within health systems...."[1] It is therefore important to define an evidence-based and quality-controlled basis for hemotherapy and related periprocedural patient care to optimize patient outcomes.

Over the last 2 decades, endeavors in multiple countries and individual hospitals have been directed toward these goals. Most efforts focused on diagnosis and treatment of preoperative anemia by optimization of erythropoiesis and preoperative hemoglobin mass, along with efforts to define transfusion thresholds for red blood cell (RBC) concentrates and preoperative, intraoperative, and postoperative minimization of blood loss.[2]

However, many clinical PBM implementation trials were not controlled or focused on the number of RBC units transfused only, rather than clinical outcomes. Thus, results of publications were sometimes contradictory. Systematic reviews, meta-analyses, and guidelines have tried to condense the current knowledge in specific parts of PBM, such as RBC transfusion thresholds in well-defined perioperative settings.[3-8]

To our knowledge, there has been no international consensus strategy analyzing the published evidence in PBM and defining recommendations after a transparent, rigorous, and quality-controlled decision-making process. The International Consensus Conference (ICC), held in Frankfurt/Main, Germany, in April 2018, was designed to address the need for evidence-based recommendations.

Key Points

Questions What is the current evidence base for patient blood management (PBM) in adults, and what international clinical recommendations can be derived for preoperative anemia, red blood cell transfusion thresholds, and PBM implementation strategies?

Findings Diagnosis and management of preoperative anemia is crucial, and iron-deficient anemia should be treated with iron supplementation. Red blood cell transfusion thresholds for critically ill, clinically stable patients (hemoglobin concentration <7 g/dL), patients undergoing cardiac surgery (hemoglobin concentration <7.5 g/dL), patients with hip fractures and cardiovascular disease or risk factors (hemoglobin concentration <8 g/dL), and hemodynamically stable patients with acute gastrointestinal bleeding (hemoglobin concentration 7-8 g/dL) are relatively well defined, although the quality of evidence is moderate to low.

Meaning Further high-quality research to support PBM is required for a range of clinical scenarios and implementation of PBM programs.

Methods

An international consortium of scientific organizations in the field of blood transfusion, including the American Association of Blood Banks (AABB), the International Society of Blood Transfusion (ISBT), the Deutsche Gesellschaft für Transfusionsmedizin und Immunhämatologie (German Blood Transfusion Society [DGTI]), the Société Française de Transfusion Sanguine (French Blood Transfusion Society [SFTS]), the Società Italiana di Medicina Transfusionale e Immunoematologia (Italian Blood Transfusion Society [SIMTI]), and the European Blood Alliance (EBA), convened a scientific committee of 23 members (eAppendix 1 in the Supplement) to coordinate an international consensus meeting on evidence-based patient blood management.

With a focus on transfusion of RBCs in adult patients, the scientific committee developed 17 questions according to the standardized Population/Intervention/Comparison/Outcome (PICO) format (population/patients/problem, intervention, comparator/comparison and outcome): 3 PICO questions addressed the diagnosis and treatment of preoperative anemia, 11 addressed the effectiveness and safety of restrictive RBC transfusion thresholds in different patient groups, and 3 addressed implementation strategies of PBM programs (**Box 1**). The analysis was confined to adult patients (typically defined as age ≥18 years), because diagnostic and treatment approaches for children are qualitatively different from those for adult patients.

Systematic reviews were conducted according to a predefined protocol to answer these 17 questions with the best available evidence.[9] Search strategies were developed in MEDLINE (PubMed interface), EMBASE, Cochrane Library, and the Transfusion Evidence Library from the time of inception until January 2018. After removing duplicates, title and abstract screening was initiated, followed by a full-text assessment based on predefined inclusion and exclusion criteria. Detailed PICO questions, search strategies, and selection criteria are reported in the eAppendix 2 in the Supplement.

Data concerning study design, population characteristics, intervention(s), and outcome measures were extracted. Effect measures and their corresponding 95% confidence intervals were inserted in Review Manager version 5.3 (Cochrane).

Meta-analyses (when possible and appropriate) were performed using a random-effects model, given the anticipated variation between studies. For dichotomous outcomes the Mantel-Haenszel method was used; for continuous outcomes, the inverse variance method was used. The pooled results were summarized in forest plots. $P < .05$ (2-sided) was considered statistically significant.

The methodological quality of included studies, as well as the overall quality of the studies for each outcome, was assessed using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) methodology.[10] The initial quality assessment corresponds to the study design, ie, "high" for experimental studies (eg, randomized clinical trials [RCTs]) and "low" for observational studies (eg, cohort studies). GRADE considers 5 factors that might downgrade the study quality: limitations in study design

Box 1. Population/Intervention/Comparison/Outcome (PICO) Questions

Preoperative Anemia

PICO 1—Adverse Events: In patients undergoing elective surgery [population], is preoperative anemia [intervention/risk factor] a risk factor for adverse clinical or economic outcome [outcomes], compared with no preoperative anemia [comparison]?

PICO 2—Definition: In patients undergoing elective surgery [population], the question "Should a specific hemoglobin cutoff [index test] vs another hemoglobin cutoff [comparator test] be used to diagnose preoperative anemia [outcome]?" was not answered because of lack in evidence.

PICO 3—Management: In patients with preoperative anemia undergoing elective surgery [population], is the use of red blood cell transfusion or iron supplementation and/or erythrocyte-stimulating agents [intervention] effective to improve clinical and economic outcomes [outcomes], compared with no intervention, placebo, or standard of care [comparison]?

Red Blood Cell (RBC) Transfusion Thresholds

PICO 4—Adult Intensive Care Patients: In critically ill but clinically stable adult intensive care patients [population], is the use of a restrictive transfusion threshold [intervention] effective to reduce mortality and improve other clinical outcomes [outcomes], compared with a liberal transfusion threshold [comparison]?

PICO 5—Orthopaedic and Noncardiac Surgery: In elderly high-risk (cardiovascular) patients undergoing orthopaedic or noncardiac surgery [population], is the use of a restrictive transfusion threshold [intervention] effective to reduce mortality and improve other clinical outcomes [outcomes], compared with a liberal transfusion threshold [comparison]?

PICO 6—Acute Gastrointestinal Bleeding: In patients with acute gastrointestinal bleeding [population], is the use of a restrictive transfusion threshold [intervention] effective to reduce mortality and improve other clinical outcomes [outcomes], compared with a liberal transfusion threshold [comparison]?

PICO 7—Coronary Heart Disease: In patients with symptomatic coronary heart disease [population], is the use of a restrictive transfusion threshold [intervention] effective to reduce mortality and improve other clinical outcomes [outcomes], compared with a liberal transfusion threshold [comparison]?

PICO 8—Septic Shock: In patients with septic shock [population], is the use of a restrictive transfusion threshold [intervention] effective to reduce mortality and improve other clinical outcomes [outcomes], compared with a liberal transfusion threshold [comparison]?

PICO 9—Cardiac Surgery: In patients undergoing cardiac surgery [population], is the use of a restrictive transfusion threshold [intervention] effective to reduce mortality and improve other clinical outcomes [outcomes], compared with a liberal transfusion threshold [comparison]?

PICO 10—Adult Hematologic Patients: In adult hematologic patients [population], is the use of a restrictive transfusion threshold [intervention] effective to reduce mortality and improve other clinical outcomes [outcomes], compared with a liberal transfusion threshold [comparison]?

PICO 11—Adult Patients With Solid Tumors: In adult patients with solid tumors [population], is the use of a restrictive transfusion threshold [intervention] effective to reduce mortality and improve other clinical outcomes [outcomes], compared with a liberal transfusion threshold [comparison]?

PICO 12—Acute Central Nervous System Injury: In patients with acute central nervous system injury [population], is the use of a restrictive transfusion threshold [intervention] effective to reduce mortality and improve other clinical outcomes [outcomes], compared with a liberal transfusion threshold [comparison]?

PICO 13—Cerebral Perfusion Disorders: In patients with cerebral perfusion disorders [population], is the use of a restrictive transfusion threshold [intervention] effective to reduce mortality and improve other clinical outcomes [outcomes], compared with a liberal transfusion threshold [comparison]?

PICO 14—Acute Bleeding: In patients with acute bleeding [population], is the use of a restrictive transfusion threshold [intervention] effective to reduce mortality and improve other clinical outcomes [outcomes], compared with a liberal transfusion threshold [comparison]?

Implementation of Patient Blood Management (PBM) Programs

PICO 15—Effectiveness of PBM Implementation: Is a PBM program [intervention] effective to improve clinical and economic outcomes [outcomes], compared with no PBM program [comparison]?

PICO 16—PBM Promotional Tools: Behavioral Interventions: Is a specific behavioral intervention to promote the implementation of a PBM program [intervention] more effective to improve clinical and economic outcomes [outcomes], compared with no/another behavioral intervention [comparison]?

PICO 17—PBM Promotional Tools: Decision Support Systems: Is a specific decision support system to promote the implementation of a PBM program [intervention] more effective to improve clinical and economic outcomes [outcomes], compared with no intervention or another decision support system/behavioral intervention [comparison]?

(which pose risk of bias), inconsistency, indirectness, imprecision, and publication bias. Three factors can upgrade the study quality: magnitude of effect, dose-response gradient, and plausible confounding.

GRADEpro software (https://www.gradepro.org) was used to create evidence profiles for the outcomes of interest.[11] Outcomes were rated for practical and clinical importance by all members of the scientific committee (n = 23) independently via an online-based questionnaire, from 1 (not critical to making a decision regarding the optimal patient care strategy) to 9 (critical to making a decision regarding optimal patient care). The final rating scores were reached by consensus during telephone conferences with all scientific committee members. The systematic reviews were performed by experienced methodologists and reviewed and approved by the entire scientific committee.

A total of 188 participants representing more than 10 clinical disciplines from 33 different countries and 5 continents participated in a 2-day consensus conference on April 24-25, 2018, in Frankfurt/Main, Germany. The ICC PBM was organized using the principles

Table 1. Clinical Recommendations: Preoperative Anemia

Clinical Recommendation	Level of Evidence
CR1—Detection and management of preoperative anemia early enough before major elective surgery	Strong recommendation, low certainty in the evidence of effects
CR2—Use of iron supplementation to reduce red blood cell transfusion rate in adult preoperative patients with iron-deficient anemia undergoing elective surgery	Conditional recommendation, moderate certainty in the evidence of effects
CR3—*Do not* use erythropoiesis-stimulating agents routinely in general for adult preoperative patients with anemia undergoing elective surgery	Conditional recommendation, low certainty in the evidence of effects
CR4—Consider short-acting erythropoietins in addition to iron supplementation to reduce transfusion rates in adult preoperative patients with hemoglobin concentrations <13 g/dL undergoing elective major orthopedic surgery	Conditional recommendation, low certainty in the evidence of effects

Abbreviation: CR, clinical recommendation.

of the National Institutes of Health consensus development conference methodology[12,13]:

1. Opening plenary session, day 1: evidence from the systematic reviews was presented by scientific committee members in 3 parallel and public open sessions according to the 3 selected topics, followed by discussion with the general audience;
2. Closed sessions without public access (invited experts, chairs, and rapporteurs only) of the 3 decision-making panels at the end of day 1 (7-15 topic experts and 2 chairs—1 topic expert and 1 methodologist) to further discuss the evidence and to formulate draft consensus recommendations;
3. Plenary session for presentation of the draft recommendations, followed by discussion and opinion poll voting (Mentimeter, https://www.menti.com/) with the general audience on day 2, including audience polling;
4. Closing executive sessions with final recommendations formulated by the decision-making panels at the end of day 2.

The process of going from the evidence (systematic review) to formulating recommendations was structured and facilitated by the GRADE methodology and its Evidence-to-Decision framework.[14]

Opinion polls were held on day 1 as well as on day 2 with the general audience using the above-mentioned online tool for voting. Draft recommendations were presented as questions to the general audience on day 2 in the morning sessions, and the online voting tool was used to get the general acceptance or dissent regarding each question. Main results of the discussion with the general audience were captured by the rapporteurs. Poll results were reviewed in closed sessions of each of the 3 panels on both days and integrated into the panel discussion and final recommendations.

Within the closed sessions of each panel, votes were by a show of hands. A majority of at least 2 of 3 panelists (number varied according to group) was considered a decisive vote.

Disclosures and potential conflicts of interest of all panelists were published online (https://icc-pbm.eu/panel-disclosures-and-cvs/) to achieve transparency.

For documentation of each session, 2 rapporteurs per group used an online version of the Evidence-to-Decision framework (GRADEpro software, https://gradepro.org/) to record feedback from the general audience in the parallel sessions and the judgments and conclusions from the decision-making panel in the closed sessions.

Since the process involved only analyses of previously published literature without individual patient data and no patient contact, the ICC was managed as a quality and educational activity, and human research ethics committee approval was not required.

Results

Study Selection

The systematic literature searches for the 17 PICO questions resulted in a total of 17 607 citations (eFigure 1 in the Supplement). The evidence reviewed included 145 studies (39 observational studies and 23 RCTs related to the 3 PICO questions on preoperative anemia; 39 RCTs and 1 observational study related to the 11 PICO questions on RBC transfusion thresholds; 42 observational studies and 1 RCT related to the 3 PICO questions on PBM implementation). The majority of studies (83%) were conducted in the region of the Americas (n = 66 studies) or Europe (n = 54). The remaining studies were from the Western Pacific (n = 15), Eastern Mediterranean (n = 5), Southeast Asia (n = 4), and Africa (n = 1). Approximately half of the studies (n = 75) were published between 2013 and 2018; 29 between 2008 and 2012; 19 between 2003-2007; 11 between 1998-2002; and 11 before 1998.

Definition, Diagnosis, and Treatment of Preoperative Anemia

Three PICO questions focused on the definition, diagnosis, and treatment of preoperative anemia and generated 4 clinical recommendations (**Table 1**; eFigure 14 in the Supplement).

Recommendation 1: Preoperative Anemia Detection and Management

The panel recommended detection and management of preoperative anemia early enough before major elective surgery (strong recommendation, low certainty in the evidence of effects).

Evidence Summary | Thirty-five cohort studies assessed whether preoperative anemia was associated with adverse events in patients scheduled for cardiac[15-29] and noncardiac[30-49] surgery. Meta-analyses showed an association between preoperative anemia and in-hospital mortality (pooled odds ratio [OR], 2.09 [95% CI, 1.48-2.95]) (eFigure 2 in the Supplement), 30-day mortality (pooled OR, 2.20 [95% CI, 1.68-2.88]) (eFigure 3 in the Supplement), acute myocardial infarction (AMI) (pooled OR, 1.39 [95% CI, 0.99-1.96]), acute ischemic stroke or central nervous system complications (pooled OR, 1.19 [95% CI, 1.02-1.39]), and acute kidney injury, renal failure/dysfunction, or urinary complications (pooled OR, 1.78 [95% CI, 1.35-2.34]). The certainty in the evidence of effect estimates ranged from moderate (for in-hospital and 30-day mortality, upgrade for strong association) to low (acute ischemic

stroke or central nervous system complications) to very low (for AMI, acute kidney injury, gastrointestinal dysfunction, or acute peripheral vascular ischemia, downgrade for inconsistency).

Rationale for the Recommendation | Despite the overall low certainty in the effect estimates, the panel formulated a strong recommendation based on the magnitude of undesirable effects of preoperative anemia on critical outcomes such as mortality, and the absence of any risk and a clear balance of effects (eTable 1 in the Supplement).

Recommendation 2: Iron Supplementation

The panel recommended use of iron supplementation in adult preoperative patients with iron-deficiency anemia undergoing elective surgery to reduce rate of RBC transfusion (conditional recommendation, moderate certainty in the evidence of effects).

Evidence Summary | One nonrandomized pilot study found that postoperative parenteral iron administration was safe and effective for reducing RBC utilization in patients undergoing total hip replacement.[50] These findings were confirmed by 3 RCTs that randomized patients with colorectal malignancies and iron-deficiency anemia who were scheduled for colorectal/major abdominal surgery to receive oral or intravenous iron supplementation or placebo or standard of care.[51-53] One additional nonrandomized study investigated the effect of oral sodium ferrous citrate compared with no treatment in patients undergoing colorectal cancer surgery.[54] Overall, 19.6% fewer patients received transfusions in the iron supplementation group compared with the control group (eFigure 4 in the Supplement). The certainty in the evidence of effect estimates was moderate for RBC utilization (upgrade for strong association).

Rationale for the Recommendation | The decision was made to formulate a conditional recommendation in favor of using preoperative iron supplementation in adult patients with iron-deficiency anemia undergoing elective surgery. It was based on favorable effects of iron supplementation on RBC utilization during surgery and the overall moderate certainty in the effect estimates (eTable 1 in the Supplement). In addition, the panel recommended that the iron formulation and route of application be individualized based on the degree of preoperative anemia, the remaining time before surgery, and the patient's ability to absorb and tolerate oral iron, which strongly influences medication adherence.

Recommendation 3: Erythropoiesis-Stimulating Agents

The panel recommended that erythropoiesis-stimulating agents (ESAs) should not be used routinely in general for adult preoperative patients with anemia undergoing elective surgery (conditional recommendation, low certainty in the evidence of effects).

Evidence Summary | One cohort study conducted in the United States in patients undergoing total hip/knee arthroplasty[55] and 1 RCT conducted in Italy in patients undergoing cardiac surgery[56] showed that erythropoietin, compared with no erythropoietin, reduced the need for postoperative RBC transfusions (relative risk [RR], 0.05 [95% CI, 0.00-0.77] for erythropoietin vs RR, 0.43 [95% CI, 0.28-0.64] for no erythropoietin). Pooled estimates from 2 RCTs showed no evidence of an erythropoietin effect on 45-day mortality (RR, 0.93 [95% CI, 0.43-2.01]), AMI (RR, 0.92 [95% CI, 0.39-2.14]), bowel ischemia (RR, 0.50 [95% CI, 0.09-2.71]), acute kidney injury (RR, 2.00 [95% CI, 0.18-21.94], or thromboembolic events (RR, 0.39 [95% CI, 0.09-1.66]).[56,57] The certainty in the evidence of effect estimates was low for all critical outcomes (RBC utilization and the clinical outcomes, downgrading for risk of bias and imprecision).

Rationale for the Recommendation | The panel gave a conditional or weak recommendation not to use ESAs routinely in general for adult preoperative patients with anemia undergoing elective surgery (low certainty of evidence; heterogeneous study results). The panel cited as justification the low rate of desirable effects and potential of undesirable effects because of a nonsignificant but potentially clinically relevant signal toward an increased risk of thromboembolic events with this approach (eTable 1 in the Supplement).

Recommendation 4: Short-Acting Erythropoietins and Iron Supplementation

The panel recommended that clinicians consider use of short-acting erythropoietins in addition to iron supplementation in adult preoperative patients with hemoglobin levels less than 13 g/dL undergoing elective major orthopedic surgery, to reduce transfusion rates (conditional recommendation, low certainty in the evidence of effects).

Evidence Summary | In 17 trials, patients were randomized either into groups receiving a combination of oral/intravenous iron supplementation in addition to erythropoietin or groups receiving placebo, no treatment, or usual care.[58-74] Most of these trials were conducted among patients undergoing orthopedic and oncologic surgical procedures (n = 12), followed by hysterectomy (n = 2), cardiac surgery (n = 2), and spinal surgery (n = 1). Results indicate that perioperative iron plus erythropoietin supplementation leads to a lower proportion of patients requiring RBC transfusions (eFigure 5 in the Supplement). This was not shown for all ESAs. For other clinically important or critical outcomes such as all-cause mortality, anemia-associated ischemic events, and thromboembolic events, the number of events was too small and the variability in results was too large to detect statistically significant and clinically relevant differences (eFigures 6-8 in the Supplement). The certainty in the evidence of effect estimates was low for all critical outcomes (for RBC utilization as well as all clinical outcomes, downgrade for risk of bias and imprecision).

Rationale for the Recommendation | In a conditional recommendation, the panel recommended that clinicians consider the use of short-acting erythropoietins plus iron supplementation in adult preoperative elective major orthopedic patients with preoperative hemoglobin levels less than 13 g/dL only. The benefit was considered low (potential reduction in RBC units transfused), while the risks (eg, thromboembolic deep vein thrombosis) were considered potentially life-threatening. However, the panel also noted that the probability of RBC transfusion, the etiology of anemia, and the thromboembolic risk of each individual patient must be considered, since the relative benefit is balanced by a potentially life-threatening complication (eTable 1 in the Supplement) (low certainty of evidence).

Table 2. Clinical Recommendations: Red Blood Cell Transfusion Thresholds

Clinical Recommendation	Level of Evidence
CR5—Restrictive RBC transfusion threshold (hemoglobin concentration <7 g/dL) in critically ill but clinically stable intensive care patients	Strong recommendation, moderate certainty in the evidence of effects
CR6—Restrictive RBC transfusion threshold (hemoglobin concentration <7.5 g/dL) in patients undergoing cardiac surgery	Strong recommendation, moderate certainty in the evidence of effects
CR7—Restrictive transfusion threshold (hemoglobin concentration <8 g/dL) in patients with hip fracture and cardiovascular disease or other risk factors	Conditional recommendation, moderate certainty in the evidence of effects
CR8—Restrictive transfusion threshold (hemoglobin concentration 7-8 g/dL) in hemodynamically stable patients with acute gastrointestinal bleeding	Conditional recommendation, low certainty in the evidence of effects

Abbreviations: CR, clinical recommendation; RBC, red blood cell.

RBC Transfusion Thresholds

Eleven PICO questions focused on RBC transfusion thresholds and generated 4 clinical recommendations (**Table 2**; eFigure 15 in the Supplement).

Recommendation 5: Intensive Care

The panel recommended a restrictive RBC transfusion threshold (hemoglobin concentration <7 g/dL) in critically ill but clinically stable intensive care patients (strong recommendation, moderate certainty in the evidence of effects).

Evidence Summary | Six RCTs conducted in intensive care patients without (4 studies) or with (2 studies) septic shock (n = 1352 patients) were included.[75-80] Overall, 31.4% fewer patients received RBC transfusions in the restrictive-threshold group compared with the liberal-threshold group. The mean number of RBC units transfused was 3 units lower and the mean hemoglobin concentration before transfusion was 1.66 g/dL lower in the restrictive-threshold group. No difference in 30-day mortality (RR, 0.97 [95% CI, 0.82-1.15]) could be demonstrated, and a statistically nonsignificant reduction in in-hospital mortality in the restrictive-threshold group (RR, 0.88 [95% CI, 0.76-1.02]) was reported (eFigures 9-10 in the Supplement). The certainty in the estimates of effects for the critical outcomes (ie, 30-day and in-hospital mortality) was moderate (downgrade for imprecision).

Rationale for the Recommendation | This strong recommendation, based on moderate certainty, was justified because of 2 findings: there was no evidence of increased survival or other desirable effects in the liberal-threshold group but a substantial reduction in RBC exposure and utilization in the restrictive-threshold group (eTable 2 in the Supplement). Of note, a hemoglobin concentration of 7 g/dL represents the transfusion threshold used in the included trials.

Recommendation 6: Cardiac Surgery

The panel recommended a restrictive RBC transfusion threshold (hemoglobin concentration <7.5 g/dL) in patients undergoing cardiac surgery (strong recommendation, moderate certainty in the evidence of effects).

Evidence Summary | Eight RCTs (n = 8679 patients) were included.[81-88] Overall, 23.3% fewer patients received transfusions in the restrictive-threshold group compared with the liberal-threshold group. The mean number of RBC units transfused was 0.87 units lower and the mean hemoglobin concentration before transfusion was 1.4 g/dL lower in the restrictive-threshold group. Mortality outcomes (30-day and in-hospital) and other clinical outcomes (ie, cardiac events, AMI, cerebrovascular accident (CVA)/stroke, rebleeding, sepsis/bacteremia, pneumonia or wound infection, and renal failure) were reported in 3 or more studies, and significant differences could not be shown between restrictive and liberal RBC transfusion strategies. The certainty in estimates of effects for critical outcomes ranged from low (for cardiac events, rebleeding, CVA/stroke, and sepsis/bacteremia, downgrade for risk of bias, indirectness, or imprecision) to moderate (for 30-day and in-hospital mortality, AMI, pneumonia or wound infection, and renal failure, downgrade for indirectness or imprecision).

Rationale for the Recommendation | Based on moderate certainty in the evidence of effects, this recommendation was justified by the same 2 findings noted above: no evidence of increased survival or other desirable effects in the liberal-threshold group but a substantial reduction in RBC exposure and utilization in the restrictive-threshold group (eTable 2 in the Supplement). Of note, a 7.5-g/dL threshold represents the value used in the included trials.

Recommendation 7: Hip Fracture

The panel recommended a restrictive transfusion threshold (hemoglobin concentration <8 g/dL) in patients with hip fracture and cardiovascular disease or other risk factors (conditional recommendation, moderate certainty in the evidence of effects).

Evidence Summary | Ten studies (n = 3907 patients) were included.[89-98] Overall, 42.6% fewer patients received transfusions in the restrictive-threshold group compared with the liberal-threshold group. The mean number of RBC units transfused was 0.08 units lower and the mean hemoglobin concentration before transfusion was 0.9 g/dL lower in the restrictive-threshold group. There were no significant differences between restrictive and liberal transfusion groups in critical outcomes, including 30-day mortality (RR, 1.27 [95% CI, 0.72-2.25]), in-hospital mortality (RR, 0.45 [95% CI, 0.09-2.28]), cardiac events (RR, 1.36 [95% CI, 1.03-1.80]), AMI (RR, 1.58 [95% CI, 0.97-2.56]), CVA/stroke (RR, 0.43 [95% CI, 0.16-1.13]), thromboembolism (RR, 0.71 [95% CI, 0.34-1.47]), renal failure (RR, 0.73 [95% CI, 0.14-3.84]), inability to walk or death at 30 days (RR, 1.04 [95% CI, 0.95-1.14]), and inability to walk or death at 60 days (RR, 0.99 [95% CI, 0.87-1.11]). The certainty in estimates of effects for critical outcomes ranged from low (for CVA/stroke, renal failure) to moderate (for 30-day and in-hospital mortality, AMI, and thromboembolism, downgrade to imprecision) to high (cardiac events).

Table 3. Clinical Recommendations: Implementation of Patient Blood Management Programs

Clinical Recommendation	Level of Evidence
CR9—Implementation of PBM programs to improve appropriate RBC utilization	Conditional recommendation, low certainty in the evidence of effects
CR10—Computerized or electronic decision support systems to improve appropriate RBC utilization	Conditional recommendation, low certainty in the evidence of effects

Abbreviations: CR, clinical recommendation; PBM, patient blood management; RBC, red blood cell.

Rationale for the Recommendation | Based on moderate level of evidence, this recommendation was justified by 1 finding: no effect on mortality (although wide confidence intervals) or functional outcomes (walking independently at 60 days) (eTable 2 in the Supplement). However, uncertainty regarding undesirable effects, in particular involving AMI, led the panel to be cautious, particularly since patients with hip fracture comprise mainly elderly people with comorbidities. Of note, a hemoglobin concentration of 8 g/dL represented the transfusion threshold used in the included trials. The panel debated the appropriateness of extrapolating trial data from older patients with hip fracture to other patients undergoing different types of orthopedic surgery or patients undergoing other nonorthopedic surgery.

Recommendation 8: Acute Gastrointestinal Bleeding

The panel recommended a restrictive transfusion threshold (hemoglobin concentration 7-8 g/dL) in hemodynamically stable patients with acute gastrointestinal bleeding (conditional recommendation, low certainty in the evidence of effects).

Evidence Summary | Three studies (n = 1522 patients) meeting the selection criteria were included.[99-101] Overall, 24.5% fewer patients received RBC transfusions in the restrictive-threshold group compared with the liberal-threshold group. The mean number of RBC units transfused was 1.79 units lower and the mean hemoglobin concentration before transfusion was 0.89 g/dL lower in the restrictive-threshold group. A significant reduction in 30-day mortality (RR, 0.65 [95% CI, 0.43-0.97]) was reported in the restrictive transfusion strategy, whereas there were no significant differences in the other critical outcomes (RR, 0.19 [95% CI, 0.01-3.67] for in-hospital mortality; 0.62 [95% CI, 0.26-1.47] for AMI; 0.50 [95% CI, 0.13-1.99] for CVA/stroke; 0.81 [95% CI, 0.62-1.05] for renal failure). The certainty in the estimates of effects for the critical outcomes ranged from low (for 30-day mortality, AMI, CVA/stroke, and renal failure, downgrade for risk of bias and imprecision) to very low (for in-hospital mortality, downgrade for risk of bias, imprecision, and indirectness).

Rationale for the Recommendation | Two PICO questions addressed acute bleeding, one specifically gastrointestinal bleeding (PICO 6), the other nonspecific bleeding (PICO 14). For patients with acute gastrointestinal bleeding who are hemodynamically stable, the panel conditionally recommended an RBC transfusion threshold of hemoglobin concentration 7 to 8 g/dL. The main justifications came from 2 trials showing lower mortality with a restrictive strategy, no evidence of undesirable effects, and a reduction in RBC exposure and utilization (eTable 2 in the Supplement). Of note, both trials used hemoglobin thresholds (eg, 7g/dL) to achieve specified hemoglobin target ranges (eg, 7-9 g/dL). In addition, both trials excluded patients with massive exsanguination. There were no trials in patients with lower gastrointestinal tract bleeding.

The evidence for RBC transfusion support in patients with acute bleeding of unspecified origin (PICO 14) was limited to 1 small RCT including 22 trauma patients, published in 1956.[102] Because of the absence of available evidence, the panel was not able to formulate any recommendation about restrictive vs liberal RBC transfusion strategies in this setting. However, the panel opinion was that hemoglobin concentration alone should not be used to determine the need for RBC transfusion in patients with acute bleeding (ie, major hemorrhage). The panel recommended that clinicians use existing protocols or guidelines for massive transfusion/major hemorrhage to guide treatment decisions.[103]

Implementation of PBM Programs

Three questions were related to PBM programs and generated 2 clinical recommendations (**Table 3**; eFigure 16 in the Supplement).

Recommendation 9: PBM Programs Implementation

The panel recommended implementation of PBM programs to improve appropriate RBC utilization (conditional recommendation, low certainty in the evidence of effects).

Evidence Summary | Twenty cohort studies investigated whether the implementation of a comprehensive PBM program (ie, at least 1 intervention for 2 of the 3 PBM pillars[2]) was effective.[104-123] The most common interventions of these PBM programs included (restrictive) RBC transfusion strategies (PBM pillar "RBC transfusion" [19 studies]), the use of pharmacologic hemostatic agents (PBM pillar "minimize blood loss" [12 studies]), and/or the use of ESA/iron therapy (PBM pillar "optimize erythropoiesis" [14 studies]).

Overall, fewer transfusions were administered after implementation of a PBM program (24 fewer RBC transfusions per 1000 patients (RR, 0.78 [95% CI, 0.73-0.85]), 4 fewer platelet concentrate (PLT) transfusions per 1000 patients (RR, 0.86 [95% CI, 0.78-0.95]), and 30 fewer fresh frozen/therapeutic plasma (FFP) transfusions per 1000 patients (RR, 0.49 [0.23-1.06]) (eFigures 11-13 in the Supplement). The mean number of blood products per transfusion was significantly lower after implementation of the PBM program (0.47 RBC units lower, 0.44 PLT units lower, and 0.67 FFP units lower).

There was no significant reduction in mortality (RR, 0.64 [95% CI, 0.23-1.74] for in-hospital mortality and 1.25 [95% CI, 0.78-2.02] for 30-day mortality) and morbidity-related outcomes (RR, 0.20 [95% CI, 0.02-1.73] for AMI; 1.03 [95% CI, 0.71-1.52] for acute ischemic stroke; 0.84 [95% CI, 0.60-1.17] for acute kidney injury). The length of hospital stay was significantly lower in the PBM group (0.50 days lower after implementation of a PBM program). The certainty in the effect estimates was "low" for the RBC utilization outcomes, whereas the certainty was labeled "very low" for all other outcomes (PLT/FFP utilization, mortality and morbidity outcomes, length of hospital stay) because of risk of bias and inconsistent results, imprecise results, or both.

Box 2. Research Recommendations

Preoperative Anemia

R1—Since published studies show major differences in the hemoglobin values used for the definition of preoperative anemia, the expert panel recommends to identify optimal hemoglobin thresholds in different patient groups as well as adequate cutoff values.

R2—The expert panel suggests to address the effects of iron supplementation in nonanemic but iron-deficient patients scheduled for major surgery.

R3—The expert panel recommends to investigate the use of short-acting erythropoietins + iron supplementation in adult preoperative patients undergoing elective surgery, with focus on long-term (un)desirable effects, optimal dose, type of surgery (particularly in cancer surgery), copresence of iron deficiency, and cost-effectiveness.

Red Blood Cell (RBC) Concentrate Transfusion Thresholds

R4—The expert panel recommends further research regarding restrictive RBC transfusion thresholds for hemodynamically stable patients with acute upper or lower gastrointestinal tract bleeding. The panel does not recommend further research in hemodynamically unstable patients with acute major bleeding.

R5-9—The expert panel suggests further research on RBC transfusion support in patients with hematologic and oncologic diseases, coronary heart diseases, noncardiac or nonorthopedic surgery, or brain injury.

Rx (no evidence): No further research on hemoglobin thresholds in patients with acute bleeding.

Implementation of Patient Blood Management (PBM) Programs

R10-12—The expert panel suggests further research on the effect of PBM programs on (A) adverse events and patient-important outcomes; (B) compliance, adherence, and acceptability; and (C) cost-effectiveness.

Reproducible definitions and outcome parameters have to be defined beforehand to evaluate the sustainability of PBM programs.

Recommendation 10: Decision Support Systems

The panel recommended computerized or electronic decision support systems to improve appropriate RBC utilization (conditional recommendation, low certainty in the evidence of effects).

Evidence Summary | One single-center RCT randomized young physicians to computerized decision support or no computerized decision support (control).[124] Three cohort studies assessed RBC usage before and after the intervention.[125-127] The RCT showed an increased appropriate transfusion rate (RBC, PLT, FFP) in the computerized decision support group compared with the control group (40.4% vs 32.5%; RR, 1.24 [95% CI, 1.13-1.37). The 3 cohort studies showed a significant reduction in overall or inappropriate RBC usage (RBC transfusions per 100 inpatient days, $P < .001$) after computerized decision support was implemented, in addition to a statistically significant reduction in overall or inappropriate RBC usage over time ($P = .01$). In addition, reduced 30-day readmission (5.2%) and mortality (2.2%) were found in 1 single-center trial (RR, 0.62 [95% CI, 0.56-0.69] for 30-day readmission and 0.60 [95% CI, 0.51-0.71] for mortality). The certainty in the effect estimates was low for the outcomes "appropriate transfusions" and "overall/inappropriate RBC usage" and was considered very low for 30-day readmission and mortality because of limited generalizability to other settings or countries.

Rationale for Recommendations 9 and 10 | Despite the low certainty in the effect of comprehensive PBM programs on RBC utilization, the panel formulated a conditional recommendation based on the moderate desirable effects on RBC utilization and the probably positive influence on equity, acceptability, and feasibility of these programs (eTable 3 in the Supplement).

Research Recommendations

In addition to the 10 clinical recommendations, the panels also developed 12 research recommendations (**Box 2**; eFigures 14-16 in the Supplement) to clarify unanswered priority questions in all 3 PBM topics. These research recommendations should guide clinical research in the field of PBM to address questions in future clinical trials.

Discussion

Blood components are lifesaving therapies but also scarce resources from human donors and must be used judiciously. Evidence-based RBC transfusion decision making can be challenging because high-quality published data are frequently lacking, studies may contain conflicting results, and recommendations are not easy to implement in clinical practice.

The ICC PBM group therefore decided to conduct a rigorous analysis of published data to define the current status of knowledge in this field, and, when possible, provide recommendations for clinical practice. The panel reviewed the current status of published evidence regarding preoperative anemia, RBC transfusion thresholds for adults, and implementation of PBM programs. The panel developed 10 clinical recommendations and 12 research recommendations using a rigorous process incorporating expert panel and audience participation. However, the quality of evidence in general was moderate to very low.

Accordingly, research recommendations were made for priority questions for areas in which evidence gaps remain (Box 2).

For preoperative anemia, a common finding in preoperative patients worldwide, 4 clinical recommendations were drafted. Preoperative anemia is an important risk factor for perioperative mortality and morbidity. The panel also stressed the need to detect and manage preoperative anemia with sufficient time before major elective surgery to ensure a clinical response. Evidence for the optimal treatment of preoperative anemia is less clear. Apart from preoperative iron supplementation in adult patients with iron-deficiency anemia undergoing elective surgery, other treatment options, such as RBC transfusion, have not been compared in a sufficiently large prospective randomized trial. Specifically, the conditional clinical recommendation 4 (consider ESAs and iron supplementation in adult preoperative patients with hemoglobin concentrations <13 g/dL undergoing elective major orthopedic surgery) elicited the greatest differences of all recommendations between the panel vote and the audience opinion poll. Because of the low-quality evidence on this topic and the different pattern in the vote of the audience (ambiguous pro and con votes: 28 [22%] accepted completely, 49 [39%]

accepted with some or major reservation, 49 [39%] rejected completely) from the panel vote, further studies are needed in this topic.

Another important finding related to this issue was the lack of agreement on the definition of hemoglobin level for the diagnosis of preoperative anemia. Published studies have used many different measurement tools and reference ranges as well as different hemoglobin thresholds for definition of anemia. The WHO definition of anemia, which is a hemoglobin level less than 13 g/dL in male patients and less than 12 g/dL in female patients, was derived in the 1960s from very small and low-quality studies.[128-134] In addition, several recent studies used point-of-care hemoglobin measurement techniques, which may produce results that differ significantly from laboratory hemoglobin "gold standard" results.[135,136] Therefore, although a hemoglobin concentration cutoff was considered in PICO question 2, the panel was unable to recommend a hemoglobin level for the diagnosis of preoperative anemia and recommended further research. Internationally accepted, evidence-based hemoglobin values for diagnosis of preoperative anemia need to be defined to make future treatment studies comparable.

For RBC transfusion thresholds, 2 strong clinical recommendations were formulated. The first was in clinically and hemodynamically stable adult patients in intensive care, including those with septic shock, who are not actively bleeding. In this group of patients, the panel recommended an RBC transfusion threshold of hemoglobin concentration less than 7 g/dL. This recommendation may not apply to patients in intensive care with acute coronary syndromes, other ischemic heart disease, or brain injury. Further research in the latter areas is recommended. For the second patient group, adult patients undergoing cardiac surgery, the panel recommended an RBC transfusion threshold of hemoglobin concentration less than 7.5 g/dL. For these 2 patient groups, there was no evidence of increased mortality or other undesirable effects when implementing the restrictive RBC transfusion threshold. There was a substantial reduction in RBC exposure and utilization applying the latter criteria. Even though the hemoglobin thresholds for RBC transfusion are slightly different between these 2 recommendations, they reflect the hemoglobin thresholds used in the included trials.

Conditional recommendations were made for 2 additional clinical scenarios. The first of these was for patients undergoing surgery for hip fracture, for whom the restrictive RBC transfusion threshold of hemoglobin level less than 8 g/dL represents the value used in the included trials. There was no effect on mortality or functional outcomes. However, most of the data were from a single trial and there is ongoing uncertainty regarding undesirable effects, in particular in patients with acute coronary syndromes. Additionally, a number of important questions remain: Can clinical trial results from patients with hip fracture be extrapolated to other older patients undergoing different orthopedic operations? Is this also true for all patients undergoing orthopedic operations? What about patients undergoing other nonorthopedic, noncardiac operations? Given the major evidence gaps in these areas, further research in these areas was also recommended. However, based on the evidence available, a restrictive RBC transfusion threshold approach seems safe and avoids overtransfusion in healthy, younger patients who require surgery.

Another patient population for which a recommendation on hemoglobin threshold for RBC transfusion was made are patients with acute upper gastrointestinal tract bleeding. For this scenario, a hemoglobin threshold of less than 7 to 8g/dL appears to be safe based on available evidence. However, the 2 recent large studies that reported lower mortality with a restrictive RBC transfusion strategy only included patients with acute upper gastrointestinal tract bleeding and at the same time excluded exsanguinating patients. There was, however, no evidence of undesirable effects. RBC exposure and utilization were reduced with a restrictive RBC transfusion approach.

In addition, based on the available evidence and aligned with other recent publications,[3,137] the panel decided to make an overarching recommendation for an RBC transfusion threshold of hemoglobin concentration 7 to 8 g/dL in most adult hospitalized patients, while underlining the importance of individual patient clinical assessment and integrating patient preferences. The panel also emphasized that measurement of hemoglobin concentration alone cannot replace clinical evaluation. Benefits of restrictive RBC transfusion strategies for patients, national blood supplies, and the blood donor population should be addressed in further studies.

Regarding PBM implementation, formulating a strong recommendation was not possible because of the lack of high-quality controlled prospective studies in contrast to the published observational studies. In particular, the risk of bias attributable to concurrent interventions or practice evolution that might have occurred during the study periods was believed to be important. Although evidence for reduction in RBC use resulting from PBM implementation was considered present, albeit with low certainty, evidence for reduction of platelet and plasma usage was found to be insufficient. Furthermore, the important issue of assessing reductions in inappropriate transfusion (as defined by current guidelines) within the reduction of blood product usage was often not addressed. Similarly, data pertaining to the effects of PBM implementation on important clinical end points such as adverse events and survival were weak.

Other notable current limitations to be addressed in future studies include the lack of concomitant health economic evaluation, including the costs of interventions as well as of the overall sustainability of PBM implementation. Specifically, the panel recommended further studies using reproducible definitions and clinical outcome parameters to provide clinicians and policy makers with evidence for comprehensive and well-structured PBM implementation strategies.

The results of this comprehensive review indicate that there are many gaps in knowledge about patient blood management. Current transfusion practice is often still based on a low level of evidence, with millions of blood units transfused daily. It is therefore important to translate international PBM guidelines into practical day-to-day recommendations for those questions for which there is strong evidence and to improve the evidence base for the remaining questions.

Limitations

This ICC PBM consensus process and conference had several limitations. First, there are challenges in interpretation of imprecision for all outcomes. Ideally, experts should discuss and decide whether the lower and upper confidence interval of an effect estimate is clinically meaningful, rather than only looking to statistical significance. For example, what is the implication if a restrictive RBC transfusion

threshold resulted in lower mortality compared with a liberal transfusion threshold (RR, 0.85 [95% CI, 0.70-1.03]) but the finding was not statistically significant?

Second, the experts also recognized considerable gaps in the published PBM evidence and recommended 5 areas in which further studies should be conducted to provide needed evidence. The paucity of high-quality clinical studies resulted in only 3 strong recommendations and 7 conditional or weak recommendations. For 3 of 10 recommendations, a moderate certainty in the evidence of effects was concluded, whereas in the remaining 7, only a low certainty in the evidence of effects was concluded (Tables 1-3). In addition, robust PBM evidence was only available from high-income countries.

Third, long-term outcome data for frail or older patients regarding quality-of-life or rehabilitation potential in relation to hemoglobin levels postoperatively or at discharge from the hospital are scarce but are the focus of the currently recruiting LIBERAL (Liberal Transfusion Strategy in Elderly Patients) trial (https://clinicaltrials.gov/ct2/show/NCT03369210). Similarly, although large amounts of RBCs are transfused to patients with hematologic and oncologic conditions, few data exist to guide clinical practice for these patient groups. This should also be a priority area for future research.

Fourth, not all of the PICO questions of interest could be addressed here. Pediatric transfusion issues were determined to warrant their own focused evaluation and these were therefore excluded from this first consensus. Similarly, platelet and plasma or plasma derivative studies were excluded from this first analysis, even though it is acknowledged that these products are frequently transfused along with RBCs. Further international consensus conferences should address these important clinical topics. In addition, PBM evidence was only analyzed for high-income countries; although hemotherapy in low- or middle-income countries comprises different, but no less important questions, even fewer high-quality data are available.

Fifth, the search strategy included studies published up to January 2018 only. However, we are unaware of any published studies since that time that would have changed our recommendations.

Conclusions

The 2018 PBM international consensus defined the current status of the PBM evidence base for clinical practice and research purposes and established 10 clinical recommendations and 12 research recommendations for preoperative anemia, RBC transfusion thresholds for adults, and implementation of PBM programs. The relative paucity of strong evidence to answer many of the PICO questions supports the need for additional research and an international consensus for accepted definitions and hemoglobin thresholds, as well as clinically meaningful end points for multicenter trials.

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Supplementary Online Content

Mueller MM, Van Remoortel H, Meybohm P, et al; ICC PBM Frankfurt 2018 Group. Patient blood management: recommendations from the 2018 Frankfurt Consensus Conference. *JAMA*. 10.1001/jama.2019.0554

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1

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Systematic Review and evidence summaries: Hans Van Remoortel (PhD) coordinated the conduct of the systematic reviews and was reviewer for PICO questions 2 and 10-17. He had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Jorien Laermans (PhD) was systematic reviewer for PICO 3, Anne-Catherine Vanhove (PhD) was systematic reviewer for PICO question 4-9, Kim Dockx (PhD) was reviewer for PICO question 1, Vere Borra (PhD), Bert Avau (PhD) and Hans Scheers (PhD) assisted in the screening of studies related to PICO question 16. All systematic reviewers are affiliated to the Centre for Evidence-Based Practice (CEBaP), Belgian Red Cross, Mechelen, Belgium.

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Scientific Committee composition

The American Association of Blood Banks (AABB), the International Society of Blood Transfusion (ISBT), the Deutsche Gesellschaft für Transfusionsmedizin und Immunhämatologie (German Blood Transfusion Society; DGTI), the Société Française de Transfusion Sanguine (French Blood Transfusion Society; SFTS), the Società Italiana di Medicina Transfusionale e Immunoematologia (Italian Blood Transfusion Society; SIMTI) and the European Blood Alliance (EBA) were the main sponsors and invited a scientific committee (SC° of 23 members: 22 experts in clinical hemother apy appointed by their respective professional organizations and one methodologist with expertise in developing evidence reviews and guidelines as well as in the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology from the Centre for Evidence-Based Practice (CEBaP) of the Belgian Red Cross.

The Conference was co-sponsored by

The American Association of Blood Banks (AABB)
The International Society of Blood Transfusion (ISBT)
Deutsche Gesellschaft für Transfusionsmedizin und Immunhämatologie (DGTI)
Société Française de Transfusion Sanguine (SFTS)
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French Society of Anesthesia and Critical Care, France (SFAR)
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eAppendix 2. PICO Questions, Search Strategies, and Selection Criteria

PREOPERATIVE ANAEMIA

PICO 1 – ADVERSE EVENTS

In elective surgery patients [Population], is preoperative anaemia [Intervention/Risk factor] a risk factor for adverse clinical or economic outcomes [Outcome] compared to no preoperative anaemia [Comparison]? [1-35]

PICO 1 - Search strategies

MEDLINE (via PubMed interface) using the following search strategy:

1. "Pre-operative"[TIAB] OR preoperative[TIAB] OR "Preoperative Period"[Mesh] OR "Preoperative Care"[Mesh]
2. "Anemia"[Mesh] OR "Anemia"[TIAB] OR "Anaemia"[TIAB]
3. 1 AND 2
4. “Elective surgical procedures”[Mesh] OR elective*[TIAB]
5. 3 AND 4

Embase (via Embase.com interface) using the following search strategy:

1. ‘Pre-operative’:ab,ti OR preoperative:ab,ti OR ‘Preoperative Period’/exp OR ‘Preoperative Care’/exp
2. Anemia/exp OR Anemia:ab,ti OR Anaemia:ab,ti
3. 1 AND 2
4. ‘Elective surgery’/exp OR elective*:ab,ti
5. 3 AND 4

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(‘Pre-operative’ OR preoperative) AND (Anemia OR Anaemia) AND (elective)

PICO 1 - Selection criteria

Population: ***Included:*** preoperative elective surgery adult patients divided into a) elective surgery in malignant disorders (all carcinomas leading to a potential blood loss (e.g. gastrointestinal or urogenital tumours) or an infiltration of the bone marrow (e.g. metastasis in tumours) and b) elective surgery in non-malignant disorders (all other non-malignant diseases in preoperative anaemic patients undergoing elective surgery) and also divided in c.) high risk of bleeding operations and d.) low risk of bleeding operations. ***Excluded:*** burns, obstetrics, trauma or transplant surgery.

Intervention/risk factor: preoperative anaemia. We will include studies that used a haemoglobin or haematocrit definition (not restricted to the WHO definition).

Comparison: no preoperative anaemia

Outcomes:

Primary outcomes: 30-day and in-hospital mortality

Secondary outcomes: acute myocardial infarction, acute ischaemic stroke, acute kidney injury, acute mesenteric ischemia and acute peripheral vascular ischemia

Language: English, French and German

PICO 2 – DEFINITION

In elective surgery preoperative patients [Population], should Hb of 130 g/L (Index test) (versus [comparator test] [Comparison]) be used to diagnose anemia [Outcome]? [36]

PICO 2 - Search strategies

MEDLINE (via PubMed interface) for diagnostic studies using the following search strategy:

1. "Elective Surgical Procedures"[Mesh] OR surg*[TIAB] OR preoperative[TIAB] OR pre-operative[TIAB]
2. "Anemia/diagnosis"[Mesh] OR "Anemia/diagnostic imaging"[Mesh] OR anemia[TIAB] OR anaemia[TIAB]
3. “Sensitivity and Specificity”[Mesh] OR “sensitivity”[TIAB] OR “specificity”[TIAB] OR “pre-test probability”[TIAB] OR “pretest probability”[TIAB] OR “post-test probability”[TIAB] OR “posttest probability”[TIAB] OR “predictive value”[TIAB] OR “predictive values”[TIAB] OR “likelihood ratio”[TIAB] OR “likelihood ratios”[TIAB]
4. 1-3 AND

Embase (via Embase.com interface) using the following search strategy:

1. ‘Elective surgery’/exp OR surg*:ab,ti OR ‘preoperative’:ab,ti OR ‘’pre-operative’:ab,ti
2. Anemia/exp OR Anemia:ab,ti OR Anaemia:ab,ti
3. ‘diagnostic accuracy’/exp OR ‘sensitivity and specificity’/exp OR sensitivity:ab,ti OR specificity:ab,ti OR ((‘pre-test’ OR pretest) NEAR/5 probability):ab,ti OR ‘post-test probability’:ab,ti OR ‘posttest probability’:ab,ti OR ‘predictive value’:ab,ti OR ‘predictive values’:ab,ti OR ‘likelihood ratio’:ab,ti OR ‘likelihood ratios’:ab,ti
5. 1-3 AND

Transfusion Evidence Library

(‘Pre-operative’ OR preoperative) AND (Anemia OR Anaemia) AND (sensitivity OR specificity OR pre-test probability OR pretest probability OR post-test probability OR posttest probability OR predictive value OR predictive values OR likelihood ratio OR likelihood ratios)

PICO 2 - Selection criteria

Population: *Include:* Pre-operative elective surgery patients

Index test: *Include:* Hb levels according to WHO definition anaemia (i.e. Hb <120 g/dL (adult females) and Hb <130 g/dL (adult males) or other Hb levels

Comparator test: *Include:* other Hb levels

Outcome: *Include:* diagnosis of preoperative anaemia (true positives, false positives, true negatives, false negatives, sensitivity, specificity), level of agreement between two methods (i.e. level of agreement).

Study design: *Include:* A systematic review: inclusion of diagnostic studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase were searched. If no systematic review of diagnostic studies is present, individual diagnostic studies (randomized controlled trial or diagnostic accuracy study) will be included.

PICO 3 – MANAGEMENT

In elective surgery patients with preoperative anemia [Population], is the use of red blood cell transfusion or iron supplementation and/or erythrocyte stimulating agents [Intervention] effective to improve clinical and economic outcomes [Outcome] compared to no intervention/placebo/standard of care [Comparison]? [37-62]

PICO 3 - Search strategies

The Cochrane Library (controlled trials) using the following search strategy:

1. [mh "Preoperative Period"] OR [mh "Preoperative care"] OR preoperat*:ti,ab,kw OR pre-operat*:ti,ab,kw OR presurg*:ti,ab,kw OR pre-surg*:ti,ab,kw OR (before NEXT surger*):ti,ab,kw OR (before NEXT surgical*):ti,ab,kw OR (before NEXT operati*):ti,ab,kw OR ("prior to" NEXT surger*):ti,ab,kw OR ("prior to" NEXT surgical*):ti,ab,kw OR ("prior to" NEXT operati*):ti,ab,kw
2. [mh "Anemia"] OR anemi*:ti,ab,kw OR anaemi*:ti,ab,kw
3. [mh "Iron"] OR [mh "Iron Compounds"] OR iron:ti,ab,kw OR dextran:ti,ab,kw OR Venofer:ti,ab,kw OR ferrous:ti,ab,kw OR ferric:ti,ab,kw OR ferrlecit:ti,ab,kw OR [mh "Erythropoietin"] OR [mh "Hematinics"] OR epo:ti,ab,kw OR erythropoiet*:ti,ab,kw OR ("erythropoiesis-stimulating" NEXT agent*):ti,ab,kw OR hematopoiet*¨:ti,ab,kw OR haematopoiet*:ti,ab,kw OR hemopoiet*:ti,ab,kw OR haemopoiet*:ti,ab,kw OR hematinic*:ti,ab,kw OR haematinic*:ti,ab,kw OR "epoetin alfa":ti,ab,kw OR Procrit:ti,ab,kw OR Epogen:ti,ab,kw OR "epoetin beta":ti,ab,kw OR NeoRecormon:ti,ab,kw OR "darbepoetin alfa":ti,ab,kw OR Mircera:ti,ab,kw OR [mh "Blood Transfusion"] OR ((blood:ti,ab,kw OR erythrocyte*:ti,ab,kw OR (red NEXT cell*):ti,ab,kw OR ("red blood" NEXT cell*):ti,ab,kw OR RBC*:ti,ab,kw) AND (transfus*:ti,ab,kw OR infus*:ti,ab,kw OR unit*:ti,ab,kw OR therap*:ti,ab,kw)) OR hemotransfus*:ti,ab,kw OR haemotransfus*:ti,ab,kw OR hemotherap*:ti,ab,kw OR haemotherap*:ti,ab,kw OR hypertransfus*:ti,ab,kw
4. 1-3 AND

MEDLINE (via PubMed interface) using the following search strategy:

1. "Preoperative Period"[Mesh] OR "Preoperative Care"[Mesh] OR preoperat*[TIAB] OR pre-operat*[TIAB] OR presurg*[TIAB] OR pre-surg*[TIAB] OR before surger*[TIAB] OR before surgical*[TIAB] OR before operati*[TIAB] OR prior to surger*[TIAB] OR prior to surgical*[TIAB] OR prior to operati*[TIAB]
2. "Anemia"[Mesh] OR anemi*[TIAB] OR anaemi*[TIAB]
3. "Iron"[Mesh] OR "Iron Compounds"[Mesh] OR iron[TIAB] OR dextran[TIAB] OR Venofer[TIAB] OR ferrous[TIAB] OR ferric[TIAB] OR ferrlecit[TIAB] OR "Erythropoietin"[Mesh] OR "Hematinics"[Mesh] OR epo[TIAB] OR erythropoiet*[TIAB] OR erythropoiesis-stimulating agent*[TIAB] OR hematopoiet*[TIAB] OR haematopoiet*[TIAB] OR hemopoiet*[TIAB] OR haemopoiet*[TIAB] OR hematinic*[TIAB] OR haematinic*[TIAB] OR "epoetin alfa"[TIAB] OR Procrit[TIAB] OR Epogen[TIAB] OR "epoetin beta"[TIAB] OR

NeoRecormon[TIAB] OR “darbepoetin alfa”[TIAB] OR Mircera[TIAB] OR “Blood transfusion”[Mesh] OR ((blood[TIAB] OR erythrocyte*[TIAB] OR red cell*[TIAB] OR red blood cell*[TIAB] OR RBC*[TIAB]) AND (transfus*[TIAB] OR infus*[TIAB] OR unit*[TIAB] OR therap*[TIAB])) OR hemotransfus*[TIAB] OR haemotransfus*[TIAB] OR hemotherap*[TIAB] OR haemotherap*[TIAB] OR hypertransfus*[TIAB]

4. (("Meta-Analysis as Topic"[Mesh] OR meta analy*[TIAB] OR metaanaly*[TIAB] OR "Meta-Analysis"[PT] OR systematic review*[TIAB] OR systematic overview*[TIAB] OR "Review Literature as Topic"[Mesh]) OR (cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR “science citation index”[TIAB] OR bids[TIAB] OR cancerlit[TIAB]) OR (reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR “relevant journals”[TIAB] OR manual search*[TIAB]) OR ((“selection criteria”[TIAB] OR “data extraction”[TIAB]) AND "Review"[PT])) NOT ("Comment"[PT] OR "Letter"[PT] OR "Editorial"[PT] OR ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh])))
5. “Controlled Clinical Trial”[PT] OR random*[TIAB] OR controll*[TIAB] OR “intervention study”[TIAB] OR “experimental study”[TIAB] OR “comparative study”[TIAB]
6. 1-4 AND (systematic reviews)
7. 1 AND 2 AND 3 AND 5 (controlled clinical trials)

Embase (via Embase.com interface) using the following search strategy:

1. ‘Preoperative period’/exp OR ‘Preoperative care’/exp OR ‘Preoperative evaluation’/exp OR preoperat*:ab,ti OR pre-operat*:ab,ti OR presurg*:ab,ti OR pre-surg*:ab,ti OR (before NEXT/1 surger*):ab,ti OR (before NEXT/1 surgical*):ab,ti OR (before NEXT/1 operati*):ab,ti OR (‘prior to’ NEXT/1 surger*):ab,ti OR (‘prior to’ NEXT/1 surgical*):ab,ti OR (‘prior to’ NEXT/1 operati*):ab,ti
2. ‘Anemia’/exp OR anemi*:ab,ti OR anaemi*:ab,ti
3. ‘Antianemic agent’/exp OR ‘Iron’/exp OR ‘Iron derivative’/exp OR iron:ab,ti OR dextran:ab,ti OR Venofer:ab,ti OR ferrous:ab,ti OR ferric:ab,ti OR ferrlecit:ab,ti OR epo:ab,ti OR erythropoiet*:ab,ti OR (‘erythropoiesis-stimulating’ NEXT/1 agent*):ab,ti OR hematopoiet*:ab,ti OR haematopoiet*:ab,ti OR hemopoiet*:ab,ti OR haemopoiet*:ab,ti OR hematinic*:ab,ti OR haematinic*:ab,ti OR ‘epoetin alfa’:ab,ti OR Procrit:ab,ti OR Epogen:ab,ti OR ‘epoetin beta’:ab,ti OR NeoRecormon:ab,ti OR ‘darbepoetin alfa’:ab,ti OR Mircera:ab,ti OR ‘Blood transfusion’/exp OR ((blood:ab,ti OR erythrocyte*:ab,ti OR (red NEXT/1 cell*):ab,ti OR (‘red blood’ NEXT/1 cell*):ab,ti OR RBC*:ab,ti) AND (transfus*:ab,ti OR infus*:ab,ti OR unit*:ab,ti OR therap*:ab,ti)) OR hemotransfus*:ab,ti OR haemotransfus*:ab,ti OR hemotherap*:ab,ti OR haemotherap*:ab,ti OR hypertransfus*:ab,ti
4. (('meta analysis (topic)'/exp OR 'meta analysis'/exp OR (meta NEXT/1 analy*):ab,ti OR metaanalys*:ab,ti OR ‘systematic review (topic)’/exp OR ‘systematic review’/exp OR (systematic NEXT/1 review*):ab,ti OR (systematic NEXT/1 overview*):ab,ti) OR (cancerlit:ab,ti OR cochrane:ab,ti OR embase:ab,ti OR psychlit:ab,ti OR psyclit:ab,ti OR psychinfo:ab,ti OR psycinfo:ab,ti OR cinahl:ab,ti OR cinhal:ab,ti OR 'science citation index':ab,ti OR bids:ab,ti) OR

('reference list*':ab,ti OR bibliograph*:ab,ti OR hand-search*:ab,ti OR (manual NEXT/1 search*):ab,ti OR 'relevant journals':ab,ti) OR (('data extraction':ab,ti OR 'selection criteria':ab,ti) AND review/it)) NOT (letter/it OR editorial/it OR ('animal'/exp NOT ('animal'/exp AND 'human'/exp)))

5. Controlled clinical trial/exp OR random*:ab,ti OR controll*:ab,ti OR "intervention study":ab,ti OR "experimental study":ab,ti OR "comparative study":ab,ti
6. 1-4 AND (systematic reviews)
7. 1 AND 2 AND 3 AND 5 (controlled clinical trials)

Transfusion Evidence Library using the following search strategy:

1. Subject Area < Clinical Practice < Management of anaemia
2. preoperative OR pre-operative OR presurgical OR pre-surgical OR "before surgery" OR "before surgical" OR "before operating" OR "prior to surgery" OR "prior to surgical" OR "prior to operating"
3. Study design < Systematic review or Randomized Controlled Trial

1-3 AND

PICO 3 – Selection criteria

Population: *Included:* preoperative elective surgery adult patients with anemia divided into a) elective surgery in malignant disorders (all carcinomas leading to a potential blood loss (e.g. gastrointestinal or urogenital tumors) or an infiltration of the bone marrow (e.g. metastasis in tumors) and b) elective surgery in non-malignant disorders (all other non-malignant diseases in preoperative anemic patients undergoing elective surgery), and also divided in c) high risk of bleeding operations and d) low risk of bleeding operations. Following the WHO definition, preoperative anemia is defined as haemoglobin (Hb) levels<13 g/dl (adult men) or Hb<12 g/dl (adult women). Studies were included if the Hb levels of the patients were covered by this definition. If studies also included patients whose Hb levels did not fall within the range of the WHO definition (e.g. 11-16 g/dl), only data from the most relevant subgroups were extracted if possible (e.g. <11.5, 11.5-12.4 and 12.5-13.4 g/dl). If no subgroup analyses were performed, the data from all patients were extracted. *Excluded:* non-elective surgery patients, non-anemic elective surgery patients, elective surgery patients with preoperative anemia which is not formally/explicitly defined, elective surgery patients with sickle-cell anemia or thalassemia, pediatric patients.

Intervention: *Included:* Intervention 1: transfusion; Intervention 2: iron supplementation (intravenous or oral); Intervention 3: ESA; Intervention 4: iron supplementation + ESA. Interventions that include the use of vitamins (e.g. folic acid, vitamin B12) as a general measure to support the production of erythrocytes in the bone marrow, are included. *Excluded:* other interventions to manage anemia such as preoperative (autologous or

homologous) transfusion and the use of tranexamic acid. Also excluded are interventions that combine one of the interventions of interest (iron supplementation and/or ESA) with these other treatments (e.g. combination of EPO and tranexamic acid).

Comparison: *Included*: Comparison 1-4: no treatment, placebo, standard of care. *Excluded:* autologous blood donation, other interventions to treat anemia such as the use of tranexamic acid.

Outcome:

Included:

Primary outcomes:

- (All-cause) mortality
- Anemia-associated ischaemic events, defined as:
    - acute myocardial infarction;
    - acute ischaemic stroke;
    - acute kidney injury;
    - acute mesenteric ischaemia;
    - acute peripheral vascular ischaemia.

Secondary outcomes:

- Length of hospital stay
- Any type of reported infection. A patient was considered to have an infection when one of the following items existed (Weber, 2005):
    - Wound infection: redness, purulent exudate or positive culture of wound fluid;
    - Wound abscess: drainage of abscess or spontaneous discharge of pus;
    - Abscess or infected haematoma in surgical area or near the implant: positive culture after collection of pus or re-exploration;
    - Urinary tract infection: abnormal urine sediment with white blood cells and/or a positive urine culture and/or clinical signs;
    - Respiratory tract infection: clinical signs according to the investigator and/or a positive sputum culture leading to treatment with antibiotics;
    - Pneumonia: clinical or radiological signs of a pulmonary infiltrate;
    - Bacteraemia: typical clinical signs (e.g. fever) and positive blood culture.
- Red blood cell utilization (units transfused, number of patients receiving a transfusion).
- Thromboembolic events, defined as deep venous/arterial thrombosis and/or pulmonary embolism.

Excluded: Hb levels, drug-related adverse events.

Study design: *Included*: Intervention 1 (transfusion): individual experimental studies; Intervention 2-3-4 (Iron and/or ESA): experimental studies that were included in the systematic reviews identified from the systematic review search, *i.e.* randomised controlled trials, quasi-randomised controlled trials, non-randomised controlled trials, controlled before and after study, or controlled interrupted time series.

For comparisons 2 and 3, the experimental studies did not provide sufficient data. Therefore, for these 2 comparisons, observational cohort studies were also included.

Excluded: studies reporting no quantitative data, studies reporting only means, but no standard deviations, effect sizes and/or p-values.

Language: English, French and German

RBC TRANSFUSION TRIGGERS

PICO 4 – ADULT INTENSIVE CARE PATIENTS

In critically ill, but clinically stable adult intensive care patients [Population], is the use of a restrictive transfusion threshold [Intervention] effective to reduce mortality and improve other clinical outcomes [Outcome] compared to a liberal transfusion threshold [Comparison]? [63-66]

PICO 4,5,6,7,8,9 - Search strategies

The Cochrane systematic review by Carson et al. (2016) and its updated/unpublished version (2018) served as a basis. An additional search in 4 databases was conducted to:

- Identify relevant experimental studies (RCT's) published after the search by Carson et al. (13th November 2017)
- Identify observational studies in case no experimental studies were available.

Databases

The Cochrane Library (systematic reviews and controlled trials) using the following search strategy (from May 2016 until June 2017):

#1 MeSH descriptor: [Blood Transfusion] this term only and with qualifier(s): [Methods - MT, Standards - ST, Trends - TD]

#2 MeSH descriptor: [Erythrocyte Transfusion] this term only and with qualifier(s): [Methods - MT, Standards - ST]

#3 ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) near/5 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practic* or indicat* or strateg* or regimen* or criteri* or standard* or management or program*))

#4 ((h?emoglobin or h?ematocrit or HB or HCT) near/5 (polic* or practic* or protocol* or trigger* or threshold* or maintain* or indicator* or strateg* or criteri* or standard*))

#5 (blood near/3 (management or program*))

#6 ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) and (critical* or intensive* or h?emorrhag* or bleed*)):ti

#7 #1 or #2 or #3 or #4 or #5 or #6

MEDLINE (via PubMed interface) for systematic reviews and experimental and observational studies using the following search strategy (from 27th May 2016 until 30th June 2017):

#1 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*) AND (trigger*[TI] OR threshold*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR aggressive*[TI] OR conservative*[TI] OR prophylactic*[TI] OR limit*[TI] OR protocol*[TI] OR policy[TI] OR policies[TI] OR practic*[TI] OR indicat*[TI] OR strateg*[TI] OR regimen*[TI] OR criteri*[TI] OR standard*[TI] OR management[TI] OR program*[TI]))

#2 ((hemoglobin[TI] OR haemoglobin[TI] OR hematocrit[TI] OR haematocrit[TI] OR HB[TI] OR HCT[TI]) AND (polic*[TI] OR practic*[TI] OR protocol*[TI] OR trigger*[TI] OR threshold*[TI] OR maintain*[TI] OR indicator*[TI] OR strateg*[TI] OR criteri*[TI] OR standard*[TI]))
#3 (blood[TI] AND (management[TI] OR program*[TI]))
#4 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*[TI]) and (critical*[TI] OR intensive*[TI] OR hemorrhag*[TI] OR haemorrhage*[TI] OR bleed*[TI]))
#5 #1 OR #2 OR #3 OR #4

Embase (via Embase.com interface) using the following search strategy (from 27th May 2016 until 30th June 2017):
#1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND (trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti))
#2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR standard*:ti))
#3 (blood:ti AND (management:ti OR program*:ti))
#4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and (critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti))
#5 #1 OR #2 OR #3 OR #4

Transfusion evidence library (from 2016 until 2017)
Red Cells AND (trigger OR threshold OR target OR restrict OR restrictive OR liberal OR aggressive OR aggressively OR conservative OR prophylactic OR limit OR limits OR protocol OR policy OR policies OR practice OR indicator OR strategy OR strategies OR regimen OR criteria OR standard OR management OR program OR programme) OR Red Cells AND title:(critical OR critically OR intensive OR intensively OR hemorrhage OR haemorrhage OR hemorrhaging OR haemorrhaging OR bleed OR bleeding)

PICO 4,5,6,7,8,9 – Selection criteria

Population (PICO 4): Included: critically ill but clinically stable adult intensive care patients. Excluded: adult intensive care patients that are not clinically/haemodynamically stable, children or neonates.

Population (PICO 5): Included: elderly high risk (cardiovascular) patients undergoing a) orthopaedic surgery (e.g. knee or hip surgery) or b) non-cardiac surgery (e.g. vascular surgery and abdominal surgery).

Population (PICO 6): Included: patients with an acute gastrointestinal bleeding.

Population (PICO 7): Included: patients with symptomatic coronary heart disease.

Population (PICO 8): Included: patients with septic shock in different settings (e.g. intensive care unit).

Population (PICO 9): Included: adult patients undergoing cardiac surgery.

Population (PICO 10): Included: adult haematological patients, a.) acute malignant haematological diseases like acute lymphatic leukemia (ALL), etc. under different therapeutic regimen: aa.) chemotherapy, ab.) hematopoietic stem cell transplantation; b.) chronic malignant haematological diseases (extremely rare in children) c.) hereditary haematological diseases (typically "benign") associated with anemia like sickle cell disease, thalassemia, etc an increasing problem in Europe! Based on the amount of evidence that will be identified, different subgroups analyses (e.g. sickle cell disease versus thalassemia) will be conducted. Excluded: children, infants or neonates.

Population (PICO 11): Included: aa: chemotherapy ab: surgery ac: radiotherapy; ad: combinations of aa to ac.

Population (PICO 12): Included: aa. traumatic brain injury; ab. Traumatic injury of the spinal cord; ac. Increase in intracranial pressure

Population (PICO 13): Included: a.) acute ischemic stroke; b.) acute intracerebral bleeding: ba: old patients (> 50yrs); bb: young pts. (< 50 yrs)

Population (PICO 14): Included: patients with acute bleeding: clinically instable bleeding patients undergoing massive transfusion: a.) trauma-induced bleeding; b.) non-trauma induced bleeding

Intervention: the use of a restrictive transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A restrictive transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 7 g/dL to 8 g/dL.

Comparison: the use of a liberal transfusion threshold as a mean of guiding allogeneic or autologous RBC transfusion. A liberal transfusion threshold most often refers to administration of blood transfusion when the haemoglobin level falls below 9 g/dL to 10 g/dL.

Outcomes: *Primary*: Mortality (e.g. 30-day mortality or in-hospital mortality, during hospital admission, at 90 days or long term) or other clinical outcomes including outcomes related to RBC transfusion use (i.e. proportion of participants exposed to transfusion, participants exposed to allogeneic or autologous transfusion, units of blood transfused (in those receiving any transfusion)) and *Secondary*: Morbidity-related outcomes that occurred during

hospitalisation (i.e. cardiac events, non-fatal and fatal myocardial infarction, congestive heart failure, stroke, renal injury, pneumonia, septic shock, rebleeding, infection, and fatigue).

Study design: The following study designs were included: 1) (cluster) randomized controlled trials included in the Cochrane review by Carson et al (May 2016) or other systematic reviews identified in the update and 2) (cluster) randomized controlled trials identified in the update. To examine the evidence for the effect of transfusion threshold on the use of RBC transfusions and the evidence for any change in clinical outcomes, we included randomized controlled trials if the comparison groups were assigned on the basis of a transfusion 'threshold' (also known as a 'trigger'), defined as a haemoglobin or haematocrit level (without haemodynamic instability) that had to be reached before a RBC transfusion was administered. We required that control group participants had to have been either transfused with allogeneic or autologous red blood cells, or both, at higher haemoglobin or haematocrit levels (transfusion threshold) than the intervention group, or transfused in accordance with current transfusion practices, which may not have included a well-defined transfusion threshold, but involved liberal rather than restrictive transfusion practices. We excluded trials that were not designed to include any clinical outcomes.

PICO 5 – ORTHOPAEDIC AND NON-CARDIAC SURGERY

In elderly high risk (cardiovascular) patients undergoing orthopaedic or non-cardiac surgery [Population], is the use of a restrictive transfusion threshold [Intervention] effective to reduce mortality and improve other clinical outcomes [Outcome] compared to a liberal transfusion threshold [Comparison]? [67-78]

PICO 5 – Search strategies

See PICO 4

PICO 5 – Selection criteria

See PICO 4

PICO 6 – ACUTE GASTROINTESTINAL BLEEDING

In patients with an acute gastrointestinal bleeding [Population], is the use of a restrictive transfusion threshold [Intervention] effective to reduce mortality and improve other clinical outcomes [Outcome] compared to a liberal transfusion threshold [Comparison]? [79-81]

PICO 6 – Search strategies

See PICO 4

PICO 6 – Selection criteria

See PICO 4

PICO 7 – CORONARY HEART DISEASE

In patients with symptomatic coronary heart disease [Population], is the use of a restrictive transfusion threshold [Intervention] effective to reduce mortality and improve other clinical outcomes [Outcome] compared to a liberal transfusion threshold [Comparison]? [82,83]

PICO 7 – Search strategies

See PICO 4

PICO 7 – Selection criteria

See PICO 4

PICO 8 – SEPTIC SHOCK

In patients with septic shock [Population], is the use of a restrictive transfusion threshold [Intervention] effective to reduce mortality and improve other clinical outcomes [Outcome] compared to a liberal transfusion threshold [Comparison]? [84,85]

PICO 8 – Search strategies

See PICO 4

PICO 8 – Selection criteria

See PICO 4

PICO 9 – CARDIAC SURGERY

In patients undergoing cardiac surgery [Population], is the use of a restrictive transfusion threshold [Intervention] effective to reduce mortality and improve other clinical outcomes [Outcome] compared to a liberal transfusion threshold [Comparison]? [86-93]

PICO 9 – Search strategies

See PICO 4

PICO 9 – Selection criteria

See PICO 4

PICO 10 – ADULT HAEMATOLOGICAL PATIENTS

In adult haematological patients [Population], is the use of a restrictive transfusion threshold [Intervention] effective to reduce mortality and improve other clinical outcomes [Outcome] compared to a liberal transfusion threshold [Comparison]? [94,95]

PICO 10 - Search strategies

The Cochrane systematic review by Carson et al. (2016) and its updated/unpublished version (2018) served as a basis. An additional search in 4 databases was conducted to:

- Identify relevant experimental studies (RCT's) published after the search by Carson et al. (13th November 2017)
- Identify observational studies in case no experimental studies were available.

Databases

The Cochrane Library (systematic reviews and controlled trials) using the following search strategy:

Systematic reviews

#1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND (trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti))

#2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR standard*:ti))

#3 (blood:ti AND (management:ti OR program*:ti))

#4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and (critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti))

#5 #1 OR #2 OR #3 OR #4

Individual experimental studies

#1 (((erythrocyte*:ti OR blood:ti) AND (unit*:ti AND trigger*:ti OR level*:ti OR threshold*:ti OR rule*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR requir*:ti OR reduc*:ti OR limit*:ti)) OR (hemotransfus*:ti OR haemotransfus*:ti OR hemotherap*:ti OR haemotherap*:ti OR "red cell*":ti OR "red blood cell*":ti OR RBC*:ti OR transfus*:ti))

#2 thrombocytopeni*:ti OR thrombocytopaeni*:ti OR leukemi*:ti OR leukaemi*:ti OR lymphom*:ti OR "aplastic anemia":ti OR "aplastic anaemia":ti OR myelodysplas*:ti OR myeloproliferat*:ti OR myeloma:ti OR lymphogranulomato*:ti OR histiocy*:ti OR granulom*:ti OR thrombocythemi*:ti OR thrombocythaemi*:ti OR polycythemi*:ti OR polycythaemi*:ti OR myelofibros*:ti OR AML:ti OR CLL:ti OR CML:ti OR Hodgkin*:ti OR burkitt*:ti OR lymphosarcom*:ti OR brill-symmer*:ti OR sezary:ti OR ((haematolog*:ti OR hematolog*:ti OR blood:ti OR red cell*:ti OR white cell*:ti OR marrow:ti OR platelet*:ti) AND (malignan*:ti OR oncolog*:ti OR cancer*:ti OR neoplasm*:ti OR carcinoma*:ti)) OR chemotherap*:ti OR radiotherap*:ti OR chemoradiotherap*:ti OR "stem cell":ti OR "stem cells" OR "progenitor cell":ti OR "progenitor cells":ti OR bone marrow transplant*:ti OR bone marrow graft*:ti OR "bone marrow rescue":ti OR rituximab:ti OR antineoplast*:ti OR anti-neoplast*:ti OR ASCT:ti OR ABMT:ti OR PBPC:ti OR PBSCT:ti OR PSCT:ti OR BMT:ti OR SCT:ti OR HSCT:ti OR

“haematology patients”:ti OR “hematology patients”:ti OR “haematological patients”:ti OR “hematological patients”:ti OR “hemato-oncology patients”:ti OR “haemato-oncology patients”:ti OR remission:ti OR ((consolidat*:ti OR induct*:ti OR maintenance:ti OR conditioning*:ti) AND (therap*:ti OR treat*:ti OR regimen*:ti OR patient*:ti)) OR ((cytosta*:ti OR cytotox*:ti) AND (therap*:ti OR treat*:ti OR regimen*:ti)) OR ((multimodal*:ti OR multi-modal*:ti) AND (treat*:ti OR therap*:ti)) OR (combi*:ti AND modalit*:ti) OR (allograft*:ti OR allo-graft*:ti OR allotransplant*:ti OR allo-transplant*:ti OR ((allogen*:ti OR allo-gen*:ti) AND (transplant*:ti OR trasplant*:ti OR graft*:ti OR rescue*)) OR homograft*:ti OR homo-graft*:ti OR homolog*:ti OR homotransplant*:ti OR homo-transplant*:ti OR homotrasplant*:ti OR homo trasplant*:ti) OR (autograft*:ti OR autograft*:ti OR autotransplant*:ti OR auto-transplant*:ti OR mini-transplant*:ti) OR (autolog*:ti AND (transplant*:ti OR graft*:ti OR trasplant*:ti OR rescu*:ti))

#3 #1 AND #2

MEDLINE (via PubMed interface) for systematic reviews and experimental and observational studies using the following search strategy:

Systematic reviews

#1 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*) AND (trigger*[TI] OR threshold*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR aggressive*[TI] OR conservative*[TI] OR prophylactic*[TI] OR limit*[TI] OR protocol*[TI] OR policy[TI] OR policies[TI] OR practic*[TI] OR indicat*[TI] OR strateg*[TI] OR regimen*[TI] OR criteri*[TI] OR standard*[TI] OR management[TI] OR program*[TI]))

#2 ((hemoglobin[TI] OR haemoglobin[TI] OR hematocrit[TI] OR haematocrit[TI] OR HB[TI] OR HCT[TI]) AND (polic*[TI] OR practic*[TI] OR protocol*[TI] OR trigger*[TI] OR threshold*[TI] OR maintain*[TI] OR indicator*[TI] OR strateg*[TI] OR criteri*[TI] OR standard*[TI]))

#3 (blood[TI] AND (management[TI] OR program*[TI]))

#4 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*[TI]) and (critical*[TI] OR intensive*[TI] OR hemorrhag*[TI] OR haemorrhage*[TI] OR bleed*[TI]))

#5 #1 OR #2 OR #3 OR #4

#6 ((((((((((Meta-Analysis as Topic[Mesh])) OR ((meta analy*[TIAB]))) OR ((metaanaly*[TIAB]))) OR ((Meta-Analysis[Publication Type]))) OR ((systematic review*[TIAB] OR systematic overview*[TIAB]))) OR ((Review Literature as Topic[Mesh])))) OR ((cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB]))) OR ((reference list*[TIAB] OR

bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB])))) OR ((((selection criteria[TIAB] OR data extraction[TIAB])) AND ((Review[PT]))))))) NOT ((Comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT (animal[Mesh] AND human[Mesh])))
#7 #5 AND #6

Individual experimental/observational studies

#1 (((erythrocyte*[TI] OR blood[TI]) AND (unit*[TI] AND trigger*[TI] OR level*[TI] OR threshold*[TI] OR rule*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR requir*[TI] OR reduc*[TI] OR limit*[TI])) OR (hemotransfus*[TI] OR haemotransfus*[TI] OR hemotherap*[TI] OR haemotherap*[TI] OR "red cell*"[TI]OR "red blood cell*"[TI] OR RBC*[TI] OR transfus*[TI]))
#2 (thrombocytopeni*[TI] OR thrombocytopaeni*[TI] OR leukemi*[TI] OR leukaemi*[TI] OR lymphom*[TI] OR "aplastic anemia"[TI] OR "aplastic anaemia"[TI] OR myelodysplas*[TI] OR myeloproliferat*[TI] OR myeloma[TI] OR lymphogranulomato*[TI] OR histiocy*[TI] OR granulom*[TI] OR thrombocythemi*[TI] OR thrombocythaemi*[TI] OR polycythemi*[TI] OR polycythaemi*[TI] OR myelofibros*[TI] OR AML[TI] OR CLL[TI] OR CML[TI] OR Hodgkin*[TI] OR burkitt*[TI] OR lymphosarcom*[TI] OR brill-symmer*[TI] OR sezary[TI] OR ((haematolog*[TI] OR hematolog*[TI] OR blood[TI] OR red cell*[TI] OR white cell*[TI] OR marrow[TI] OR platelet*[TI]) AND (malignan*[TI] OR oncolog*[TI] OR cancer*[TI] OR neoplasm*[TI] OR carcinoma*[TI])) OR chemotherap*[TI] OR radiotherap*[TI] OR chemoradiotherap*[TI] OR "stem cell"[TI] OR "stem cells" OR "progenitor cell"[TI] OR "progenitor cells"[TI] OR bone marrow transplant*[TI] OR bone marrow graft*[TI] OR "bone marrow rescue"[TI] OR rituximab[TI] OR antineoplast*[TI] OR anti-neoplast*[TI] OR ASCT[TI] OR ABMT[TI] OR PBPC[TI] OR PBSCT[TI] OR PSCT[TI] OR BMT[TI] OR SCT[TI] OR HSCT[TI] OR "haematology patients"[TI] OR "hematology patients"[TI] OR "haematological patients"[TI] OR "hematological patients"[TI] OR "hemato-oncology patients"[TI] OR "haemato-oncology patients"[TI] OR remission[TI] OR ((consolidat*[TI] OR induct*[TI] OR maintenance[TI] OR conditioning*[TI]) AND (therap*[TI] OR treat*[TI] OR regimen*[TI] OR patient*[TI])) OR ((cytosta*[TI] OR cytotox*[TI]) AND (therap*[TI] OR treat*[TI] OR regimen*[TI])) OR ((multimodal*[TI] OR multi-modal*[TI]) AND (treat*[TI] OR therap*[TI])) OR (combi*[TI] AND modalit*[TI]) OR (allograft*[TI] OR allo-graft*[TI] OR allotransplant*[TI] OR allo-transplant*[TI] OR ((allogen*[TI] OR allo-gen*[TI]) AND (transplant*[TI] OR trasplant*[TI] OR graft*[TI] OR rescue*)) OR homograft*[TI] OR homo-graft*[TI] OR homolog*[TI] OR homotransplant*[TI] OR homo-transplant*[TI] OR homotrasplant*[TI] OR homo trasplant*[TI]) OR (autograft*[TI] OR autograft*[TI] OR

autotransplant*[TI] OR auto-transplant*[TI] OR mini-transplant*[TI]) OR (autolog*[TI] AND (transplant*[TI] OR graft*[TI] OR trasplant*[TI] OR rescu*[TI]))

#3 ("Epidemiologic Studies"[Mesh] OR “case control”[TIAB] OR “case-control”[TIAB] OR ((case[TIAB] OR cases[TIAB]) AND (control[TIAB] OR controls[TIAB)) OR “cohort study”[TIAB] OR “cohort analysis”[TIAB] OR “follow up study”[TIAB] OR “follow-up study”[TIAB] OR “observational study”[TIAB] OR “longitudinal”[TIAB] OR “retrospective”[TIAB] OR “cross sectional”[TIAB] OR “cross-sectional”[TIAB] OR questionnaire[TIAB] OR questionnaires[TIAB] OR survey[TIAB])

#4 (random* OR blind* OR “control group” OR placebo* OR controlled OR groups OR trial* OR “systematic review” OR “metaanalysis” OR metaanalysis OR “literature search” OR medline OR cochrane OR embase) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])

#5 #3 OR #4

#6 #1 AND #2 AND #5

Embase (via Embase.com interface) using the following search strategy:

Systematic reviews

#1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND (trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti))

#2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR standard*:ti))

#3 (blood:ti AND (management:ti OR program*:ti))

#4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and (critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti))

#5 #1 OR #2 OR #3 OR #4

#6 (systematic reviews) ‘meta analysis (topic)’/exp OR ‘meta analysis’/exp OR ‘meta analysis’:ab,ti OR ‘meta-analysis’:ab,ti OR ‘systematic review (topic)’/exp OR ‘systematic review’/exp OR ‘cochrane’:ab,ti OR ‘embase’:ab,ti OR ‘pubmed’:ab,ti OR ‘medline’:ab,ti OR ‘reference list’:ab,ti OR ‘reference lists’:ab,ti OR ‘bibliography’:ab,ti OR ‘bibliographies’:ab,ti OR ‘hand-search’:ab,ti OR ‘manual search’:ab,ti OR ‘relevant journals’:ab,ti OR ‘selection criteria’:ab,ti OR ‘data extraction’:ab,ti

#7 #5 AND #6

Individual experimental/observational studies

#1 (((erythrocyte*:ti OR blood:ti) AND (unit*:ti AND trigger*:ti OR level*:ti OR threshold*:ti OR rule*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR requir*:ti OR reduc*:ti OR limit*:ti)) OR (hemotransfus*:ti OR haemotransfus*:ti OR hemotherap*:ti OR haemotherap*:ti OR "red cell*":ti OR "red blood cell*":ti OR RBC*:ti OR transfus*:ti))

#2 thrombocytopeni*:ti OR thrombocytopaeni*:ti OR leukemi*:ti OR leukaemi*:ti OR lymphom*:ti OR "aplastic anemia":ti OR "aplastic anaemia":ti OR myelodysplas*:ti OR myeloproliferat*:ti OR myeloma:ti OR lymphogranulomato*:ti OR histiocy*:ti OR granulom*:ti OR thrombocythemi*:ti OR thrombocythaemi*:ti OR polycythemi*:ti OR polycythaemi*:ti OR myelofibros*:ti OR AML:ti OR CLL:ti OR CML:ti OR Hodgkin*:ti OR burkitt*:ti OR lymphosarcom*:ti OR brill-symmer*:ti OR sezary:ti OR ((haematolog*:ti OR hematolog*:ti OR blood:ti OR red cell*:ti OR white cell*:ti OR marrow:ti OR platelet*:ti) AND (malignan*:ti OR oncolog*:ti OR cancer*:ti OR neoplasm*:ti OR carcinoma*:ti)) OR chemotherap*:ti OR radiotherap*:ti OR chemoradiotherap*:ti OR "stem cell":ti OR "stem cells" OR "progenitor cell":ti OR "progenitor cells":ti OR bone marrow transplant*:ti OR bone marrow graft*:ti OR "bone marrow rescue":ti OR rituximab:ti OR antineoplast*:ti OR anti-neoplast*:ti OR ASCT:ti OR ABMT:ti OR PBPC:ti OR PBSCT:ti OR PSCT:ti OR BMT:ti OR SCT:ti OR HSCT:ti OR "haematology patients":ti OR "hematology patients":ti OR "haematological patients":ti OR "hematological patients":ti OR "hemato-oncology patients":ti OR "haemato-oncology patients":ti OR remission:ti OR ((consolidat*:ti OR induct*:ti OR maintenance:ti OR conditioning*:ti) AND (therap*:ti OR treat*:ti OR regimen*:ti OR patient*:ti)) OR ((cytosta*:ti OR cytotox*:ti) AND (therap*:ti OR treat*:ti OR regimen*:ti)) OR ((multimodal*:ti OR multi-modal*:ti) AND (treat*:ti OR therap*:ti)) OR (combi*:ti AND modalit*:ti) OR (allograft*:ti OR allo-graft*:ti OR allotransplant*:ti OR allo-transplant*:ti OR ((allogen*:ti OR allo-gen*:ti) AND (transplant*:ti OR trasplant*:ti OR graft*:ti OR rescue*)) OR homograft*:ti OR homo-graft*:ti OR homolog*:ti OR homotransplant*:ti OR homo-transplant*:ti OR homotrasplant*:ti OR homo trasplant*:ti) OR (autograft*:ti OR autograft*:ti OR autotransplant*:ti OR auto-transplant*:ti OR mini-transplant*:ti) OR (autolog*:ti AND (transplant*:ti OR graft*:ti OR trasplant*:ti OR rescu*:ti))

#3 ('clinical study'/exp OR 'cohort analysis'/exp OR 'case control':ab,ti OR 'case-control':ab,ti OR ((case:ab,ti OR cases:ab,ti) AND (control:ab,ti OR controls:ab,ti)) OR 'cohort study':ab,ti OR 'cohort analysis':ab,ti OR 'follow up study':ab,ti OR 'follow-up study':ab,ti OR 'observational study':ab,ti OR 'longitudinal':ab,ti OR 'retrospective':ab,ti OR 'cross sectional':ab,ti OR 'cross-sectional':ab,ti OR questionnaire:ab,ti OR questionnaires:ab,ti OR survey:ab,ti OR 'epidemiological study':ab,ti)

#4 ('randomized controlled trial'/exp OR 'clinical trial'/exp OR 'comparative study'/exp OR random*:ab,ti OR control*:ab,ti OR 'intervention study':ab,ti OR 'experimental study':ab,ti

OR ‘comparative study’:ab,ti OR trial:ab,ti OR evaluat*:ab,ti OR ‘before and after’:ab,ti OR ‘interrupted time series’:ab,ti) NOT ('animal'/exp NOT 'human'/exp)
#5 #3 OR #4
#6 #1 AND #2 AND #5

Transfusion evidence library

Systematic reviews

#1 Red Cells AND (trigger OR threshold OR target OR restrict OR restrictive OR liberal OR aggressive OR aggressively OR conservative OR prophylactic OR limit OR limits OR protocol OR policy OR policies OR practice OR indicator OR strategy OR strategies OR regimen OR criteria OR standard OR management OR program OR programme) OR Red Cells AND title:(critical OR critically OR intensive OR intensively OR hemorrhage OR haemorrhage OR hemorrhaging OR haemorrhaging OR bleed OR bleeding)
#2 systematic review filter
#3 #1 AND #2

Individual experimental studies

#1 Clinical specialty: Haematology and oncology
#2 restrict* OR liberal OR trigger* OR threshold* OR hemoglobin OR haemoglobin OR hematocrit* OR haematocrit* OR hb OR ht
#3 #1 AND #2

PICO 10 – Selection criteria

See PICO 4

PICO 11 – ADULT PATIENTS WITH SOLID TUMOURS

In adult patients with solid tumours [Population], is the use of a restrictive transfusion threshold [Intervention] effective to reduce mortality and improve other clinical outcomes [Outcome] compared to a liberal transfusion threshold [Comparison]?[96-98]

PICO 11 – Search strategies

The Cochrane systematic review by Carson et al. (2016) and its updated/unpublished version (2018) served as a basis. An additional search in 4 databases was conducted to:

- Identify relevant experimental studies (RCT’s) published after the search by Carson et al. (13th November 2017)

- Identify observational studies in case no experimental studies were available.

Databases

The Cochrane Library (systematic reviews and controlled trials) using the following search strategy:

Systematic reviews

#1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND (trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti))

#2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR standard*:ti))

#3 (blood:ti AND (management:ti OR program*:ti))

#4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and (critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti))

#5 #1 OR #2 OR #3 OR #4

Individual experimental studies

#1 (((erythrocyte*:ti OR blood:ti) AND (unit*:ti AND trigger*:ti OR level*:ti OR threshold*:ti OR rule*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR requir*:ti OR reduc*:ti OR limit*:ti)) OR (hemotransfus*:ti OR haemotransfus*:ti OR hemotherap*:ti OR haemotherap*:ti OR “red cell*”:ti OR “red blood cell*”:ti OR RBC*:ti OR transfus*:ti))

#2 neoplas*:ti OR tumor*:ti OR tumour*:ti OR Krebsti OR cancer*ti OR malignan*ti OR carcino*ti OR karzino*ti OR sarcom*ti OR leukaem*ti OR leukam*ti OR leuc*ti OR lymphom*ti OR melano*ti OR metastas*ti OR mesothelio*ti OR mesotelio*ti OR carcinomatous*ti OR gliom*ti OR glioblastom*ti OR osteo*sarcom*ti OR blastom*ti OR neuroblastom*ti OR adenocarcinoma*ti OR choriocarcinoma*ti OR teratoma*ti

#3 #1 AND #2

MEDLINE (via PubMed interface) for systematic reviews and experimental and observational studies using the following search strategy:

Systematic reviews

#1 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*) AND (trigger*[TI] OR threshold*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR aggressive*[TI] OR conservative*[TI] OR prophylactic*[TI] OR limit*[TI] OR protocol*[TI] OR

policy[TI] OR policies[TI] OR practic*[TI] OR indicat*[TI] OR strateg*[TI] OR regimen*[TI] OR criteri*[TI] OR standard*[TI] OR management[TI] OR program*[TI]))

#2 ((hemoglobin[TI] OR haemoglobin[TI] OR hematocrit[TI] OR haematocrit[TI] OR HB[TI] OR HCT[TI]) AND (polic*[TI] OR practic*[TI] OR protocol*[TI] OR trigger*[TI] OR threshold*[TI] OR maintain*[TI] OR indicator*[TI] OR strateg*[TI] OR criteri*[TI] OR standard*[TI]))

#3 (blood[TI] AND (management[TI] OR program*[TI]))

#4 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*[TI]) and (critical*[TI] OR intensive*[TI] OR hemorrhag*[TI] OR haemorrhage*[TI] OR bleed*[TI]))

#5 #1 OR #2 OR #3 OR #4

#6 ((((((((((Meta-Analysis as Topic[Mesh])) OR ((meta analy*[TIAB]))) OR ((metaanaly*[TIAB]))) OR ((Meta-Analysis[Publication Type]))) OR ((systematic review*[TIAB] OR systematic overview*[TIAB]))) OR ((Review Literature as Topic[Mesh])))) OR ((cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB]))) OR ((reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB]))) OR ((((selection criteria[TIAB] OR data extraction[TIAB])) AND ((Review[PT]))))) NOT ((Comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT (animal[Mesh] AND human[Mesh])))

#7 #5 AND #6

Individual experimental/observational studies

#1 (((erythrocyte*[TI] OR blood[TI]) AND (unit*[TI] AND trigger*[TI] OR level*[TI] OR threshold*[TI] OR rule*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR requir*[TI] OR reduc*[TI] OR limit*[TI])) OR (hemotransfus*[TI] OR haemotransfus*[TI] OR hemotherap*[TI] OR haemotherap*[TI] OR “red cell*”[TI]OR “red blood cell*”[TI] OR RBC*[TI] OR transfus*[TI]))

#2 “Neoplasms by histologic type”[Mesh] OR “Neoplasms by site”[Mesh] OR neoplas*[TI] OR tumor*[TI] OR tumour*[TI] OR Krebs[TI] OR cancer*[TI] OR malignan*[TI] OR carcino*[TI] OR karzino*[TI] OR sarcom*[TI] OR leukaem*[TI] OR leukam*[TI] OR leuc*[TI] OR lymphom*[TI] OR melano*[TI] OR metastas*[TI] OR mesothelio*[TI] OR mesotelio*[TI] OR carcinomatous*[TI] OR gliom*[TI] OR glioblastom*[TI] OR osteo*sarcom*[TI] OR blastom*[TI] OR neuroblastom*[TI] OR adenocarcinoma*[TI] OR choriocarcinoma*[TI] OR teratoma*[TI]

#3 ("Epidemiologic Studies"[Mesh] OR “case control”[TIAB] OR “case-control”[TIAB] OR ((case[TIAB] OR cases[TIAB]) AND (control[TIAB] OR controls[TIAB)) OR “cohort

study”[TIAB] OR “cohort analysis”[TIAB] OR “follow up study”[TIAB] OR “follow-up study”[TIAB] OR “observational study”[TIAB] OR “longitudinal”[TIAB] OR “retrospective”[TIAB] OR “cross sectional”[TIAB] OR “cross-sectional”[TIAB] OR questionnaire[TIAB] OR questionnaires[TIAB] OR survey[TIAB])
#4 (random* OR blind* OR “control group” OR placebo* OR controlled OR groups OR trial* OR “systematic review” OR “metaanalysis” OR metaanalysis OR “literature search” OR medline OR cochrane OR embase) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])
#5 #3 AND #4
#6 #1 AND #2 AND #5

Embase (via Embase.com interface) using the following search strategy:

Systematic reviews

#1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND (trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti))
#2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR standard*:ti))
#3 (blood:ti AND (management:ti OR program*:ti))
#4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and (critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti))
#5 #1 OR #2 OR #3 OR #4
#6 (systematic reviews) ‘meta analysis (topic)’/exp OR ‘meta analysis’/exp OR ‘meta analysis’:ab,ti OR ‘meta-analysis’:ab,ti OR ‘systematic review (topic)’/exp OR ‘systematic review’/exp OR ‘cochrane’:ab,ti OR ‘embase’:ab,ti OR ‘pubmed’:ab,ti OR ‘medline’:ab,ti OR ‘reference list’:ab,ti OR ‘reference lists’:ab,ti OR ‘bibliography’:ab,ti OR ‘bibliographies’:ab,ti OR ‘hand-search’:ab,ti OR ‘manual search’:ab,ti OR ‘relevant journals’:ab,ti OR ‘selection criteria’:ab,ti OR ‘data extraction’:ab,ti
#7 #5 AND #6

Individual experimental/observational studies

#1 (((erythrocyte*:ti OR blood:ti) AND (unit*:ti AND trigger*:ti OR level*:ti OR threshold*:ti OR rule*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR requir*:ti OR reduc*:ti OR limit*:ti))

OR (hemotransfus*:ti OR haemotransfus*:ti OR hemotherap*:ti OR haemotherap*:ti OR “red cell*”:ti OR “red blood cell*”:ti OR RBC*:ti OR transfus*:ti))

#2 neoplas*:ti OR tumor*:ti OR tumour*:ti OR Krebsti OR cancer*ti OR malignan*ti OR carcino*ti OR karzino*ti OR sarcom*ti OR leukaem*ti OR leukam*ti OR leuc*ti OR lymphom*ti OR melano*ti OR metastas*ti OR mesothelio*ti OR mesotelio*ti OR carcinomatous*ti OR gliom*ti OR glioblastom*ti OR osteo*sarcom*ti OR blastom*ti OR neuroblastom*ti OR adenocarcinoma*ti OR choriocarcinoma*ti OR teratoma*ti

#3 (‘clinical study’/exp OR ‘cohort analysis’/exp OR ‘case control’:ab,ti OR ‘case-control’:ab,ti OR ((case:ab,ti OR cases:ab,ti) AND (control:ab,ti OR controls:ab,ti)) OR ‘cohort study’:ab,ti OR ‘cohort analysis’:ab,ti OR ‘follow up study’:ab,ti OR ‘follow-up study’:ab,ti OR ‘observational study’:ab,ti OR ‘longitudinal’:ab,ti OR ‘retrospective’:ab,ti OR ‘cross sectional’:ab,ti OR ‘cross-sectional’:ab,ti OR questionnaire:ab,ti OR questionnaires:ab,ti OR survey:ab,ti OR ‘epidemiological study’:ab,ti)

#4 ('randomized controlled trial'/exp OR 'clinical trial'/exp OR 'comparative study'/exp OR random*:ab,ti OR control*:ab,ti OR ‘intervention study’:ab,ti OR ‘experimental study’:ab,ti OR ‘comparative study’:ab,ti OR trial:ab,ti OR evaluat*:ab,ti OR ‘before and after’:ab,ti OR ‘interrupted time series’:ab,ti) NOT ('animal'/exp NOT 'human'/exp)

#5 #3 OR #4

#6 #1 AND #2 AND #5

Transfusion evidence library

Systematic reviews

#1 Red Cells AND (trigger OR threshold OR target OR restrict OR restrictive OR liberal OR aggressive OR aggressively OR conservative OR prophylactic OR limit OR limits OR protocol OR policy OR policies OR practice OR indicator OR strategy OR strategies OR regimen OR criteria OR standard OR management OR program OR programme) OR Red Cells AND title:(critical OR critically OR intensive OR intensively OR hemorrhage OR haemorrhage OR hemorrhaging OR haemorrhaging OR bleed OR bleeding)

#2 systematic review filter

#3 #1 AND #2

Individual experimental studies

#1 Clinical specialty: Haematology and oncology

#2 restrict* OR liberal OR trigger* OR threshold* OR hemoglobin OR haemoglobin OR hematocrit* OR haematocrit* OR hb OR ht

#3 #1 AND #2

PICO 11 – Selection criteria

See PICO 4

PICO 12 – ACUTE CENTRAL NERVOUS SYSTEM INJURY

In patients with acute central nervous system (CNS) injury [Population], is the use of a restrictive transfusion threshold [Intervention] effective to reduce mortality and improve other clinical outcomes [Outcome] compared to a liberal transfusion threshold [Comparison]? [99,100]

PICO 12 – Search strategies

The Cochrane systematic review by Carson et al. (2016) and its updated/unpublished version (2018) served as a basis. An additional search in 4 databases was conducted to:

- Identify relevant experimental studies (RCT's) published after the search by Carson et al. (13th November 2017)
- Identify observational studies in case no experimental studies were available.

Databases

The Cochrane Library (systematic reviews and controlled trials) using the following search strategy:

Systematic reviews

#1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND (trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti))

#2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR standard*:ti))

#3 (blood:ti AND (management:ti OR program*:ti))

#4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and (critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti))

#5 #1 OR #2 OR #3 OR #4

Individual experimental studies

#1 (((erythrocyte*:ti OR blood:ti) AND (unit*:ti AND trigger*:ti OR level*:ti OR threshold*:ti OR rule*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR requir*:ti OR reduc*:ti OR limit*:ti)) OR (hemotransfus*:ti OR haemotransfus*:ti OR hemotherap*:ti OR haemotherap*:ti OR "red cell*":ti OR "red blood cell*":ti OR RBC*:ti OR transfus*:ti))

#2 [mh “Central Nervous System Diseases”]

#3 (Disease*:ti,ab OR disorder*:ti,ab OR injury:ti,ab OR injuries:ti,ab) AND (brain:ti,ab OR “spinal cord”:ti,ab OR “central nervous system”:ti,ab OR CNS:ti,ab)

#4 #2 OR #3

#5 #1 AND #4

MEDLINE (via PubMed interface) for systematic reviews and experimental and observational studies using the following search strategy:

Systematic reviews

#1 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*) AND (trigger*[TI] OR threshold*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR aggressive*[TI] OR conservative*[TI] OR prophylactic*[TI] OR limit*[TI] OR protocol*[TI] OR policy[TI] OR policies[TI] OR practic*[TI] OR indicat*[TI] OR strateg*[TI] OR regimen*[TI] OR criteri*[TI] OR standard*[TI] OR management[TI] OR program*[TI]))

#2 ((hemoglobin[TI] OR haemoglobin[TI] OR hematocrit[TI] OR haematocrit[TI] OR HB[TI] OR HCT[TI]) AND (polic*[TI] OR practic*[TI] OR protocol*[TI] OR trigger*[TI] OR threshold*[TI] OR maintain*[TI] OR indicator*[TI] OR strateg*[TI] OR criteri*[TI] OR standard*[TI]))

#3 (blood[TI] AND (management[TI] OR program*[TI]))

#4 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*[TI]) and (critical*[TI] OR intensive*[TI] OR hemorrhag*[TI] OR haemorrhage*[TI] OR bleed*[TI]))

#5 #1 OR #2 OR #3 OR #4

#6 ((((((((((Meta-Analysis as Topic[Mesh])) OR ((meta analy*[TIAB]))) OR ((metaanaly*[TIAB]))) OR ((Meta-Analysis[Publication Type]))) OR ((systematic review*[TIAB] OR systematic overview*[TIAB]))) OR ((Review Literature as Topic[Mesh])))) OR ((cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB]))) OR ((reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB]))) OR ((((selection criteria[TIAB] OR data extraction[TIAB])) AND ((Review[PT]))))) NOT ((Comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT (animal[Mesh] AND human[Mesh])))

#7 #5 AND #6

Individual experimental/observational studies

#1 (((erythrocyte*[TI] OR blood[TI]) AND (unit*[TI] AND trigger*[TI] OR level*[TI] OR threshold*[TI] OR rule*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR requir*[TI] OR reduc*[TI] OR limit*[TI])) OR (hemotransfus*[TI] OR haemotransfus*[TI] OR hemotherap*[TI] OR haemotherap*[TI] OR “red cell*”[TI]OR “red blood cell*”[TI] OR RBC*[TI] OR transfus*[TI]))

#2 "Central Nervous System Diseases"[Mesh]

#3 (Disease*[TIAB] OR disorder*[TIAB] OR injury[TIAB] OR injuries[TIAB]) AND (brain[TIAB] OR “spinal cord”[TIAB] OR “central nervous system”[TIAB] OR CNS[TIAB])

#4 #2 OR #3

#5 ("Epidemiologic Studies"[Mesh] OR “case control”[TIAB] OR “case-control”[TIAB] OR ((case[TIAB] OR cases[TIAB]) AND (control[TIAB] OR controls[TIAB)) OR “cohort study”[TIAB] OR “cohort analysis”[TIAB] OR “follow up study”[TIAB] OR “follow-up study”[TIAB] OR “observational study”[TIAB] OR “longitudinal”[TIAB] OR “retrospective”[TIAB] OR “cross sectional”[TIAB] OR “cross-sectional”[TIAB] OR questionnaire[TIAB] OR questionnaires[TIAB] OR survey[TIAB])

#6 (random* OR blind* OR “control group” OR placebo* OR controlled OR groups OR trial* OR “systematic review” OR “metaanalysis” OR metaanalysis OR “literature search” OR medline OR cochrane OR embase) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])

#7 #5 AND #6

#8 #1 AND #4 AND #7

Embase (via Embase.com interface) using the following search strategy:

Systematic reviews

#1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND (trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti))

#2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR standard*:ti))

#3 (blood:ti AND (management:ti OR program*:ti))

#4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and (critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti))

#5 #1 OR #2 OR #3 OR #4

#6 (systematic reviews) ‘meta analysis (topic)’/exp OR ‘meta analysis’/exp OR ‘meta analysis’:ab,ti OR ‘meta-analysis’:ab,ti OR ‘systematic review (topic)’/exp OR ‘systematic review’/exp OR ‘cochrane’:ab,ti OR ‘embase’:ab,ti OR ‘pubmed’:ab,ti OR ‘medline’:ab,ti OR ‘reference list’:ab,ti OR ‘reference lists’:ab,ti OR ‘bibliography’:ab,ti OR ‘bibliographies’:ab,ti OR ‘hand-search’:ab,ti OR ‘manual search’:ab,ti OR ‘relevant journals’:ab,ti OR ‘selection criteria’:ab,ti OR ‘data extraction’:ab,ti

#7 #5 AND #6

Individual experimental/observational studies

#1 (((erythrocyte*:ti OR blood:ti) AND (unit*:ti AND trigger*:ti OR level*:ti OR threshold*:ti OR rule*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR requir*:ti OR reduc*:ti OR limit*:ti)) OR (hemotransfus*:ti OR haemotransfus*:ti OR hemotherap*:ti OR haemotherap*:ti OR “red cell*”:ti OR “red blood cell*”:ti OR RBC*:ti OR transfus*:ti))

#2 (Disease*:ab,ti OR disorder*:ab,ti OR injury:ab,ti OR injuries:ab,ti) AND (brain:ab,ti OR “spinal cord”:ab,ti OR “central nervous system”:ab,ti OR CNS)

#3 (‘clinical study’/exp OR ‘cohort analysis’/exp OR ‘case control’:ab,ti OR ‘case-control’:ab,ti OR ((case:ab,ti OR cases:ab,ti) AND (control:ab,ti OR controls:ab,ti)) OR ‘cohort study’:ab,ti OR ‘cohort analysis’:ab,ti OR ‘follow up study’:ab,ti OR ‘follow-up study’:ab,ti OR ‘observational study’:ab,ti OR ‘longitudinal’:ab,ti OR ‘retrospective’:ab,ti OR ‘cross sectional’:ab,ti OR ‘cross-sectional’:ab,ti OR questionnaire:ab,ti OR questionnaires:ab,ti OR survey:ab,ti OR ‘epidemiological study’:ab,ti)

#4 ('randomized controlled trial'/exp OR 'clinical trial'/exp OR 'comparative study'/exp OR random*:ab,ti OR control*:ab,ti OR ‘intervention study’:ab,ti OR ‘experimental study’:ab,ti OR ‘comparative study’:ab,ti OR trial:ab,ti OR evaluat*:ab,ti OR ‘before and after’:ab,ti OR ‘interrupted time series’:ab,ti) NOT ('animal'/exp NOT 'human'/exp)

#5 #3 OR #4

#6 #1 AND #2 AND #5

Transfusion evidence library

Systematic reviews

#1 Red Cells AND (trigger OR threshold OR target OR restrict OR restrictive OR liberal OR aggressive OR aggressively OR conservative OR prophylactic OR limit OR limits OR protocol OR policy OR policies OR practice OR indicator OR strategy OR strategies OR regimen OR criteria OR standard OR management OR program OR programme) OR Red Cells AND title:(critical OR critically OR intensive OR intensively OR hemorrhage OR haemorrhage OR hemorrhaging OR haemorrhaging OR bleed OR bleeding)

#2 systematic review filter

#3 #1 AND #2

Individual experimental studies

#1 Clinical specialty: Medicine – Neurological disorders

#2 restrict* OR liberal OR trigger* OR threshold* OR hemoglobin OR haemoglobin OR hematocrit* OR haematocrit* OR hb OR ht

#3 #1 AND #2

PICO 12– Selection criteria

See PICO 4

PICO 13 – CEREBRAL PERFUSION DISORDERS

In patients with cerebral perfusion disorders [Population], is the use of a restrictive transfusion threshold [Intervention] effective to reduce mortality and improve other clinical outcomes [Outcome] compared to a liberal transfusion threshold [Comparison]?[101]

PICO 13 – Search strategies

The Cochrane systematic review by Carson et al. (2016) and its updated/unpublished version (2018) served as a basis. An additional search in 4 databases was conducted to:

- Identify relevant experimental studies (RCT's) published after the search by Carson et al. (13th November 2017)
- Identify observational studies in case no experimental studies were available.

Databases

The Cochrane Library (systematic reviews and controlled trials) using the following search strategy:

Systematic reviews

#1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND (trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti))

#2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR standard*:ti))

#3 (blood:ti AND (management:ti OR program*:ti))

#4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and (critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti))

#5 #1 OR #2 OR #3 OR #4 Results #hits

Individual experimental studies

#1 (((erythrocyte*:ti OR blood:ti) AND (unit*:ti AND trigger*:ti OR level*:ti OR threshold*:ti OR rule*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR requir*:ti OR reduc*:ti OR limit*:ti)) OR (hemotransfus*:ti OR haemotransfus*:ti OR hemotherap*:ti OR haemotherap*:ti OR "red cell*":ti OR "red blood cell*":ti OR RBC*:ti OR transfus*:ti))

#2 [mh stroke] OR [mh "cerebral hemorrhage"]

#3 (cerebral:ti,ab OR intracerebral:ti,ab) AND hemorrhage*:ti,ab

#4 CVA:ti,ab OR stroke:ti,ab OR "cerebrovascular accident":ti,ab OR "cerebrovascular accidents":ti,ab

#5 #2 OR #3 OR #4

#6 #1 AND #5

MEDLINE (via PubMed interface) for systematic reviews and experimental and observational studies using the following search strategy:

Systematic reviews

#1 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*) AND (trigger*[TI] OR threshold*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR aggressive*[TI] OR conservative*[TI] OR prophylactic*[TI] OR limit*[TI] OR protocol*[TI] OR policy[TI] OR policies[TI] OR practic*[TI] OR indicat*[TI] OR strateg*[TI] OR regimen*[TI] OR criteri*[TI] OR standard*[TI] OR management[TI] OR program*[TI]))

#2 ((hemoglobin[TI] OR haemoglobin[TI] OR hematocrit[TI] OR haematocrit[TI] OR HB[TI] OR HCT[TI]) AND (polic*[TI] OR practic*[TI] OR protocol*[TI] OR trigger*[TI] OR threshold*[TI] OR maintain*[TI] OR indicator*[TI] OR strateg*[TI] OR criteri*[TI] OR standard*[TI]))

#3 (blood[TI] AND (management[TI] OR program*[TI]))

#4 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*[TI]) and (critical*[TI] OR intensive*[TI] OR hemorrhag*[TI] OR haemorrhage*[TI] OR bleed*[TI]))

#5 #1 OR #2 OR #3 OR #4

#6 ((((((((((Meta-Analysis as Topic[Mesh])) OR ((meta analy*[TIAB]))) OR ((metaanaly*[TIAB]))) OR ((Meta-Analysis[Publication Type]))) OR ((systematic review*[TIAB] OR systematic overview*[TIAB]))) OR ((Review Literature as Topic[Mesh])))) OR ((cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB]))) OR ((reference list*[TIAB] OR

bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB]))) OR ((((selection criteria[TIAB] OR data extraction[TIAB])) AND ((Review[PT]))))))) NOT ((Comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT (animal[Mesh] AND human[Mesh])))

#7 #5 AND #6

Individual experimental/observational studies

#1 (((erythrocyte*[TI] OR blood[TI]) AND (unit*[TI] AND trigger*[TI] OR level*[TI] OR threshold*[TI] OR rule*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR requir*[TI] OR reduc*[TI] OR limit*[TI])) OR (hemotransfus*[TI] OR haemotransfus*[TI] OR hemotherap*[TI] OR haemotherap*[TI] OR “red cell*”[TI]OR “red blood cell*”[TI] OR RBC*[TI] OR transfus*[TI]))

#2 stroke[Mesh] OR “cerebral hemorrhage”[Mesh]

#3 (cerebral[TIAB] OR intracerebral[TIAB]) AND hemorrhage*[TIAB]

#4 CVA[TIAB] OR stroke[TIAB] OR “cerebrovascular accident”[TIAB] OR “cerebrovascular accidents”[TIAB]

#5 #2 OR #3 OR #4

#6 ("Epidemiologic Studies"[Mesh] OR “case control”[TIAB] OR “case-control”[TIAB] OR ((case[TIAB] OR cases[TIAB]) AND (control[TIAB] OR controls[TIAB)) OR “cohort study”[TIAB] OR “cohort analysis”[TIAB] OR “follow up study”[TIAB] OR “follow-up study”[TIAB] OR “observational study”[TIAB] OR “longitudinal”[TIAB] OR “retrospective”[TIAB] OR “cross sectional”[TIAB] OR “cross-sectional”[TIAB] OR questionnaire[TIAB] OR questionnaires[TIAB] OR survey[TIAB])

#7 (random* OR blind* OR “control group” OR placebo* OR controlled OR groups OR trial* OR “systematic review” OR “metaanalysis” OR metaanalysis OR “literature search” OR medline OR cochrane OR embase) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])

#8 #6 OR #7

#9 #1 AND #5 AND #8

Embase (via Embase.com interface) using the following search strategy:

Systematic reviews

#1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND (trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti))

#2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR standard*:ti))
#3 (blood:ti AND (management:ti OR program*:ti))
#4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and (critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti))
#5 #1 OR #2 OR #3 OR #4
#6 (systematic reviews) 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti
#7 #5 AND #6

Individual experimental/observational studies

#1 (((erythrocyte*:ti OR blood:ti) AND (unit*:ti AND trigger*:ti OR level*:ti OR threshold*:ti OR rule*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR requir*:ti OR reduc*:ti OR limit*:ti)) OR (hemotransfus*:ti OR haemotransfus*:ti OR hemotherap*:ti OR haemotherap*:ti OR "red cell*":ti OR "red blood cell*":ti OR RBC*:ti OR transfus*:ti))
#2 'cerebrovascular accident'/exp OR 'brain hemorrhage'/exp
#3 (cerebral:ab,ti OR intracerebral:ab,ti) AND hemorrhage*:ab,ti
#4 CVA:ab,ti OR stroke:ab,ti OR 'cerebrovascular accident':ab,ti OR 'cerebrovascular accidents':ab,ti
#5 #2 OR #3 OR #4
#6 ('clinical study'/exp OR 'cohort analysis'/exp OR 'case control':ab,ti OR 'case-control':ab,ti OR ((case:ab,ti OR cases:ab,ti) AND (control:ab,ti OR controls:ab,ti)) OR 'cohort study':ab,ti OR 'cohort analysis':ab,ti OR 'follow up study':ab,ti OR 'follow-up study':ab,ti OR 'observational study':ab,ti OR 'longitudinal':ab,ti OR 'retrospective':ab,ti OR 'cross sectional':ab,ti OR 'cross-sectional':ab,ti OR questionnaire:ab,ti OR questionnaires:ab,ti OR survey:ab,ti OR 'epidemiological study':ab,ti)
#7 ('randomized controlled trial'/exp OR 'clinical trial'/exp OR 'comparative study'/exp OR random*:ab,ti OR control*:ab,ti OR 'intervention study':ab,ti OR 'experimental study':ab,ti OR 'comparative study':ab,ti OR trial:ab,ti OR evaluat*:ab,ti OR 'before and after':ab,ti OR 'interrupted time series':ab,ti) NOT ('animal'/exp NOT 'human'/exp)
#8 #6 OR #7
#9 #1 AND #5 AND #8

Transfusion evidence library

Systematic reviews

#1 Red Cells AND (trigger OR threshold OR target OR restrict OR restrictive OR liberal OR aggressive OR aggressively OR conservative OR prophylactic OR limit OR limits OR protocol OR policy OR policies OR practice OR indicator OR strategy OR strategies OR regimen OR criteria OR standard OR management OR program OR programme) OR Red Cells AND title:(critical OR critically OR intensive OR intensively OR hemorrhage OR haemorrhage OR hemorrhaging OR haemorrhaging OR bleed OR bleeding)

#2 systematic review filter

#3 #1 AND #2

Individual experimental studies

#1 Clinical specialty: Medicine – Neurological disorders

#2 restrict* OR liberal OR trigger* OR threshold* OR hemoglobin OR haemoglobin OR hematocrit* OR haematocrit* OR hb OR ht

#3 #1 AND #2

PICO 13 – Selection criteria

See PICO 4

PICO 14 – ACUTE BLEEDING

In patients with acute bleeding [Population], is the use of a restrictive transfusion threshold [Intervention] effective to reduce mortality and improve other clinical outcomes [Outcome] compared to a liberal transfusion threshold [Comparison]?[102]

PICO 14 – Search strategies

The Cochrane systematic review by Carson et al. (2016) and its updated/unpublished version (2018) served as a basis. An additional search in 4 databases was conducted to:

- Identify relevant experimental studies (RCT's) published after the search by Carson et al. (13th November 2017)
- Identify observational studies in case no experimental studies were available.

Databases

The Cochrane Library (systematic reviews and controlled trials) using the following search strategy:

Systematic reviews

#1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND (trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti))

#2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR standard*:ti))

#3 (blood:ti AND (management:ti OR program*:ti))

#4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and (critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti))

#5 #1 OR #2 OR #3 OR #4

Individual experimental studies

#1 (((erythrocyte*:ti OR blood:ti) AND (unit*:ti AND trigger*:ti OR level*:ti OR threshold*:ti OR rule*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR requir*:ti OR reduc*:ti OR limit*:ti)) OR (hemotransfus*:ti OR haemotransfus*:ti OR hemotherap*:ti OR haemotherap*:ti OR “red cell*”:ti OR “red blood cell*”:ti OR RBC*:ti OR transfus*:ti))

#2 (acute:ti,ab OR massive:ti,ab) AND (bleeding:ti,ab OR hemorrhage*:ti,ab OR “blood loss”:ti,ab)

#3 #1 AND #2

MEDLINE (via PubMed interface) for systematic reviews and experimental and observational studies using the following search strategy:

Systematic reviews

#1 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*) AND (trigger*[TI] OR threshold*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR aggressive*[TI] OR conservative*[TI] OR prophylactic*[TI] OR limit*[TI] OR protocol*[TI] OR policy[TI] OR policies[TI] OR practic*[TI] OR indicat*[TI] OR strateg*[TI] OR regimen*[TI] OR criteri*[TI] OR standard*[TI] OR management[TI] OR program*[TI]))

#2 ((hemoglobin[TI] OR haemoglobin[TI] OR hematocrit[TI] OR haematocrit[TI] OR HB[TI] OR HCT[TI]) AND (polic*[TI] OR practic*[TI] OR protocol*[TI] OR trigger*[TI] OR threshold*[TI] OR maintain*[TI] OR indicator*[TI] OR strateg*[TI] OR criteri*[TI] OR standard*[TI]))

#3 (blood[TI] AND (management[TI] OR program*[TI]))

#4 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*[TI]) and (critical*[TI] OR intensive*[TI] OR hemorrhag*[TI] OR haemorrhage*[TI] OR bleed*[TI]))
#5 #1 OR #2 OR #3 OR #4
#6 ((((((((((Meta-Analysis as Topic[Mesh])) OR ((meta analy*[TIAB]))) OR ((metaanaly*[TIAB]))) OR ((Meta-Analysis[Publication Type]))) OR ((systematic review*[TIAB] OR systematic overview*[TIAB]))) OR ((Review Literature as Topic[Mesh])))) OR ((cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB]))) OR ((reference list*[TIAB] OR bibliograph*[TIAB] OR hand-search*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB]))) OR ((((selection criteria[TIAB] OR data extraction[TIAB])) AND ((Review[PT]))))) NOT ((Comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT (animal[Mesh] AND human[Mesh])))
#7 #5 AND #6

Individual experimental/observational studies

#1 (((erythrocyte*[TI] OR blood[TI]) AND (unit*[TI] AND trigger*[TI] OR level*[TI] OR threshold*[TI] OR rule*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR requir*[TI] OR reduc*[TI] OR limit*[TI])) OR (hemotransfus*[TI] OR haemotransfus*[TI] OR hemotherap*[TI] OR haemotherap*[TI] OR “red cell*”[TI]OR “red blood cell*”[TI] OR RBC*[TI] OR transfus*[TI]))
#2 (acute[TIAB] OR massive [TIAB]) AND (bleeding[TIAB] OR hemorrhage*[TIAB] OR “blood loss”[TIAB])
#3 ("Epidemiologic Studies"[Mesh] OR “case control”[TIAB] OR “case-control”[TIAB] OR ((case[TIAB] OR cases[TIAB]) AND (control[TIAB] OR controls[TIAB)) OR “cohort study”[TIAB] OR “cohort analysis”[TIAB] OR “follow up study”[TIAB] OR “follow-up study”[TIAB] OR “observational study”[TIAB] OR “longitudinal”[TIAB] OR “retrospective”[TIAB] OR “cross sectional”[TIAB] OR “cross-sectional”[TIAB] OR questionnaire[TIAB] OR questionnaires[TIAB] OR survey[TIAB])
#4 (random* OR blind* OR “control group” OR placebo* OR controlled OR groups OR trial* OR “systematic review” OR “metaanalysis” OR metaanalysis OR “literature search” OR medline OR cochrane OR embase) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])
#5 #3 OR #4
#6 #1 AND #2 AND #5

Embase (via Embase.com interface) using the following search strategy:

Systematic reviews

#1 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*) AND (trigger*:ti OR threshold*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR aggressive*:ti OR conservative*:ti OR prophylactic*:ti OR limit*:ti OR protocol*:ti OR policy:ti OR policies:ti OR practic*:ti OR indicat*:ti OR strateg*:ti OR regimen*:ti OR criteri*:ti OR standard*:ti OR management:ti OR program*:ti))

#2 ((hemoglobin:ti OR haemoglobin:ti OR hematocrit:ti OR haematocrit:ti OR HB:ti OR HCT:ti) AND (polic*:ti OR practic*:ti OR protocol*:ti OR trigger*:ti OR threshold*:ti OR maintain*:ti OR indicator*:ti OR strateg*:ti OR criteri*:ti OR standard*:ti))

#3 (blood:ti AND (management:ti OR program*:ti))

#4 ((transfus*:ti OR red cell*:ti OR red blood cell*:ti OR RBC*:ti OR PRBC*:ti) and (critical*:ti OR intensive*:ti OR hemorrhag*:ti OR haemorrhage*:ti OR bleed*:ti))

#5 #1 OR #2 OR #3 OR #4

#6 (systematic reviews) 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR 'data extraction':ab,ti

#7 #5 AND #6

Individual experimental/observational studies

#1 (((erythrocyte*:ti OR blood:ti) AND (unit*:ti AND trigger*:ti OR level*:ti OR threshold*:ti OR rule*:ti OR target*:ti OR restrict*:ti OR liberal*:ti OR requir*:ti OR reduc*:ti OR limit*:ti)) OR (hemotransfus*:ti OR haemotransfus*:ti OR hemotherap*:ti OR haemotherap*:ti OR "red cell*":ti OR "red blood cell*":ti OR RBC*:ti OR transfus*:ti))

#2 (acute:ab,ti OR massive:ab,ti) AND (bleeding:ab,ti OR hemorrhage*:ab,ti OR "blood loss":ab,ti)

#3 ('clinical study'/exp OR 'cohort analysis'/exp OR 'case control':ab,ti OR 'case-control':ab,ti OR ((case:ab,ti OR cases:ab,ti) AND (control:ab,ti OR controls:ab,ti)) OR 'cohort study':ab,ti OR 'cohort analysis':ab,ti OR 'follow up study':ab,ti OR 'follow-up study':ab,ti OR 'observational study':ab,ti OR 'longitudinal':ab,ti OR 'retrospective':ab,ti OR 'cross sectional':ab,ti OR 'cross-sectional':ab,ti OR questionnaire:ab,ti OR questionnaires:ab,ti OR survey:ab,ti OR 'epidemiological study':ab,ti)

#4 ('randomized controlled trial'/exp OR 'clinical trial'/exp OR 'comparative study'/exp OR random*:ab,ti OR control*:ab,ti OR 'intervention study':ab,ti OR 'experimental study':ab,ti

OR ‘comparative study’:ab,ti OR trial:ab,ti OR evaluat*:ab,ti OR ‘before and after’:ab,ti OR ‘interrupted time series’:ab,ti) NOT ('animal'/exp NOT 'human'/exp)
#5 #3 OR #4
#6 #1 AND #2 AND #5

Transfusion evidence library

Systematic reviews

#1 Red Cells AND (trigger OR threshold OR target OR restrict OR restrictive OR liberal OR aggressive OR aggressively OR conservative OR prophylactic OR limit OR limits OR protocol OR policy OR policies OR practice OR indicator OR strategy OR strategies OR regimen OR criteria OR standard OR management OR program OR programme) OR Red Cells AND title:(critical OR critically OR intensive OR intensively OR hemorrhage OR haemorrhage OR hemorrhaging OR haemorrhaging OR bleed OR bleeding)
#2 systematic review filter
#3 #1 AND #2

Individual experimental studies

#1 restrict* OR liberal OR trigger* OR threshold* OR hemoglobin OR haemoglobin OR hematocrit* OR haematocrit* OR hb OR ht
#2 (acute OR massive) AND (bleeding OR hemorrhage* OR “blood loss”)
#3 #1 AND #2

PICO 14 – Selection criteria

See PICO

PBM IMPLEMENTATION

PICO 15 – EFFECTIVENESS PBM IMPLEMENTATION

Is a PBM program [Intervention] effective to improve clinical and economic outcomes [Outcome] compared to no PBM program [Comparison]?[103-122]

PICO 15 – Search strategies

Databases

The Cochrane Library (systematic reviews and controlled trials) using the following search strategy:

1. "Patient Blood Management":ti,ab,kw
2. [mh Education] OR educat*:ti,ab,kw OR implement*:ti,ab,kw OR monitor*:ti,ab,kw OR [mh "information dissemination"] OR disseminat*:ti,ab,kw OR adopt*:ti,ab,kw OR [mh "quality improvement"] OR improv*:ti,ab,kw OR [mh "organizational innovation"] OR change*:ti,ab,kw OR program*:ti,ab,kw OR practice*:ti,ab,kw OR scal*:ti,ab,kw OR diffusion:ti,ab,kw OR incorporation:ti,ab,kw OR adherence:ti,ab,kw OR transformation:ti,ab,kw OR translation:ti,ab,kw OR transfer:ti,ab,kw OR uptake:ti,ab,kw OR sustainab*:ti,ab,kw OR institutionali*:ti,ab,kw OR routin*:ti,ab,kw OR maintenance:ti,ab,kw OR capacity:ti,ab,kw OR integration:ti,ab,kw
3. 1 AND 2

MEDLINE (via PubMed interface) using the following search strategy:

1. "Patient Blood Management"[TIAB]
2. Education[Mesh] OR educat*[TIAB] OR implement*[TIAB] OR monitor*[TIAB] OR "information dissemination"[Mesh] OR disseminat*[TIAB] OR adopt*[TIAB] OR "quality improvement"[Mesh] OR improv*[TIAB] OR "organizational innovation"[Mesh] OR change*[TIAB] OR program*[TIAB] OR practice*[TIAB] OR scal*[TIAB] OR diffusion[TIAB] OR incorporation[TIAB] OR adherence[TIAB] OR transformation[TIAB] OR translation[TIAB] OR transfer[TIAB] OR uptake[TIAB] OR sustainab*[TIAB] OR institutionali*[TIAB] OR routin*[TIAB] OR maintenance[TIAB] OR capacity[TIAB] OR integration[TIAB]
3. 1 AND 2

Embase (via Embase.com interface) using the following search strategy:

1. 'Patient Blood Management':ab,ti
2. Education/exp OR educat*:ab,ti OR implement*:ab,ti OR monitor*:ab,ti OR 'information dissemination'/exp OR disseminat*:ab,ti OR adopt*:ab,ti OR 'total quality management'/exp OR improv*:ab,ti OR change*:ab,ti OR program*:ab,ti OR practice*:ab,ti OR scal*:ab,ti OR diffusion:ab,ti OR incorporation:ab,ti OR adherence:ab,ti OR transformation:ab,ti OR translation:ab,ti OR transfer:ab,ti OR uptake:ab,ti OR sustainab*:ab,ti OR institutionali*:ab,ti OR routin*:ab,ti OR maintenance:ab,ti OR capacity:ab,ti OR integration:ab,ti
3. 1 AND 2

Transfusion Evidence Library using the following search strategy:

1. Patient blood management (#hits on July 18: 307)

2. educat* OR implement* OR monitor* OR disseminat* OR adopt* OR improv* OR "organizational innovation" OR change* OR program* OR practice* OR scal* OR diffusion OR incorporation OR adherence OR transformation OR translation OR transfer OR uptake OR sustainab* OR institutionali* OR routin* OR maintenance OR capacity OR integration
3. 1 AND 2

After removing duplicates, 674 papers were screened on title and abstract
In addition to the current search strategies, the first 20 related citations of all included papers were screened and included (if appropriate).

PICO 15 – Selection criteria

Population: *Included:* patients who might need transfusion (surgical and non-surgical patients/ acute and chronic disease patients/ adults and children).

Intervention: *Included:* Patient blood management (PBM) is a patient-focused, evidence-based and systematic approach to optimize the management of patient and transfusion of blood products for quality and effective patient care. It is designed to improve patient outcomes through the safe and rational use of blood and blood products and by minimizing unnecessary exposure to blood products. Patient Blood Management focuses on three pillars of care during the pre-, intra- and post-operative phase: 1) optimizing erythropoiesis, 2) minimizing blood loss and 3) management of anemia. We only include PBM programs that contained at least one intervention for 2 or 3 pillars. *Excluded:* programs that only focused on interventions in 1 pillar (e.g. restrictive RBC transfusion strategies).

Comparison: no PBM program

Outcome: *Included:* Clinical outcomes including blood product utilization, hospital stay, morbidity (acute myocardial infarction, acute ischaemic stroke, acute kidney injury, acute mesenteric ischemia and acute peripheral vascular ischemia) and mortality (30-day and in-hospital mortality), and economic outcomes including costs.

Composite measures, if relevant, were used. If composite measure were not relevant or available, individual measures were included. Data on relevant subgroup analyses (e.g. type of surgery), if available, were extracted/included. When papers reported outcomes for different periods (e.g. per year), we decided to only include the outcomes of the longest/latest period unless it was possible to pool the outcomes of all periods together. Exclude: outcomes with no raw data and/or effect estimated (e.g. only p-values, percentages).

Study design: Include: a systematic review: inclusion of the studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase are searched.

An experimental study: inclusion in case of one of the following study types: (quasi or non-) randomised controlled trial, controlled before and after study or controlled interrupted time series, and the data are available.

An observational study: inclusion in case of one of the following study types: cohort and case-control study, (un)controlled before and after study or (un)controlled interrupted time series, and the data are available.

Exclude: case series, cross-sectional studies**,** animal studies, *ex vivo* or *in vitro* studies, studies reporting no quantitative data, studies reporting only means, but no SDs, effect sizes, p-values.

Language: English, French and German

PICO 16 – PBM PROMOTIONAL TOOLS: BEHAVIOURAL INTERVENTIONS

Is a specific behavioural intervention to promote the implementation of a PBM program [Intervention] more effective to improve clinical and economic outcomes [Outcome] compared

to no/another behavioural intervention[Comparison]?[123-141]

PICO 16 – Search strategies

See PICO 15

PICO 16 – Selection criteria

Population: *Included:* patients who might need transfusion (surgical and non-surgical patients/ acute and chronic disease patients/ adults and children).

Intervention: *Included:* the following behavioural interventions to promote the implementation of a PBM program:

- Behavioral interventions intended to promote appropriate blood usage.
  - ➔ Guidelines
  - ➔ Educational sessions (group or individual)
  - ➔ A reminder system (computer aids or transfusion forms containing reminders of appropriate criteria for transfusion)
  - ➔ Audit with feedback (retrospective audits with feedback given to individuals or groups after the transfusion)
  - ➔ Audit with approval (audit with approval needed before transfusion of products).

  If guidelines were disseminated or accompanied by educational sessions, then the study interventions were classified as guidelines and education.

Comparison: another or no intervention

Outcome: *Included:* Tinmouth systematic review (effectiveness behavioural interventions to reduce blood product utilization): the number of units transfused and the proportion of patients who received transfusions. Additional outcome: financial outcomes. *Excluded:* papers that only narratively/descriptively reported on blood product utilization outcomes (i.e. no raw data and/or effect estimated, only p-values, percentages).

Study design: Include: 1) we used the systematic review by Tinmouth et al (2005), the thesis that performed an update of the Tinmouth review until 2010 and we performed an update of the Tinmouth review between 2010 and 2017. Included individual studies involve both an intervention group and a control group. Controlled clinical trials that mandated adherence to a specific transfusion trigger or protocol were excluded.

Language: English, French and German

PICO 17 – PBM PROMOTIONAL TOOLS: DECISION SUPPORT SYSTEMS

Is a specific decision support system to promote the implementation of a PBM program [Intervention] more effective to improve clinical and economic outcomes [Outcome] compared to no intervention or another decision support system/behavioural intervention [Comparison]?[142-145]

PICO 17 – Search strategies

We used the evidence from the Cochrane systematic review by Fisher et al. 'Computer decision support systems to promote appropriate use of blood products.', which will be published in 2018.

PICO 17 – Selection criteria

Population: *Included:* all people (adults and children) who are considered for transfusion of red blood cells (RBCs), platelets, plasma, cryoprecipitate, or granulocytes in any clinical setting. *Excluded:* people who receive other blood products e.g. intravenous immunoglobulin, factor VIII.

Intervention: *Included:* Any electronic/computerised DSS that provides clinicians with recommendations on RBC, platelet, plasma, cryoprecipitate, or granulocyte ordering at the time the decision to order a transfusion is being made based on individual patient characteristics.

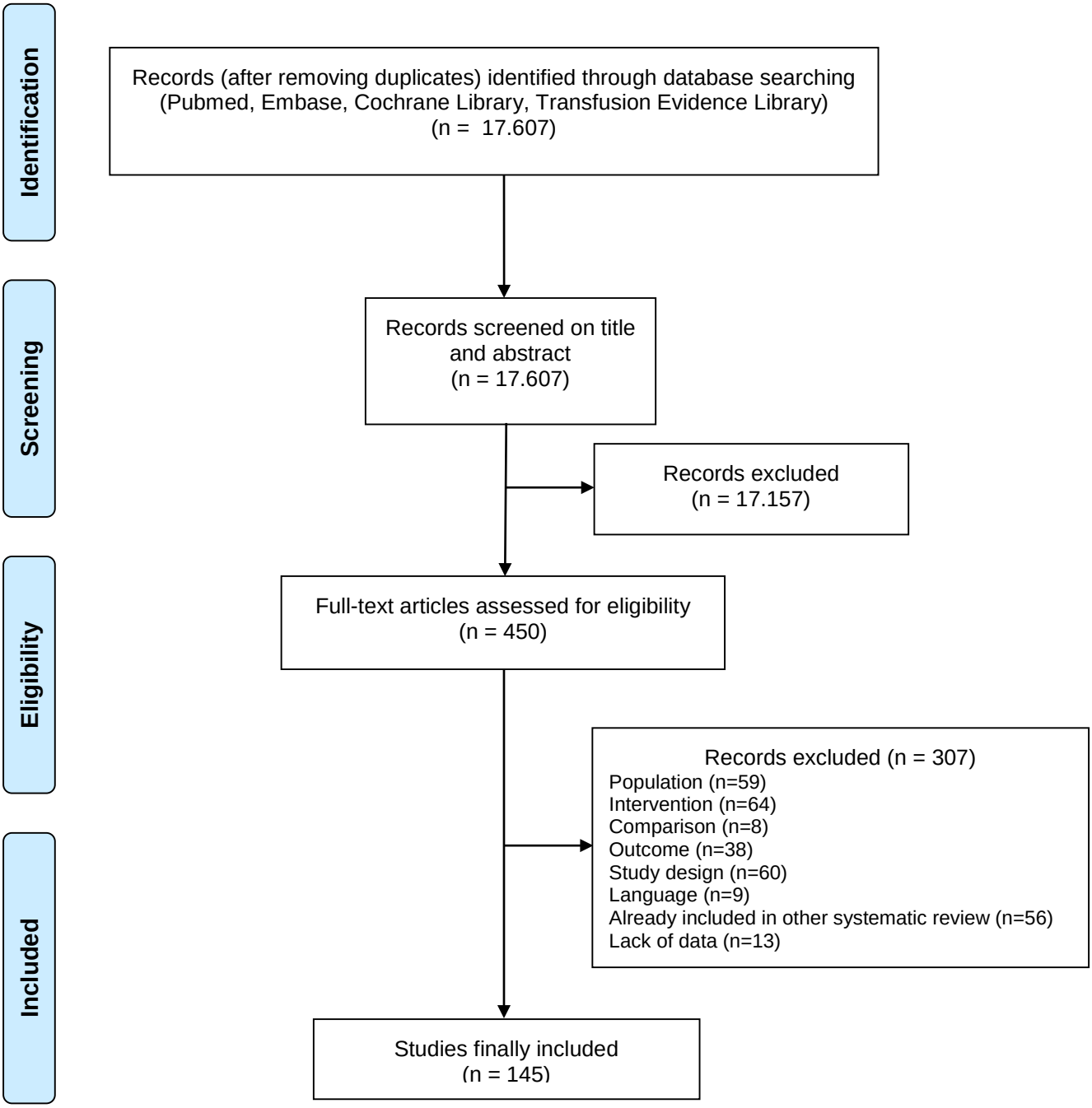
Comparison: no DSS

Outcome: *Included:*

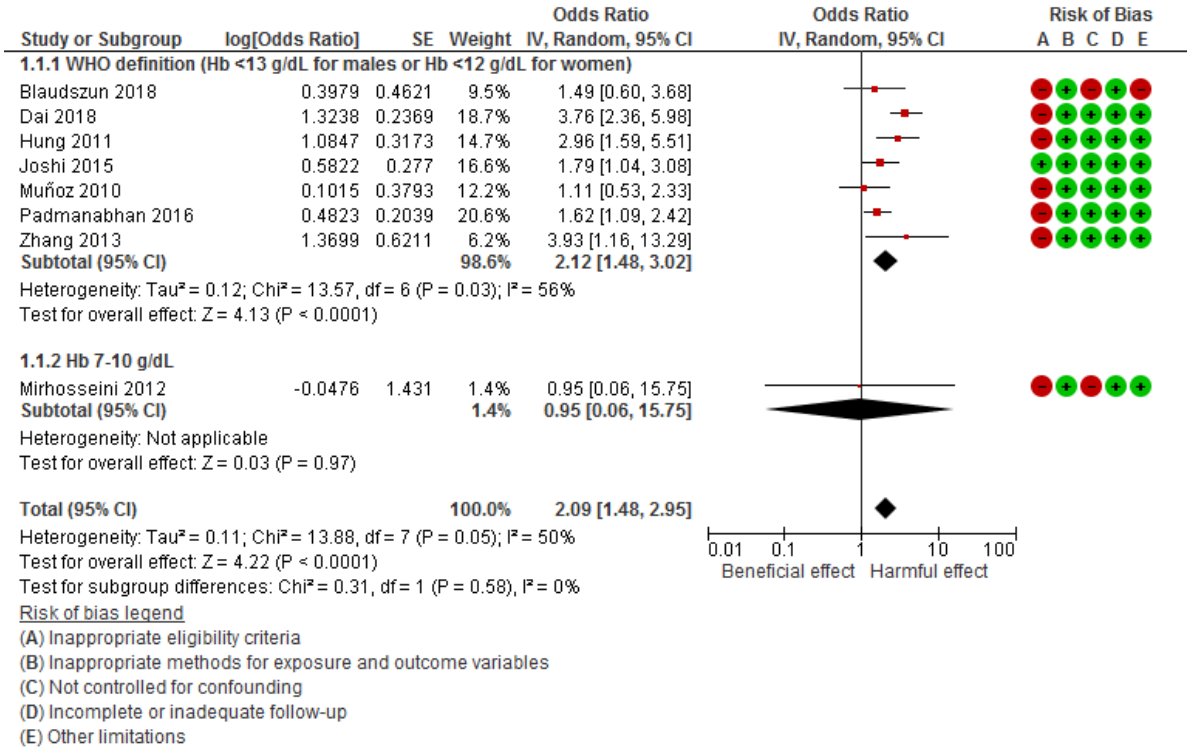
- Primary outcomes
  - ➔ Proportion of participants who receive transfusions
  - ➔ Amount of blood product used per participant (number of units in adults and volume in mL in infants and children)
  - ➔ Serious adverse event (1) transfusion-related, transfusion-transmitted infection, transfusion-associated circulatory overload, transfusion-associated dyspnea, acute transfusion reactions, 2) bleeding (including WHO grade 3 or 4, or equivalent or bleeding that requires an operation), 3) infection, 4) arterial or venous thromboembolism (including deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction).
- Secondary outcomes
  - ➔ Number of transfusions compliant with institutional transfusion guidelines
  - ➔ Blood count or coagulation parameter (e.g. haematocrit, haemoglobin, prothrombin time, partial thromboplastin time, or platelet count) preceding and after the transfusion.
  - ➔ Length of participant stay (in-hospital)
  - ➔ Length of participant stay (ICU)
  - ➔ All-cause mortality

Clinician workflow (additional time per intervention implemented)

eFigure 1. Flowchart Representing the Study-Selection Process of the Systematic Reviews



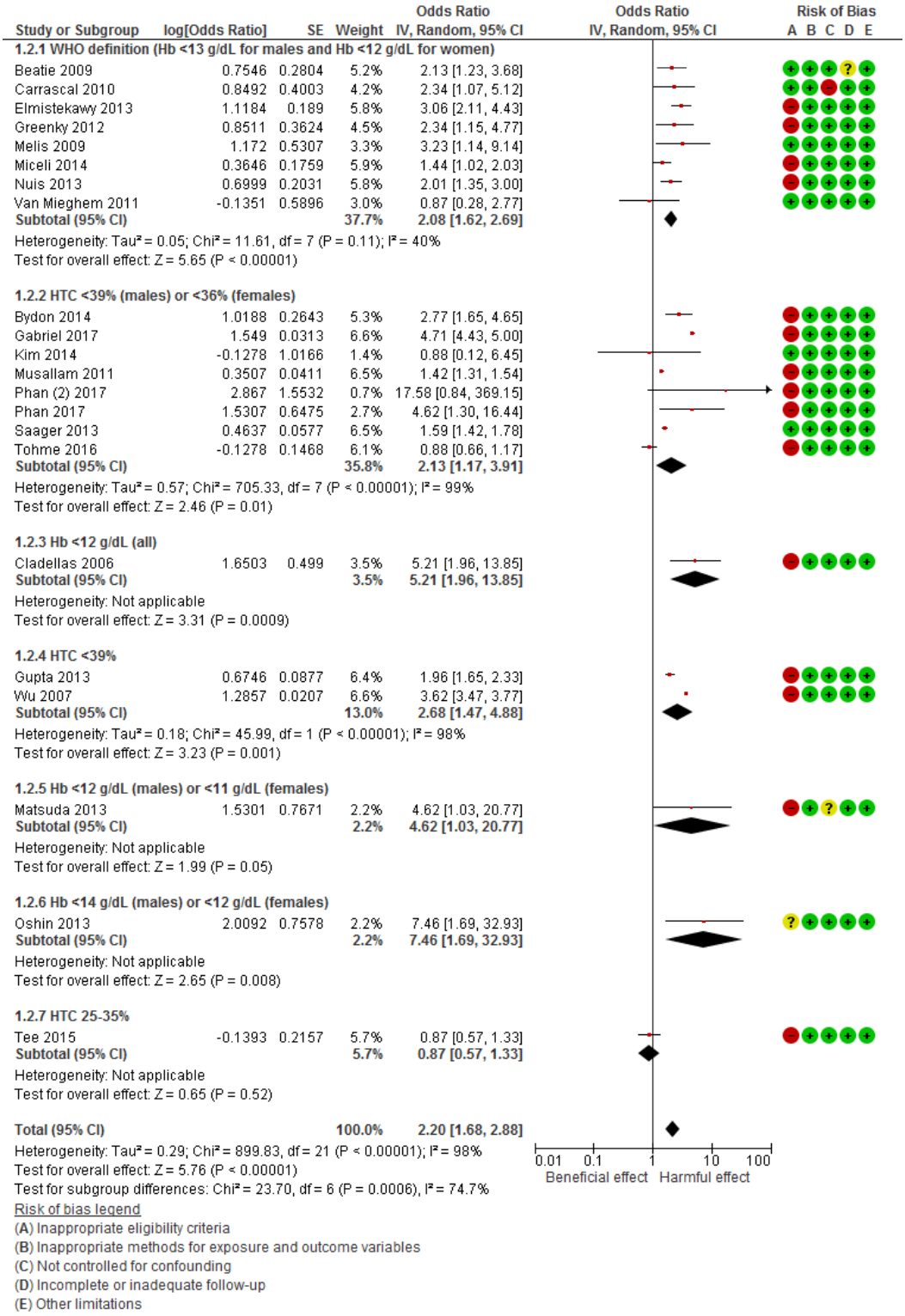
eFigure 2. Study-Specific Association Between Preoperative Anemia and Hospital Mortality



Each dot represents the OR of the respective study together with the 95% CI. The size of the box represents the weight of the study in the meta-analysis. Weights are from random-effects analysis.

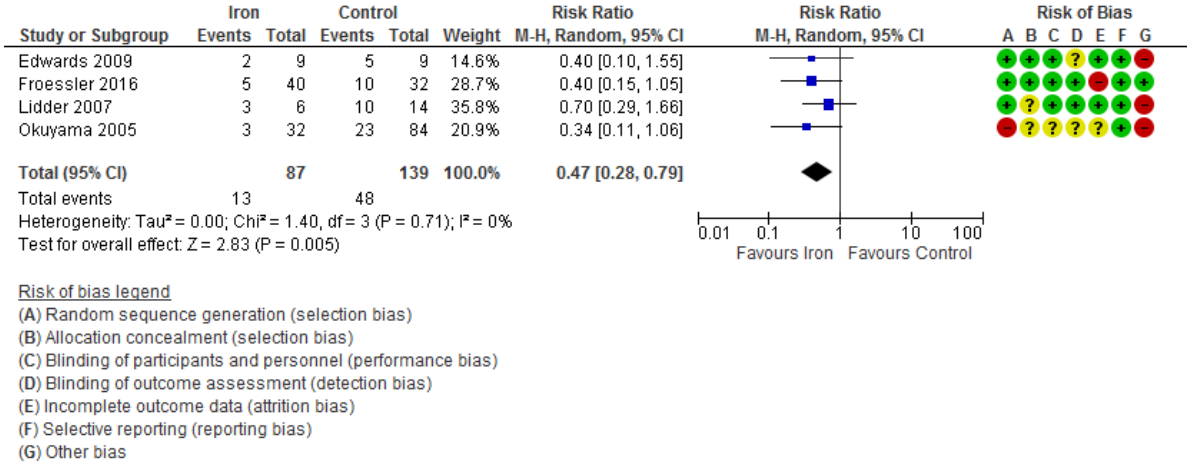
Low risk of bias, high risk of bias, unclear.

eFigure 3. Study-Specific Association Between Preoperative Anaemia and 30-Day Mortality



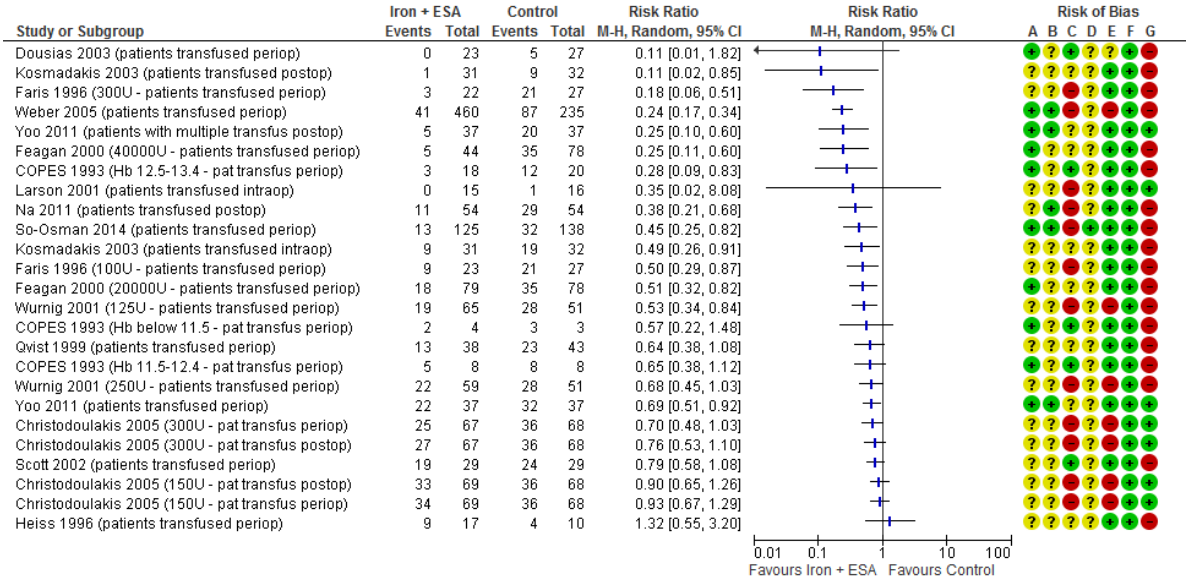
Each dot represents the OR of the respective study together with the 95% CI. The size of the box represents the weight of the study in the meta-analysis. Weights are from random-effects analysis. Low risk of bias, high risk of bias, unclear.

eFigure 4. Study-Specific Risk Ratios Representing the Association Between Iron Supplementation (Compared to Placebo/Usual Care) and the Number of RBC Transfusions



Each dot represents the RR of the respective study together with the 95% CI. The size of the box represents the weight of the study in the meta-analysis. Weights are from random-effects analysis. + Low risk of bias, − high risk of bias, ? unclear.

eFigure 5. Study-Specific Risk Ratios Representing the Association Between Iron+ESA Supplementation (Compared to Placebo/No Treatment/Usual Care) and the Number of RBC Transfusions

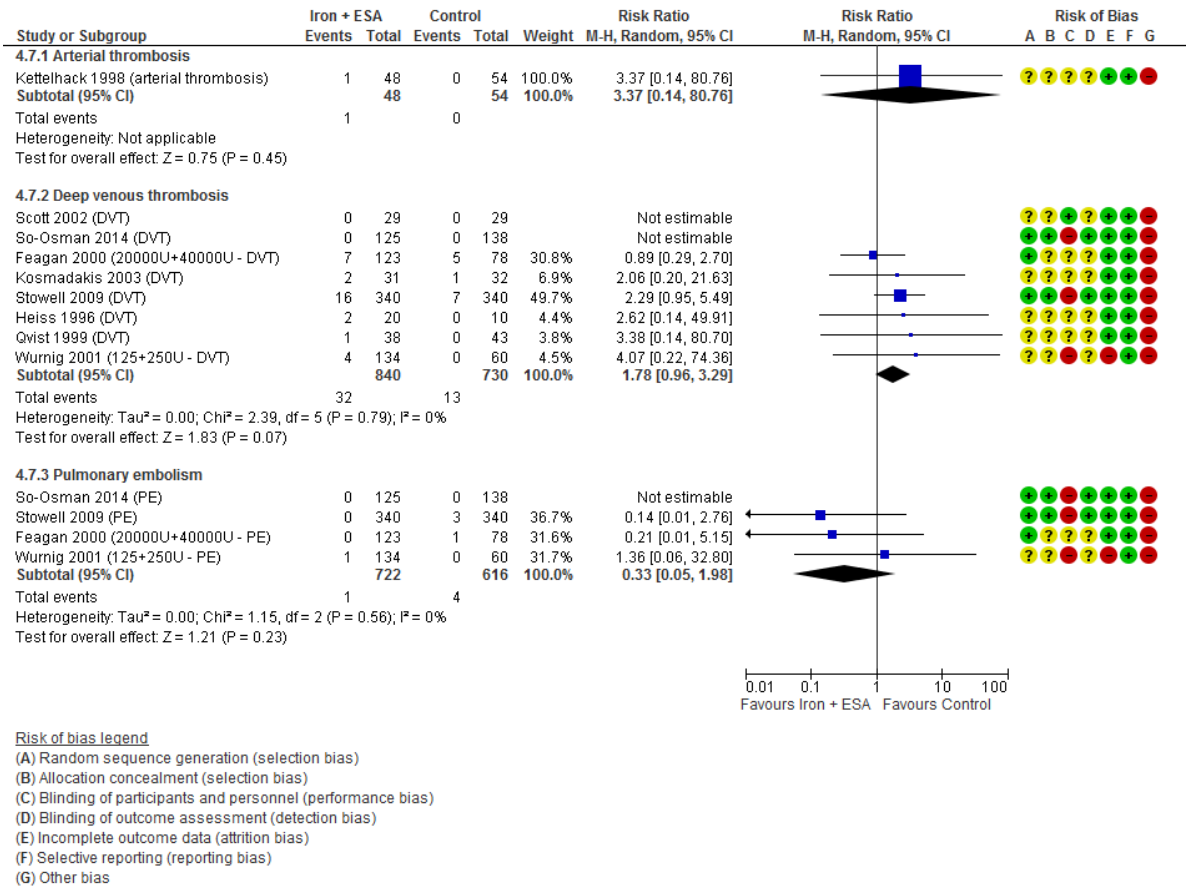


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

Each dot represents the RR of the respective study together with the 95% CI. The size of the box represents the weight of the study in the meta-analysis. Weights are from random-effects analysis.

+ Low risk of bias, − high risk of bias, ? unclear.

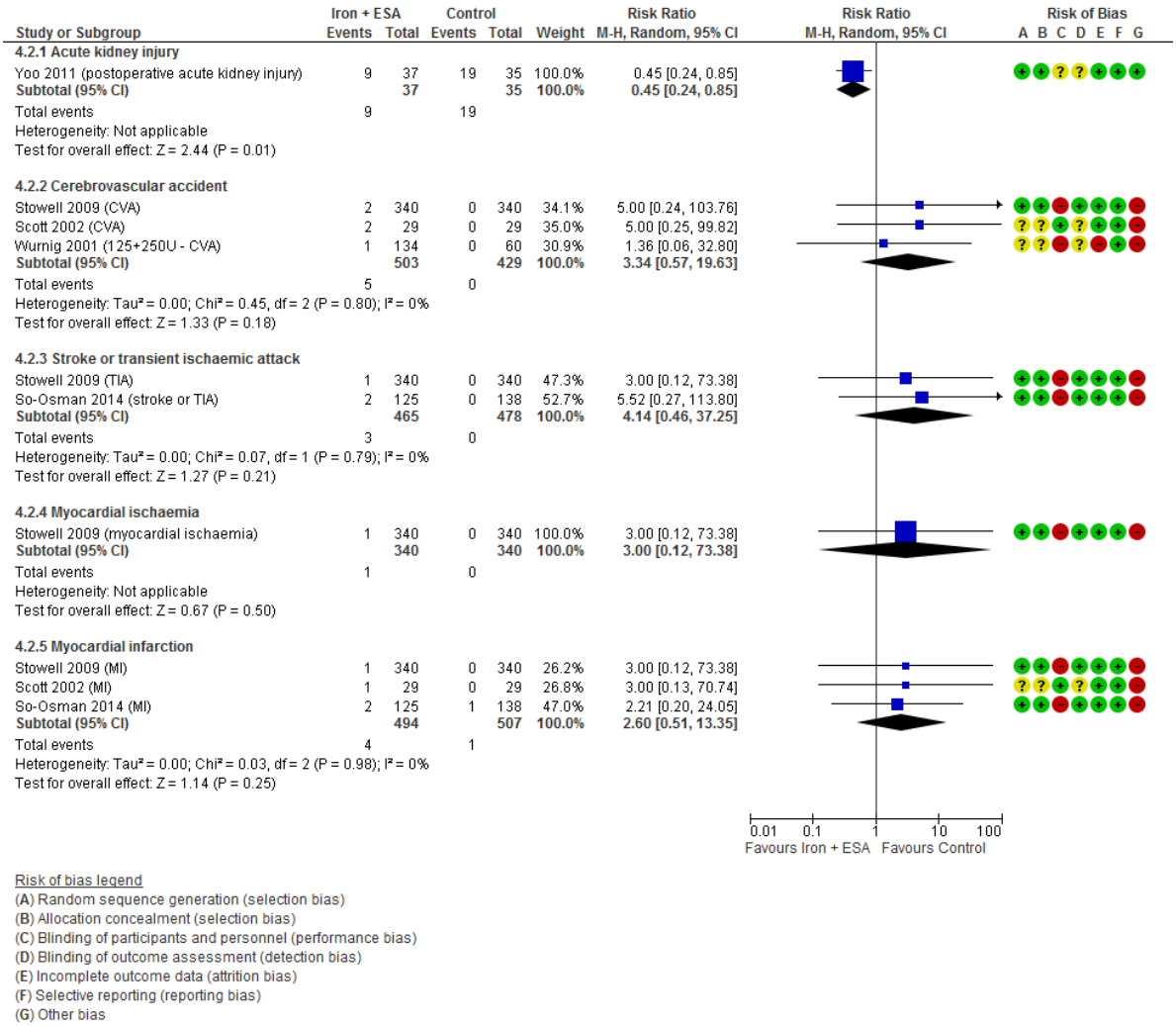
eFigure 6. Study-Specific Risk Ratios Representing the Association Between Iron+ESA Supplementation (Compared to Placebo/No Treatment/Usual Care) and the Number of Thromboembolic Events



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

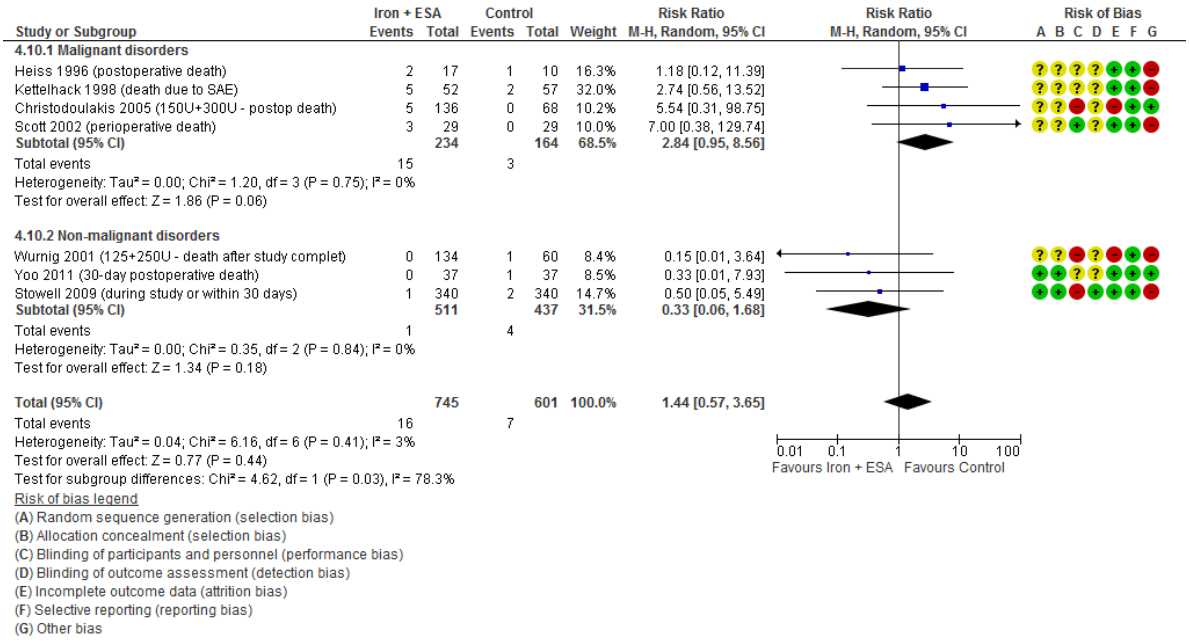
Each dot represents the RR of the respective study together with the 95% CI. The size of the box represents the weight of the study in the meta-analysis. Weights are from random-effects analysis. + Low risk of bias, − high risk of bias, ? unclear.

eFigure 7. Study-Specific Risk Ratios Representing the Association Between Iron+ESA Supplementation (Compared to Placebo/No Treatment/Usual Care) and the Number of Anaemia-Associated Ischaemic Events



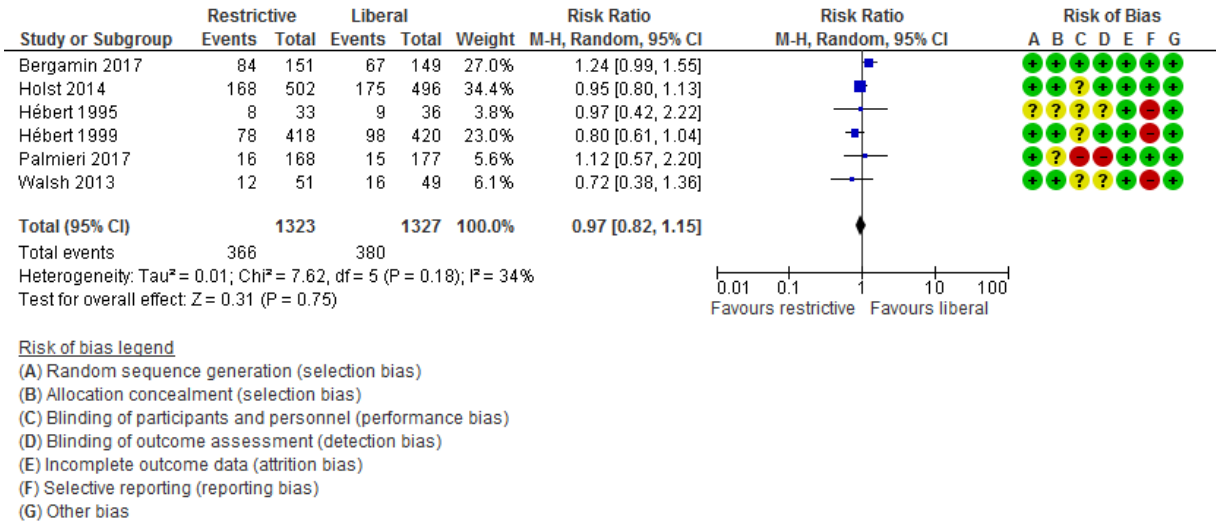
Each dot represents the RR of the respective study together with the 95% CI. The size of the box represents the weight of the study in the meta-analysis. Weights are from random-effects analysis. Low risk of bias, high risk of bias, unclear.

eFigure 8. Study-Specific Risk Ratios Representing the Association Between Iron+ESA Supplementation (Compared to Placebo/No Treatment/Usual Care) and All-Cause Mortality Rates



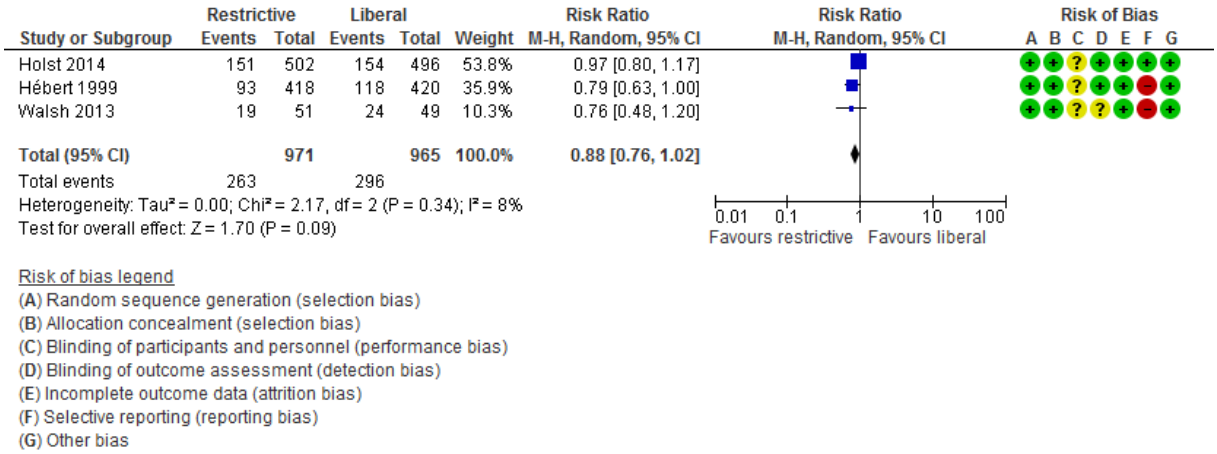
Each dot represents the RR of the respective study together with the 95% CI. The size of the box represents the weight of the study in the meta-analysis. Weights are from random-effects analysis. + Low risk of bias, − high risk of bias, ? unclear.

eFigure 9. Study-Specific Risk Ratios Representing the Association Between the Use of a More Restrictive RBC Transfusion Strategy (Compared to a More Liberal RBC Transfusion Strategy) and 30-day Mortality in Critically Ill, But Clinically Stable Intensive Care Patients



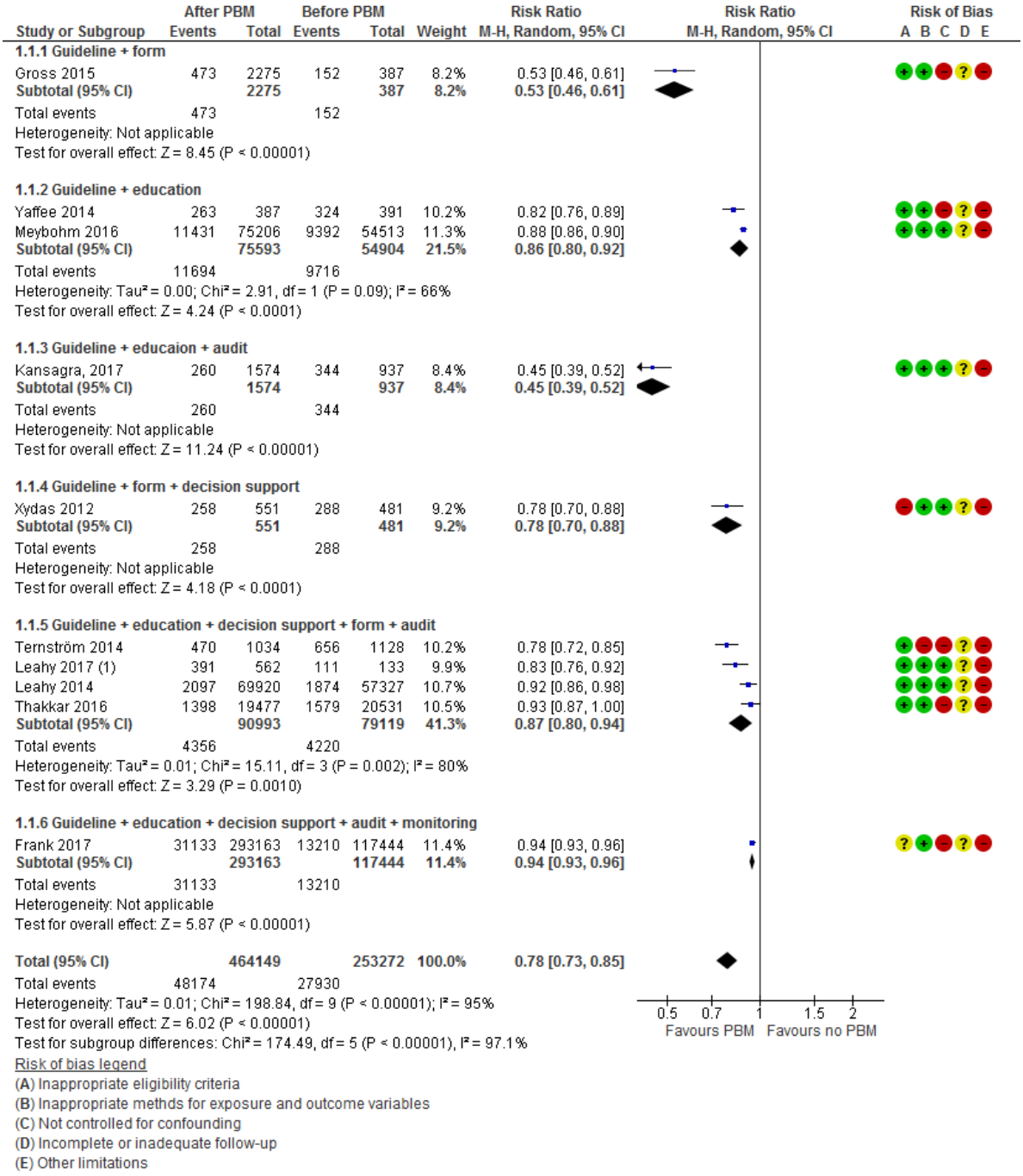
Each dot represents the RR of the respective study together with the 95% CI. The size of the box represents the weight of the study in the meta-analysis. Weights are from random-effects analysis. + Low risk of bias, − high risk of bias, ? unclear.

eFigure 10. Study-Specific Risk Ratios Representing the Association Between the Use of a More Restrictive RBC Transfusion Strategy (Compared to a More Liberal RBC Transfusion Strategy) and 30-day Mortality in Critically Ill, But Clinically Stable Intensive Care Patients



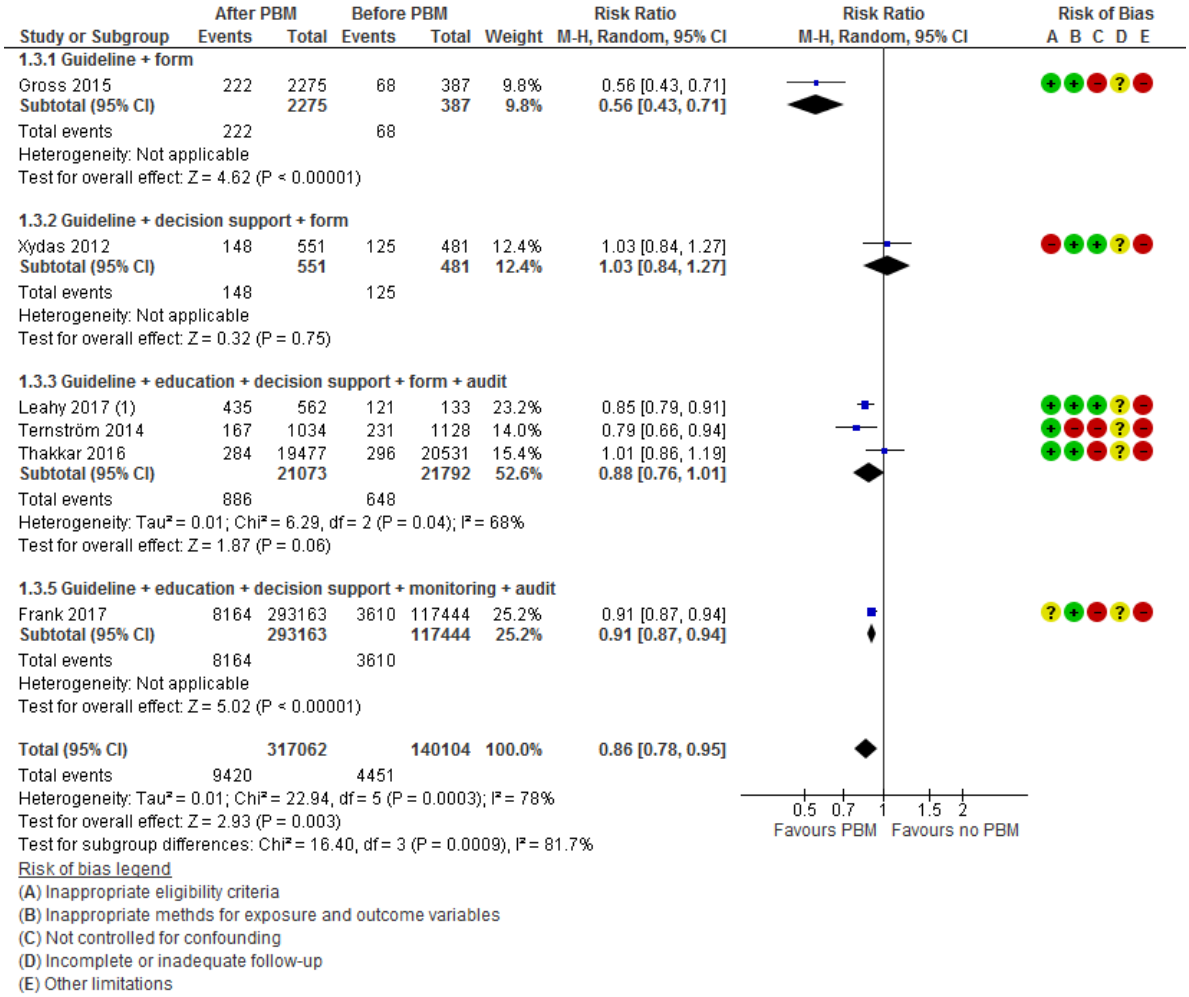
Each dot represents the RR of the respective study together with the 95% CI. The size of the box represents the weight of the study in the meta-analysis. Weights are from random-effects analysis. + Low risk of bias, − high risk of bias, ? unclear.

eFigure 11. Study-Specific Risk Ratios Representing the Association Between the Implementation of a Comprehensive PBM Program (Compared to Before the Implementation) and the Number of Patients Receiving RBC Transfusion



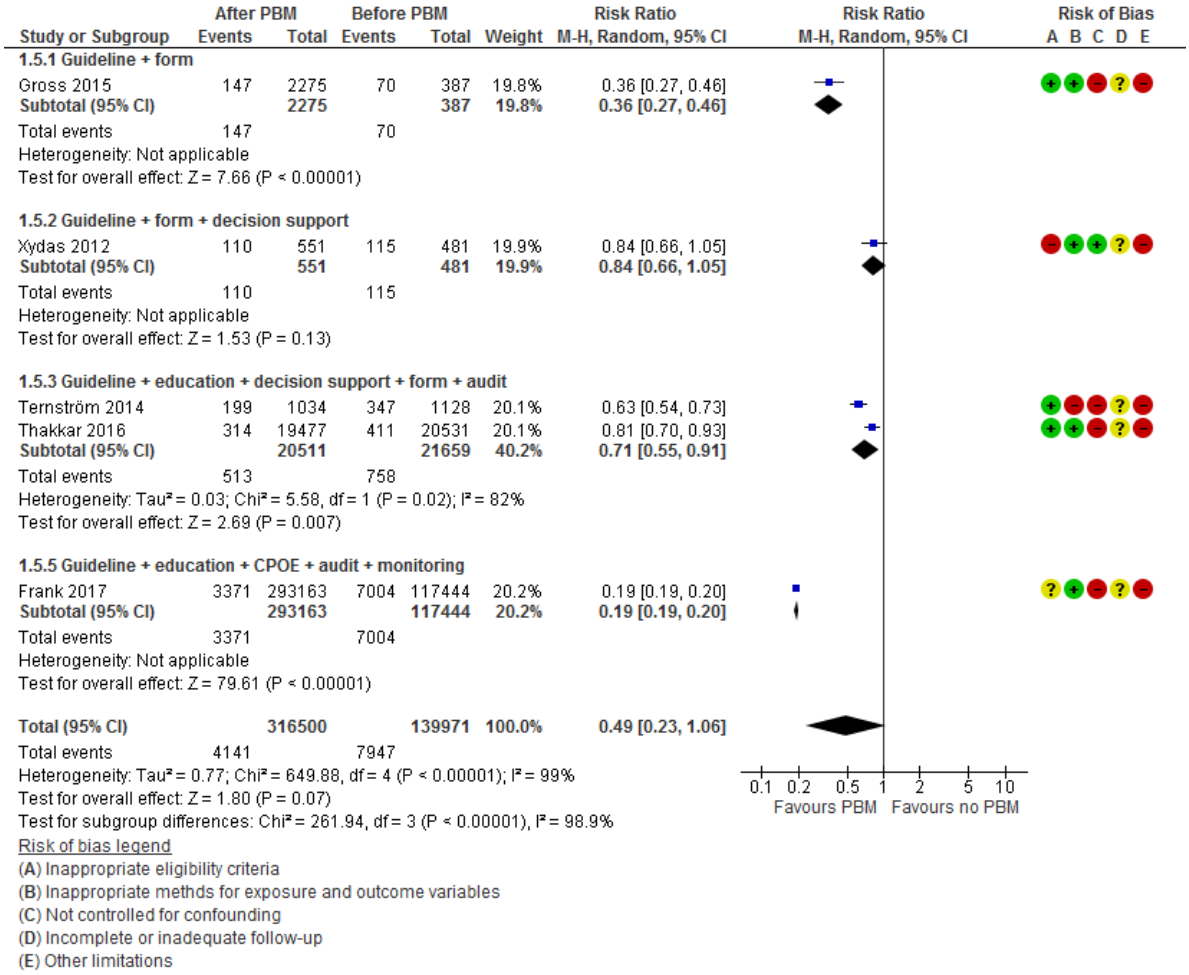
Each dot represents the RR of the respective study together with the 95% CI. The size of the box represents the weight of the study in the meta-analysis. Weights are from random-effects analysis. + Low risk of bias, − high risk of bias, ? unclear.

eFigure 12. Study-Specific Risk Ratios Representing the Association Between the Implementation of a Comprehensive PBM Program (Compared to Before the Implementation) and the Number of Patients Receiving PLT Transfusion



Each dot represents the RR of the respective study together with the 95% CI. The size of the box represents the weight of the study in the meta-analysis. Weights are from random-effects analysis. Low risk of bias, high risk of bias, unclear.

eFigure 13. Study-Specific Risk Ratios Representing the Association Between the Implementation of a Comprehensive PBM Program (Compared to Before the Implementation) and the Number of Patients Receiving FFP Transfusion



Each dot represents the RR of the respective study together with the 95% CI. The size of the box represents the weight of the study in the meta-analysis. Weights are from random-effects analysis. + Low risk of bias, − high risk of bias, ? unclear

eFigure 14. Clinical and Research Recommendations: Preoperative Anemia

- Strong recommendation, low-quality evidence
- Conditional recommendation, moderate-quality evidence
- Conditional recommendation, low-quality evidence
- Research recommendation, low-quality evidence
- Research recommendation, no evidence included

Abbreviation

ESAs	Erythropoiesis Stimulating Agents
Hb	Hemoglobin
RBC	(packed) Red Blood Cells

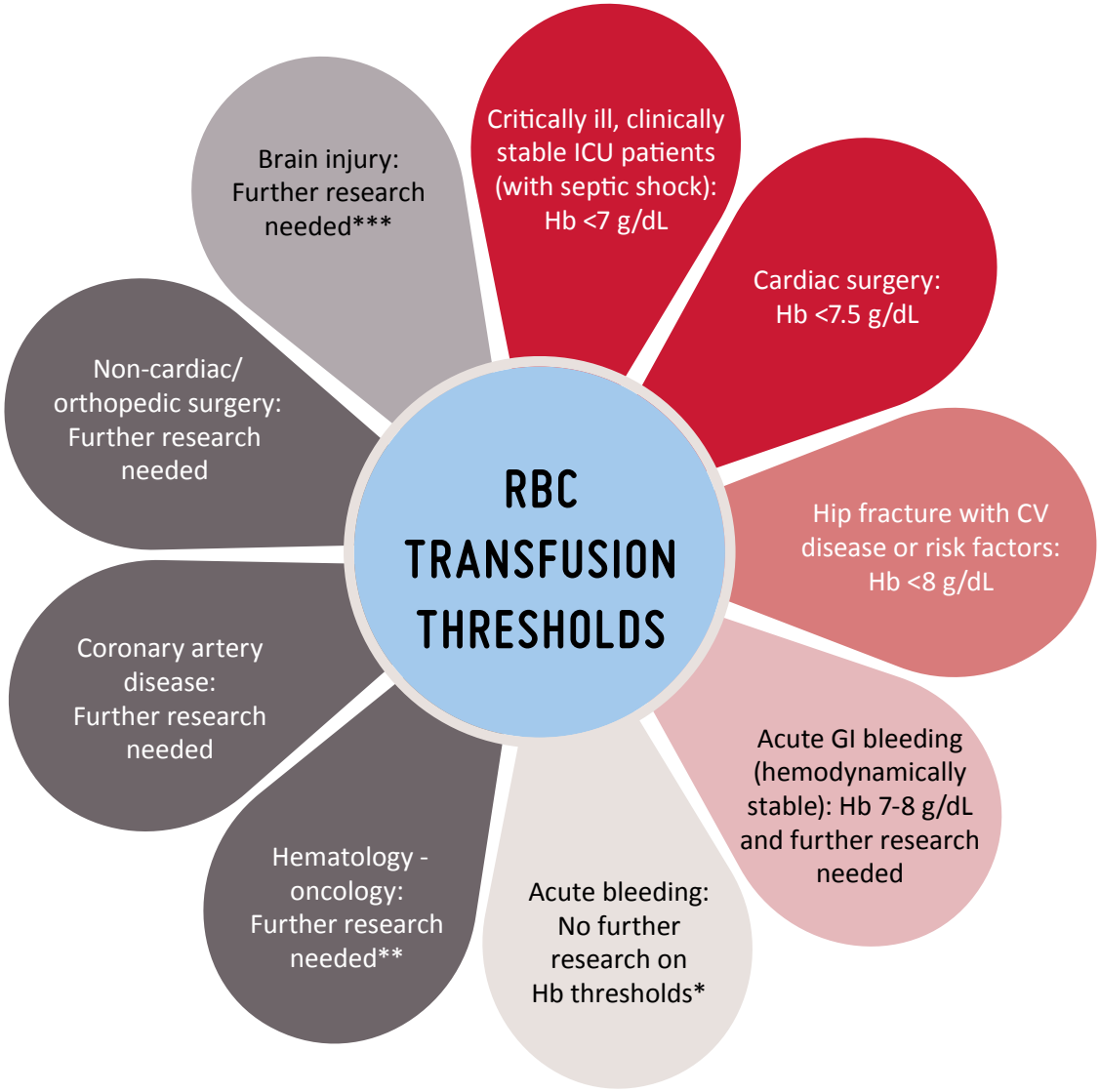
* Choice of iron formulation and administration based on the degree of anemia, time to surgery procedure and the ability to absorb and tolerate oral iron

** Take individual transfusion probability, etiology of anemia and thromboembolic risk into account

*** Focus on long term (un-)desirable effects, optimal dose, type of surgery (particular in cancer surgery), co-presence of iron-deficiency, and cost-effectiveness

eFigure 15. Clinical and Research Recommendations: RBC Transfusion Thresholds

- Strong recommendation, moderate-quality evidence
- Conditional recommendation, moderate-quality evidence
- Conditional + research recommendation, low-quality evidence
- Research recommendation, low-quality evidence
- Research recommendation, very-low quality evidence
- No evidence found



Abbreviation

CV	Cardiovascular
GI	Gastro-intestinal
Hb	Hemoglobin
ICU	Intensive Care Unit
RBC	(packed) Red Blood Cells

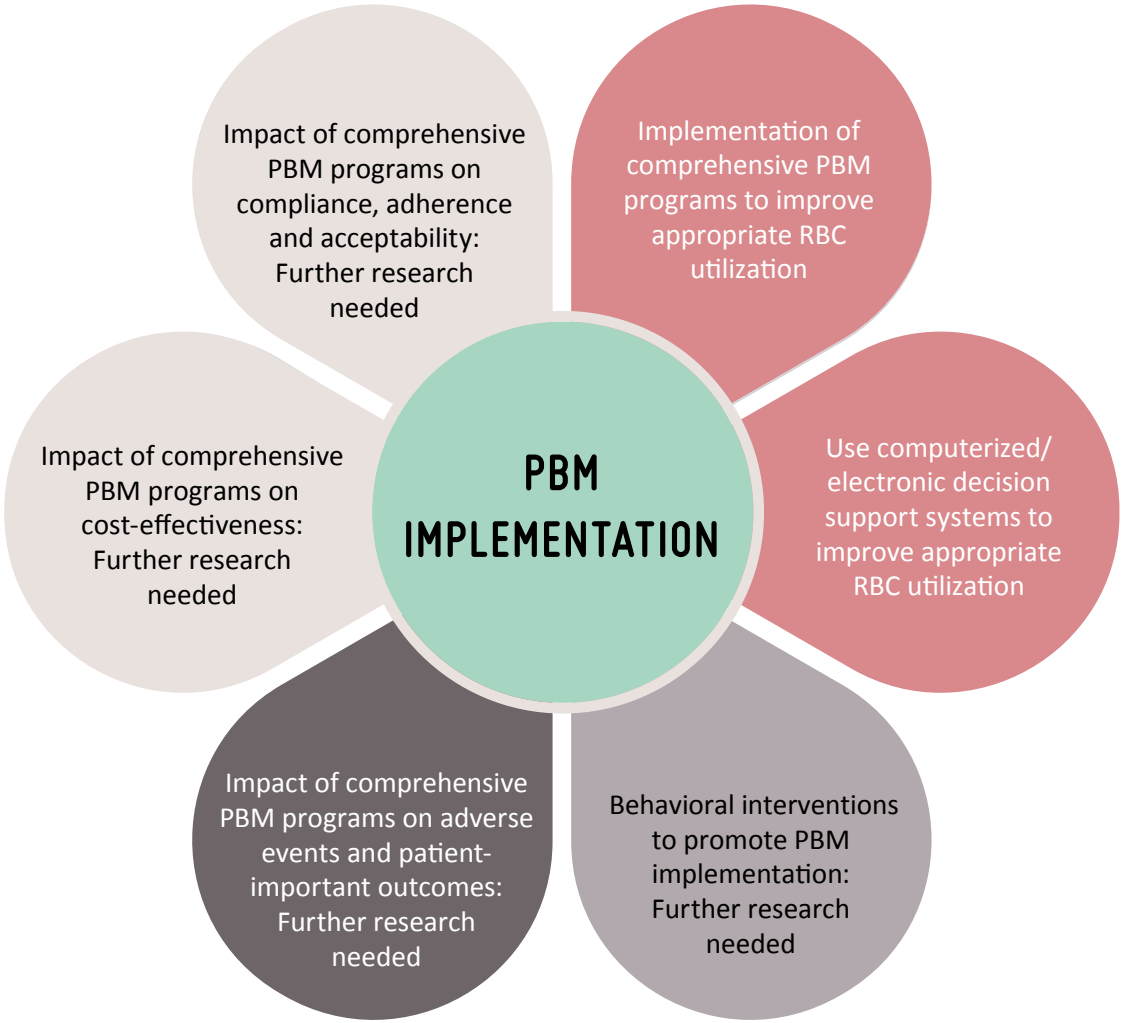
* For patients with critical bleeding (major blood loss), Hb level is not the most important, or deciding, factor in transfusion management. It is difficult to perform studies in exsanguinating patients, and they have been excluded from most trials. Stopping the bleeding is the priority – refer to published national/international guidelines on management of massive hemorrhage requiring transfusion support.

** Future research should focus on patients with non-malignant hematological disorders and patients undergoing chemotherapy, not surgery for solid tumors.

*** Patients with cerebral perfusion disorders or acute central nervous system injury (excluded: sickle cell disease)

eFigure 16. Clinical and Research Recommendations: PBM Implementation

- Conditional recommendation, low-quality evidence
- Research recommendation, low-quality evidence
- Research recommendation, very-low quality evidence
- Research recommendation, no evidence included



Abbreviation

PBM Patient Blood Management
RBC (packed) Red Blood Cells

eTable 1. Summary of Results of the ICC PBM Panel Decisions for PICO Questions 1 to 3: Preoperative Anaemia

PICO question 1: In elective surgery patients [Population], is preoperative anaemia [Intervention/Risk factor] a risk factor for adverse clinical or economic outcomes [Outcome] compared to no preoperative anaemia [Comparison]?

PICO question 2: In elective surgery preoperative patients [Population], should Hb of 130 g/L (Index test) (versus [comparator test] [Comparison]) be used to diagnose anemia [Outcome]?

Importance of outcomes
Critical outcomes: 30-day mortality, hospital mortality, acute myocardial infarction, acute ischaemic stroke, acute kidney injury
Important outcomes: acute mesenteric ischaemia, acute peripheral vascular ischaemia

Overview judgements 10 items Evidence-to-Decision framework

desirable effects	undesirable effects	certainty of evidence	values	balance of effects	resources	cost effectiveness	equity	acceptability	feasibility
Trivial	moderate	low	no important uncertainty/variability **Opinion poll results (n=35)** • Important uncertainty or variability (n=10) • Possibly important uncertainty or variability (n=5) • Probably no important uncertainty or variability (n=9) • No important uncertainty or variability (n=11)	favors the comparison	n.a. (no intervention)	n.a. (no intervention)	n.a. (no intervention)	n.a. (no intervention)	n.a. (no intervention)

Conclusions

- *Recommendation 1: The ICC-PBM expert panel recognizes preoperative anaemia as an important risk factor for perioperative mortality and morbidity, and therefore recommends to detect and manage preoperative anemia early enough before major elective surgery. (strong recommendation, low certainty in the evidence of effects).*

General justification: Based on the magnitude of the undesirable effects, the absence of any desirable effect, the absence of any risk, the low certainty of evidence, and clear balance of effects.
Detailed justification: Desirable effects: none; Undesirable effects: moderate to large; substantial; Certainty of evidence: conditional recommendation due to low quality evidence with imprecise estimate.
Results opinion poll draft recommendation (plenary session with general audience, n=150 voters): 119 accept completely, 22 accept with some reservation, 7 accept with major reservation, 2 reject with reservation.

- *Research recommendation (including PICO question 2):The ICC-PBM guideline panel noted that the haemoglobin thresholds for definition of anaemia are heterogeneous in the literature. Therefore, the optimal thresholds and adequate cut-offs of hemoglobin levels need to be adressed in future studies.*

PICO question 3 A: In elective surgery patients with preoperative anemia [Population], is the use of prophylactic RBC transfusion [Intervention] effective to improve clinical and economic outcomes [Outcome] compared to no intervention/placebo/standard of care [Comparison]?

Importance of outcomes
Critical outcomes: mortality, acute myocardial infarction, acute ischaemic stroke, acute kidney injury
Important outcomes: acute mesenteric ischaemia, acute peripheral vascular ischaemia, length of hospital stay, any type of reported infection, RBC utilization, thromboembolic events.

Overview judgements 10 items Evidence-to-Decision framework

desirable effects	undesirable effects	certainty of evidence	values	balance of effects	resources	cost effectiveness	equity	acceptability	feasibility
Trivial	trivial	very low	no important uncertainty/variability **Opinion poll results (n=31)** • Important uncertainty or variability (n=6) • Possibly important uncertainty or variability (n=8) • Probably no important uncertainty or variability (n=6) • No important uncertainty or variability (n=11)	neither inter-vention, nor comparison favored	moderate costs	no included studies	probably reduced **Opinion poll results (n=29)** • Reduced (n=7) • Probably reduced (n=5) • Probably no impact (n=2) • Probably increased (n=6) • Increased (n=4) • Varies (n=3) • Don't know (n=2)	no **Opinion poll results (n=24)** • No (n=12) • Probably no (n=5) • Probably yes (n=2) • Yes (n=2) • Varies (n=2) • Don't know (n=1)	Yes **Opinion poll results (n=24)** No (n=6) Probably no (n=7) Probably yes (n=6) Yes (n=1) Varies (n=3) Don't know (n=1)

Conclusions
The ICC-PBM guideline panel decided to formulate no recommendation on the use of routine preoperative prophylactic transfusion in adult elective surgery patients with anaemia because there is no evidence of an advantage for this approach.
Results opinion poll draft recommendation (plenary session with general audience, n=150 voters): 96 accept completely, 39 accept with some reservation, 9 accept with major reservation, 5 reject with reservation, 1 reject completely.

PICO question 3 B: In elective surgery patients with preoperative anemia [Population], is iron supplementation [Intervention] effective to improve clinical and economic outcomes [Outcome] compared to no intervention/placebo/standard of care [Comparison]?

Importance of outcomes
Critical outcomes: mortality, acute myocardial infarction, acute ischaemic stroke, acute kidney injury
Important outcomes: acute mesenteric ischaemia, acute peripheral vascular ischaemia, length of hospital stay, any type of reported infection, RBC utilization, thromboembolic events.

Overview judgements 10 items Evidence-to-Decision framework

desirable effects	undesirable effects	certainty of evidence	values	balance of effects	resources	cost effectiveness	equity	acceptability	feasibility
Large	small	low	no important uncertainty/variability **Opinion poll results (n=31)** • Important uncertainty or variability (n=6) • Possibly important uncertainty or variability (n=8) • Probably no important uncertainty or variability (n=6) • No important uncertainty or variability (n=11)	probably favors intervention	varies	no included studies	probably increased **Opinion poll results (n=25)** • Reduced (n=1) • Probably reduced (n=2) • Probably no impact (n=3) • Probably increased (n=6) • Increased (n=5) • Varies (n=6) • Don't know (n=2)	yes **Opinion poll results (n=24)** No (n=0) Probably no (n=2) Probably yes (n=8) Yes (n=12) Varies (n=1) Don't know (n=1)	probably yes **Opinion poll results (n=24)** No (n=0) Probably no (n=0) Probably yes (n=7) Yes (n=12) Varies (n=4) Don't know (n=1)

Conclusions

- *Recommendation 2: The ICC-PBM expert panel suggests using iron supplementation in adult preoperative elective surgery patients with iron-deficient anaemia to reduce red blood cell transfusion rate (conditional recommendation, moderate certainty in the evidence of effects). The choice of the iron formulation and route should be based on the degree of anaemia, time to surgical procedure and ability to absorb and tolerate oral iron.*

General justification: High desirable effects, small undesirable effects,but low certainty of evidence.
Results opinion poll draft recommendation (plenary session with general audience, n=140 voters): 97 accept completely, 26 accept with some reservation, 11 accept with major reservation, 4 reject with reservation, 2 reject completely.

PICO question 3 C: In elective surgery patients with preoperative anemia [Population], are erythropoiesis-stimulating agents (ESAs) [Intervention] effective to improve clinical and economic outcomes [Outcome] compared to no intervention/placebo/standard of care [Comparison]?

Importance of outcomes
Critical outcomes: mortality, acute myocardial infarction, acute ischaemic stroke, acute kidney injury
Important outcomes: acute mesenteric ischaemia, acute peripheral vascular ischaemia, length of hospital stay, any type of reported infection, RBC utilization, thromboembolic events.

Overview judgements 10 items Evidence-to-Decision framework

desirable effects	undesirable effects	certainty of evidence	values	balance of effects	resources	cost effectiveness	equity	acceptability	feasibility
Moderate	trivial	very low	no important uncertainty/variability **Opinion poll results (n=31)** • Important uncertainty or variability (n=6) • Possibly important uncertainty or variability (n=8) • Probably no important uncertainty or variability (n=6) • No important uncertainty or variability (n=11)	unknown	varies	no included studies	not known **Opinion poll results (n=24)** • Reduced (n=0) • Probably reduced (n=5) • Probably no impact (n=1) • Probably increased (n=8) • Increased (n=3) • Varies (n=4) • Don't know (n=3)	not known **Opinion poll results (n=24)** • No (n=1) • Probably no (n=1) • Probably yes (n=10) • Yes (n=4) • Varies (n=6) • Don't know (n=2)	not known **Opinion poll results (n=23)** • No (n=0) • Probably no (n=1) • Probably yes (n=9) • Yes (n=5) • Varies (n=7) • Don't know (n=1)

Conclusions

- *Recommendation 3: The ICC-PBM expert panel suggests against the use of* erythropoiesis-stimulating agents (*ESA) routinely in general adult preoperative elective surgery patients with anaemia (conditional recommendation, low certainty in the evidence of effects).*

General justification: Heterogeneous desirable effects, low event rate for undesirable effects, unknown certainty of evidence**.**
Results opinion poll draft recommendation (plenary session with general audience, n=135 voters): 96 accept completely, 26 accept with some reservation, 10 accept with major reservation, 0 reject with reservation, 3 reject completely.

PICO question 3 D: In elective surgery patients with preoperative anemia [Population], is the use of iron supplementation + erythropoiesis-stimulating agents (ESAs) [Intervention] effective to improve clinical and economic outcomes [Outcome] compared to no intervention/placebo/standard of care [Comparison]?

Importance of outcomes
Critical outcomes: mortality, acute myocardial infarction, acute ischaemic stroke, acute kidney injury
Important outcomes: acute mesenteric ischaemia, acute peripheral vascular ischaemia, length of hospital stay, any type of reported infection, RBC utilization, thromboembolic events.

Overview judgements 10 items Evidence-to-Decision framework

desirable effects	undesirable effects	certainty of evidence	values	balance of effects	resources	cost effectiveness	equity	acceptability	feasibility
moderate	moderate	low	no important uncertainty/variability **Opinion poll results (n=31)**	neither inter-vention, nor comparison favored	not known	no included studies	not known **Opinion poll results (n=24)** • Reduced (n=0)	probably yes **Opinion poll results (n=24)** • No (n=1)	probably yes **Opinion poll results (n=23)** • No (n=0)

			• Important uncertainty or variability (n=6) • Possibly important uncertainty or variability (n=8) • Probably no important uncertainty or variability (n=6) • No important uncertainty or variability (n=11)				• Probably reduced (n=5) • Probably no impact (n=1) • Probably increased (n=8) • Increased (n=3) • Varies (n=4) • Don't know (n=3)	• Probably no (n=1) • Probably yes (n=10) • Yes (n=4) • Varies (n=6) • Don't know (n=2)	• Probably no (n=1) • Probably yes (n=9) • Yes (n=5) • Varies (n=7) • Don't know (n=1)

Conclusions

- *Recommendation 4: The ICC-PBM guideline panel suggests to consider the use of short-acting erythropoietins in addition to iron supplementation in adult preoperative elective major orthopedic surgery patients with haemoglobin levels < 13 g/dL, taking into account the individual transfusion probability, etiology of anemia and individual thromboembolic risk to reduce transfusion rates (conditional recommendation, low certainty in the evidence of effects).*

General justification: Low desirable effects but potential undesirable effects (because of a strong signal of increased risk of thromboembolic events), low certainty of evidence, unbalanced effects

Results opinion poll draft recommendation (plenary session with general audience, n=126 voters): 28 accept completely, 31 accept with some reservation, 18 accept with major reservation, 26 reject with reservation, 23 reject completely.

- *Research recommendation: The ICC-PBM expert panel called for further research to investigate the impact of using short-acting erythropoietins + iron supplementation in adult preoperative elective surgery patients with focus on long term (un)desirable effects, optimal dose, type of surgery (particular in cancer surgery), co-presence of iron deficiency, and cost effectiveness.*

n.a. = not applicable; “conditional“ = „weak“

eTable 2. Summary of Results of the ICC PBM Panel Decisions for PICO Questions 4 to 14: RBC Transfusion Triggers

PICO question 4: In critically ill, but clinically stable adult intensive care patients [Population], is the use of a restrictive transfusion threshold [Intervention] effective to reduce mortality and improve other clinical outcomes [Outcome] compared to a liberal transfusion threshold [Comparison]?

Importance of outcomes

Critical outcomes: 30-day mortality, hospital mortality, cardiac events, myocardial infarction,

Important outcomes: participants exposed to blood transfusion, units of blood transfused, haemoglobin concentration, congestive heart failure, sepsis-bacteraemia, pneumonia, pneumonia or wound infection, number of RBC transfusions, blood stream infections, wound infections, urinary tract infections,

Overview judgements 10 items Evidence-to-Decision framework

desirable effects	undesirable effects	certainty of evidence	values	balance of effects	resources	cost effectiveness	equity	acceptability	feasibility
Moderate	trivial	moderate	important uncertainty or variability **Opinion poll results (n=56)** • Important uncertainty or variability (n=26) • Possibly important uncertainty or variability (n=20) • Probably no important uncertainty or variability (n=8) • No important uncertainty or variability (n=2)	probably favors the interventions	Varies **Opinion poll results (n=56)** • Large costs (n=3) • Moderate costs (n=6) • Negligible costs and savings (n=5) • Moderate savings (n=16) • Large savings (n=10) • Varies (n=5) • Don't know (n=11)	no included studies	Varies **Opinion poll results (n=55)** • Reduced (n=2) • Probably reduced (n=3) • Probably no impact (n=16) • Probably increased (n=16) • Increased (n=2) • Varies (n=7) • Don't know (n=9)	probably yes **Opinion poll results (n=55)** • No (n=0) • Probably no (n=4) • Probably yes (n=23) • Yes (n=16) • Varies (n=8) • Don't know (n=4)	probably yes **Opinion poll results (n=53)** • No (n=0) • Probably no (n=1) • Probably yes (n=19) • Yes (n=28) • Varies (n=3) • Don't know (n=2)

Conclusions

Recommendation 5: The ICC-PBM expert panel recommends a restrictive RBC transfusion threshold (Hb <7 g/dL) in critically ill, but clinically stable intensive care patients (strong recommendation, moderate certainty in the evidence of effects).

General justification: This recommendation was justified by two main elements: there is no evidence of increased mortality or other undesirable effects, and there is a substantial reduction in red cell exposure and utilization.

Detailed justification: Of note, Hb 7g/dL threshold represents the value used in the included trials.

Results opinion poll draft recommendation (plenary session with general audience, n=110 voters): 77 accept completely, 25 accept with some reservation, 7 accept with major reservation, 1 reject with reservation.

PICO question 5: In elderly high risk (cardiovascular) patients undergoing orthopaedic or non-cardiac surgery [Population], is the use of a restrictive transfusion threshold [Intervention] effective to reduce mortality and improve other clinical outcomes [Outcome] compared to a liberal transfusion threshold [Comparison]?

Importance of outcomes

Critical outcomes: 30-day mortality, hospital mortality, 90-day mortality, cardiac events, myocardial infarction, CVA/stroke, thromboembolism, renal failure, inability to walk or death at 30/60 days

Important outcomes: patients exposed to RBC transfusion, RBC units transfused, haemoglobin concentration, congestive heart failure, sepsis-bacteraemia, pneumonia, pneumonia or wound infection, mental confusion, lower extremity physical activities of daily living at 30/60 days, instrumental activities of daily living at 30/60 days, energy/fatigue at 30/60 days, timed up and go test.

Overview judgements 10 items Evidence-to-Decision framework

desirable effects	undesirable effects	certainty of evidence	values	balance of effects	resources	cost effectiveness	equity	acceptability	feasibility
moderate	small	moderate	important uncertainty or variability **Opinion poll results (n=56)** • Important uncertainty or variability (n=26) • Possibly important uncertainty or variability (n=20) • Probably no important uncertainty or variability (n=8) • No important uncertainty or variability (n=2)	probably favors the intervention	Varies **Opinion poll results (n=56)** • Large costs (n=3) • Moderate costs (n=6) • Negligible costs and savings (n=5) • Moderate savings (n=16) • Large savings (n=10) • Varies (n=5) • Don't know (n=11)	no included studies	Varies **Opinion poll results (n=55)** • Reduced (n=2) • Probably reduced (n=3) • Probably no impact (n=16) • Probably increased (n=16) • Increased (n=2) • Varies (n=7) • Don't know (n=9)	probably yes **Opinion poll results (n=55)** • No (n=0) • Probably no (n=4) • Probably yes (n=23) • Yes (n=16) • Varies (n=8) • Don't know (n=4)	Yes **Opinion poll results (n=53)** • No (n=0) • Probably no (n=1) • Probably yes (n=19) • Yes (n=28) • Varies (n=3) • Don't know (n=2)

Conclusions

Recommendation 7: The ICC-PBM expert panel suggest a restrictive transfusion threshold (Hb <8 g/dL) in patients with hip fracture with cardiovascular disease or risk factors (conditional recommendation, moderate certainty in the evidence of effects).

General justification: No effect on mortality (although wide CI) or functional outcomes (walk independently at 60 days). However, uncertainty regarding undesirable effects, in particular AMI. Therefore weak recommendation. Patients with hip fracture comprise mainly of elderly people with comorbidity.
Results opinion poll draft recommendation (plenary session with general audience, n=111 voters): 52 accept completely, 40 accept with some reservation, 15 accept with major reservation, 2 reject with reservation, 2 reject completely.

PICO question 6: In patients with an acute gastrointestinal bleeding [Population], is the use of a restrictive transfusion threshold [Intervention] effective to reduce mortality and improve other clinical outcomes [Outcome] compared to a liberal transfusion threshold [Comparison]?

Importance of outcomes
Critical outcomes: 30-day mortality, hospital mortality, myocardial infarction, CVA/stroke, renal failure
Important outcomes: patients exposed to RBC transfusion, RBC units transfused, haemoglobin concentration, congestive heart failure, rebleeding, pneumonia, pneumonia or wound infection, function and fatigue

Overview judgements 10 items Evidence-to-Decision framework

desirable effects	undesirable effects	certainty of evidence	values	balance of effects	resources	cost effectiveness	equity	acceptability	feasibility
moderate	trivial	low	possibly important uncertainty or variability **Opinion poll results (n=56)** • Important uncertainty or variability (n=26) • Possibly important uncertainty or variability (n=20) • Probably no important uncertainty or variability (n=8) • No important uncertainty or variability (n=2)	probably favors the intervention	Varies **Opinion poll results (n=56)** • Large costs (n=3) • Moderate costs (n=6) • Negligible costs and savings (n=5) • Moderate savings (n=16) • Large savings (n=10) • Varies (n=5) • Don't know (n=11)	no included studies	Varies **Opinion poll results (n=55)** • Reduced (n=2) • Probably reduced (n=3) • Probably no impact (n=16) • Probably increased (n=16) • Increased (n=2) • Varies (n=7) • Don't know (n=9)	probably yes **Opinion poll results (n=55)** • No (n=0) • Probably no (n=4) • Probably yes (n=23) • Yes (n=16) • Varies (n=8) • Don't know (n=4)	Yes **Opinion poll results (n=53)** • No (n=0) • Probably no (n=1) • Probably yes (n=19) • Yes (n=28) • Varies (n=3) • Don't know (n=2)

Conclusions

Recommendation 8: The ICC-PBM expert panel suggests to use a restrictive transfusion threshold (Hb 7-8 g/dL) in acute GI bleeding patients (conditional recommendation, low certainty in the evidence of effects)

General justification: Two trials, both excluded exsanguinating patients. Lower mortality with restrictive strategy. No evidence of undesirable effects. Reduction in RBC exposure and utilisation.

Notes:

•PICO was "acute GI bleeding". But the study populations were limited to acute *upper* GI bleeding. •"Massive exsanguinating" patients excluded from the trials. No trials identified in lower GI bleeding. •Guidelines should emphasise that in the acutely bleeding patient, Hb is not the deciding factor for transfusion. •Trials used Hb triggers (e.g. Hb 7) to achieve specified Hb target ranges (e.g. Hb 7-9).

Results opinion poll draft recommendation (plenary session with general audience, n=140 voters): 97 accept completely, 26 accept with some reservation, 11 accept with major reservation, 4 reject with reservation, 2 reject completely.

PICO question 7: In patients with symptomatic coronary heart disease [Population], is the use of a restrictive transfusion threshold [Intervention] effective to reduce mortality and improve other clinical outcomes [Outcome] compared to a liberal transfusion threshold [Comparison]?

Importance of outcomes

Critical outcomes: 30-day mortality, hospital mortality, myocardial infarction, congestive heart failure, CVA/stroke, thromboembolism

Important outcomes: participants exposed to RBC transfusion, RBC units transfused, haemoglobin concentration, sepsis-bacteraemia, pneumonia, pneumonia or wound infection

Overview judgements 10 items Evidence-to-Decision framework

desirable effects	undesirable effects	certainty of evidence	values	balance of effects	resources	cost effectiveness	equity	acceptability	feasibility
small	moderate	low	important uncertainty or variability **Opinion poll results (n=56)** • Important uncertainty or variability (n=26) • Possibly important uncertainty or variability (n=20) • Probably no important uncertainty or	probably favors the comparison	Varies **Opinion poll results (n=56)** • Large costs (n=3) • Moderate costs (n=6) • Negligible costs and savings (n=5) • Moderate savings (n=16) • Large savings (n=10) • Varies (n=5)	no included studies	Varies **Opinion poll results (n=55)** • Reduced (n=2) • Probably reduced (n=3) • Probably no impact (n=16) • Probably increased (n=16) • Increased (n=2) • Varies (n=7) • Don't know (n=9)	probably yes **Opinion poll results (n=55)** • No (n=0) • Probably no (n=4) • Probably yes (n=23) • Yes (n=16) • Varies (n=8) • Don't know (n=4)	Yes **Opinion poll results (n=53)** • No (n=0) • Probably no (n=1) • Probably yes (n=19) • Yes (n=28) • Varies (n=3) • Don't know (n=2)

			variability (n=8) • No important uncertainty or variability (n=2)		• Don't know (n=11)				

Conclusions

The ICC-PBM guideline panel decided to formulate no recommendation on the use of restrictive transfusion threshold in adult patients with acute coronary syndrome or other ischemic heart disease because of the concern over the possibility for undesirable effects in the restrictive group.

Results opinion poll draft recommendation (plenary session with general audience, n=119 voters): 107 accept completely, 7 accept with some reservation, 4 accept with major reservation, 1 reject completely.

PICO question 8: In patients with septic shock [Population], is the use of a restrictive transfusion threshold [Intervention] effective to reduce mortality and improve other clinical outcomes [Outcome] compared to a liberal transfusion threshold [Comparison]?

Importance of outcomes, overview judgements 10 items Evidence-to-Decision framework and conclusions

See PICO question 4: The ICC-PBM panel decided to combine the evidence of PICO questions 4 and 8 because of overlap in populations (critically ill intensive care patients with septic shock).

PICO question 9: In patients undergoing cardiac surgery [Population], is the use of a restrictive transfusion threshold [Intervention] effective to reduce mortality and improve other clinical outcomes [Outcome] compared to a liberal transfusion threshold [Comparison]?

Importance of outcomes

Critical outcomes: 30-day mortality, hospital mortality, 90-day mortality, cardiac events, myocardial infarction, CVA/stroke, renal failure

Important outcomes: patients exposed to RBC transfusion, RBC units transfused, haemoglobin concentration, congestive heart failure, rebleeding, sepsis-bacteraemia, pneumonia, pneumonia or wound infection, thromboembolism, health-related quality of life, vascular morbidity, pulmonary morbidity, gastrointestinal morbidity, reoperative morbidity.

Overview judgements 10 items Evidence-to-Decision framework

desirable effects	undesirable effects	certainty of evidence	values	balance of effects	resources	cost effectiveness	equity	acceptability	feasibility
moderate	trivial	moderate	important uncertainty or variability **Opinion poll results (n=56)** • Important uncertainty or variability (n=26)	probably favors the intervention	Varies **Opinion poll results (n=56)** • Large costs (n=3) • Moderate costs (n=6)	no included studies	Varies **Opinion poll results (n=55)** • Reduced (n=2) • Probably reduced (n=3)	probably yes **Opinion poll results (n=55)** • No (n=0) • Probably no (n=4) • Probably yes (n=23)	probably yes **Opinion poll results (n=53)** • No (n=0) • Probably no (n=1) • Probably yes (n=19)

			• Possibly important uncertainty or variability (n=20) • Probably no important uncertainty or variability (n=8) • No important uncertainty or variability (n=2)		• Negligible costs and savings (n=5) • Moderate savings (n=16) • Large savings (n=10) • Varies (n=5) • Don't know (n=11)		• Probably no impact (n=16) • Probably increased (n=16) • Increased (n=2) • Varies (n=7) • Don't know (n=9)	• Yes (n=16) • Varies (n=8) • Don't know (n=4)	• Yes (n=28) • Varies (n=3) • Don't know (n=2)

Conclusions

Recommendation 6: The ICC-PBM expert panel recommends a restrictive RBC transfusion threshold (Hb <7.5 g/dL) in cardiac surgery patients (strong recommendation, moderate certainty in the evidence of effects).

General justification: No difference in mortality or other undesirable effects, and substantial reduction in red cell exposure and utilisation.

Results opinion poll draft recommendation (plenary session with general audience, n=114 voters): 74 accept completely, 26 accept with some reservation, 11 accept with major reservation, 3 reject with reservation.

PICO question 10: In adult haematological patients [Population], is the use of a restrictive transfusion threshold [Intervention] effective to reduce mortality and improve other clinical outcomes [Outcome] compared to a liberal transfusion threshold [Comparison]?

Importance of outcomes

Critical outcomes: 30-day mortality

Important outcomes: patients exposed to RBC transfusion, RBC units transfused, bleeding events, length of hospital stay, fatigue scale score

Overview judgements 10 items Evidence-to-Decision framework

desirable effects	undesirable effects	certainty of evidence	values	balance of effects	resources	cost effectiveness	equity	acceptability	feasibility
Trivial	trivial	low	important uncertainty or variability **Opinion poll results (n=56)** • Important uncertainty or variability (n=26)	does not favor either the intervention or the comparison	Varies **Opinion poll results (n=56)** • Large costs (n=3) • Moderate costs (n=6)	no included studies	Varies **Opinion poll results (n=55)** • Reduced (n=2) • Probably reduced (n=3)	probably yes **Opinion poll results (n=55)** • No (n=0) • Probably no (n=4) • Probably yes (n=23)	probably yes **Opinion poll results (n=53)** • No (n=0) • Probably no (n=1) • Probably yes (n=19)

			• Possibly important uncertainty or variability (n=20) • Probably no important uncertainty or variability (n=8) • No important uncertainty or variability (n=2)		• Negligible costs and savings (n=5) • Moderate savings (n=16) • Large savings (n=10) • Varies (n=5) • Don't know (n=11)		• Probably no impact (n=16) • Probably increased (n=16) • Increased (n=2) • Varies (n=7) • Don't know (n=9)	• Yes (n=16) • Varies (n=8) • Don't know (n=4)	• Yes (n=28) • Varies (n=3) • Don't know (n=2)

Conclusions

The ICC-PBM guideline panel decided to formulate a recommendation for further research on RBC transfusion support in adult haematology patients (including non-malignant conditions e.g. haemoglobinopathies)

Results opinion poll draft recommendation (plenary session with general audience, n=124 voters): 89 accept completely, 27 accept with some reservation, 5 accept with major reservation, 3 reject with reservation.

PICO question 11: In adult patients with solid tumours [Population], is the use of a restrictive transfusion threshold [Intervention] effective to reduce mortality and improve other clinical outcomes [Outcome] compared to a liberal transfusion threshold [Comparison]?

Importance of outcomes

Critical outcomes: 30-day mortality, renal failure, myocardial infarction, cardiac events, CVA-stroke, thromboembolism, complications from RBC transfusions

Important outcomes: Patients exposed to RBC transfusions, congestive heart failure, sepsis-bacteraemia, pneumonia, pneumonia or wound infection, transfusion-related hemolysis, transfusion-related fever, transfusion-related pulmonary oedema, transfusion-related new alloantibodies

Overview judgements 10 items Evidence-to-Decision framework

desirable effects	undesirable effects	certainty of evidence	values	balance of effects	resources	cost effectiveness	equity	acceptability	feasibility
don't know	don't know	no included studies	important uncertainty or variability **Opinion poll results (n=56)** • Important uncertainty or	don't know	Varies **Opinion poll results (n=56)** • Large costs (n=3) • Moderate costs (n=6)	nincluded studies	Varies **Opinion poll results (n=55)** • Reduced (n=2) • Probably reduced (n=3)	probably yes **Opinion poll results (n=55)** • No (n=0) • Probably no (n=4)	probably yes **Opinion poll results (n=53)** • No (n=0) • Probably no (n=1)

			variability (n=26) • Possibly important uncertainty or variability (n=20) • Probably no important uncertainty or variability (n=8) • No important uncertainty or variability (n=2)		• Negligible costs and savings (n=5) • Moderate savings (n=16) • Large savings (n=10) • Varies (n=5) • Don't know (n=11)		• Probably no impact (n=16) • Probably increased (n=16) • Increased (n=2) • Varies (n=7) • Don't know (n=9)	• Probably yes (n=23) • Yes (n=16) • Varies (n=8) • Don't know (n=4)	• Probably yes (n=19) • Yes (n=28) • Varies (n=3) • Don't know (n=2)

Conclusions

The ICC-PBM guideline panel decided to formulate no recommendation on the use of restrictive transfusion threshold in adult patients with solid tumours because the only available study was in post-op surgical oncology setting in ICU – considered in surgical (PICO 5).

In a closed session of the panel there was a consensus to consider that research on transfusion triggers could not be a priority in this setting. Consequently the research recommendation was deleted. The panel also advised to replace 'trigger' by 'threshold'.

Results opinion poll draft recommendation (plenary session with general audience, n=115 voters): 94 accept completely, 16 accept with some reservation, 5 accept with major reservation.

PICO question 12: In patients with acute central nervous system (CNS) injury [Population], is the use of a restrictive transfusion threshold [Intervention] effective to reduce mortality and improve other clinical outcomes [Outcome] compared to a liberal transfusion threshold [Comparison]?

Importance of outcomes

Critical outcomes: 30/60/90-day mortality, Hospital mortality, ARDS/ALI, DVT/PE

Important outcomes: Patients with GCS score ≤8 that received RBC transfusion, ICU length of stay, days requiring mechanical ventilation, days with fever, patients exposed to RBC transfusion, multiple organ dysfunction, infection

Overview judgements 10 items Evidence-to-Decision framework

desirable effects	undesirable effects	certainty of evidence	values	balance of effects	resources	cost effectiveness	equity	acceptability	feasibility
small	trivial	very low	possibly important uncertainty or variability	does not favor either the intervention or the comparison	-	No included studies	-	-	-

			Opinion poll results (n=56) • Important uncertainty or variability (n=26) • Possibly important uncertainty or variability (n=20) • Probably no important uncertainty or variability (n=8) • No important uncertainty or variability (n=2)						

Conclusions
The ICC-PBM guideline panel decided to formulate a recommendation for further research on the use of a restrictive transfusion trigger in patients with brain injury.
General justification: Very low level of evidence for all outcomes
Notes: Post hoc analysis of TRICC study (67 patients, randomised to Hb trigger of 7 or 10g/dL). No undesirable effects observed. Two ongoing studies referred to.
Results opinion poll draft recommendation (plenary session with general audience, n=108 voters): 92 accept completely, 12 accept with some reservation, 3 accept with major reservation, 1 reject with reservation.

PICO question 13: In patients with cerebral perfusion disorders [Population], is the use of a restrictive transfusion threshold [Intervention] effective to reduce mortality and improve other clinical outcomes [Outcome] compared to a liberal transfusion threshold [Comparison]?

Importance of outcomes
Critical outcomes: any adverse event related to transfusion, pulmonary edema or respiratory distress
Important outcomes: any packed RBC transfusion given, number of separate packed RBC transfusion per patient, packed RBC units per transfusion, total packed RBC units given per patient, ventilator-free days, any cerebral infarction on MRI, delayed cerebral infarction

Overview judgements 10 items Evidence-to-Decision framework

desirable effects	undesirable effects	certainty of evidence	values	balance of effects	resources	cost effectiveness	equity	acceptability	feasibility
don't know	don't know	no included studies	-	don't know	-	no included studies	-	-	-

Conclusions

The ICC-PBM guideline panel decided to formulate a recommendation for further research on the use of restrictive transfusion trigger in patients with brain injury.

Note that this PICO question excludes studies of patients with sickle cell disease and cerebral perfusion disorders.

General justification: No evidence for any outcomes related to restrictive transfusion strategy because participants randomised to Hb trigger of 10 or 11.5 g/dL. Not considered a restrictive strategy.

Results opinion poll draft recommendation (plenary session with general audience, n=115 voters): 101 accept completely, 10 accept with some reservation, 3 accept with major reservation, 1 reject completely.

PICO question 14: In patients with acute bleeding [Population], is the use of a restrictive transfusion threshold [Intervention] effective to reduce mortality and improve other clinical outcomes [Outcome] compared to a liberal transfusion threshold [Comparison]?

Importance of outcomes

Critical outcomes: -

Important outcomes: blood usage (units), number of participants transfused

Overview judgements 10 items Evidence-to-Decision framework

desirable effects	undesirable effects	certainty of evidence	values	balance of effects	resources	cost effectiveness	equity	acceptability	feasibility
don't know	don't know	no included studies	-	don't know	-	no included studies	-	-	-

Conclusions

The ICC-PBM guideline panel decided to formulate no recommendation for a specific (restrictive) Hb trigger in patients with acute bleeding

General justification: No evidence. One pseudo-randomised trial from 1956 identified.

Notes:

•Panel view is that a Hb concentration alone should not be used to determine the need for transfusion in an acutely bleeding (i.e. major haemorrhage) scenario. Recommend refer to existing massive transfusion/major haemorrhage protocols/guidelines)

•ICC PBM Guidelines should emphasise that in the acutely bleeding patient, Hb is not the deciding factor for transfusion.

Results opinion poll draft recommendation (plenary session with general audience, n=102 voters): 83 accept completely, 11 accept with some reservation, 6 accept with major reservation, 1 reject with reservation, 1 reject completely.

eTable 3. Summary of Results of the ICC PBM Panel Decisions for PICO Questions 15 to 17: Implementation of PBM Programs

PICO question 15: Is a PBM program [Intervention] effective to improve clinical and economic outcomes [Outcome] compared to no PBM program [Comparison]?

Importance of outcomes
Critical outcomes: RBC utilization, PLT utilization, FFP utilization, acute myocardial infarction, acute ischaemic stroke, acute kidney injury, hospital mortality, 30-day mortality
Important outcomes: Cryoprecipitate utilization, length of hospital stay

Overview judgements 10 items Evidence-to-Decision framework

desirable effects	undesirable effects	certainty of evidence	values	balance of effects	resources	cost effectiveness	equity	acceptability	feasibility
moderate	don't know	low	probably no important uncertainty or variability **Opinion poll results (n=45)** • Important uncertainty or variability (n=7) • Possibly important uncertainty or variability (n=20) • Probably no important uncertainty or variability (n=11) • No important uncertainty or variability (n=7)	probably favors the intervention	varies	no included studies	probably increased **Opinion poll results (n=42)** • Reduced (n=0) • Probably reduced (n=5) • Probably no impact (n=8) • Probably increased (n=7) • Increased (n=3) • Varies (n=16) • Don't know (n=3)	Probably yes	Probably yes

Conclusions

- *Recommendation 9: The ICC-PBM expert panel suggests implementation of a comprehensive PBM program to improve appropriate RBC utilization (conditional recommendation, low certainty in the evidence of effects).*

General justification: Moderate desirable effects, low-quality evidence and probably positive effect on equity, acceptability and feasibility.

Results opinion poll draft recommendation (plenary session with general audience, n=128 voters): 100 accept completely, 20 accept with some reservation, 3 accept with major reservation, 3 reject with reservation, 2 reject completely.

PICO question 16: Is a specific behavioural intervention to promote the implementation of a PBM program [Intervention] more effective to improve clinical and economic outcomes [Outcome] compared to no/another behavioural intervention[Comparison]?

Importance of outcomes
Critical outcomes: RBC utilization, FFP utilization, PLT utilization
Important outcomes: Cryoprecipitate utilization

Overview judgements 10 items Evidence-to-Decision framework

desirable effects	undesirable effects	certainty of evidence	values	balance of effects	resources	cost effectiveness	equity	acceptability	feasibility
moderate	don't know	very low	probably no important uncertainty or variability **Opinion poll results (n=45)** • Important uncertainty or variability (n=7) • Possibly important uncertainty or variability (n=20) • Probably no important uncertainty or variability (n=11) • No important uncertainty or variability (n=7)	probably favors the intervention	varies	no included studies	probably increased **Opinion poll results (n=42)** • Reduced (n=0) • Probably reduced (n=5) • Probably no impact (n=8) • Probably increased (n=7) • Increased (n=3) • Varies (n=16) • Don't know (n=3)	Yes **Opinion poll results (n=39)** • No (n=0) • Probably no (n=0) • Probably yes (n=18) • Yes (n=14) • Varies (n=5) • Don't know (n=2)	probably yes **Opinion poll results (n=39)** • No (n=1) • Probably no (n=1) • Probably yes (n=17) • Yes (n=12) • Varies (n=8) • Don't know (n=0)

Conclusions
The ICC-PBM guideline panel decided to formulate no recommendation on the use of a specific behavioural intervention (e.g.. audit, transfusion form, education) to promote implementation of a comprehensive PBM program the evidence is of very low quality.

Results opinion poll draft recommendation (plenary session with general audience, n=122 voters): 84 accept completely, 28 accept with some reservation, 8 accept with major reservation, 1 reject with reservation, 1 reject completely.

PICO question 17: Is a specific decision support system to promote the implementation of a PBM program [Intervention] more effective to improve clinical and economic outcomes [Outcome] compared to no intervention or another decision support system/behavioural intervention [Comparison]?

Importance of outcomes
Critical outcomes: RBC utilization, FFP utilization, PLT utilization, Transfusion-related/transfusion-transmitted infections, transfusion-associated circulatory overload, transfusion-associated dyspnea, acute transfusion reactions, bleeding, arterial or venous thromboembolism, number of transfusions compliant with institutional transfusion guidelines, all-cause mortality
Important outcomes: Cryoprecipitate utilization, infection, blood count or coagulation parameter, length of hospital ICU/hospital stay, clinician workflow

Overview judgements 10 items Evidence-to-Decision framework

desirable effects	undesirable effects	certainty of evidence	values	balance of effects	resources	cost effectiveness	equity	acceptability	feasibility
moderate	trivial	low	probably no important uncertainty or variability **Opinion poll results (n=45)** • Important uncertainty or variability (n=7) • Possibly important uncertainty or variability (n=20) • Probably no important uncertainty or variability (n=11) • No important uncertainty or variability (n=7)	probably favors the intervention	varies	no included studies	probably increased **Opinion poll results (n=42)** • Reduced (n=0) • Probably reduced (n=5) • Probably no impact (n=8) • Probably increased (n=7) • Increased (n=3) • Varies (n=16) • Don't know (n=3)	probably yes **Opinion poll results (n=39)** • No (n=0) • Probably no (n=0) • Probably yes (n=19) • Yes (n=14) • Varies (n=6) • Don't know (n=0)	Varies **Opinion poll results (n=39)** • No (n=0) • Probably no (n=2) • Probably yes (n=14) • Yes (n=10) • Varies (n=12) • Don't know (n=0)

Conclusions

- *Recommendation 10: The ICC-PBM expert panel suggests computerized/electronic decision support systems to improve appropriate RBC utilization (conditional recommendation, low certainty in the evidence of effects).*

General justification: Moderate desirable effects on RBC utilization, low-quality evidence.
Results opinion poll draft recommendation (plenary session with general audience, n=122 voters): 81 accept completely, 35 accept with some reservation, 3 accept with major reservation, 2 reject with reservation, 1 reject completely.

General research recommentation (**PICO 15-16-17**)
The ICC-PBM expert panel called for further research to study the impact of comprehensive PBM programs on 1) adverse events and patient-important outcomes, 2) compliance, adherence and acceptability and 3) the cost-effectiveness. Special considerations were given by the panel to the importance of design and implementation of well-conducted observational studies, the use of reproducible definitions and descriptions/outcome parameters for such strategies as well as patient engagement and options to evaluate the sustainability of PBM programs.