ICC PBM: Méthodes; recommandations

pour les seuils transfusionnels (1)

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Merci au Prof. Erhard Seifried, pour l'autorisation d'utiliser les dias de l'ICC PBM

Présentations ppt de l'ICC PBM
https://icc-pbm.eu/recommendations-materials/

- Conflit d'intérêt: aucun

INTERNATIONAL CONSENSUS CONFERENCE
ICC·PBM
FRANKFURT
2018

PROCESS OF DEVELOPING RECOMMENDATIONS:
THE USE OF A FORMAL CONSENSUS FORMAT AND EVIDENCE-BASED METHODOLOGY

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Patient Blood Management:
3 topics of interest & 17 PICO questions

P	I	C	O
Population Patient Problem	Intervention Or Exposure	Comparison	Outcome
Who are the patients? What is the problem?	What do we do to them? What are they exposed to?	What do we compare the intervention with?	What happens? What is the outcome?

Patient Blood Management: 3 topics of interest

Topic 1: Preoperative anaemia

- ✓ Definition and diagnosis (PICO 1 and PICO 2)
- ✓ Treatment (PICO 3)

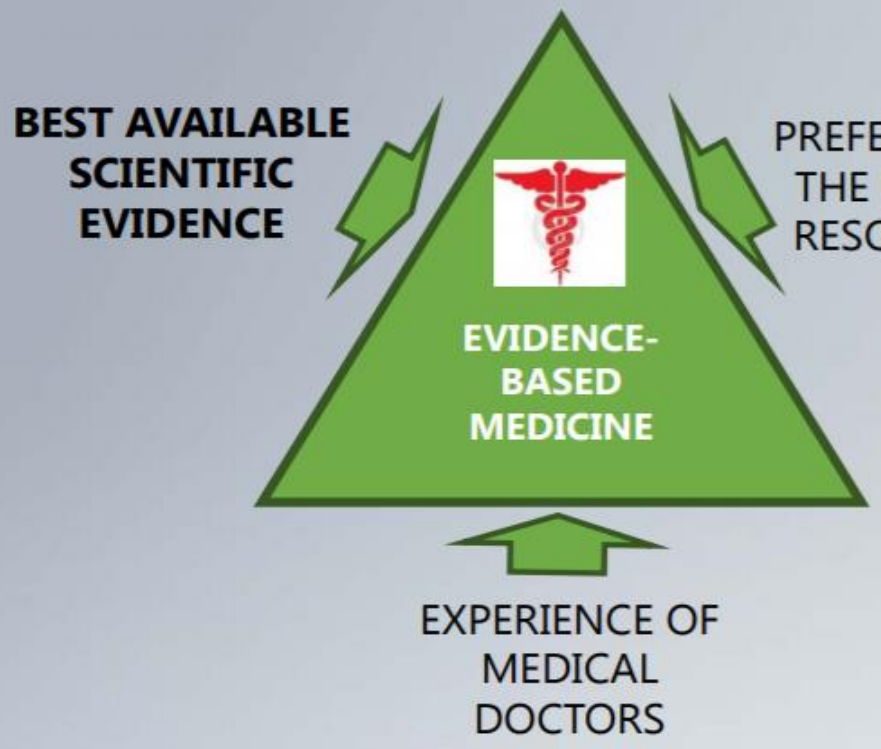
Topic 2: RBC transfusion triggers

- ✓ Intensive care and acute interventions (PICO 4-9 & PICO 14)
- ✓ Haematology and oncology (PICO 10 & PICO 11)
- ✓ Neurology (PICO 12 & PICO 13)

Topic 3: PBM implementation

- ✓ Effectiveness implementation of 'comprehensive' PBM programs (PICO 15)
- ✓ Effectiveness behavioural interventions (PICO 16)
- ✓ Effectiveness decision support systems (PICO 17)

Evidence-based methodology



GRADE

http://www.gradeworkinggroup.org/

- **G**rading of **R**ecommendations **A**ssessment, **D**evelopment and **E**valuation
- Common, sensible and transparent approach to grading:
  - Quality (or certainty) of evidence
  - Strength of recommendations

GRADE approach

From evidence to recommendations – transparent and sensible

March 2017 – February 2018

Screening ~18.000 references in 4 databases from date of inception until January 2018 with **142 studies** finally included

PubMed

embase BIOMEDICAL ANSWERS

Cochrane Library

Transfusion Evidence Library

Formulate question

Select outcomes

Rate importance

P
I
C
O

Outcome Critical

Outcome Critical

Outcome Important

Outcome Not important

Systematic review

Evidence-based by **CEBaP**

Scientific Committee

Evidence-to-Decision framework

CRITERIA	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
1. DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?**	EVIDENCE	Rapporteurs Audience
2. UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?**		Rapporteurs Audience
3. CERTAINTY OF EVIDENCE	**What is the overall quality of the evidence of effects?**	EVIDENCE	Rapporteurs Audience
4. VALUES	Is there important uncertainty about or variability in how much people value the critical outcomes?	OPINION POLL	Rapporteurs Audience
5. BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?**	EVIDENCE	Rapporteurs Audience
6. RESOURCES REQUIRED	**How large are the resource requirements (costs)?**	EVIDENCE	Rapporteurs Audience
7. COST EFFECTIVENESS	Does the cost-effectiveness of the intervention favor the intervention or the comparison?		Rapporteurs Audience
8. EQUITY	What would be the impact on health equity?	OPINION POLL	Rapporteurs Audience
9. ACCEPTABILITY	Is the intervention acceptable to key stakeholders?	OPINION POLL	Rapporteurs Audience
10. FEASIBILITY	Is the intervention feasible to implement?	OPINION POLL	Rapporteurs Audience

GRADE approach

From evidence **to recommendations** – transparent and sensible

Guideline development

Strong/conditional recommendation
No recommendation
Research recommendation

By considering balance of consequences (evidence to recommendation)

- ❑ Quality of evidence
- ❑ Balance benefits/harms
- ❑ Values and preferences
- ❑ Resource use (cost(-effectiveness)
- ❑ Equity – Acceptability - Feasibility

EtD framework

Guideline

Formulate recommendations

- "We recommend using…"
- "We recommend against using…"
- "We suggest using…"
- "We suggest against using…"

Transparency, clear, actionable
Research?

GRADE approach

From evidence **to recommendations** – transparent and sensible

Guideline development

Decision-making panelists

Formulation of a recommendation (option 1)

- For or against (direction) ↑↓
- Strong or conditional/weak (strength)

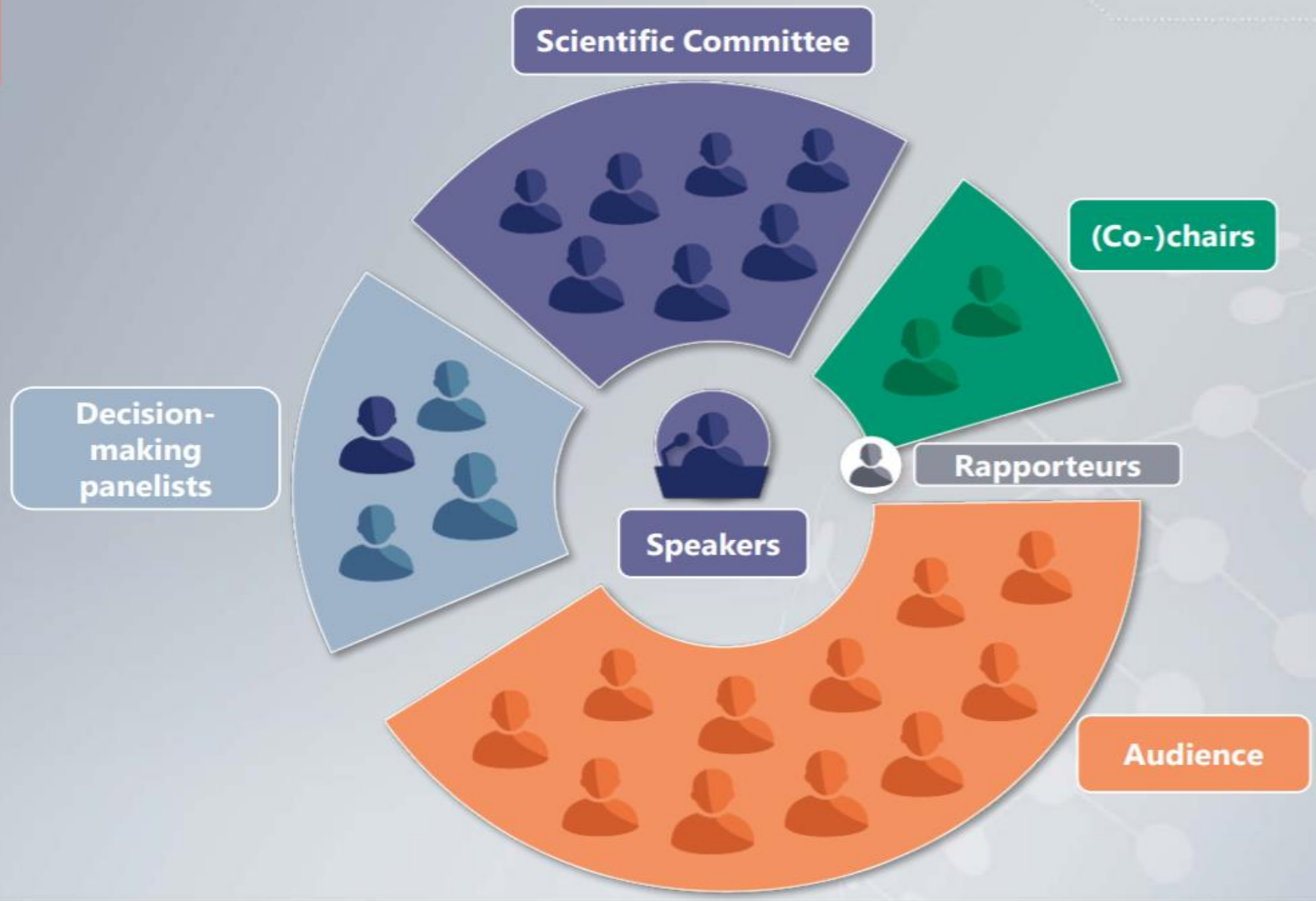
No recommendation (option 2)

- Very low quality evidence
- Trade offs closely balanced

Research recommendation (option 3)

- Insufficient evidence
- Further research has a large potential for reducing the uncertainty about the effect of the intervention

Consensus Development Conference (CDC)



RBC transfusion thresholds: 11 P*ICO questions

4. Critically ill but clinically stable intensive care patients
5. Orthopaedic / non-cardiac surgery patients
6. Acute gastrointestinal bleeding
7. Patients with symptomatic/acute coronary heart disease
8. Septic shock
9. Cardiac surgery
10. Haematological patients
11. Patients with solid tumours
12. Acute central nervous system injury
13. Cerebral perfusion disorders
14. Acute bleeding patients

* All adult patients

Transfusion thresholds : formulation of PICO questions

In patients undergoing … (Population), is the use of a restrictive transfusion threshold (Intervention) effective to reduce mortality and improve other clinical outcomes (Outcomes) compared to a liberal transfusionthreshold (Comparison)?

RBC transfusion thresholds: 12 PICO questions

Intervention/comparison

- More restrictive: 7 -8 g/dL
- More liberal : 9-10 g/dL

Outcomes

- **Mortality: 30-day**, hospital
- Participants exposed to tx, units transfused, number of tx
- Hb concentration
- Myocardial infarction, congestive heart failure, sepsis/bacteraemia, pneumonia …

Haematology, oncology: study characteristics

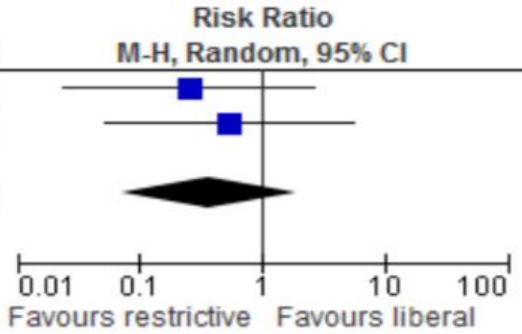
Author, year, country	Study design	Population	Restrictive RBC transfusion trigger	Liberal RBC transfusion trigger
Haematology				
DeZern, 2016, USA	RCT	89 acute leukaemia participants (acute myeloid leukaemia, acute lymphoblastic leukaemia/lymphoma, acute promyelocytic leukaemia, treatment-related myeloid neoplasm, highgrade myelodysplastic syndrome)	Single-unit RBC transfusion if Hb <7 g/dL	Single-unit RBC transfusion if Hb <8 g/dL
Webert, 2008, Canada	RCT	60 adult participants with acute leukaemia	2- unit RBC transfusion if Hb <8 g/dL, with a target range of 8.5 to 9.5 g/dL	2-unit RBC transfusion if Hb <12 g/dL
Oncology				
De Almeida, 2015, Brazil	RCT	198 adult participants who underwent a major surgical procedure for abdominal cancer and required postoperative care in the ICU	RBC transfusion if Hb <7 g/dL	RBC transfusion if Hb <9 g/dL
Park, 2008, South Korea	RCT	87 adult patients with a confirmed diagnosis of measurable advanced gastric cancer and scheduled to receive 5-fluorouracil-based first-line chemotherapy for metastatic/recurrent disease	RBC transfusion if Hb <10 g/dL	RBC transfusion if Hb <12 g/dL
Yakymenko, 2017, Denmark	RCT	133 patients with a confirmed diagnosis of malignant solid tumour and planned treatment with chemotherapy	RBC transfusion if Hb <9.7 g/dL	RBC transfusion if Hb <11.5 g/dL (females) or <13.1 g/dL (males)

Adult haematological patients

30-day mortality

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
DeZern 2016	1	59	2	30	49.7%	0.25 [0.02, 2.69]
Webert 2008	1	29	2	31	50.3%	0.53 [0.05, 5.58]
Total (95% CI)		**88**		**61**	**100.0%**	**0.37 [0.07, 1.95]**
Total events	2		4			

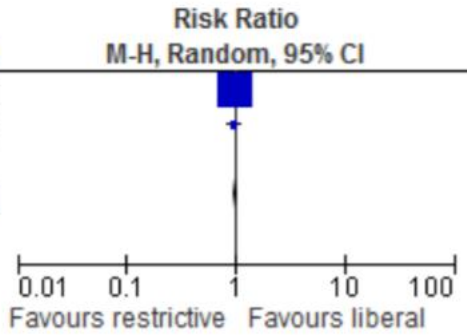
Heterogeneity: Tau² = 0.00; Chi² = 0.19, df = 1 (P = 0.66); I² = 0%
Test for overall effect: Z = 1.17 (P = 0.24)



Participants exposed to transfusion

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
DeZern 2016	59	59	30	30	90.3%	1.00 [0.95, 1.05]
Webert 2008	26	29	29	31	9.7%	0.96 [0.82, 1.12]
Total (95% CI)		**88**		**61**	**100.0%**	**1.00 [0.95, 1.05]**
Total events	85		59			

Heterogeneity: Tau² = 0.00; Chi² = 0.55, df = 1 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.17 (P = 0.87)



Haematology

IMPORTANT OUTCOMES

Desirable effects?

Outcomes	Difference (restrictive (<7/8 g/dL) versus liberal (<8/12 g/dL) RBC transfusion triggers)	Relative effect (95% CI)
RBC transfusion (units)	MD **3.1 RBC units lower** (5.31 lower to 0.89 lower)	-
Patients received RBC transfusion	**0 fewer per 1.000** (48 fewer to 48 more)	**RR 1.00** (0.95 to 1.05)
Episodes of neutropenic fever (0-1 vs 2-5)	**88 fewer per 1.000** (249 fewer to 125 more)	**RR 0.88** (0.66 to 1.17)
Length of inpatient stay (days)	median **0.5 days lower** (0 to 0)	-
Fatigue scale score	median **0.3 points higher** (0 to 0)	-

Undesirable effects?

Outcomes	Difference (restrictive (<7/8 g/dL) versus liberal (<8/12 g/dL) RBC transfusion triggers)	Relative effect (95% CI)
Bleeding events (by grade: 0-1 vs 2-4)	**17 more per 1.000** (133 fewer to 192 more)	**RR 1.02** (0.84 to 1.23)

Haematology & Oncology

Quality of the body of evidence (critical outcomes)?

Haematology

Outcomes	Certainty of the evidence (GRADE)
30-day mortality	⊕⊕◯◯ LOW[a,b]

a. Limited sample size or low number of events
b. Large variability of results

Oncology

Outcomes	Certainty of the evidence (GRADE)
30-day mortality	⊕◯◯◯ VERY LOW[a,b]
Renal failure	⊕◯◯◯ VERY LOW[a,b]
Myocardial infarction	⊕◯◯◯ VERY LOW[a,b]
Cardiac events	⊕⊕◯◯ LOW[a,b]
CVA-stroke	⊕◯◯◯ VERY LOW[a,b]
Thromboembolism	⊕◯◯◯ VERY LOW[a,b]

a. Indirectness: Lack of generalizibility: evidence from 1 Brazilian (feasibility) study
b. Imprecision: Limited sample size, low number of events and/or large variability of results
c. Indirectness: Lack of generalizibility: evidence from 1 Danish study

Haematology (PICO 10)

No Hb trigger recommendation

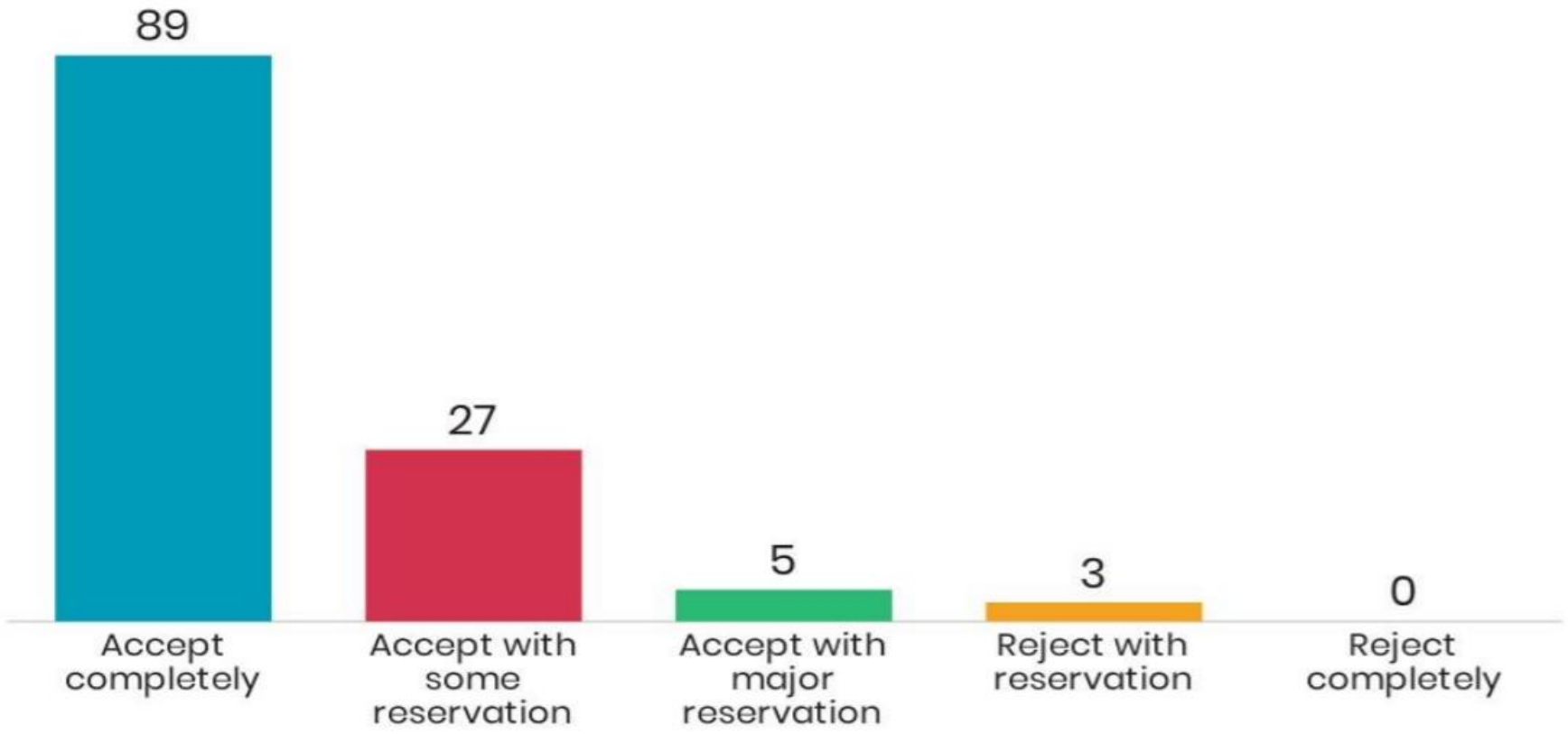
Plus: The ICC-PBM guideline panel decided to formulate a recommendation for further research on the use of restrictive transfusion trigger in haematology patients (including non-malignant conditions) (Y/N)

Justification: Insufficient evidence (two pilot studies in acute leukaemia, total 149 patients). No signal for undesirable effects.

Notes: Hb trigger in the two included trials was 7-8g/dL

No Hb trigger recommendation (PICO 10)

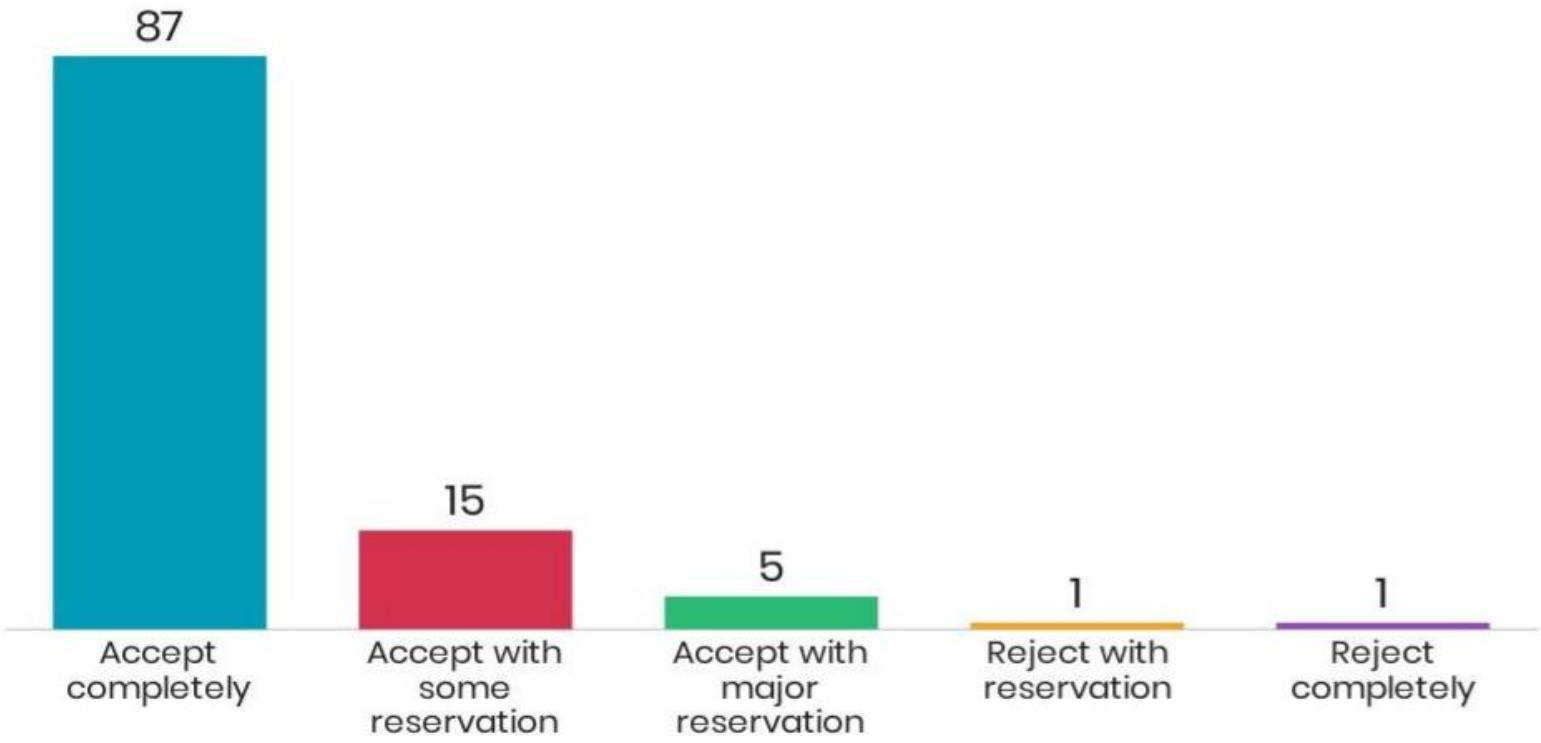
Mentimeter



124

recommendation for further research on the use of restrictive transfusion trigger in haematology patients

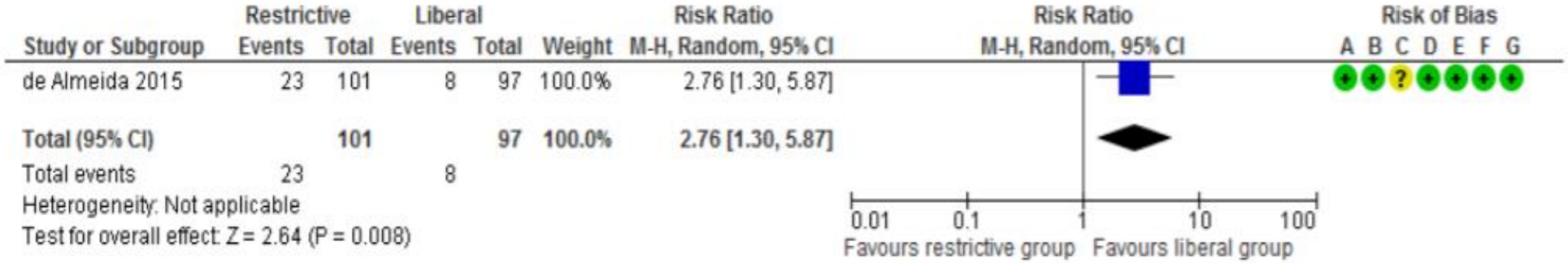
Mentimeter



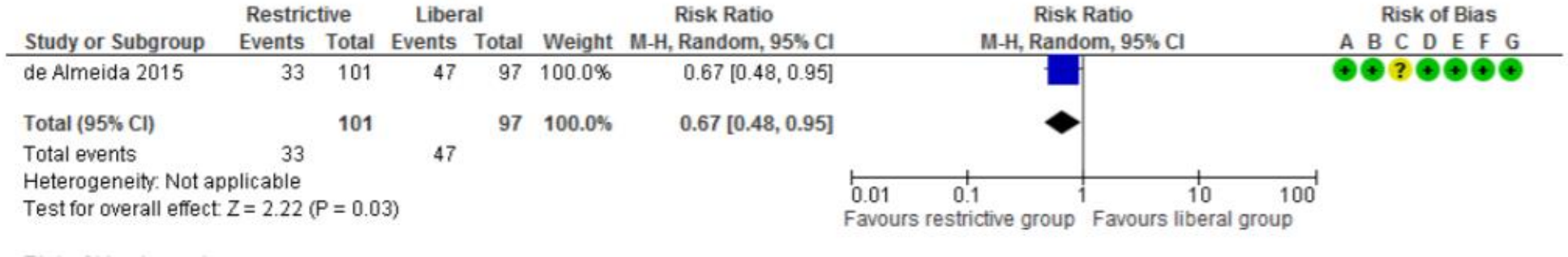
109

Patients with solid tumours

30-day mortality



Participants exposed to transfusion



Oncology (PICO 11)

No recommendation for Hb trigger (Y/N)

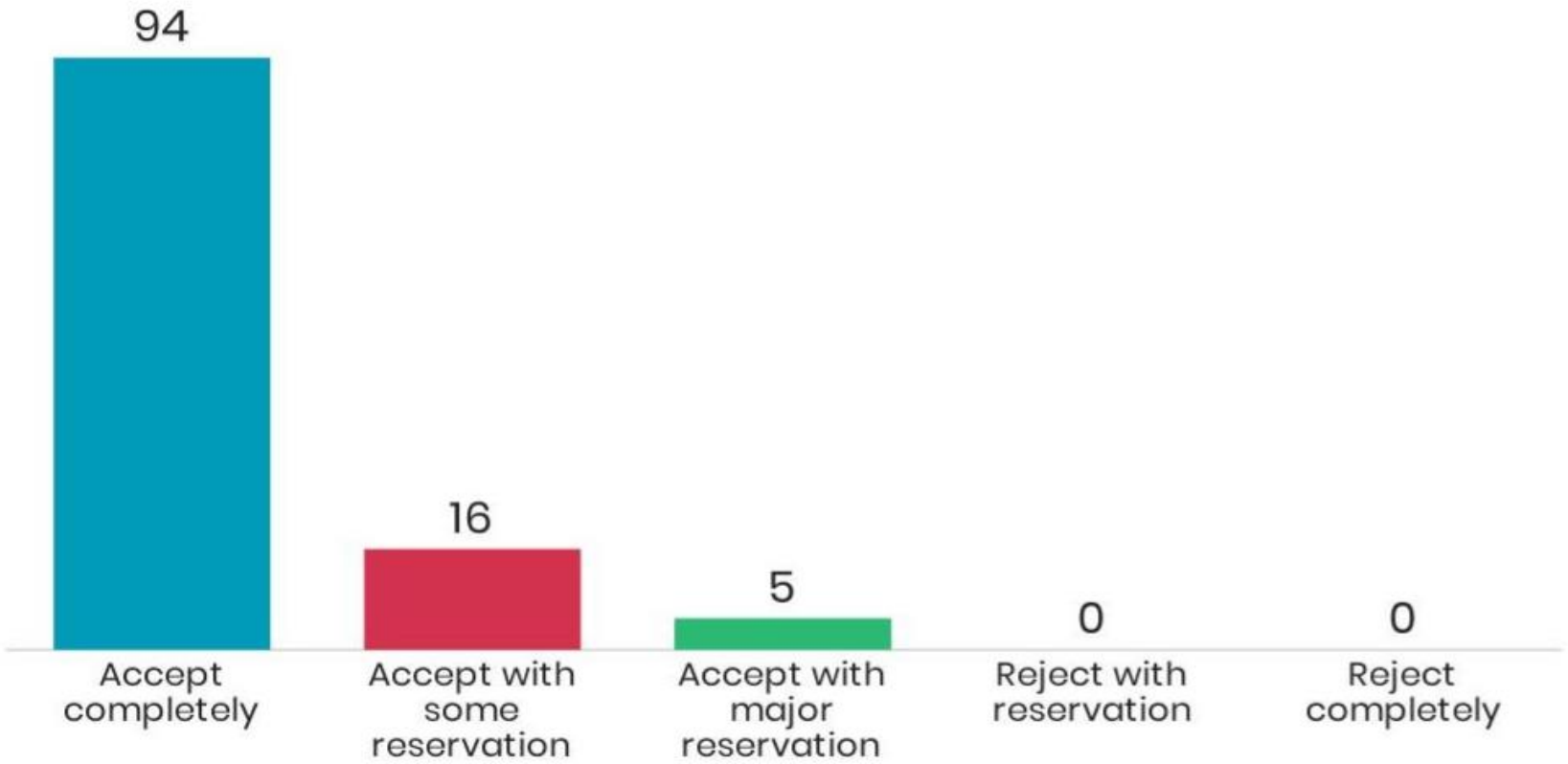
The ICC-PBM guideline panel decided to formulate a recommendation for further research on the use of restrictive transfusion trigger in oncology patients (Y/N)

Justification: No evidence

Notes: Only available study was in post-op surgical oncology setting in ICU – considered in surgical (PICO 5)

No Hb trigger recommendation (PICO 11)

Mentimeter



115

Neurology: study characteristics

study characteristics

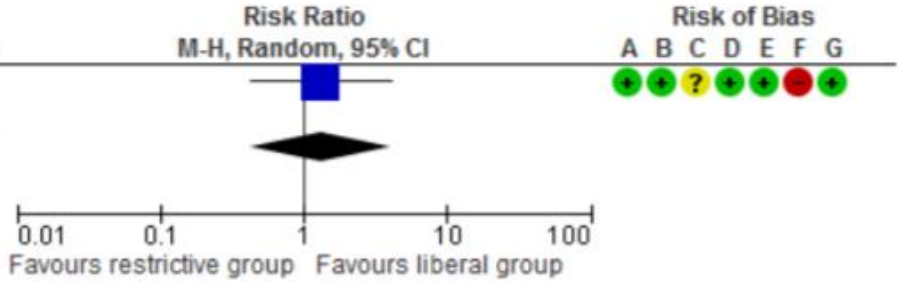
Author, year, country	Study design	Population	Restrictive RBC transfusion trigger	Liberal RBC transfusion trigger
Patients with acute central nervous injury				
McIntyre, 2006, Canada	RCT	67 multiple trauma patients with a closed head injury	Single-unit RBC transfusion if Hb <7 g/dL	Single-unit RBC transfusion if Hb <10 g/dL
Ngwenya, 2017, USA	Cohort study	1565 consecutive patients with a diagnosis of traumatic brain injury	Hb <7 g/dL	Hb <10 g/dL
Patients with cerebral perfusion disorders				
Naidech, 2010, USA	RCT	44 patients with subarachnoid hemorrhage and high risk for vasospasm	Hb <10 g/dL	Hb <11.5 g/dL

Patients with acute central nervous system injury

30-day mortality

Study or Subgroup	Restrictive trigger Events	Total	Liberal trigger Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
McIntyre 2006	5	29	5	38	100.0%	1.31 [0.42, 4.10]
Total (95% CI)		**29**		**38**	**100.0%**	**1.31 [0.42, 4.10]**
Total events	5		5			

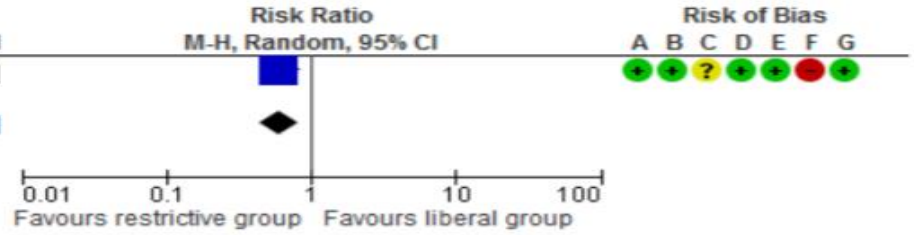
Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.64)



Proportion transfused

Study or Subgroup	Restrictive trigger Events	Total	Liberal trigger Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
McIntyre 2006	17	29	38	38	100.0%	0.59 [0.44, 0.80]
Total (95% CI)		**29**		**38**	**100.0%**	**0.59 [0.44, 0.80]**
Total events	17		38			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.39 (P = 0.0007)



Central nervous system injury (PICO 12)

No Hb trigger recommendation (Y/N)

Plus: The ICC-PBM guideline panel decided to formulate a recommendation for further research on the use of restrictive transfusion trigger in patients with CNS injury (Y/N)

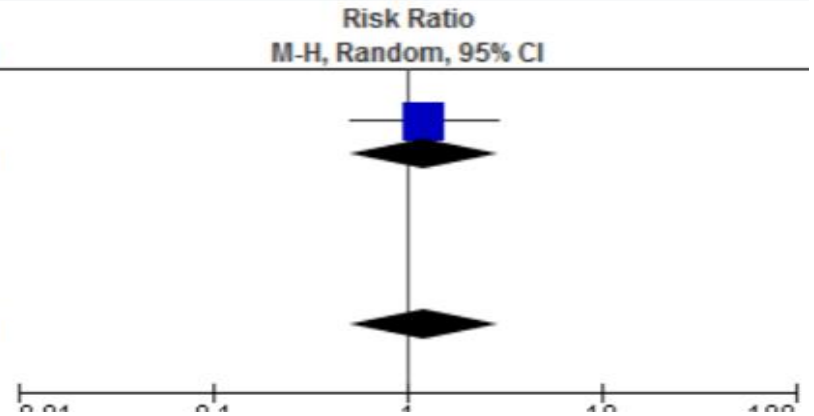
Justification: Very low level of evidence for all outcomes

Notes: *Post hoc* analysis of TRICC study (67 patients, randomised to Hb trigger of 7 or 10g/dL). No undesirable effects observed

Patients with cerebral perfusion disorders

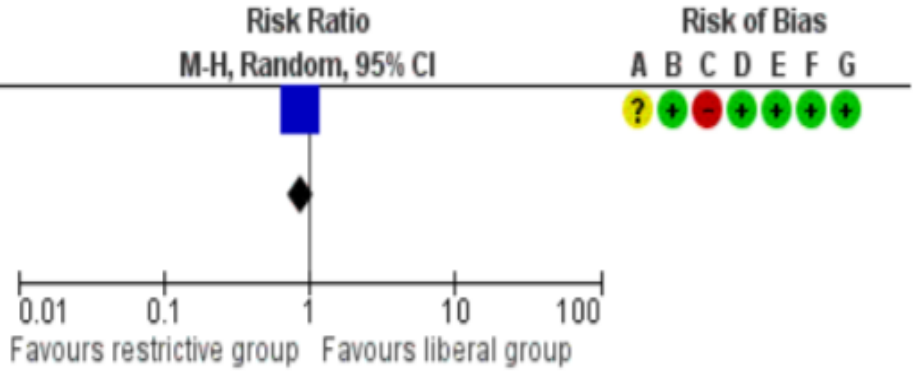
No mortality data available
CRITICAL OUTCOME: any adverse event related to transfusion

Study or Subgroup	Restrictive group Events	Total	Liberal group Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Cerebral perfusion disorders						
Naidech 2010	8	23	6	21	100.0%	1.22 [0.51, 2.93]
Subtotal (95% CI)		**23**		**21**	**100.0%**	**1.22 [0.51, 2.93]**
Total events	8		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.44 (P = 0.66)						
Total (95% CI)		**23**		**21**	**100.0%**	**1.22 [0.51, 2.93]**
Total events	8		6			
Heterogeneity: Not applicable						



Any packed RBC transfusion given

Study or Subgroup	Restrictive group Events	Total	Liberal group Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Naidech 2010	19	23	20	21	100.0%	0.87 [0.70, 1.07]
Total (95% CI)		**23**		**21**	**100.0%**	**0.87 [0.70, 1.07]**
Total events	19		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.32 (P = 0.19)						



Cerebral perfusion disorders (PICO 13)

Recommendations:
No Hb trigger recommendation (Y/N)
The ICC-PBM guideline panel decided to formulate a recommendation for further research on the use of restrictive transfusion trigger in patients with cerebral perfusion disorders (Y/N)

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.

Notes: One study of 44 patients with subarachnoid haemorrhage No undesirable effects observed.

Remerciements aux « SFTS delegates »

- Scientific committee member: **Cécile Aubron** (Brest)
- Co-chair POA : **Yves Ozier** (Brest)
- Panelist POA: **Sigismond Lasocki** (Angers)
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- Rep of French Intensive Care Society (**SRLF**): **Frédéric Pène** (Paris)
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- Rep of French Blood Establishment (**EFS**): **Christophe Besiers** (St Denis)
- Rep of National Institute of Blood Transfusion (**INTS**): **Olivier Garraud**

Merci de votre attention!