The systematic use of evidence-based methodologies and technologies enhances shared decision-making in the 2018 International Consensus Conference on Patient Blood Management

Hans Van Remoortel,1 Kari Aranko,2,3 Markus M. Mueller,4 Emmy De Buck,1,5 Dana Devine,6 Gilles Folléa,7 Patrick Meybohm,8 Pierre Tiberghien,9 Erica M. Wood,10,11 Philippe Vandekerckhove5,12 Erhard Seifried2,4,10

1 Centre for Evidence-Based Practice (CEBaP), Belgian Red Cross, Mechelen, Belgium
2 European Blood Alliance (EBA), Amsterdam, The Netherlands
3 Finnish Red Cross Blood Service, Helsinki, Finland
4 German Red Cross Blood Transfusion Service, Frankfurt/Main, Germany
5 Department of Public Health and Primary Care, Faculty of Medicine, KU Leuven, Leuven, Belgium
6 Canadian Blood Services, Ottawa, ON, Canada
7 Société Française de Transfusion Sanguine (SFTS), Paris, France
8 Department of Anaesthesiology, Intensive Care Medicine and Pain Therapy, University Hospital Frankfurt, Frankfurt/Main, Germany
9 Établissement Français du Sang (EFS), Saint-Denis, France
10 International Society of Blood Transfusion (ISBT), Amsterdam, The Netherlands
11 Transfusion Research Unit, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Vic, Australia
12 Belgian Red Cross, Mechelen, Belgium

Background and objectives Patient Blood Management (PBM) aims to optimize the care of patients who might need a blood transfusion. The International Consensus Conference on PBM (ICC-PBM) aimed to develop evidence-based recommendations on three topics: preoperative anaemia, red blood cell transfusion thresholds and implementation of PBM programmes. This paper reports how evidence-based methodologies and technologies were used to enhance shared decision-making in formulating recommendations during the ICC-PBM.

Materials & Methods Systematic reviews on 17 PICO (Population, Intervention, Comparison, Outcomes) questions were conducted by a Scientific Committee (22 international topic experts and one methodologist) according to GRADE (Grades of Recommendation, Assessment, Development and Evaluation) methodology. Evidence-based recommendations were formulated using Consensus Development Conference methodology.

Results We screened 17 607 references and included 145 studies. The overall certainty in the evidence of effect estimates was generally low or very low. During the ICC, plenary sessions (100–200 stakeholders from a range of clinical disciplines and community representatives) were followed by closed sessions where multidisciplinary decision-making panels (>50 experts and patient organizations) formulated recommendations. Two chairs (content-expert and methodologist) moderated each session and two rapporteurs documented the discussions. The Evidence-to-Decision template (GRADEpro software) was used as the central basis in the process of formulating recommendations.
Conclusion

This ICC-PBM resulted in 10 clinical and 12 research recommendations supported by an international stakeholder group of experts in blood transfusion. Systematic, rigorous and transparent evidence-based methodology in a formal consensus format should be the new standard to evaluate (cost-) effectiveness of medical treatments, such as blood transfusion.

Key words: anemia, patient blood management, red cell components, transfusion.

Introduction

Patient Blood Management (PBM) is a patient-focused, evidence-based and multidisciplinary approach to optimize both 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].

Key areas in PBM include diagnosing and treating perioperative anaemia, implementing blood-saving measures throughout the course of diagnosis and treatment, and transfusing patients according to accepted and evidence-based transfusion thresholds.

To develop rigorous evidence-based guidelines, according to the AGREE II checklist [2], systematic literature searches should form the basis of the guidelines. The methodology to conduct these systematic reviews, including an assessment in the certainty of the body of evidence, and the translation of the evidence into clinical, evidence-based recommendations can be performed using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach.

GRADE is a transparent framework for developing and presenting summaries of evidence and provides a systematic approach for making clinical practice recommendations [3–5]. To bridge the gap between research and clinical practice, the engagement of a multidisciplinary expert panel is key. Formal group consensus methods have been developed to organize subjective judgements and to synthesize them with the available evidence [6].

The National Institutes of Health (NIH) has developed a consensus development conference format to evaluate biomedical technologies and practices and to disseminate these results to health professionals and the public [6,7]. NIH consensus development conferences include participation by speakers who present the evidence, an audience that has the opportunity to comment on the evidence, and a panel that deliberates and produces a written statement based on its judgement [6]. The strengths of the NIH consensus development process are its potential to translate a large body of evidence into practical clinical policy, to bring together apparently conflicting viewpoints, with the evidence as the “common denominator”, to draw public as well as professional attention to important clinical issues, to obtain front-line practitioner input on the feasibility of evidence-generated clinical policy and to increase the exposure of all parties to the existing research evidence in an area [9].

A diverse, international group of policymakers, managers, their support staff and other stakeholders indicated that the systematic consideration of the best available evidence would help to improve health system decision-making processes [10]. To improve the trustworthiness of claims about the effects of treatments and to formulate evidence-based clinical recommendations, the systematic and transparent use of a methodological approach/framework and a formal consensus methodology is highly recommended [11,12].

Therefore, in order to enhance shared decision-making and to formulate evidence-based recommendations in three PBM topics (preoperative anaemia, red blood cell (RBC) transfusion thresholds and implementation of PBM programmes), an international consortium of European, American, Canadian and Australian organizations in the field of blood transfusion organized a 2-day (24 and 25 April 2018) International Consensus Conference on Patient Blood Management in Frankfurt/Main, Germany (ICC-PBM 2018). The key results and conclusions/recommendations of this meeting were published elsewhere [13]. The aim of this methodology paper was to report the ICC-PBM 2018 proceedings and provide more insight how evidence-based methodologies and technologies were used to enhance shared decision-making when formulating clinical recommendations. This information will inform and guide all stakeholders involved in making and using evidence-based recommendations.

Materials & methods

A Scientific Committee was established consisting of 23 members including one methodologist from the Centre for Evidence-Based Practice, Belgian Red Cross (Belgium) with expertise in conducting systematic reviews and 22 subject matter experts that were appointed by the following sponsoring and participating organizations: German Red Cross Blood Transfusion Services (Germany); Grenoble University.
A stepwise, rigorous and transparent process was used to evidence-based methodology strategies are published elsewhere.[13]. PICO questions, selection criteria and corresponding search tion of PBM programmes. Detailed information about the decision support systems (PICO 17) to promote the implementa tion of ‘comprehensive’ PBM programmes (PICO 15) and behavioural interventions (PICO 16) or deci sion support systems (PICO 17) to promote the implementation of PBM programmes. The 17 PICO ques tions were related to (1) definition (PICO 1), diagnosis (PICO 2) and management (PICO 3) of preoperative anaemia in adult elective surgery patients, (2) the use of RBC transfusion thresholds in intensive care and acute interventions (PICO 4–9, & PICO 14), haematology and oncology (PICO 10 & PICO 11) and neurology (PICO 12 & PICO 13) and (3) the implementation of PBM programmes (3 PICO questions). The 17 PICO questions were formulated after reviewing the evidence (February 2018) and revisions were done by the Scientific Committee. Detailed methodological principles to conduct the evidence reviews in the context of a clinical guideline project are published in a methodological charter [14]. The GRADE approach was used to rate the certainty of evidence in the reviews and to translate the evidence from the reviews to conditional/weak, strong or research recommendations [5].

Starting from the PICO questions and the selection of outcomes, the Scientific Committee members independently assessed the relative importance of outcomes numerically on a 1–9 scale (7–9, critical; 4–6 important; and 1–3, of limited importance). Ranking outcomes by their relative importance can help guideline developers to focus attention, when formulating recommendations, on those outcomes that are considered most important [15]. This rating exercise was performed after reviewing the evidence (February 2018) and detailed information can be found in Appendix 2. About 60–70% of the Scientific Committee members completed the rating scores for all outcomes related to the PICO questions of preoperative anaemia (n = 16, 70%), RBC transfusion thresholds (n = 16, 70%) and PBM implementation (n = 14, 61%). Based on the calculation of the mean rating scores and a discussion within the Scientific Committee in case of discrepant results (i.e. large variability in rating scores), final rating scores were provided.

A standard evidence summary template (in Word) was used to describe the PICO question, the search strategies, the search date, the selection criteria, the characteristics of included studies, the synthesis of findings, the quality of the evidence, the certainty of the body of evidence, the conclusion(s) and the references of the included studies [14]. Additionally, evidence profiles were created with the GRADEpro software (https://gradepro.org/) to enable a summary of findings including an estimate of effect for each outcome and a quality rating of the evidence for each outcome according to the 8 GRADE criteria (five criteria that might potentially downgrade the quality: risk of bias, inconsistency, indirectness, imprecision, publication bias; and three criteria that might potentially upgrade the quality: large effect, dose–response and confounders).[3]

When developing recommendations, the GRADE approach recommends that an expert panel should use
the evidence reviews as the fundamental source of information (including the quality of the evidence and the importance of outcomes) and recommends that an expert panel should subsequently formulate a conditional/weak of strong recommendation (strength) for or against an intervention (direction). In order to formulate appropriate recommendations, several items need to be considered such as the balance between benefits and harms, the quality of the evidence, values and preferences, resource use and the feasibility, equity and acceptability. These items are collected in an Evidence-to-Decision (EtD) framework available in the GRADEpro software which facilitates this consideration and enhances the formulation of recommendations in a clear and transparent manner [12,16]. Table 1 represents the 10 items and judgement questions of the EtD framework that were used as a central thread to formulate recommendations during the ICC-PBM 2018. In general, the different evidence reviews answered whether a specific intervention is effective (or not). Therefore, the source of information for EtD items one (desirable effects), two (undesirable effects), three (certainty of evidence) and five (balance of effects) was the evidence reviews. The other items (4, 6, 8, 9, 10) were not ignored but were introduced and discussed in the different sessions and indicative opinion polls were organized (see below). The Scientific Committee decided to exclude item 7 (cost-effectiveness) from the discussion because this item is too context- and healthcare specific.

Formal consensus methodology

The use of the NIH consensus development conference methodology resulted in the following four consecutive major steps:

1. At day 1, evidence reviews were presented by Scientific Committee members in three parallel public (open) sessions (according to the three selected topics) followed by discussion with the general audience. The general audience was divided over these three sessions (according to their preference which was recorded during the registration and for the conference): 46 people attended the ‘preoperative anaemia’ session, 68 people attended the session on ‘RBC transfusion thresholds’ and 61 people attended the ‘PBM implementation’ session. Each session was chaired by two experts (one subject matter expert and one methodologist), and two Scientific Committee members (per session) served as the Rapporteurs by recording the key points from the discussion with the general audience. Before the ICC-PBM 2018, the speakers, chairs and rapporteurs were trained in the GRADE methodology and the Consensus Conference methodology via an online webinar. A detailed list of the speakers, chairs and rapporteurs can be found in Appendix 3. After having the evidence reviews presented by different speakers (mainly Scientific Committee members), the chairs introduced the nine Evidence-to-Decision framework items to the audience: desirable effects (item 1), undesirable effects (item 2), certainty of the evidence (item 3), values (item 4), balance of effects (item 5), resources required (item 6), equity (item 8), acceptability (item 9), feasibility (item 10). These items served as the central themes during the discussion with the audience. Items 1, 2, 3 and 5 were covered by the evidence reviews which were used as the fundamental source of information. The remaining items (items 4, 6, 8, 9, 10; item 7 was not discussed cfr. supra) were also part of the discussion and indicative opinion polls of the audience were collected via the Mentimeter™ software (www.menti.com, Stockholm, Sweden, application via smartphone or laptop). We summarized the results from the indicative opinion polls by expressing a range (%) of different answers from one or more items. Since these opinion polls were not binding but rather indicative for the decision-making panels, no consensus definition was used. The rapporteurs used the GRADEpro software to insert the additional considerations by the general audience directly into the EtD framework (Table 1).

2. At the end of day 1, further deliberation on the evidence and additional considerations by the general audience was done by the three decision-making panels (one panel per topic) during three separate and closed (executive) sessions. The decision-making panels consisted of 10–15 subject matter experts (including 2–3 Scientific Committee members) together with the same chairs (one subject matter expert and one methodologist) as for the open sessions. Key information from the evidence reviews together with important additional considerations of the general audience was presented via the EtD framework (directly in the GRADEpro software) by the chairs after which discussion among the decision-making panelists was started and judgements on the different EtD items were completed. The two rapporteurs (per session) recorded the judgement decisions into the summary of judgement template of the GRADEpro software. Finally, based on this summary of judgements, a conclusion was drafted including the formulation of a conditional, strong or research recommendation (using standard wording) together with the underlying justifications.

3. At day 2, a general plenary session with all conference attendees was organized and moderated by three chairs (Appendix 3). During this session, the chairs of the open/parallel sessions (day 1) presented the
Table 1 GRADE's Evidence-to-Decision framework used during the ICC-PBM 2018

| ITEMS (introduced by the chairs in the open sessions) | JUDGEMENT questions (answered by the decision-making panels during the private sessions) | Source of information | Additional considerations |
|------------------------------------------------------|----------------------------------------------------------------------------------------|-----------------------|----------------------------|
| 1. Desirable effects                                  | How substantial are the desirable anticipated effects?                                | Presentation of evidence reviews (including evidence profiles created by the GRADEpro software) by the Scientific Committee | The rapporteurs directly inserted the additional considerations by the general audience in the EtD template in word or in the GRADEpro software |
|                                                      |                                         |                       |                             |
|                                                      | Trivial                               |                       |                             |
|                                                      | Small                                 |                       |                             |
|                                                      | Moderate                              |                       |                             |
|                                                      | Large                                 |                       |                             |
|                                                      | Varies                                |                       |                             |
|                                                      | Don't know                            |                       |                             |
| 2. Undesirable effects                                | How substantial are the undesirable anticipated effects?                              | Presentation of evidence reviews (including evidence profiles created by the GRADEpro software) by the Scientific Committee | The rapporteurs directly inserted the additional considerations by the general audience in the EtD template in word or in the GRADEpro software |
|                                                      | Large                                 |                       |                             |
|                                                      | Moderate                              |                       |                             |
|                                                      | Small                                 |                       |                             |
|                                                      | Trivial                              |                       |                             |
|                                                      | Varies                               |                       |                             |
|                                                      | Don't know                           |                       |                             |
| 3. Certainty of evidence                              | What is the overall certainty of the evidence of effects?                            | Presentation of evidence reviews (including evidence profiles created by the GRADEpro software) by the Scientific Committee | The rapporteurs directly inserted the additional considerations by the general audience in the EtD template in word or in the GRADEpro software |
|                                                      | Very low                              |                       |                             |
|                                                      | Low                                   |                       |                             |
|                                                      | Moderate                              |                       |                             |
|                                                      | High                                  |                       |                             |
|                                                      | No included studies                   |                       |                             |
| 4. Values                                             | Is there important uncertainty about or variability in how much people value the main outcomes? | Opinion poll voting with the general audience via Mentimeter™, www.menti.com, Stockholm, Sweden | The rapporteurs directly inserted the additional considerations by the general audience in the EtD template in word or in the GRADEpro software |
|                                                      | Important uncertainty or variability  |                       |                             |
|                                                      | Possibly important uncertainty or variability |                       |                             |
|                                                      | Probably no important uncertainty or variability |                       |                             |
|                                                      | No important uncertainty or variability |                       |                             |
| 5. Balance of effects                                 | Does the balance between desirable and undesirable effects favour the intervention or the comparison? | Presentation of evidence reviews (including evidence profiles created by the GRADEpro software) by the Scientific Committee | The rapporteurs directly inserted the additional considerations by the general audience in the EtD template in word or in the GRADEpro software |
|                                                      | Favour the comparison                  |                       |                             |
|                                                      | Probably favours the comparison        |                       |                             |
|                                                      | Does not favour either the intervention or the comparison |                       |                             |
|                                                      | Probably favours the intervention      |                       |                             |
|                                                      | Favour the intervention                |                       |                             |
|                                                      | Varies                                |                       |                             |
|                                                      | Don't know                            |                       |                             |
| ITEMS (introduced by the chairs in the open sessions) | JUDGEMENT questions (answered by the decision-making panels during the private sessions) | Source of information | Additional considerations |
|----------------------------------------------------|------------------------------------------------------------------------------------------|-----------------------|--------------------------|
| 6. Resources required                               | How large are the resource requirements (costs)?                                          | Opinion poll voting with the general audience via Mentimeter™, www.menti.com, Stockholm, Sweden | The rapporteurs directly inserted the additional considerations by the general audience in the EtD template in word or in the GRADEpro software |
|                                                    | Large costs                                                                             |                       |                          |
|                                                    | Moderate costs                                                                          |                       |                          |
|                                                    | Negligible costs and savings                                                           |                       |                          |
|                                                    | Moderate savings                                                                        |                       |                          |
|                                                    | Large savings                                                                           |                       |                          |
|                                                    | Varies                                                                                 |                       |                          |
|                                                    | Don’t know                                                                             |                       |                          |
| 7. cost-effectiveness                              | Does the cost-effectiveness of the intervention favour the intervention or the comparison? | The Scientific Committee decided to exclude this item from the discussion because too context- and healthcare system-specific |
|                                                    | Favour the comparison                                                                   |                       |                          |
|                                                    | Probably favours the comparison                                                         |                       |                          |
|                                                    | Does not favour either the intervention or the comparison                               |                       |                          |
|                                                    | Probably favours the intervention                                                      |                       |                          |
|                                                    | Favour the intervention                                                                 |                       |                          |
|                                                    | Varies                                                                                 |                       |                          |
|                                                    | Don’t know                                                                             |                       |                          |
| 8. Equity                                           | What would be the impact on health equity?                                              | Opinion poll voting with the general audience via Mentimeter™, www.menti.com, Stockholm, Sweden | The rapporteurs directly inserted the additional considerations by the general audience in the EtD template in word or in the GRADEpro software |
|                                                    | Reduced                                                                                |                       |                          |
|                                                    | Probably reduced                                                                       |                       |                          |
|                                                    | Probably no impact                                                                      |                       |                          |
|                                                    | Probably increased                                                                     |                       |                          |
|                                                    | Increased                                                                              |                       |                          |
|                                                    | Varies                                                                                 |                       |                          |
|                                                    | Don’t know                                                                             |                       |                          |
| 9. Acceptability                                    | Is the intervention acceptable to key stakeholders?                                     | Opinion poll voting with the general audience via Mentimeter™, www.menti.com, Stockholm, Sweden | The rapporteurs directly inserted the additional considerations by the general audience in the EtD template in word or in the GRADEpro software |
|                                                    | No                                      |                       |                          |
|                                                    | Probably no                                                                            |                       |                          |
|                                                    | Probably yes                                                                           |                       |                          |
|                                                    | Yes                                      |                       |                          |
|                                                    | Varies                                                                                 |                       |                          |
|                                                    | Don’t know                                                                             |                       |                          |
| 10. Feasibility                                     | Is the intervention feasible to implement?                                              | Opinion poll voting with the general audience via Mentimeter™, www.menti.com, Stockholm, Sweden | The rapporteurs directly inserted the additional considerations by the general audience in the EtD template in word or in the GRADEpro software |
|                                                    | No                                      |                       |                          |
|                                                    | Probably no                                                                            |                       |                          |
|                                                    | Probably yes                                                                           |                       |                          |
|                                                    | Yes                                      |                       |                          |
|                                                    | Varies                                                                                 |                       |                          |
|                                                    | Don’t know                                                                             |                       |                          |
At the end of day 2, three separate and final closed sessions were organized with the decision-making panels. Based on the plenary session presentations (i.e. GRADE’s EtD framework), discussions with the general audience and indicative opinion poll votes on the draft recommendations, consensus among the decision-making panelists was defined as a two-thirds majority (via hand raising).

Results

A total number of 186 persons from five continents and 35 countries were registered for the 2-day Conference (Appendix 4). The attendees represented different medical disciplines, including transfusion medicine, clinical haematology, pathology, anaesthesiology, oncology, cardiology, neurology, surgery, and critical care medicine and methodological expertise in conducting systematic reviews. The attendees were affiliated to 63 (University/Academic) Hospitals, 28 Blood Services, 23 (Patient) Organizations, 12 (Pharmaceutical) Companies, and 5 Governmental Bodies. All contributing Institutions are listed in Appendix 5. The different co-sponsors of the ICC-PBM were acknowledged followed by a brief introduction of the three PBM topics, and the composition of the three corresponding decision-making panels tasked to formulate evidence-based recommendations were presented. A detailed list of these decision-making panels can be found in Appendix 6. Figure 1 summarizes how shared decision-making was promoted by the use of the Consensus Development Conference format, the GRADE’s EtD framework/software and indicative opinion polls via a smartphone/laptop application (Mentimeter™ software).

Day 1: three parallel sessions and a draft consensus statement

The screening of 17,607 references resulted in the final inclusion of 145 studies [13]. In the ‘preoperative anaemia’ session, the evidence of 62 studies regarding the definition and diagnosis of preoperative anaemia (PICOs 1–2: 36 observational studies) and the treatment of preoperative anaemia in adult elective surgery patients (PICO 3: 3 observational studies and 23 experimental studies) were presented. The mean response rate of the indicative opinion poll was 56% (range 50–76%). About 55% of the respondents decided that there is (probably) no important uncertainty or variability in how people/patients value the critical outcomes. About 40% of the people believe that prophylactic transfusion has a reduced impact on health equity whereas only 12–21% of the respondents felt that this reduction is present in case of iron monotherapy or ESA+iron therapy, respectively. The majority of people (50–70%) said that prophylactic transfusion is (probably) not acceptable or feasible to key stakeholders whereas ~60–80% mentioned that iron monotherapy or ESA+iron therapy is (probably) acceptable and feasible.

The ‘RBC transfusion thresholds’ session started with an introductory keynote presentation by Prof. Dr. Jeffrey L. Carson (Robert Wood Johnson Medical School, Rutgers University, New Brunswick, NJ, USA) followed by the presentation of the evidence from 40 studies that investigated the effectiveness of a more restrictive transfusion threshold compared to a more liberal transfusion threshold in the following adult patient populations: critically ill but clinically stable intensive care (PICO 4: four experimental studies), orthopaedic and non-cardiac surgery (PICO 5: 11 experimental studies), acute (gastrointestinal) bleeding (PICOs 6 and 14: four experimental studies), symptomatic coronary heart disease (PICO 7: two experimental studies), septic shock (PICO 8: two experimental studies), cardiac surgery (PICO 9: eight experimental studies), haematology (PICO 10: two experimental studies), oncology (PICO 11: three experimental studies), neurology (PICOs 12 and 13: one observational study and two experimental studies).

The mean response rate of the indicative opinion poll was 81% (range 77–82%). About 82% of the respondents decided that there is (probably) important uncertainty or variability in how people/patients value the critical outcomes. Fifty-four per cent indicated that the use of restrictive RBC transfusion thresholds will result in negligible costs/savings to moderate/large savings. About 60% of the people believe that the use of restrictive RBC transfusion thresholds will probably have no impact or even an increased impact on health equity. The majority of people (70–90%) said that restrictive RBC transfusion strategies are probably acceptable and feasible to key stakeholders.

In the ‘PBM implementation’ session, the evidence of 43 studies regarding the implementation of comprehensive PBM programmes (PICO 15: 20 observational studies) and potential behavioural interventions (PICO 16: 19 observational studies) or computerized decision support...
systems (PICO 17: 3 observational studies and one experimental study) was presented. Detailed information of all evidence reviews and presentations is available at the ICC-PBM website [17]. The mean response rate of the indicative opinion poll was 65% (range 56–80%). About 60% of the respondents decided that there is (probably) important uncertainty or variability in how people/patients value the critical outcomes. About half of the people believe that the impact of PBM programmes on health equity varies. The majority of people (63–85%) said that behavioural interventions and decision support systems are probably acceptable and feasible to key stakeholders. Detailed information about the indicative opinion polls can be downloaded from the ICC-PBM website [17].

During the second part of the three parallel sessions, a closed/executive session with the decision-making panels took place. Based on the evidence reviews, the additional considerations and the indicative polling of the audience, the decision-making panels made final judgements on the different EtD criteria. A summary of judgements for the 17 PICO questions can be found in Appendix 7. The draft recommendations/conclusions of the decision-making panels can be found in Appendix 8.

Day 2: general plenary session and a final consensus statement

The draft recommendations and underlying justifications from the decision-making panels were presented to the general audience. Detailed information of these presentations and the indicative opinion poll results is available at the ICC-PBM website [17]. The median response rate of the indicative opinion poll on these draft recommendations was 68 [IQR: 10]% in summary, the majority of the audience accepted the draft recommendations completely of the diagnosis and management of preoperative anaemia (74 [IQR: 7]%), the use RBC transfusion thresholds (81 [IQR: 16]%) and PBM implementation (69 [IQR: 6]%) completely, except one recommendation which was accepted completely by only ~20% of the audience. This recommendation was related to the management of anaemia and the use of ESAs in addition to iron supplementation in adult preoperative elective major orthopaedic surgery patients with haemoglobin levels <13 g/dl. Major concerns from the audience were that this recommendation did cover a (too) big number of different anaemia causes and it does not cover the caveats/contraindications and the costs of ESAs. It was also mentioned that clinical
outcomes should be considered as the critical outcomes rather than reduction in RBC transfusion since it only replaces one treatment by another. Because transfusion rate in orthopaedic surgery dropped dramatically over the past years, the included older studies overestimate the effect of ESA+iron therapy on RBC reduction and may make the recommendation obsolete. The audience also commented that the avoidance of RBC transfusion reported in published studies depends on the transfusion rate (number of patients transfused), which is dependent on the time of publication, patient population and disease/operation planned. Finally, the audience indicated that ethical considerations, patient preferences, financial and equity consideration are key aspects when formulating this recommendation.

At the end of the second day, the decision-making panels formulated final recommendations. For preoperative anaemia, four clinical and three research recommendations were formulated, including a strong recommendation to detect and manage anaemia sufficiently early before major elective surgery. For RBC transfusion thresholds, four clinical and six research recommendation were developed, including two strong clinical recommendations for critically ill but clinically stable intensive care patients with or without septic shock (recommended threshold for RBC transfusion, haemoglobin concentration <7 g/dl) as well as for patients undergoing cardiac surgery (recommended threshold for RBC transfusion, haemoglobin concentration <7.5 g/dl). For implementation of PBM programmes, two clinical and three research recommendations were developed, including recommendations to implement comprehensive PBM programmes and to use electronic decision support systems (both conditional recommendations) to improve appropriate RBC utilization. Detailed information about the final recommendations is published elsewhere.[13].

Discussion

Numerous consensus conference formats have been used to address issues in medical care [18]. The most well-developed consensus conference format has been used by the US National Institutes of Health (NIH) Consensus Conference format [19]. Consensus conferences are designed to minimize the ability of individual opinions to dominate a group discussion and limit the influence of other social pressures and constructs. These features may be particularly relevant when the topics under discussion are contentious.

For the first time in the field of PBM, and after two years of preparation, clinical bedside experts from anaesthesiology, haemostasis and thrombosis, intensive care medicine, transfusion medicine, internal medicine, neurology, clinical laboratory medicine, haematology, clinical immunology, oncology, neurosurgery, vascular, cardiac and oncological surgery, gynaecology and obstetrics met with nurses, patient and blood banking representatives, representatives of blood transfusion services and government authorities, Evidence-Based Medicine methodologists as well as epidemiologists for a two-day intensive exchange guided by the GRADE methodology. Prior to the meeting, significant deliberation was put into the framing of the questions to be addressed. Consistent with the NIH model, the ICC-PBM relied on a broad-based independent panel to bring balanced perspectives and relevant knowledge to the process. In addition to subject matter experts, both practitioners and methodologists as well as representatives of blood recipients participated. Information was presented in an open meeting format with opportunity for both panellists and audience to question and discuss. Lastly, draft recommendations (consensus statement) were generated at the end of the first day and presented to the entire group of participants on the second day for discussion and refinement. Because of the use of the GRADE methodology, the ICC-PBM spent less time on expert presentations than is typical for most NIH Consensus Conferences. Consensus conferences are dependent on acceptance of the scientific method and a robust application of scientific rigour generates trust in the process. By thoroughly training all members of the Scientific Committee, all panellists, chairs, rapporteurs and speakers in the GRADE and EtD methodologies as well as in the use of the GRADEpro software by establishing more than ten webinars in addition to the regular teleconferences before the conference, we were able to facilitate the whole process. All critical partners had a deep and thorough methodology knowledge before attending the ICC. Furthermore, use of GRADE methodology, including a thorough assessment of the relevant literature, provided a solid foundation for consideration of the PICO questions.

Together with the active involvement of the audience comprising about another 150 clinical experts, the three panels evaluated the outcome of the literature search performed following the predefined PICO questions. The panellists were able to agree on the above-mentioned recommendations in the three predefined PBM topics on the diagnosis and treatment of preoperative anaemia, RBC transfusion thresholds and the implementation of PBM programmes [13].

The GRADE and EtD methodology enabled the three panels to integrate evidence-based literature searches into a discussion on practical bedside implementation and guided the drafting of evidence-based recommendations. Employing the tools described above to maintain academic rigour through the process, the three panels were
able to take a holistic view of PBM. One of the major outcomes of this process are the recommendations, which go beyond the simple interpretation of the published literature to give concise advice to the bedside clinician and to patients potentially requiring RBC transfusion, ESA and/or iron support while keeping in line with the published evidence.

Several challenges or limitations regarding the use of the Consensus Conference format and the GRADE approach were present. Firstly, although an enormous effort was made to inform and educate all people involved in the evidence-based methodology (i.e. GRADE approach), the formulation of straightforward PICO questions and selection criteria, including rating the importance of outcomes, was a difficult discussion between the methodologists and the subject matter experts. This is part of the lumping–splitting debate where subject matter experts are more lumping the review questions, that is addressing a wide range of populations, interventions and outcomes. Lumped review questions are time-consuming but will better inform decisions about which interventions to implement when there may be a range of options. On the other hand, methodologists are more in favour of splitting the review questions, that is addressing a narrow range of populations, interventions and outcomes. These type of questions are less time-consuming. However, these reviews can only inform decisions about whether or not to implement narrowly focused interventions. Given the tight time schedule (i.e. 1 year) to complete the 17, predominantly lumped evidence reviews, in addition to the technical preparation of the ICC-PBM 2018, we might have missed some relevant studies (selection bias). Therefore, a face-to-face meeting at the beginning of the project with the formulation and final approval of clinically relevant and feasible PICO questions (given the available time and resources) together with the preparation of an a priori data analysis plan should have been better to conduct evidence reviews in the most efficient way. To further improve the engagement of the Scientific Committee members, the decision-making panels, chairs and
rapporteurs, a second online/face-to-face meeting with the Scientific Committee, the rapporteurs and the decision-making panels could be organized after conducting the evidence reviews to discuss the results, critical appraisal and the conclusions of these evidence reviews. Secondly, the formulation of the recommendations is the key task for decision-making panels. Therefore, a rigorous procedure is required to select panellists that accept the principles of Evidence-Based Medicine and to manage potential conflicts of interest in a fair, judicious and transparent manner [20]. Where substantial disagreement on the formulation of recommendation exists (i.e. ICC-PBM recommendation on the use of ESAs and iron in preoperative major orthopaedic surgery patients with Hb <13 g/dl), a formal and blinded voting system among the decision-making panels (e.g. via the GRADEpro software) could be helpful to avoid the (negative) impact of biased/strong individual opinions. Thirdly, to maximize participation and minimize the costs, consensus conferences could be held in conjunction with other educational or scientific meetings.

**Conclusion**

The use of a formal Consensus Conference format in combination with the GRADE approach provides a powerful framework to formulate evidence-based recommendations based on the best available evidence, patient perspectives and clinical expertise. This first international consensus conference on PBM could open ways to future developments in this field. First, it provides a tool to help evaluate the outcomes from this consensus conference (e.g. changes in clinical practices, published clinical studies according to the ICC-PBM recommendations). Second, the emitted recommendations should be reviewed and updated at least every 5 years according to the same methodology. The systematic use of evidence-based methodologies should be the new standard to evaluate (cost-) effectiveness of medical treatments in order to avoid recommendations based on expert opinion solely and/or strongly held opinions on religious (e.g. Jehovah Witnesses) or commercial (e.g. pharmaceutical companies) grounds. Third, future consensus conferences using the same methodology should be organized to elaborate other recommendations in areas not covered by the first ICC-PBM such as PBM for platelet and plasma transfusion or PBM in paediatrics or obstetrics.

**Acknowledgements**

The authors thank all participants, (co-)sponsors and contributors of the 1st International Consensus Conference (ICC) on Patient Blood Management (PBM) in Frankfurt, Germany, on 24 and 25 April 2018 (ICC-PBM 2018). Members of the Scientific Committee, decision-making panels, chairs and speakers are listed in Appendices 1, 4 and 6. The authors also thank Martina Päßl, Sophie Hamburger and Willemijn Kramer for technical arrangements at the ICC-PBM2018.
References

1 World Health Organization: WHO global forum for blood safety: patient blood management, 2011. https://www.who.int/bloodsafety/events/gfbs_01_pbm/en/. (Last accessed 27 September 2019).

2 Brouwers MC, Kho ME, Browman GP, et al.: AGREE II: advancing guideline development, reporting and evaluation in health care. CMAJ 2010; 182:E839–E842

3 Guyatt G, Oxman AD, Akl EA, et al.: Grade guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011; 64:383–394

4 Guyatt GH, Oxman AD, Kunz R, et al.: What is "quality of evidence" and why is it important to clinicians? BMJ 2008; 336:995–998

5 Guyatt GH, Oxman AD, Vist GE, et al.: GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008; 336:924–926

6 Nair R, Aggarwal R, Khanna D: Methods of formal consensus in classification/diagnostic criteria and guideline development. Semin Arthritis Rheum 2011; 41:95–105

7 Sher GD, Devine DV: The consensus development process in transfusion medicine: does it add value? Transfusion 2007; 47:2176–2179

8 Consensus Development at the NIH: Improving the Program. The National Academies Collection: Reports funded by National Institutes of Health. Washington (DC),1990

9 Lomas J: The consensus process and evidence dissemination. CMAJ 1986; 134:1340–1341

10 Vogel JP, Oxman AD, Glenton C, et al.: Policymakers’ and other stakeholders’ perceptions of key considerations for health system decisions and the presentation of evidence to inform those considerations: an international survey. Health Res Policy Syst 2013; 11:19

11 Chalmers I, Oxman AD, Austvoll-Dahlgren A, et al.: Key Concepts for Informed Health Choices: a framework for helping people learn how to assess treatment claims and make informed choices. BMJ Evid Based Med 2018; 23:29–33

12 Moher J, Oxman AD, Rosenbaum S, et al.: The GRADE Evidence to Decision (EtD) framework for health system and public health decisions. Health Res Policy Syst 2018; 16:45

13 Mueller MM, Van Remoortel H, Meybohm P, et al.: Patient blood management: recommendations from the 2018 Frankfurt consensus conference. JAMA 2019; 321:983–997

14 De Buck E, Pauwels NS, Dieltjens T, et al.: Use of evidence-based practice in an aid organisation: a proposal to deal with the variety in terminology and methodology. Int J Evid Based Healthc 2014; 12:39–49

15 Guyatt GH, Oxman AD, Kunz R, et al.: GRADE guidelines: 2. Framing the question and deciding on important outcomes. J Clin Epidemiol 2011; 64:395–400

16 Li SA, Alexander PE, Reljic T, et al.: Evidence to Decision framework provides a structured “roadmap” for making GRADE guidelines recommendations. J Clin Epidemiol 2018; 104:103–112

17 The International Consensus Conference on Patient Blood Management (Frankfurt G): Recommendations & Materials. 2018. https://icc-pbm.eu/recommendations-materials/. (Last accessed 27 September 2019).

18 McGlynn EA, Kosecoff J, Brook RH: Format and conduct of consensus development conferences. Multi-nation comparison. Int J Technol Assess Health Care 1990; 6:450–469

19 Waggone J, Carlile JD, Durning SJ: Is there a consensus on consensus methodology? Descriptions and recommendations for future consensus research. Acad Med 2016; 91:663–668

20 Schunemann HJ, Al-Ansary LA, Forland F, et al.: Guidelines International Network: principles for disclosure of interests and management of conflicts in guidelines. Ann Intern Med 2015; 163:548–553

Supporting Information

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

Appendix S1 Overview of the 23 Scientific Committee Members.

Appendix S2 Rating the importance of outcomes for all PICO questions by the Scientific Committee members

Appendix S3 Chairs, presenters and rapporteurs of the three parallel sessions (day 1) and the general plenary session (day 2)

Appendix S4 List of continents and countries included in the participation list of the ICC-PBM 2018

Appendix S5 List of Institutions/Organizations that co-sponsored or contributed during the ICCPBM 2018

Appendix S6 Composition decision-making panels

Appendix S7 Summary of judgements of the Evidence-to-Decision framework items relevant to the 17 PICO questions

Appendix S8 Draft recommendations of the decision-making panels at the end of day 1