19th Expert Committee on The Selection and Use of Essential Medicines
April 8-12 2013

Expert peer review on application for WHOLE BLOOD/RED BLOOD CELLS (Reviewer 1)

INTRODUCTION
This is an application from the American Association of Blood Banks, the American Red Cross, the Canadian Blood Services and the International Society of Blood Transfusion. It follows discussions at the meeting of the WHO Expert Committee on Biological Standards (October 2012) and the 15th ICDRA meeting. At the time of preparing this review, there are many comments both for and against the proposal on the WHO Essential Medicines website. The arguments in the comments are summarized under point 7, below.

1. Assessment of efficacy
a. Have all relevant studies on efficacy been included
   Yes  No (if no, please provide reference and information)
NO.
The literature on blood transfusion is enormous and the application has highlighted some of the key references in relation to indications and use of whole blood and red blood cells. However, a very rapid search of the Cochrane Database of Systematic Reviews identified at least 12 potentially relevant systematic reviews – an annex with these citations is attached. While reviewing the literature in its entirety is clearly not reasonable or sensible, the following additional studies to those mentioned in the application should be noted:
   • Severe anaemia in children with malaria - evaluated in Meremikwu and Smith, 1999
   • Sickle cell anaemia and use of transfusion to prevent stroke - see also Hirst et al, 2002; Hirst and Williamson, 2012; the Cochrane reviews also cover acute chest pain syndrome (Alhashimi et al, 2010; Cho and Hambleton, 2011); use in pregnancy (Kassam, 2006)
The Cochrane reviews also describe the impact of blood transfusions in anaemia in patients with advanced cancer (Preston et al), upper gastrointestinal haemorrhage (Jairath et al, 2010), anaemia in HIV (Martincarvajal et al, 2011) post partum haemorrhage (Moussa and Alfirvic, 2007).

b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable

The evidence and experience of use of blood transfusion clearly show that it is life saving for management of acute hemorrhage from various causes and that it is effective with respect to other outcomes in a variety of inherited hemoglobin disorders. The role of transfusion in management of severe anaemia from various causes is also generally clear, as is the use of red cell in supportive care in patients with haematological malignancies. The only relevant comparator for some of these indications currently on the WHO EML is the crystalloids that can be used as an interim management strategy in acute hypovolaemia. Exogenous erythropoietin is not listed on the EML.
What is unclear is the ‘threshold’ hemoglobin (or haematocrit) for initiating transfusion in non-acute settings, and the role of transfusion in anemia of chronic diseases, such as cancer. Some of the comments on the application raise concerns about ‘commodification’ of whole blood and red blood cells if it is listed on the EML – there is also the risk of overuse of transfusion.

c. Please provide any additional relevant information with reference

The number of studies and protocols for studies registered in relation to transfusion indicate that the evidence for efficacy and safety and optimal use of red blood cells is still evolving. The appropriate use of transfusions is not nearly as clear as is portrayed in the application and this changing evidence would need to be considered in guideline development. See the list of planned Cochrane reviews in the Reference attachment for examples.

2. Assessment of safety
a. Have all relevant studies on safety been included
   Yes   No (if no, please provide reference and information)

Transfusion associated risks are not quantified in the application but are well defined in Madjdpour and Spahn, 2005.

An additional systematic review that is relevant to the application is: Whyte R, Kirpalani H. Low versus high haemoglobin concentration threshold for blood transfusion for preventing morbidity and mortality in very low birth weight infants. The Cochrane Database of Systematic Reviews. DOI: 10.1002/14651858.CD000512.

This review identified 4 trials with 619 infants, comparing restrictive and liberal transfusion thresholds. As one of the risks of transfusion is inappropriate use, evidence supporting no benefit from liberal thresholds is important to consider to guide appropriate use. So far, the evidence tends to support the use of restrictive thresholds as a way of reducing risks of transfusion.

b. Summarize the data on safety, in comparison to what is listed in EML where applicable.

There is no relevant comparator on the EML

The risks of transfusion include: acute reactions, volume overload transmission of viral infection, iron overload. The work of Carson and others in describing risks associated with potentially unnecessary transfusion is covered in the application. However, the application overstates the safety; the benefits do not always clearly outweigh the risks as is claimed on page 17.

The application also highlights that one reason to include whole blood and red blood cells is to improve the safety of manufacture of blood products.

c. Please provide any additional relevant information with reference

3. Assessment of cost and availability
a. Have all relevant data on cost provided
   Yes   No (if no, please provide reference and information)

The application provides some of the evidence concerning cost of production and cost of transfusion. It estimates that the cost in Zimbabwe for a quality assured unit of whole blood is USD 128, based on WHO costing guidelines.
b. Summarize the data on cost and cost effectiveness, in comparison to what is listed in EML where applicable

There is no relevant comparator on the EML.

There are many other cost-analyses – for example, Abraham and Sun (2012) estimated that the cost of a 2 unit transfusion in 6 European countries averaged 877 EU. A relevant cost-effectiveness analysis is Beliaev et al (2012), which estimated that the incremental cost-effectiveness of allogeneic transfusion in severe anaemia was (2011) USD 22515/death averted. In summary, while the costs of transfusion may be known, they are significant. Many countries are adopting strategies to reduce the use of transfusion wherever possible and this also needs to be taken into account in evaluating costs and effects.

c. Please provide any additional relevant information with reference

d. Is the product available in several low and middle income countries?

YES

4. Assessment of public health need
a. Please provide the public health need for this product

This is adequately covered in the application.

b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones?

There are numerous guidelines that deal with transfusion. However, the current questions are use in chronic conditions and at what threshold to transfuse. WHO does not yet have specific guidelines addressing these issues.

5. Are there special requirements for use or training needed for safe/effective use?
If yes, please provide details in 1-2 sentences

YES. These are covered in the application and mainly relate to the requirements for safe collection of donated blood and safe processing. There are also requirements for ABO matching but these are extremely well understood.

6. Is the proposed product registered by a stringent regulatory authority?

Yes No Not applicable

Many countries manage blood products through the national medicines regulatory authority.

7. Any other comments

From the responses from interested associations and transfusions services published on the WHO meeting website, it is clear that there are strong views both for and against including blood and red blood cells on the WHO EML. The arguments against inclusion of whole blood and red blood cells on the WHO EML are:

- Increased commodification of blood/blood products
- The risk of undermining voluntary donations
- That it may reduce countries self-sufficiency
- That it will increase the risk of overuse of blood
• That it will destroy the ‘spirituality’ of the gift of donating blood
• That based on the experience of including Factor VIII and Factor IX on the WHO EML, it is unlikely to have any positive effect on availability, safety and use of blood.

These views reflect the values and preferences of some national groups/authorities and no evidence is provided to support the claims. It would be useful to have data concerning the uptake of the Factor VIII/IX listing, but as Factor VIII and IX deficiencies are rare disease it may not be a useful comparison.

The political and advocacy value of adding blood and red blood cells to the EML is also a consideration. Many of the comments stress this aspect of the application, but it can also be argued that WHO has many political and advocacy documents/resolutions/guidelines relating to blood and blood products. It is not therefore not at all clear that adding whole blood and red blood cells to the EML will achieve any significant public health or clinical gains and WHO should be prepared to undertake an evaluation of the impact if the additions are made.

8. What is your recommendation to the committee (please provide the rationale)

The application has made the case that (1) whole blood and red blood cells meet the general definition of a ‘medicine’ (2) that they meet the criteria for the WHO Essential Medicines List:

“Essential medicines are those that satisfy the priority health care needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness. Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford. “

As there is already a Section of the List for Blood and Blood Products, my recommendation is that the Committee:

1) add whole blood and red blood cells to Section 11, Blood Products and Plasma Substitutes
2) review the continued listing of Factor VIII concentrate and Factor IX complex, as it is not clear that these 2 products meet the criteria for essential medicines.

Additional References

1. Potentially relevant Cochrane reviews.


Meremikwu Martin M, Smith Helen J. Blood transfusion for treating malarial anaemia. Cochrane Database of Systematic Reviews 1999 DOI: 10.1002/14651858.CD001475

Alhashimi Dunia, Fedorowicz Zbys, Alhashimi Fatima, Dastgiri Saeed. Blood transfusions for treating acute chest syndrome in people with sickle cell disease. Cochrane Database of Systematic Reviews 2010 DOI: 10.1002/14651858.CD007843.pub2


Potentially relevant protocols:


Haas Barbara, Gomez David, Steel Andrew, Nathens Avery. Ratio of units of red blood cells to fresh frozen plasma for severely injured patients undergoing massive transfusion. Cochrane Database of Systematic Reviews 2011. DOI: 10.1002/14651858.CD009033


Sarai Michael, Tejani Aaron M. Loop diuretics for patients receiving blood transfusions. Cochrane Database of Systematic Reviews 2012. DOI: 10.1002/14651858.CD010138

Safety data

Madjdpour C, Spahn DR. Allogeneic red blood cell transfusions: efficacy, risks, alternatives and indications. BJA 2005:95 (1)33-42.

Relevant economic citations
