Expert peer review on application for whole blood and red blood cells

The application is for the addition of Whole Blood and Red Blood Cells (RBC) the WHO EML and WHO EMLc. This application follows discussions held on this issue during meetings of the WHO Expert Committee on Biological Standardization, the European Committee on Blood Transfusion of the European Directorate for the Quality of Medicines and Heath Care in the Council of Europe and the International Conference of Drug Regulatory Authorities.

The initial part of this application is dedicated to demonstrating that blood and blood products are medications. Since WHO has defined medicine as “any substance or pharmaceutical product for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient” it is stated in the application that blood meets the generic definition of a substance used to treat, mitigate, or prevent disease, therefore it can be classified as a medicine. Blood components are biologicals that share many attributes with medicines. In addition, the anticoagulant and preservative solutions and the process and quality controls inherent in blood collection, processing and distribution, render blood transfusion less like a “transplant” and more like the administration of a medicine. In addition, the units of whole blood and red blood cells transfused contain pharmaceuticals that require licensing.

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

Blood and Red Blood Cells are transfused is indicated in patients with life-threatening anaemia and severe tissue hypoxia. The dosage regimens and the duration of treatment depend on the underlying reasons for transfusion and to each patient’s condition.

The efficacy of whole blood and red blood cells (RBC) transfusion is a vast topic, so it is unrealistic to expect that all the relevant, well designed studies to be included in this application. However, some critical reviews and other large studies which should have been included were not considered. They are:

Critical reviews:


Other studies:
In cells. disorders

There may be variations among countries in patient factors and the quality of healthcare that could affect the safety of transfusion.

b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

In most clinical situations where red cells are transfused, the rationale is to increase the oxygen carrying capacity of the blood, ultimately to deliver additional oxygen to the tissues.

The need for transfusion is particularly important if the patient is unable to compensate for the lack of red cells. Unfortunately, there is not enough information to determine when this point has been reached: The patient’s haemoglobin level is a way to measure the severity of anaemia, but it is only a reliable indicator of tissue hypoxia when it is very low (< 5-6 g/dL). Some patients may function well in low levels of haemoglobin, while patients with cardiovascular disease may show signs and symptoms of tissue oxygen deprivation and may require transfusion at higher haemoglobin levels.

There is sufficient evidence indicating that blood transfusion is effective in the treatment of haemoglobin disorders and that it is life saving for management of acute haemorrhage due to different causes. Trials also demonstrated a significantly reduced risk of stroke in patients with sickle cell receiving regular blood transfusions. Data from a follow-up trial indicate individuals may revert to former risk status if transfusion is discontinued.

The evidence of efficacy of transfusion in patients with less severe anaemia, usually defined as haemoglobin levels between 7 and 10 g/dL is weak.

c. Please provide any additional relevant information with reference

Studies indicate that fatigue and breathlessness in patients with advanced cancer can be improved immediately after the transfusion. However, this benefit wanes after 2 weeks. (see Preston et al 2012 in 1a)

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

b. Summarize the data on safety, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

Blood is a biological product and there is inherent variability in the source of the product, the safety of Whole Blood and Red Blood Cells will vary from country to country depending upon the transfusion transmissible disease incidence and prevalence rates in the local blood donor population, as well as upon the specific test kits (e.g., HIV and hepatitis) used to identify collected units at risk. The safety and quality of the biological product is, therefore, dependent on quality assurance processes (including GMPs) that ensure the quality and safety of the final biological product to be transfused into patients. Finally, there may be
There is no known substitution for whole blood and RBC (several unsuccessful clinical trials of blood substitutes have been halted). The only known replacement, when appropriately administered, is erythropoietin, which has limited applicability.

The application states that the safety profile of Whole Blood and Red Blood Cells is widely acknowledged to represent a favourable therapeutic index and that because transfusion has been carried out so widely and for so many years, the adverse events are well-recognized and have been carefully quantified and studied.

c. Please provide any additional relevant information with reference

Marik and Corwin (see 1a) reviewed literature found in MEDLINE, Embase, Cochrane Register of Controlled Trials, and citation review of relevant primary and review articles. The CR, which included 45 studies (272,596 patients), indicate that in adult, intensive care unit, trauma, and surgical patients, RBC transfusions are associated with increased morbidity and mortality. In 42 studies the risks of RBC transfusion outweighed the benefits; the risk was neutral in two studies with the benefits outweighing the risks in a subgroup of a single study (elderly patients with an acute myocardial infarction and a hematocrit <30%). Seventeen of 18 studies, demonstrated that RBC transfusions were an independent predictor of death; the pooled odds ratio (12 studies) was 1.7 (95% confidence interval, 1.4–1.9). Twenty-two studies examined the association between RBC transfusion and nosocomial infection; in all these studies blood transfusion was an independent risk factor for infection. The pooled odds ratio (nine studies) for developing an infectious complication was 1.8 (95% confidence interval, 1.5–2.2). RBC transfusions similarly increased the risk of developing multi-organ dysfunction syndrome (three studies) and acute respiratory distress syndrome (six studies). The pooled odds ratio for developing acute respiratory distress syndrome was 2.5 (95% confidence interval, 1.6–3.3).

From the study by Pape et al (see 1a), the data indicates that systematic evidence on the clinical effectiveness of blood transfusions is limited. The results of clinical studies investigating the effects of blood transfusion on morbidity are at least as inconsistent as those regarding the effects on mortality. The most relevant clinical studies report inconsistent effects of blood transfusion on morbidity and mortality as primary outcome parameters.

Three major studies [TRICC (included in the application), ABC and CRIT (see 1a)] reported increases in morbidity and mortality of patients who received blood transfusions than in those who did not, while in the Sepsis Occurrence in Acutely Ill Patients (SOAP) study reported that the 30-day survival rate was significantly higher in transfused patients. Vincent et al. demonstrated that blood transfusion was associated with an increased time spent in the ICU and a higher incidence of organ failure, as assessed by the sequential organ failure assessment (SOFA) score.

There is insufficient data to be sure whether routinely giving blood to clinically stable children with severe anaemia in endemic malarious areas reduces death, or results in higher haematocrit measured at one month. (see Meremikwu and Smith in 1a)

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

b. Summarize the data on cost and cost effectiveness, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)
The comparative costs of Whole Blood and Red Blood Cells must be based on the collection of a unit of Whole Blood, rather than the individual component costs. In most countries that collect, test, process and distribute blood, the cost of a unit of Whole Blood and Red Blood Cells is based on a cost recovery model, i.e., the costs required to collect, test, process and distribute. For that reason, costs vary from country to country. The application includes the average cost of producing a unit of quality assured Whole Blood in Zimbabwe is USD $128.00.

c. Please provide any additional relevant information with reference
A study in the USA found that the actual blood transfusion costs range between $522 and $1,183 per-unit—37% higher than estimated by prior studies and 3.2 to 4.8-fold higher than reported blood product acquisition costs.

d. Is the product available in several low and middle income countries?
Yes. Ninety countries (20 high-income, 45 middle-income and 25 low income) contributing data to the 2011 WHO Global Database on Blood Safety reported that more than 9 million patients received blood transfusions during the reported year (based on 2008 data or the latest data available since 2006 if 2008 data were not available.)

4. Assessment of public health need
a. Please provide the public health need for this product (1-2 sentences)
The WHO Global Database on Blood Safety (based on 2008 data) establishes that about 8000 centres in 159 countries reported that they collect blood.

As described in the application, the Pan American Health Organization (PAHO) identified four conditions which may result in underlying need for blood:
- Clinical conditions, such as anaemia and diseases of the blood; leukaemia and lymphomas; non-hematologic malignant tumours, and anaemia associated with gastrointestinal bleeding
- Surgical interventions, such as cardiovascular surgery, injury, poisoning and other consequences of external causes; orthopaedics and general surgery;
- Obstetric and gynaecological conditions; and
- Neonatal Conditions

b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable.

WHO has developed guidelines for the collection, processing and quality control of blood, blood components and plasma derivatives:

5. Are there special requirements for use or training needed for safe/effective use?
If yes, please provide details in 1-2 sentences
Yes.
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They are mostly related to the requirements for safe collection of donated blood and safe processing. The Whole Blood, or Red Blood Cells and Plasma, must remain in quarantine until testing has been completed and the results are found acceptable. These tests include ABO and Rh type, hepatitis B, hepatitis C and HIV. Temperature during storage and transport (distribution to the transfusion facility) must be maintained within a strict cold range.

6. Is the proposed product registered by a stringent regulatory authority?
   Yes X  No

Blood is a strategic resource and blood donation from voluntary non remunerated donors (VNRD) occurs in all countries while regulatory status is provided for several (but not all) countries. In the US, Canada and Germany, Whole Blood and Red Blood Cells are directly regulated as biologic medicines. In Switzerland, Whole Blood and Red Blood Cells are considered medicinal products, and regulated by the law on therapeutic products and the ordinances referred to by the law. In Japan, Whole Blood and Red Blood Cells are regulated as safety measures by the “Pharmaceutical Affairs Law” and under the “Law on Securing a Stable Supply of Safe Blood Products”.
In Australia, Whole Blood and Red Blood Cell blood establishment manufacturers are subject to licensing to assure that the products meet standards as per the Council of Europe “Guide”. In France, Whole Blood and Red Blood Cells are covered in an overall national drug legislative framework that has specific references to regulation of them

7. Any other comments

This application has generated a large amount of responses, both in favour and against the addition of Whole Blood and Red Blood Cells in the EML and EML(c). Several letters and position statements from organizations and governments have been received by the WHO Secretariat.

It is clear that many governments and organizations have worked over several years to establish safe and sustainable blood programs based on the principle of voluntary, non remunerated blood donors.

Some of the arguments in favour of this application include:

It is argued that the inclusion of Whole Blood and Red Blood Cells on the WHO EML accomplishes a number of critical objectives in blood safety and efficacy, in furtherance of WHA Resolution 63.12:

- Increases awareness of the need for blood in every country and of the role of blood in protecting the public health.
- underscores the government’s responsibility for ensuring financially sustainable funding and support for a safe and adequate supply of blood that is accessible to patients in need and creates a favourable environment for governments to support a National Regulatory Authority specifically pertinent to blood, and to invest in infrastructure, systems and governance for blood establishments.
- Underscores the need for effective and efficient procurement systems to provide equipment, supplies and reagents to collect, process, test, store and transport blood.
- Emphasizes the need to ensure that blood is cost-effective, affordable AND available.
- Underscores the importance of, and enables appropriate regulatory oversight of, blood collection, processing, testing, storage and distribution to ensure the safety and quality of blood and the safety and efficacy of blood transfusion.
- Brings visibility to the need for adherence to universally accepted and evidence-based clinical guidelines.

Some arguments against this application include:
Placing blood and blood products in the EML and EML(c) carries the risk of making it a commodity which may result in its commercialization which in turn, may result in decreased availability. This could affect national self-sufficiency and VNRD.

The commercial market for plasma products which are already listed in the WHO EML, not necessarily has resulted in increased availability but rather in over-consumption in some countries and under-consumption in countries with limited resources.

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

It is my opinion that there are two dimensions to this decision: One is related to the moral and ethical aspects, and another is the evidence on safety and efficacy of whole blood and RBC transfusion.

While the application states that whole blood and red blood cells are the most carefully studied medications and remain widely used precisely because the benefits so clearly outweigh the risks, the systematic reviews indicate that the level of evidence is weak and that there needs to be more, careful studies and evaluations. As patients requiring blood transfusions are usually supposed to be sicker than non-transfused patients and blood transfusions are not administered on the basis of a prospective randomisation, the study populations are very likely to have differed in many other variables than only the treatment intervention. While it is difficult (and in most cases, morally unacceptable) to design prospective, randomized controlled trials to study the safety and efficacy of whole blood and RBC transfusion, the most relevant clinical studies report inconsistent effects of blood transfusion on morbidity and mortality as primary outcome parameters.

The moral and ethical aspects are based on the concerns expressed by governments, organizations and individuals, on how the inclusion of whole blood and Red Blood Cells could negatively affect voluntary non-remunerated donations and the perception that blood could become a commodity which may result in its commercialization for profit. Three ethical elements are relevant in this discussion and have been raised:

Blood transfusion safety should be based on the principle of VNRD; a profit motive should not be the basis for the establishment and running of a blood service; and blood is a public resource and access should not be restricted. In addition, an issue which has not been raised in the application and should also be considered is the fact that some people find blood transfusion offensive or contrary to their religious values.

While I am supportive of the overall intent to recognise the essential nature of blood in health care and the importance to increase global access to and availability of safe blood, my recommendation is to postpone the decision to allow more time to identify additional clinical evidence and to allow for a broader, more comprehensive discussion among all the stakeholders to reach an informed decision.