December 14, 2012

Secretary of the Expert Committee on the Selection and Use of Essential Medicines
World Health Organization
Office of the EML Secretariat
Medicine Access and Rational Use (MAR)
Department of Essential Medicines and Health Products
20 Avenue Appia
CH-1211 Geneva 27

Re: Application for the addition of Whole Blood and Red Blood Cells to the WHO Model Essential Medicines List and the WHO Model Essential Medicines List for children

Dear Sir:

I am writing on behalf of AABB (formerly the American Association of Blood Banks), the American Red Cross, Canadian Blood Services and the International Society of Blood Transfusion to request the addition of Whole Blood and Red Blood Cells to the essential medicines lists (WHO EML and WHO EMLc). Our organizations strongly believe that the placement of important medicines on the EML results in a higher quality of care for patients, better management and use of medicines and more cost-effective use of health resources. The provision of safe, adequate and cost-effective Whole Blood and Red Blood Cells that are appropriately transfused is a key component of the public health infrastructure in every country.

The specific benefits of placement on the EML are included in the Summary Statement of the formal submission for Whole Blood and Red Blood Cells, which is attached. We thank you for your consideration of this request and hope, for the sake of donors and patients, that our request will be endorsed by the WHO Expert Committee.

Sincerely,

Karen L. Shoos, JD
Chief Executive Officer
AABB

On behalf of:

Dr. Richard Benjamin  Dr. Graham Sher  Dr. Peter Flanagan
Chief Medical Officer  Chief Executive Officer  President
American Red Cross  Canadian Blood Services  International Society of Blood Transfusion
Application for the inclusion of WHOLE BLOOD and RED BLOOD CELLS in the WHO Model List of Essential Medicines

Submitted by

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Application for Inclusion of Whole Blood/Red Blood Cells as a Medicine in the WHO Model List of Essential Medicines

1. **Summary Statement of the proposal for inclusion**

Applicants propose that Whole Blood and Red Blood Cells be included in the WHO Model List of Essential Medicines (WHO EML and WHO EMLc). The applicants believe that the addition of Whole Blood and Red Blood Cells to the EML will serve as an important tool to support the sixty-third World Health Assembly (WHA 63) resolution on Availability, safety and quality of blood products (WHA63.12) Geneva, 17-21 May 2010).

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.” (http://www.who.int/medicines/areas/quality_safety/regulation_legislation/blue_book/en/index.htm)

Blood meets the generic definition of a substance used to treat, mitigate, or prevent disease. Whole Blood and Red Blood Cells differ from the small molecule medicines in their inherent biological variability unit to unit. Blood components are biologicals that share many attributes with those medicines.

Although blood transfusion evolved initially as a medical practice or service, transfused literally from the vein of the donor to the vein of the patient, two important developments significantly changed the nature of blood transfusion. First, the identification by Karl Landsteiner in 1901 of the major blood groups and the subsequent introduction of compatibility testing by agglutination facilitated the characterization of blood units. Second, the introduction of anticoagulant solutions that enabled storage (that is, banking) of blood in lieu of donor to patient transfusion, made it possible to think of whole blood and its labile components as products that must meet defined standards. Today, the anticoagulant 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.

Technical and regulatory developments during the past half century have also led to the “manufacture” of blood to ensure purity, potency and safety. The blood donor is qualified as the source of raw material by rigorous selection and testing standards. Units undergo in-process quarantine, quality control to ensure that reagents, equipment and methods perform as expected, temperature monitoring, batch release after suitability determination, and labeling for identity, content, expiration date and intended use. Once issued, blood components are subject to standards for traceability. Like other medicines, blood has defined medical indications, recognized adverse effects, and may be administered only by a doctor’s order or prescription.
Today, 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. Moreover, the units of whole blood and red blood cells transfused contain, in addition to the blood itself, pharmaceuticals that require licensure, specifically anticoagulants (e.g., citrate), nutrients (e.g., dextrose), buffers (e.g., phosphate), and preservatives (e.g., adenine).

Many countries regulate blood and its components as a “medicine.” As an example, in the United States, blood has been regulated as a medicine under the Food and Drug Cosmetic Act since 1938 and in 1972 became subject to the regulations applicable to the manufacturing of pharmaceutical drugs. In Canada, blood components are subject to the Food and Drugs Act and drugs are defined as “any substance or mixture of substances… (a) for use in the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms…or (b) restoring, correcting or modifying functions in human beings....” Additional information on existing national regulations is included in Section 13.

Whole Blood and Red Blood Cells cannot be characterized by an exact chemical formula or a purified bulk substance, as they are biologic materials that can vary due to the inherent biological variations among individual blood donors. However, the development and adoption of internationally recognized standards for whole blood and blood components have evolved over time and these products now share fundamental features with medicines. Specifically, although the composition of units cannot be uniform, maximal standardization is achieved through process controls that are comparable to medicine preparation processes. Raw material qualification through the application of donor selection criteria and testing, in-process quarantine, batch release of each blood unit to ensure that all donor and product requirements are met before release, quality control procedures to ensure that reagents, equipment and methods perform as expected, expiration dating and traceability requirements are all part of blood and medicine preparation. Like most medicines, blood can only be administered on a physician’s order or prescription. Blood components also have well defined medical indications and contraindications. And each unit is specifically labeled for identity, content (including additive medicines such as anticoagulants, nutrients, buffers and preservative solutions) and intended use. Examples of Whole Blood and Red Blood Cell standards are included in the references section of the application.

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.

- Placement on the WHO EML brings heightened awareness of the need for blood in every country and of the role of blood in protecting the public health.
• Placement on the WHO EML 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 favorable environment for governments to support a National Regulatory Authority specifically pertinent to blood, and to invest in infrastructure, systems and governance for blood establishments.

• Placement on the WHO EML underscores the need for effective and efficient procurement systems to provide equipment, supplies and reagents to collect, process, test, store and transport blood.

• Placement on the WHO EML emphasizes the need to ensure that blood is cost-effective, affordable AND available.

• Placement on the WHO EML 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.


• Placement on the EML brings visibility to the need for adherence to universally accepted and evidence-based clinical guidelines.

2. The focal point in WHO supporting the application is the Expert Committee on Biological Standardization.

The concept of Whole Blood and Red Blood Cells as essential medicines has been endorsed by the WHO Expert Committee on Biological Standardization—blood products and in vitro diagnostics track, the WHO Blood Regulators Network and the International Conference of Drug Regulatory Authorities at their respective meetings in October 2012. The WHO Department serving as secretariat for the above Committees, network and forum is the Department of Essential Medicines and Health Products. The focal person is Dr. Ana Padilla, Programme Manager Blood Products and Related Biologicals.

3. The organizations supporting the application include the following:

AABB (formerly the American Association of Blood Banks), the American Red Cross, Canadian Blood Services and the International Society of Blood Transfusion.
4. The International Nonproprietary Name (INN, generic name) of the medicine


5. Formulation proposed for inclusion; including adult and pediatric doses.

Adults:

Whole Blood (from which Red Blood Cells can be derived) can be collected in containers of different sizes, ranging from 300 to 500 mL for adults.

Each container is considered to be a unit. A single dose of Whole Blood is generally considered to be one unit of Whole Blood and, with respect to Red Blood Cells, the Red Blood Cells that are separated from one unit of Whole Blood. Each unit of Whole Blood and each unit of Red Blood Cells holds approximately 147-278 mg of iron, most in the form of hemoglobin. The number of doses (units) required is dependent on the underlying condition of the patient.

Requirements relating to blood donor qualifications, approved containers and approved preservatives and anticoagulants vary from country to country, although product formulations generally conform to the characteristics stated above. This is because composition of the product is standardized through control of donor screening, blood collection, testing, processing (product manufacture), storage and administration processes.

Pediatrics:

Whole Blood and Red Blood Cells derived from a single collection in one plastic container (300-500mL) can be separated in a closed system into multiple pediatric packs of approximately 50-80mL each. For neonates and infants, Whole Blood and Red Blood Cells can also be removed from the single collection set or a pediatric-sized container by syringe for transfusion.

A pediatric dose can be either administered as one pediatric unit or alternatively 10-15 mLs per Kilogram, depending on the practice in the country and/or the availability of pediatric collection sets. (Roseff 2006)


First, a review of what is involved in “manufacture” of Whole Blood and Red Blood Cells may be in order. Whole blood is collected by venipuncture from a suitable volunteer. Suitability determination involves two aspects: safety of the volunteer in donating and safety to the patient to be transfused. This is determined by assessing the volunteer’s vital signs, and by questioning the individual regarding past and current health, as well as behaviors associated with risk of infections that can be transmitted
by transfusion. Along with several tubes of blood for testing, a pre-determined volume of whole blood is collected into a sterile, single-use, plastic collection set already containing anticoagulant and preservatives, buffer and nutrients. For Whole Blood and Red Blood Cells production, the collected blood is then cooled and refrigerated, and initially kept in quarantine. For Red Blood Cells production, the Whole Blood is placed in a refrigerated centrifuge, to sediment the red blood cells to the bottom of the collection set. The centrifuged whole blood is then placed in a plasma expressor, which expresses the supernatant plasma (or platelet-rich plasma (PRP) if a platelet component is to also be produced) through integrally connected tubing into a separate container. This separated plasma must then be frozen promptly; it can either be used later for direct transfusion, or used as starting material for further manufacture into plasma derivatives, e.g., immunoglobulin or anti-hemophilic factor. (Note that these two plasma derivatives are already on WHO’s EML, and that they can also use whole blood as the source material.)

The Whole Blood, or Red Blood Cells and Plasma, must remain in quarantine, until results of testing of the associated tubes of blood has been completed and found acceptable. These tests include, at least, ABO and Rh type, hepatitis B, hepatitis C and HIV. Records of processing must be reviewed to ensure all procedures have been followed correctly and that test results are acceptable, before the Whole Blood or Red Cell Unit can be released from quarantine and labeled as acceptable for distribution. Temperature during storage and transport (distribution to the transfusion facility) must be maintained within a strict cold range. One example of manual whole blood processing is depicted in the following schematic:
All of these activities must be performed in conformance with Good Manufacturing Practices, which include quality control, quality assurance, and traceability. Adherence to GMPs is much more likely to occur where there is strict, pertinent regulation by a National Regulatory Authority. This lesson has been learned the hard way in developing countries, as awareness of HIV transmission by transfusion became apparent in the 1980’s. This development precipitated government regulators in developed countries, most notably in the US, to apply more strict regulations initially developed solely for the medical pharmaceutical industry, to blood establishments, inspecting these facilities more frequently, and even imposing enforcement actions including product seizures, plant closures, fines and prison sentences for responsible employees. These measures have resulted in a much better practices in blood establishments, a safer blood supply, and have helped decrease the potential risk for subsequent other transfusion risks (e.g., HCV WNV, vCJD).

WHO has developed guidelines in this regard:

WHO requirements for the collection, processing and quality control of blood, blood components and plasma derivatives. In: WHO Expert Committee on Biological Standardization (1994) http://www.who.int/entity/bloodproducts/publications/WHO_TRS_840A2.pdf; and


Whole Blood and Red Blood Cells can be and are manufactured in virtually every country in the world and are generally available, although the safety, quality and availability of these products is currently variable. Blood components are manufactured by blood establishments in their respective countries, generally under the coordination of a national programme. The World Health Assembly Resolution 63.12 on availability, safety and quality of blood products, adopted in May 2012 (http://apps.who.int/gb/ebwha/pdf_files/WHA63-REC1/WHA63_REC1-en.pdf), urged Member States to “update their national regulations ...in order to ensure that regulatory control in the area of Quality and safety of blood products across the entire transfusion chain meets internationally recognized standards.” WHO is requested to guide Member States to meet these standards.

The WHO Global Database on Blood Safety (based on 2008 data) establishes that about 8000 centers in 159 countries reported that they collect blood. A total of 164 countries, representing 92% of the world’s population, responded to the survey. Whole Blood and all blood components, including Red Blood Cells, are not generally shipped cross national borders, with the exception of rare units and in cases of emergency. This application is not intended to, and does not contemplate, a change in that practice.

This application to include Whole Blood and Red Blood Cells in the WHO Model Lists of Essential Medicines is also not intended to change, and will not require that any country change, its reliance on volunteer non remunerated blood donors.
7. **Listing is requested as an individual medicine or as an example of a therapeutic group.**

   Not applicable.

8. **Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)**

   While there are not good validated data on the uses of Whole Blood and Red Blood Cells in developed and developing countries, the 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.) The same database revealed that there is significant variation in the age distribution of transfused patients between developed and developing countries, as there are different underlying disease burdens. Specifically, in high-income countries, transfusion was reported as most commonly used for supportive care in cardiovascular and transplant surgery, massive trauma and therapy for solid and hematological malignancies. In low-and middle-income countries transfusion was reported as used more often in pregnancy-related complications and severe childhood anemia.

   Several smaller studies in both developed and developing countries reinforce the vailidity of these conclusions. In the United States, the National Blood Collection and Utilization Survey, funded by the U.S. Department of Health and Human Services and conducted by AABB, concluded that more that 15 million units of Red Blood Cells were transfused in the U.S. in 2008. The two highest uses of Red Blood Cells were attributed to General Medicine (28.2% of all Red Blood Cells transfused in the U.S.) and Surgery, including general, orthopedic and cardiac surgeries, combined (23.6%), although these calculations could have been confounded by the use of self-defined categories by reporting hospitals. Whole Blood transfusions in the U.S., as a percentage of total transfusions, are significantly fewer in the U.S. than in the developing world (0.03% of total transfusions, or approximately 5,000 units). (NBCUS 2010)

   In the developing world, there are few studies to validate the uses of Red Blood Cells reported in the 2011 WHO Global Database on Blood Safety Summary report, although there are ongoing efforts to estimate blood needs.

   The Pan American Health Organization (PAHO) has proposed a methodology and instrument to assess the underlying needs for blood in the region. Both the methodology and the instrument were validated by 20 professionals in 9 hospitals in Nicaragua. The proposed methodology recommended that patients who receive transfusions be assigned to one of the following four groups:
• Clinical conditions, such as anemias and diseases of the blood; leukemias and lymphomas; non-hematologic malignant tumors, and anemia associated with gastrointestinal bleeding
• Surgical interventions, such as cardiovascular surgery, injury, poisoning and other consequences of external causes; orthopedics and general surgery;
• Obstetric and gynecological conditions; and
• Neonatal Conditions (PAHO Estimating Blood Needs)

These groups were further elaborated as follows:

**Clinical conditions**
*Anemias and diseases of the blood*
*Leukemias and lymphomas*
*Non-hematologic malignant tumors (clinical needs)*
*Anemia associated with gastrointestinal bleeding*

**Surgical interventions**
*Cardiovascular surgery*
*Injury, poisoning, and other consequences of external causes*
*Orthopedics*
*General surgery*

**Obstetric and gynecological conditions**
*Obstetrics*
*Gynecology*

**Neonatal conditions**

The results of the validation survey conducted in Nicaragua are summarized as follows:
In addition, the following observations were noted:

- In the general hospitals included in the validation exercise, women received a higher percentage of blood transfusions than men, although the male/female ratio of transfusions varied from hospital to hospital.
- Patients aged 15-64 received the highest percentage of transfusion, with variations from hospital to hospital.
- The percentage of transfusion recipients and number of units used depended on the clinical condition (Centano Mena RA, Sanchez Lopez ML).
- The need for Red Blood Cells is related to the prevalent conditions in the community, the age structure of the population, and patterns of blood use.

The overall conclusion was that, given the number of underlying conditions for which Whole Blood and Red Blood Cells are given, the target population for receipt of these therapies will be different in each country.

In addition to these data, in section 10, the effectiveness of Red Blood Cell transfusion in the treatment of thalassemia and sickle cell anemia is described. These hereditary conditions, which can require major (lifelong) Red Blood Cell use vary in prevalence geographically (both often in parallel with the prevalence of malaria).

The “thalassemia belt” includes the Mediterranean shores, the Arabian peninsula, and especially Thailand, Cambodia, and southern China, where prevalence can range from 2.5% to 15%.
In tropical Africa, the heterozygous sickle cell trait can be found in up to 20% to 40% in some areas. Sickle cell disease is also prevalent in the Mediterranean area, the Middle East, India and Southeast Asia.

9. **Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostic or treatment facilities and skills).**

Dosage regimens and the duration of treatment depend on the underlying reasons for Red Blood Cell transfusion. Red Blood Cells are transfused to correct anemia in patients. There are multiple Clinical Guidelines that govern the appropriate use of Red Blood Cells. See section 9 references.

No special diagnostic or treatment facilities are needed, however, special capabilities of the transfusing entity include cold storage (and effective cold chains) and ABO compatibility testing. Moreover, clinician education on the appropriate use of blood, including Whole Blood and Red Blood Cells and education and training on the proper administration of Whole Blood and Red Blood Cells is required if blood is to be transfused safely. Inclusion of Whole Blood and Red Blood Cells in the WHO Model Essential Medicines List will draw much needed attention to these needs and emphasize to national regulatory authorities and health ministries that such guidelines should be audited and enforced.

10. **Summary of comparative effectiveness in a variety of clinical settings:**

Hemoglobin binds oxygen in the lungs at high oxygen tension and releases oxygen in the tissues at low oxygen tension. The hemoglobin oxygen binding characteristics are determined by the hemoglobin molecule itself as well as by factors such as pH, carbon dioxide concentration, and 2-3 DPG levels. Oxygen delivery is the product of the arterial oxygen content and the cardiac output, and tissue oxygen consumption is the fraction of the arterial oxygen content which is extracted by the tissues.

In otherwise healthy patients, compensatory mechanisms occur to preserve tissue oxygen consumption in the face of increasingly severe anemia. Decreased blood viscosity and sympathetic stimulation lead to increased cardiac output both by increasing stroke volume and heart rate. Blood flow is redistributed so that preference is given to critical organs such as the heart and brain. In addition, oxygen extraction in the tissues is increased, allowing tissue oxygen consumption to be maintained at acceptable level in spite of decreases in oxygen delivery. However, there are limits to the ability of the body to compensate.

**Red Blood Cell transfusion to increase oxygen delivery to the tissues**

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. Severe anemia may occur as a result of a variety of clinical conditions including major surgery, trauma, obstetrical hemorrhage, malaria, gastrointestinal bleeding, or various hematological disorders, clinical situations which occur both in the developed and underdeveloped world. The need for transfusion is
particularly important if the patient is so anemic that the body’s ability to compensate for the lack of red cells has been exceeded. Unfortunately there is no gold standard against which to measure when this point has been reached. The patient’s hemoglobin level is the simplest gauge of the severity of the anemia, but it is only a reliable indicator of tissue hypoxia when it is very low (< 5-6 g/dL). Patients who are otherwise healthy can often tolerate chronic hemoglobin levels as low as 5-6 gm/dL, whereas patients with comorbidities such as cardiovascular disease may exhibit signs and symptoms of tissue oxygen deprivation and may require transfusion at much higher hemoglobin levels. The mortality of untransfused anemic patients with underlying cardiovascular disease is substantially higher than patients without cardiovascular disease (Carson 1996). Modest inadequate tissue oxygenation may be indicated by symptoms such as weakness and exertional fatigue, symptoms which do not usually prompt transfusion. However patients with more serious indicators of inadequate oxygen delivery, such as dyspnea, tachypnea, or mental status changes should be transfused.

Blood transfusion has been used for nearly 100 years to treat patients with life-threatening anemia and severe tissue hypoxia. The usefulness of transfusion in these settings is so clearly evident that controlled trials to determine efficacy would be considered unethical and have not been performed. A few observational studies have supported the need for transfusion in severe anemia. In a study of transfusion of children with severe anemia in Kenya (English 2002), most of whom had malaria but for whom blood was not always available, transfusion resulted in a marked and statistically significant improvement in mortality. Eighty nine percent (8/9) of non-transfused children with prostration, respiratory distress, and a hemoglobin less than 4g/dL died, whereas only 23% (15/65) of those transfused died. A retrospective observational study of 1928 surgical patients who refused transfusion for religious reasons demonstrated a direct relationship between the degree of anemia and mortality with 28% of the deaths being attributed to anemia (Carson 1996).

The benefit of transfusion for patients with less severe anemia, usually defined as hemoglobin levels between 7 and 10 g/dL, has been the subject of a number of controlled studies. Hebert et al (Hebert 1999) randomized 838 intensive care unit patients to a restrictive or liberal transfusion strategy. Patients in the liberal arm were transfused for hemoglobin levels > 10g/dL and the hemoglobin level maintained at the 10-12 g/dL level. Patients in the restrictive arm were transfused when the hemoglobin was < 7 g/dL to maintain hemoglobin levels between 7 and 9 g/dL. No statistically significant differences were seen between the groups in terms of mortality or the severity of organ dysfunction. Carson et al (Carson 2011) studied 2016 patients whose hemoglobin level was <10g/dL after hip fracture surgery. All patients were over the age of 50 and had a history of either cardiovascular disease or cardiovascular risk factors. The patients were randomized to a liberal (transfuse for hemoglobin < 10g/dL) or restrictive (transfuse for hemoglobin < 8g/dL or for symptoms of anemia) strategy. No differences were seen between the groups in terms of mortality or ability to walk across the room without assistance 60 days after the surgery. The results indicated no advantage to the liberal transfusion strategy and suggested that it was reasonable to limit transfusion, in the absence of symptoms of anemia, to those patients with hemoglobin < 8 g/dL. A Cochrane Summary of the existing literature evaluated 19 controlled studies comparing restrictive vs liberal transfusion strategies involving 6264 patients. Restrictive strategies were not associated with an increase in patient adverse events such as cardiovascular incidents or mortality. (Carson 2012).
Whether these same findings will apply to other groups of patients such as those with significant cardiovascular disease, acute coronary syndromes, severe trauma, or those undergoing hematopoietic stem cell transplantation has yet to be determined.

**Red Blood Cell transfusion unrelated to oxygen delivery**

**Transfusion in Thalassemia**

Severe thalassemia is characterized by massive ineffective erythropoiesis with a hyperplastic marrow, skeletal abnormalities with a typical facies, hepatosplenomegaly, stunted growth, increased iron absorption resulting in iron overload, cardiomegaly with eventual cardiac failure, and early death. As with other disorders, patients with severe anemia due to thalassemia do require transfusion to maintain minimal physical activity, and this was the primary role of transfusion in this disorder until the 1960s. At that time it was observed that hypertransfusion, transfusing patients to much higher hematocrit levels than necessary to maintain basic oxygen delivery, had a profound effect on the clinical manifestations of the disease. With this transfusion strategy, designed to suppress increased erythropoiesis and its effects, several investigators demonstrated that bony abnormalities could be avoided, cardiomegaly and cardiac failure avoided or even reversed, hepatosplenomegaly minimized, iron absorption reduced, and normal growth patterns achieved. Wolman (Woman 1964) first observed that children who had been more heavily transfused were taller and had less hepatosplenomegaly, bony abnormalities, and cardiac problems. Piomelli (Piomelli 1969) described four patients transfused to maintain hemoglobin levels of 10-12 g/dL. No patient developed either the typical bone changes or marked hepatosplenomegaly. A follow-up study (Piomelli 1974) confirmed that patients who were maintained at a hematocrit of at least 28% from the time of diagnosis did not develop the typical facies, experienced regression of any bone changes within one year and regression of cardiomegaly within six months. Kattamis (Kattamis 1970) studied 74 patients and demonstrated that growth rates depended on the level of hemoglobin concentration achieved; patients maintained at a hemoglobin level of > 8 g/dL had a normal growth rates. Subsequent studies and debates have focused on the optimal target hemoglobin levels. Transfusion to even higher levels (hemoglobin >14) has been advocated; this strategy does provide additional suppression of erythropoiesis but at the expense of additional iron overload, and most experts do not recommend it. Cazzola et al (Cazzola 1997) studied 32 patients on chelation therapy who had been maintained at an average pre-transfusion hemoglobin level of 11.3 g/dL and examined the effect of switching to an average pre-transfusion hemoglobin level of 9.4. They noted a substantial decrease in red cell requirements, decreased iron accumulation, an increase in spontaneous prepubertal development (indicating less iron toxicity), and levels of erythroid activity not exceeding 2-3 times the normal level.

The result of these developments was that the treatment of thalassemia was dramatically changed, at least in those parts of the world where transfusion and chelation therapy was available. The downside of this approach was that additional iron accumulation occurred as a result of the frequent transfusions, a problem that can be successfully handled by modern iron chelation therapy.
Red Blood Cell Transfusion in Sickle Cell Disease

Transfusion is used in patients with severe anemia for the same reason that it’s used in other patients, to increase the oxygen carrying capacity of the blood. But it is also often used for an entirely different purpose, to decrease the fraction of sickle red cells. One of the devastating consequences of sickle cell disease is the high incidence of stroke and other cerebrovascular events. Approximately 6-10% of sickle cell patients experience strokes, and once a patient has had a stroke, there is a 60-70% chance that additional strokes will occur, usually within the next year or two. It was observed by in the 1970’s that the incidence of stroke could be reduced by regular transfusion (Lusher 1976). Twenty one patients with previous strokes were transfused regularly for up to six years with no recurrent events. The one patient who did have a recurrent stroke was not transfused regularly. Russell et al studied 30 patients with a history of stroke (Russell 1984). Twenty three of the patients had multiple cerebral vessel abnormalities by angiography; these patients were placed on a transfusion program designed to keep the hemoglobin concentration between 12-14 g/dL and the % hemoglobin S < 30%. The result was marked decrease in the incidence of recurrent stroke when compared to historical controls (10% vs 90%). Wilimas et al showed that if such a transfusion program is discontinued after 1-2 years, the incidence of recurrent stroke rapidly returns to the previous high level (Wilimas 1980).

Adams et al measured transcranial Doppler (TCD) ultrasonography (a measure of cerebral blood flow) in 190 children (age 3-18) with sickle cell disease and followed them for an average 29 months. Twenty three had an abnormal TCD; there were six strokes in this group of patients. One hundred sixty seven had normal TCD; only one of these had a stroke in the follow-up period. These results indicated a 44 fold increase in risk for those patients with abnormal TCD (Adams 1992). These observations were followed by the SOP trial, a randomized controlled trial designed to prevent initial strokes by instituting chronic transfusion programs in patients with an abnormal TCD (Adams 1998). 130 patients were randomized to receive either standard care or chronic transfusion to keep the Hemoglobin S concentration less than 30%. With a mean follow-up of 19.6 months, there were 10 strokes in the control group and 1 in the transfused group. This study was stopped early because the efficacy of transfusion therapy had been proven. Follow-up analysis of the STOP study showed that compliance with the aggressive transfusion strategy also significantly lowered hospitalization rates for acute chest syndrome and for pain crises (Miller 2001) as well as resulting in improved growth rates (Wang 2005). A follow-up study, STOP II, was designed to determine whether the transfusion programs could be curtailed after a certain time. Children eligible for this study were those who had completed at least 30 months of transfusion therapy and whose Doppler measurements had revered to normal. Seventy nine patients were randomized to continue transfusion or to stop. The end points were stroke or conversion to a high risk Doppler pattern. Of the 41 patients randomized to no transfusion, 2 had strokes and 14 converted to high risk Doppler pattern. Neither of these end points was seen in the 389 patients randomized to continue transfusion (Adams 2008). The study was stopped short of the intended 100 patients.

In summary, these studies have indicated that transfusion plays an important and ever-increasing role in the optimal treatment of patients with sickle cell anemia. Much of the effect seems related to replacing sickle cells with normal cells, a rationale quite different than merely supplying additional oxygen carrying capacity. While some of the claimed effects of transfusion will need additional
confirmation, the role of transfusion in preventing the catastrophic neurologic complications have been clearly demonstrated.

**DATA CHARTS**

**Severe Childhood Anemia in Africa**

**Comparison: Death**

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<thead>
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<th>Study</th>
<th>Transfused</th>
<th>Not transfused</th>
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**Transfusion Trigger**

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<th>Restrictive</th>
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<td>0.11</td>
<td></td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>93/418</td>
<td>118/420</td>
<td>0.79</td>
<td>----</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Hosp LOS</td>
<td>34.8</td>
<td>35.5</td>
<td>----</td>
<td>-0.7</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td>ICU LOS</td>
<td>11.0</td>
<td>11.5</td>
<td>----</td>
<td>-0.5</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>Cardiac event</td>
<td>55/418</td>
<td>88/420</td>
<td>0.63</td>
<td>----</td>
<td>&lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>22/418</td>
<td>45/420</td>
<td>0.49</td>
<td>----</td>
<td>&lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>pneumonia</td>
<td>87/418</td>
<td>86/420</td>
<td>1.02</td>
<td>----</td>
<td>0.92</td>
<td></td>
</tr>
</tbody>
</table>

**Study: Carson (2011)**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Restrictive</th>
<th>Liberal</th>
<th>Risk ratio</th>
<th>Mean difference</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 day mortality</td>
<td>43/1009</td>
<td>52/1007</td>
<td>0.83</td>
<td>----</td>
<td></td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>14/1003</td>
<td>20/999</td>
<td>0.70</td>
<td>----</td>
<td></td>
</tr>
<tr>
<td>Hosp LOS</td>
<td>4.0</td>
<td>3.7</td>
<td>----</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>30 d inability to walk</td>
<td>481/1000</td>
<td>459/995</td>
<td>1.04</td>
<td>----</td>
<td></td>
</tr>
<tr>
<td>Cardiac events</td>
<td>76/1009</td>
<td>52/1007</td>
<td>1.46</td>
<td>----</td>
<td></td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>35/1009</td>
<td>27/1007</td>
<td>1.29</td>
<td>----</td>
<td></td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>3/1009</td>
<td>8/1007</td>
<td>0.37</td>
<td>----</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>48/1009</td>
<td>60/1007</td>
<td>0.8</td>
<td>----</td>
<td></td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>8/1009</td>
<td>12/1007</td>
<td>0.67</td>
<td>----</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>56/1009</td>
<td>74/1007</td>
<td>0.76</td>
<td>----</td>
<td></td>
</tr>
</tbody>
</table>

★ No differences are statistically significant

**Thalassemia**

**Analysis 1.**

**Study: Kattamis (1970)**

<table>
<thead>
<tr>
<th>Hgb Levels maintained (g/dL)</th>
<th>&lt;6</th>
<th>6-8</th>
<th>&gt;8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height centile</td>
<td>7.0</td>
<td>22.2</td>
<td>55.9</td>
</tr>
<tr>
<td>Weight centile</td>
<td>9.9</td>
<td>22.5</td>
<td>61.2</td>
</tr>
</tbody>
</table>
Analysis 2.
Study: Cazzola (1997)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Hgb 9.4</th>
<th>Hgb 11.3</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusion requirement (ml/kg/yr)</td>
<td>104</td>
<td>137</td>
<td>0.0001</td>
</tr>
<tr>
<td>Ferritin (ug/L)</td>
<td>816</td>
<td>2448</td>
<td>0.0001</td>
</tr>
<tr>
<td>Erythropoiesis (xN)</td>
<td>2.4</td>
<td>----</td>
<td>----</td>
</tr>
</tbody>
</table>

Sickle Cell Disease

Analysis 1.
Comparison: Stroke/TIA/Silent Infarct

<table>
<thead>
<tr>
<th>Study</th>
<th>Transfused</th>
<th>Not transfused</th>
<th>Risk ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lusher (1976)</td>
<td>0/21</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Russell (1984)</td>
<td>2/20</td>
<td>9/10</td>
<td>0.11</td>
<td>0.001</td>
</tr>
<tr>
<td>Wilimas (1980)</td>
<td>0/10</td>
<td>7/10</td>
<td>0.00</td>
<td>----</td>
</tr>
<tr>
<td>Adams (1998)</td>
<td>1/63</td>
<td>11/67</td>
<td>0.10</td>
<td>0.001</td>
</tr>
<tr>
<td>Adams (2005)</td>
<td>0/38</td>
<td>16/41</td>
<td>0.00</td>
<td>0.001</td>
</tr>
<tr>
<td>Abboud (2011)</td>
<td>3/37</td>
<td>11/40</td>
<td>0.29</td>
<td>0.03</td>
</tr>
</tbody>
</table>

★ Development of stroke or high risk transcranial Doppler pattern

Analysis 2.
Comparison: Acute Chest Syndrome

<table>
<thead>
<tr>
<th>Study</th>
<th>Transfused</th>
<th>Not transfused</th>
<th>Risk ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miller (2001)</td>
<td>2.2/100 pt yrs</td>
<td>15.7/100 pt yrs</td>
<td>0.14</td>
<td>0.0001</td>
</tr>
<tr>
<td>Styles (2006)</td>
<td>0/7</td>
<td>5/8</td>
<td>0.00</td>
<td>0.026</td>
</tr>
</tbody>
</table>

Analysis 3.
Comparison: Pain crises

<table>
<thead>
<tr>
<th>Study</th>
<th>Transfused</th>
<th>Not transfused</th>
<th>Risk ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miller (2001)</td>
<td>9.7/100 pt yrs</td>
<td>27.1/100 pt yrs</td>
<td>0.36</td>
<td>0.014</td>
</tr>
</tbody>
</table>

11. Summary of comparative evidence on safety:

11.1 Identification of variation in safety due to health systems and patient factors.

Because blood and blood components such as Red Blood Cells are produced in countries with differing levels of health care practitioner, laboratory, and technical education, training and skills, the safety of Whole Blood and Red Blood Cell transfusions may differ from country to country. One purpose in requesting placement of Whole Blood and Red
Blood Cells on the WHO Model List of Essential Medicines is to standardize the processes followed to make and use this medicine, so that the product itself becomes more standardized (and safer). Another purpose is to encourage the standardization of clinical guidelines, to improve patient care.

Moreover, because 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 variations among countries in patient factors and the quality of healthcare that could affect the safety of transfusion.

11.2 Summary of comparative safety against comparators

There have been no controlled clinical trials of Whole Blood and Red Blood Cells against placebo. Today, such a trial would be unethical given that the historical experience in transfusing Whole Blood goes back to the 19th century and modern blood transfusion, including the identification of major blood groups and the development of anticoagulant-preservative solutions, began during World War I.

There is no known medicine that currently substitutes for Whole Blood and Red Blood Cells. Worldwide, seven clinical trials involving blood substitutes have been halted because of unacceptable toxicity to the recipients. (Natanson 2008)

The sole known replacement for Whole blood and Red Blood Cell transfusion, when appropriately administered, is erythropoietin. Erythropoietin, and its analogues, were initially approved for treatment of the anemia of chronic renal disease, and used specifically in patients on long-term hemodialysis. The National Institute for Health and Clinical Excellence (NICE) in England has since issued guidance which states that epoetin alfa, epoetin beta and darbepoetin alfa (erythropoietin analogues) should be used only in limited circumstances. Specifically, they are not recommended for routine use in the management of cancer treatment-induced anaemia, but may be considered in combination with intravenous iron:

- for the management of cancer treatment-induced anaemia in women receiving platinum-based chemotherapy for ovarian cancer who have symptomatic anaemia and a haemoglobin level of 8 g/100 ml or lower
• for people who cannot be given blood transfusions and who have profound cancer treatment-related anaemia that is likely to have an impact on survival.

Recent data have shown that the adverse affects associated with the administration of erythropoietin are much greater than originally reported. As a consequence, erythropoietin is currently used more judiciously than when it was first licensed and is not widely used as a substitute for Red Blood Cells, particularly not in developing countries where its high cost is also a great impediment to use.

The safety profile of Whole Blood and Red Blood Cells is widely acknowledged to represent a favorable therapeutic index. 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. Recognition of adverse events has resulted in continuous improvements in safety and manufacture. Whole Blood and Red Blood Cells are arguably the most carefully studied medications and remain widely used precisely because the benefits so clearly outweigh the risks.

12. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutics group:

12.1 Range of costs of the proposed medicine.

For a number of valid safety, as well as logistical reasons, Whole Blood and Red Blood Cell preparations are collected, processed, distributed and transfused within the same country. With the exceptions of rare units and emergency requests for blood, blood is not routinely shipped between countries.

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 Whole Blood and Red Blood Cells. For that reason, costs vary from country to country. For purposes of determining and comparing the costs of blood, however, two things are important:

1. 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. Basing the comparative cost of Whole Blood and Red Blood Cells on the costs of collecting a unit of blood is important as methods of allocating costs among components can vary from country to country.

2. The cost comparisons must be based on an understanding of all costs associated with the production of a unit of blood. WHO has developed materials that both assist in
understanding the costs of providing blood, as well as a template for determining the
That publication includes the following description of costs to be included in
determining the cost of a unit of blood.

Chart 1

**BLOOD TRANSFUSION SERVICE**

*Costs Allocated by Activity*

<table>
<thead>
<tr>
<th>Total Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Donor</td>
</tr>
<tr>
<td>Recruitment</td>
</tr>
<tr>
<td>Capital costs + Recurrent costs</td>
</tr>
</tbody>
</table>

| Blood Collection |
| Capital costs + Recurrent costs |

| Blood Processing |
| Capital costs + Recurrent costs |

| Blood Storage & Distribution |
| Capital costs + Recurrent costs |
As a point of reference, applying this model, the average cost of producing a unit of quality assured Whole Blood in Zimbabwe is USD $128.00.

<table>
<thead>
<tr>
<th>EXPENDITURE:</th>
<th>AMOUNT</th>
<th>% Expenditure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Payroll</td>
<td>$ 2,663,226</td>
<td>33.6%</td>
</tr>
<tr>
<td>Blood Procurement</td>
<td>$ 1,405,180</td>
<td>17.7%</td>
</tr>
<tr>
<td>Coordination</td>
<td>$ 68,759</td>
<td>0.9%</td>
</tr>
<tr>
<td>Finance &amp; Administration</td>
<td>$ 1,205,593</td>
<td>15.2%</td>
</tr>
<tr>
<td>Laboratory Operations</td>
<td>$ 1,473,120</td>
<td>18.6%</td>
</tr>
<tr>
<td>Planning, Information and Research</td>
<td>$ 207,119</td>
<td>2.6%</td>
</tr>
<tr>
<td>Public Affairs &amp; Communication</td>
<td>$ 178,347</td>
<td>2.3%</td>
</tr>
<tr>
<td>Safety, Health Environment &amp; Quality</td>
<td>$ 111,675</td>
<td>1.4%</td>
</tr>
<tr>
<td>Capital</td>
<td>$ 612,035</td>
<td>7.7%</td>
</tr>
<tr>
<td>Total</td>
<td>$ 7,925,055</td>
<td>100.0%</td>
</tr>
</tbody>
</table>
12.2 Comparative Cost effectiveness

There have been several published economic analyses of the comparative cost effectiveness of several erythropoetin analogues versus the use of blood transfusion, but only in patients with various types and stages of cancer, and not generally applicable in developing countries. There are no empirical data on the cost-effectiveness of erythropoietin analogues in people who cannot receive blood transfusions.

13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)

Blood is a strategic resource and blood donation from voluntary non remunerated blood donors occurs in all countries. Shipment of Whole Blood or Red Blood Cells for transfusion from one country to another is now an uncommon event, and primarily occurs only in the case of emergency shortages or for the purpose of providing rare units to patients with very difficult cross-matching challenges in transfusion. The “country of origin” is, therefore, potentially every country, and, as a consequence, the 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 – since 2002 – are 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.

While laws and regulations pertinent to Whole Blood and Red Blood Cells exist in many other countries, there is variation in their specificity and enforcement, particularly in developing countries.

As mentioned earlier, enforcement of blood-specific regulations by National Regulatory Authorities have resulted in dramatic improvements in the safety of blood for transfusion. The WHO document “Assessment Criteria for National Blood Regulatory Systems” is a very pertinent and useful reference for countries to consider.

14. **Availability of pharmacopoeial standards**

Whole Blood and Red Blood Cells are both listed in Japan’s Pharmacopeia. Red Blood Cells have been listed in the US Pharmacopoeia, but the information there is in need of updating now (2012).

15. **Proposed new text for the WHO Model Formulary:**

The complete text for Whole Blood and Red Blood Cells is contained in Annex A.

**REFERENCES (by section)**

1. **Summary Statement**


Website link: http://www.who.int/entity/bloodproducts/NationalBloodRegSystems.pdf


5. **Formulation proposed...**

6. International availability...
WHO recommendations for the production, control and regulation of human plasma for fractionation.
Africa Society for Blood Transfusion, Standards Step-Wise Accreditation Program, DRAFT (2011)
PAHO/WHO Estandares de Trabajo para Bancos de Sangre (Segunda Edicion) (1999); PAHO/WHO Caribbean Regional Standards for Blood Banks and Transfusion Services (Second Edition 2011)

8. Information supporting public health relevance...


9. Treatment details...
Adults:
WHO The Clinical Use of Blood in General Medicine, Obstetrics, Paediatrics, Surgery & Anaesthesia, Trauma & Burns 2001

British Committee for Standards in Haematology 2001
10. Summary of comparative effectiveness...


11. Summary of comparative evidence on safety:

Natanson, C; Kern, S; Lurie, P; Banks, S; Wolfe, S. Cell-Free Hemoglobin-Based Blood Substitutes and Risk of Myocardial Infarction and Death: A Meta-analysis. JAMA 2008; 299 (19): 2304-2312


WHO Global Database for Blood Safety. 2011


12. Comparative cost effectiveness

15. Proposed new text for the WHO Model Formulary
General
Circular of Information for the use of human blood and blood components (US) revised December 2009.


Malaria
Kitchen AD, Chiodini PL. Malaria and blood transfusion. Vox Sang 2006;90:77-84.

TA-GVHD/Irradiation

TRALI

Circulatory Overload

Febrile Nonhemolytic Transfusion Reactions

Citrate Toxicity
Anaphylaxis
Sandler SG. How I manage patients suspected of having had an IgA anaphylactic transfusion reaction. Transfusion 2006;46:10-13.

Red Blood Cells
Luban NLC, Strauss RG, Hume HA. Commentary on the safety of red cells preserved in extended storage media for neonatal transfusions. Transfusion 1991;31:229-35.
Yang X, Alexander KP, Chen AY, et al for the CRUSADE Investigators. The implications of
Annex A

Blood products and plasma substitutes

Blood products:

Whole Blood and Red Blood Cells

Whole Blood and Red Blood Cell components are biologic products. Red blood cells contain hemoglobin and serve as the primary agent for transport of oxygen to tissues. The primary red-cell-containing transfusion component is Red Blood Cells. This component is prepared by centrifugation or sedimentation of Whole Blood to remove much of the plasma. Depending upon the collection system used, a single whole blood donation typically contains either 450 mL (10%) or 500 mL (10%) of blood collected from blood donors with a minimum hematocrit of 38%, withdrawn in a sterile container that includes an anticoagulant solution licensed for this component. In some countries, units of smaller volumes are collected and those volumes are stated on the label. Red-cell-containing components can be stored for an interval (“shelf life”) determined by the properties of the anticoagulant-preservation solution. Whole Blood units are prepared in an aseptic manner in a ratio of 14 mL of anticoagulant-preservation solution per 100 mL of whole blood collected. After plasma is removed, the resulting component is Red Blood Cells, which has a hematocrit of 65% to 80% and a usual volume between 225 mL and 350 mL.

Donor Qualifications

Whole Blood and Red Blood Cell components described in this document have been collected from volunteer blood donors for use in other patients (allogeneic transfusions). The donors have been questioned about risk factors for transmissible infectious agents, have satisfactorily completed a health assessment that includes a questionnaire on past and present illnesses and have satisfied minimum physiologic criteria.

Testing of Donor Blood

Testing of a sample of donor blood is performed before units of Whole Blood or Red Blood Cell components are distributed for routine transfusion. The donor’s ABO group and Rh type have been determined, including testing for the presence of weak D antigen. A sample from each donation intended for allogeneic use has been tested by tests approved by the National Regulatory Authority (NRA), and found to be nonreactive for antibodies to human immunodeficiency virus (anti-HIV) and hepatitis C virus (anti-HCV), and nonreactive for hepatitis B surface antigen (HBsAg). Depending on the local epidemiology of potentially transfusion transmissible infections in the donor population, other tests may be advisable as well.

Tests for unexpected antibodies against red cell antigens have been performed on samples from all donors. The results of these tests are negative or have been determined to be clinically insignificant unless otherwise indicated on the label. Other tests may have been performed on donor blood as indicated by information that has been provided by the blood bank or transfusion service on an additional label or tie tag.
Good Manufacturing Practices
A strong GMP culture in the blood establishment is essential, not just in donor testing, but also in all aspects of blood collection, production, quarantine, storage, labeling and distribution. These practices should be in keeping with national regulations and international guidelines.

Whole Blood and Red Blood Cell Component Labeling
Whole Blood and Red Blood Cell components have the International Society of Blood Transfusion (ISBT) 128 product name listed first and other recognized component names in parentheses. Whole Blood and Red Blood Cell component labels will contain the following information:
1. The proper name, whole blood or red blood cells, including an indication of any qualification or modification.
2. The method by which the blood component was prepared.
3. The temperature range in which the whole blood or red blood cell component is to be stored.
4. The preservatives and anticoagulant used in the preparation of the whole blood or red blood cell component, when appropriate.
5. The standard contents or volume is assumed unless otherwise indicated on the label.
6. The name, address and registration number (if applicable) of the collection and processing location.
7. The expiration date (and time if applicable), which varies with the method of preparation (open or closed system) and the preservatives and anticoagulant used. When the expiration time is not indicated, the product expires at midnight.
8. The donation (unit) identification number.
9. The donor category (paid or volunteer).
10. ABO group and Rh type.
11. Special handling information, as required.
12. Statements regarding recipient identification, infectious disease and other risks, and prescription requirement.

Blood Products

1. WHOLE BLOOD is mostly used in developing countries. In situations where Whole Blood is indicated but Red Blood Cells are used, a suitable plasma volume expander should be administered.

2. RED BLOOD CELLS are prepared from blood collected into any of the anticoagulant-preservative solutions approved by the National Regulatory Authority (NRA), and separated from the plasma by centrifugation or sedimentation. Separation may be done at any time during the allowable storage interval (“shelf life”). Red Blood Cells may contain from 160 to 275 mL of red cells (50-80 g of hemoglobin) suspended in varying quantities of residual plasma.

Uses:
Red-cell-containing components are indicated for treatment of symptomatic or critical deficit of oxygen-carrying capacity. They are also indicated for red cell exchange transfusion.
Red Blood Cell components and Whole Blood increase the recipient’s oxygen-carrying capacity by increasing the mass of circulating red cells. Processing and/or storage deplete the component of virtually all potential therapeutic benefit attributable to the functions of white cells and platelets; cellular elements remain in these blood components and may cause adverse immunologic or physiologic consequences. Residual plasma in the component provides the recipient with volume expansion and nonlabile plasma proteins to the extent that residual plasma is present in the preparation. Depending on the method of production, Red Blood Cells may contain approximately 20 to 100 mL of residual plasma.

**Contraindications:**
Whole Blood and Red Blood Cell components should not be used to treat anemias that can be corrected with specific hematonic medications such as iron, vitamin B12, folic acid, or erythropoietin. Red Blood Cell components or Whole Blood should not be used solely for volume expansion or to increase oncotic pressure of circulating blood.

**Precautions:**
The following general instructions pertain to Whole Blood and Red Blood Cell components:
1. All Whole Blood and Red Blood Cell components must be maintained in a controlled environment and stored under appropriate conditions as described in the AABB Standards for Blood Banks and Transfusion Services.
2. The intended recipient and the blood container must be properly identified before the transfusion is started.
3. Aseptic technique must be employed during preparation and administration. If the container is entered in a manner that violates the integrity of the system, the component expires 4 hours after entry if maintained at room temperature (20-24 C), or 24 hours after entry if refrigerated (1-6 C).
4. Whole Blood and Red Blood Cell components must be transfused through a filter designed to remove clots and aggregates (generally a standard 170- to 260-micron filter).
5. Whole Blood and Red Blood Cell components should be mixed thoroughly before use.
6. Whole Blood and Red Blood Cell components must be inspected immediately before use. If, upon visual inspection, the container is not intact or the appearance is abnormal (presence of excessive hemolysis, a significant color change in the blood bag as compared with the tubing segments, floccular material, cloudy appearance, or other problems), the blood or blood component must not be used for transfusion and appropriate follow-up with the transfusion service must be performed.
7. No medications or solutions may be routinely added to or infused through the same tubing with Whole Blood or Red Blood Cell components with the exception of 0.9% Sodium Chloride, Injection, unless 1) they have been approved for this use by the NRA or 2) there is documentation available to show that the addition is safe and does not adversely affect the Whole Blood or Red Blood Cell component.
8. Lactated Ringer’s, Injection or other solutions containing calcium should never be added to or infused through the same tubing with blood or blood components containing citrate.
9. Whole Blood and Red Blood Cell components should be warmed if clinically indicated for situations such as exchange or massive transfusions, or for patients with cold-reactive antibodies. Warming must be accomplished using an NRA-cleared warming device so as not to cause hemolysis.

10. Some life-threatening reactions occur after the infusion of only a small volume of Whole Blood or Red Blood Cell components. Therefore, unless otherwise indicated by the patient’s clinical condition, the rate of infusion should initially be slow.

11. Periodic observation and recording of vital signs should occur during and after the transfusion to identify suspected adverse reactions. If a transfusion reaction occurs, the transfusion must be discontinued immediately and appropriate therapy initiated. The infusion should not be restarted unless approved by transfusion service protocol.

12. Specific instructions concerning possible adverse reactions shall be provided to the patient or a responsible caregiver when direct medical observation or monitoring of the patient will not be available after transfusion.

13. Transfusion should be started before component expiration and completed within 4 hours.

14. All adverse events related to transfusion, including possible bacterial contamination of Whole Blood or Red Blood Cell component or suspected disease transmission, must be reported to the transfusion service according to local protocol.

**Dose:**
Each unit of Red Blood Cells or Whole Blood contains enough hemoglobin to increase the hemoglobin concentration in an average-sized adult by approximately 1 g/dL (increase hematocrit by 3%). Smaller aliquots can be made available for use with neonatal or pediatric patients, or adults with special transfusion needs.

**ADMINISTRATION.**
The ABO group of Red Blood Cell components must be compatible with ABO antibodies in the recipient’s plasma. Whole Blood must be ABO identical with the recipient; Red Blood Cell components, which contain a reduced volume of antibody-containing plasma, need not be ABO identical. Serologic compatibility between recipient and donor must be established before any Whole Blood or Red Blood Cell component is transfused. This may be accomplished by performing ABO/Rh typing, antibody screening, and crossmatching by serologic technique or use of a computer crossmatch.

In cases when delay in transfusion will be life-threatening, uncrossmatched group O Red Blood Cells or ABO group-specific Red Blood Cells may be transfused before completion of pretransfusion compatibility testing.

The initial portion of each unit transfused should be infused cautiously and with sufficient observation to detect onset of acute reactions. Thereafter, the rate of infusion can be more rapid, as tolerated by the patient’s circulatory system. It is undesirable for Whole Blood or Red Blood Cell components to remain at room temperature longer than 4 hours. If the anticipated infusion rate must be so slow that the entire unit cannot be infused within 4 hours, it is appropriate to order smaller aliquots for transfusion.

**Adverse effects primarily specific to Whole Blood and Red Blood Cells:**

1. **Hemolytic transfusion reaction** is the immunologic destruction of transfused red cells, nearly always the result of incompatibility of antigen on the transfused cells with antibody in
the recipient’s circulation (see item 5 below for discussion of nonimmunologic hemolysis).
The most common cause of severe, acute hemolytic reactions is transfusion of ABO incompatible
blood, resulting from identification errors occurring at some point(s) in the
transfusion process. Serologic incompatibility undetected during pretransfusion testing is a
much less common cause of acute hemolysis. If a transfusion reaction is suspected, the
transfusion must be stopped and the transfusion service laboratory notified immediately.
Information identifying the patient, the transfusion component, and associated forms and
labels must be reviewed promptly to detect possible errors. A postreaction blood sample,
preferably drawn from a site other than the transfusion access, must be sent to the laboratory
along with the implicated unit of blood and administration set.

**Acute hemolytic reactions** characteristically begin with an increase in temperature and pulse
rate; symptoms may include chills, dyspnea, chest or back pain, abnormal bleeding, or shock.
Instability of blood pressure is frequent, the direction and magnitude of change depending
upon the phase of the reaction and the magnitude of compensatory mechanisms. In
anesthetized patients, hemoglobinuria, hypotension, and evidence of disseminated
intravascular coagulopathy (DIC) may be the first signs of incompatibility. Laboratory findings can
include hemoglobinemia and/or hemoglobinuria, followed by elevation of serum bilirubin. The direct
antiglobulin test (DAT) is usually positive, with rare exceptions (ie, complete hemolysis of
incompatible red cells). Treatment includes measures to maintain or correct arterial blood pressure;
correct coagulopathy, if present; and promote and maintain urine flow. Lack of symptoms does not
exclude an acute hemolytic reaction.

**Delayed hemolytic reactions** occur in previously red-cell-alloimmunized patients in whom antigens on
transfused red cells provoke anamnestic production of antibody. The anamnestic response reaches a
significant circulating level while the transfused cells are still present in the circulation; the usual time
frame is 2 to 14 days after transfusion. Signs may include
unexplained fever, development of a positive DAT, and unexplained decrease in
hemoglobin/hematocrit. Hemoglobinemia and hemoglobinuria are uncommon, but elevation
of lactate dehydrogenase (LDH) or bilirubin may be noted. Most delayed hemolytic reactions
have a benign course and require no treatment.

**Hemolytic transfusion reactions in patients with sickle cell anemia** may be particularly
severe, with destruction of autologous as well as transfused red cells. In such patients,
serologic investigations may not reveal the specificity of the causative antibody. Prospective
matching for Rh and Kell antigens may decrease risk.

2. Antigens on transfused red cells may cause red cell **alloimmunization** of the recipient.
Clinically significant antibodies to red cell antigens will usually be detected in pretransfusion
antibody screening tests. For most patients, red cell antigen matching beyond ABO and Rh is
unnecessary.

3. **Transfusion associated circulatory overload** (TACO), resulting in pulmonary edema, can accompany
transfusion of any component at a rate more rapid than the recipient’s cardiac output can
accommodate. Whole Blood creates more of a risk than Red Blood Cells because the transfused
plasma adds volume without increasing oxygen-carrying capacity. Patients with chronic anemia have
increased plasma volumes and are at increased risk for circulatory overload.
4. **Iron overload** is a long-term complication of repeated Red Blood Cell transfusions. Each transfusion contributes approximately 250 mg of iron. Patients requiring multiple transfusions for aplastic anemia, thalassemias, or hemoglobinopathies are at far greater risk than patients transfused for hemorrhagic indications, because blood loss is an effective means of iron excretion. Patients with predictably chronic transfusion requirements should be considered for treatment with iron-chelating agents or a program of exchange transfusion therapy, if applicable.

5. **Nonimmunologic hemolysis** occurs rarely, but can result from: 1) introduction of hypotonic fluids into the circulation, 2) effects of drugs co-administered with transfusion, 3) effects of bacterial toxins, 4) thermal injury to transfusion components, by either freezing or overheating, 5) metabolic damage to cells, as from hemoglobinopathies or enzyme deficiencies, or 6) development of physical or osmotic stresses. Examples of situations capable of causing nonimmune red cell hemolysis include: exposure to excessive heat by non-NRA-approved warming methods, mixture with hypotonic solutions, or transfusion under high pressure through small-gauge or defective needles.

**Adverse effects pertinent to all blood components, including Whole Blood and Red Blood Cells:**

**Immunologic Complications, Immediate**

1. **Hemolytic transfusion reaction**, the destruction of red cells, is discussed in detail in the section above on adverse effects primarily specific to Whole Blood and Red Blood Cells, but can also occur with plasma containing components.

2. **Febrile nonhemolytic reaction** is typically manifested by a temperature elevation of $\geq 1$°C occurring during or shortly after a transfusion and in the absence of any other pyrexic stimulus. This may reflect the action of antibodies against white cells or the action of cytokines, either present in the transfused component or generated by the recipient in response to transfused elements. Febrile reactions may occur in approximately 1% of transfusions, and they occur more frequently in patients previously alloimmunized by transfusion or pregnancy. No routinely available pre- or posttransfusion tests are helpful in predicting or preventing these reactions. Antipyretics usually provide effective symptomatic relief. Patients who experience repeated, severe febrile reactions may benefit from receiving leukocyte-reduced components. If these reactions are caused by cytokines in the component, prestorage leukocyte reduction may be beneficial.

3. **Allergic reactions** frequently occur as mild or self-limiting urticaria or wheezing that usually respond to antihistamines. More severe manifestations including respiratory and cardiovascular symptoms are more consistent with anaphylactoid/anaphylactic reactions and may require more aggressive therapy (see below). No laboratory procedures are available to predict these reactions.

4. **Anaphylactoid/anaphylactic reactions**, characterized by hypotension, tachycardia, nausea, vomiting and/or diarrhea, abdominal pain, severe dyspnea, pulmonary and/or laryngeal edema, and bronchospasm and/or laryngospasm, are rare but dangerous complications requiring immediate treatment with epinephrine. These reactions have been reported in IgA-deficient patients who develop IgA antibodies. Such patients may not have been previously transfused and may develop symptoms after infusion of very small amounts of IgA-containing
plasma, in any blood component. Similar reactions have also been described in patients with haptoglobin deficiency. In certain circumstances, patients might benefit from the use of washed cellular components to prevent or reduce the severity of allergic reactions not minimized by treatment with medication alone.

5. **Transfusion-related acute lung injury (TRALI)** is the acute onset of hypoxemia within 6 hours of a blood or blood component transfusion and is the most commonly reported cause of transfusion-related deaths in the United States. In addition to hypoxemia, criteria for diagnosis include the presence of bilateral infiltrates on frontal chest radiographs and the exclusion of TACO, or preexisting acute lung injury. The exact mechanism of TRALI is not known, but hypotheses include donor antibodies that react against white cell antigens (HLA or human neutrophil antigens) and the sequestration of neutrophils by the pulmonary endothelium (caused by the recipient’s underlying condition) that are subsequently activated by the infusion of substances in the donor plasma such as antibodies or other biologically active substances. In far fewer cases, antibodies in the recipient that may react with antigens on transfused white cells have been implicated. Laboratory testing does not alter management of this reaction, which is diagnosed mainly on clinical and radiographic findings. Treatment of TRALI requires aggressive respiratory support, frequently requiring mechanical ventilation.

**Immunologic Complications, Delayed**

1. **Delayed hemolytic reaction** is described in detail in the section above, adverse effects primarily specific to Whole Blood and Red Blood Cells.

2. **Alloimmunization** to antigens of red cells, white cells, platelets, or plasma proteins may occur unpredictably after transfusion. Blood components may contain certain immunizing substances other than those indicated on the label. For example, Whole Blood and Red Blood Cell components may also contain platelets and white cells. Primary immunization does not become apparent until days or weeks after the immunizing event, and does not usually cause symptoms or physiologic changes. If Whole Blood or Red Blood Cell components that express the relevant antigen are subsequently transfused, there may be accelerated removal of cellular elements from the circulation and/or systemic symptoms. Clinically significant antibodies to red cell antigens will ordinarily be detected by pretransfusion testing. Alloimmunization to antigens of white cells, platelets, or plasma proteins can be detected only by specialized testing.

3. **Posttransfusion purpura (PTP)** is a rare syndrome characterized by the development of dramatic, sudden, and self-limited thrombocytopenia, typically 7 to 10 days after a blood transfusion, in a patient with a history of sensitization by either pregnancy or transfusion. Although the immune specificity may be to a platelet-specific antigen the patient lacks, both autologous and allogeneic platelets are destroyed. High-dose Immune Globulin, Intravenous (IGIV) may correct the thrombocytopenia.

4. **Transfusion-associated graft-vs-host disease (TA-GVHD)** is a rare but extremely dangerous condition that occurs when viable T lymphocytes in the transfused component engraft in the recipient and react against recipient tissue antigens. TA-GVHD can occur if the host does not recognize and reject the foreign transfused cells, and it can follow transfusion of any component that contains even very small numbers of viable T lymphocytes. Recipients with severe cellular immunodeficiency (except for HIV infection) are at greatest risk (eg, fetuses
receiving intrauterine transfusions, recipients of hematopoietic progenitor cell transplants, and selected patients with severe immunodeficiency conditions), but TA-GVHD has also been reported in recipients receiving fludarabine for oncologic and rheumatologic diseases, and in immunologically normal recipients who are heterozygous for a tissue antigen haplotype for which the donor is homozygous. Tissue antigen haplotype sharing is most likely to occur when the transfused component is from a blood relative or has been selected for HLA compatibility. TA-GVHD remains a risk with leukocyte-reduced components because they contain sufficient residual T lymphocytes. Irradiation of the component renders T lymphocytes incapable of proliferation and is presently the only approved means to prevent TA-GVHD.

Nonimmunologic Complications

1. Because Whole Blood and Red Blood Cell components are made from human blood, they may carry a risk of transmitting infectious agents [eg, viruses, bacteria, parasites, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the classic CJD agent]. Careful donor selection and available laboratory tests do not totally eliminate the hazard. Also, septic and toxic reactions can result from transfusion of bacterially contaminated Whole Blood and Red Blood Cell components. Such reactions are infrequent, but may be life-threatening. This may occur despite careful selection of donors and testing of blood. Donor selection criteria are designed to screen out potential donors with increased risk of infection with HIV and hepatitis, as well as other agents (see section on Testing of Donor Blood). These procedures do not totally eliminate the risk of transmitting these agents.

Cytomegalovirus (CMV) may, unpredictably, be present in white-cell-containing components from donors previously infected with this virus, which can persist lifelong despite the presence of serum antibodies. Up to 70% of donors may be anti-CMV positive. Transmission of CMV by transfusion may be of concern in low-birthweight (≤1200 g) premature infants born to CMV-seronegative mothers and in certain other categories of immunocompromised individuals, if they are CMV seronegative. For at-risk recipients, the risk of CMV transmission by cellular components can be reduced by transfusing CMV-seronegative or leukocyte-reduced components.

Trypanosoma cruzi has been transmitted by whole blood and platelet transfusion; testing for antibody to this agent is available, and should be considered if the donor population includes individuals at risk. For other infectious agents (eg, Babesia spp, Leishmania spp, and Plasmodia spp) there are no routinely available tests to predict or prevent disease transmission. All potential blood donors are subjected to screening procedures intended to reduce to a minimum the risk that they will transmit infectious agents.

2. Bacterial sepsis occurs rarely but can cause acute, severe, sometimes life-threatening effects. Onset of high fever (≥2°C increase in temperature), severe chills, hypotension, or circulatory collapse during or shortly after transfusion should suggest the possibility of bacterial contamination and/or endotoxin reaction. Red Blood Cell components stored for several weeks at 1 to 6°C have been implicated. Both gram-positive and gram-negative organisms have been identified as causing septic reactions. Organisms capable of multiplying at low temperatures (eg, Yersinia enterocolitica) and those using citrate as a nutrient are most often associated with components
containing red cells. Endotoxemia in recipients has resulted from multiplication of gram-negative bacteria in blood components.

Prompt recognition of a possible septic reaction is essential, with immediate discontinuation of the transfusion and aggressive therapy with broad-spectrum antimicrobials and vasopressor agents, if necessary. In addition to prompt sampling of the patient’s blood for cultures, investigation should include examination of material from the blood container by Gram’s stain, and cultures of specimens from the container and the administration set. It is important to report all febrile transfusion reactions to the transfusion service. Follow-through from the transfusion service to the blood collection facility may facilitate retrieval of other components associated with the collection.

3. **TACO**, leading to pulmonary edema, can occur after transfusion of excessive volumes or at excessively rapid rates. This is a particular risk in the very young and the elderly and in patients with chronic severe anemia in whom low red cell mass is associated with high plasma volume. Small transfusion volumes can precipitate symptoms in at-risk patients who already have a positive fluid balance. Pulmonary edema should be promptly and aggressively treated, and infusion of colloid preparations, including plasma components and the suspending plasma in cellular components, reduced to a minimum.

4. **Hypothermia** carries a risk of cardiac arrhythmia or cardiac arrest and exacerbation of coagulopathy. Rapid infusion of large volumes of cold Whole Blood or Red Blood Cell components can depress body temperature, and the danger is compounded in patients experiencing shock or surgical or anesthetic manipulations that disrupt temperature regulation. A blood warming device should be considered if rapid infusion of Whole Blood or Red Blood Cell components is needed. Warming must be accomplished using a NRA-approved warming device so as not to cause hemolysis.

5. **Metabolic complications** may accompany large-volume transfusions, especially in neonates and patients with liver or kidney disease.
   
a. Citrate “toxicity” reflects a depression of ionized calcium caused by the presence in the circulation of large quantities of citrate anticoagulant. Because citrate is promptly metabolized by the liver, this complication is rare. Patients with severe liver disease or those with circulatory collapse that prevents adequate hepatic blood flow may have physiologically significant hypocalcemia after rapid, large-volume transfusion. Citrated Whole Blood or Red Blood Cell components administered rapidly through central intravenous access may reach the heart so rapidly that ventricular arrhythmias occur. Standard measurement of serum calcium does not distinguish ionized from complexed calcium. Ionized calcium testing or electrocardiogram monitoring is more helpful in detecting physiologically significant alteration in calcium levels.

b. Other metabolic derangements can accompany rapid or large-volume transfusions, especially in patients with preexisting circulatory or metabolic problems. These include acidosis or alkalosis (deriving from changing concentrations of citric acid and its subsequent conversion to pyruvate and bicarbonate) and hyper- or hypokalemia.
Additional Information for applicants

1. **Minimum criteria for acceptance of an application for consideration by the Expert Committee:**
   a. The application must present scientific evidence on comparative safety and efficacy. Summary evidence tables of key trials should be included in the application and the original data should be available in the public domain. See section 10 in the Application, above. All of the data cited are in the public domain.
   b. The application must include information on the public health need for the medicine. See section 8 in the Application, above.
   c. The medicine being proposed for inclusion must have a composition of product defined in a way that is reproducible.

Whole Blood (from which Red Blood Cells can be derived) can be collected in plasticized containers of different sizes, ranging from 300 to 500 mL for adults. (500 mL containers generally contain up to 510 total volume and 450 mL of donor blood.) Each bag is considered to be a unit. A single dose of Whole Blood is generally considered to be one unit of Whole Blood and, with respect to Red Blood Cells, the Red Blood Cells that are separated from one unit of Whole Blood. Each unit of Whole Blood and each unit of Red Blood Cells contain approximately 147-278 mg of iron, most in the form of hemoglobin. The number of doses required is dependent on the underlying condition of the patient.

Requirements relating to blood donor qualifications, approved containers and approved preservatives and anticoagulants do vary from country to country, although products generally conform to the characteristics stated above. This is because composition of the product is standardized through control of donor screening, blood collection, testing, product manufacture, storage and administration processes.

2. **Where appropriate evidence of comparative effectiveness and safety should be presented in tabular form using Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tables.**

See section 10 on Comparative Efficacy in the Application, above. The use of GRADE tables with respect to Whole Blood and Red Blood Cells is appropriate only with respect to the comparison of transfusion triggers for particular uses of Red Blood Cells. The historical use of Whole Blood and Red Blood Cells makes the use of randomized controlled clinical trials comparing Red Blood Cell transfusion with no transfusion unethical.

Copies of the key trials that are referenced to support the application are included in Annex B.

3. **All applications must evaluate data for both adults and children**

See section 10 of the Application, above.
4. The application should provide a detailed specification of the active pharmaceutical ingredient, dosage forms and strength for the proposed medicine for inclusion

The active pharmaceutical ingredient for both Whole Blood Cells and Red Blood Cells is Red Blood Cells. Dosage forms are contained in section 5 of the Application, above. The dosages are or can be available in any country. See section 6 of the Application, above.

5. The application must provide a summary of the regulatory status of the medicine(s) proposed for inclusion. This should include the regulatory status in the country of origin and preferably other countries as well. The summary should also specify the indications that the medicine is licensed for.

The regulatory of Whole Blood and Red Blood Cells is described in section 13 of the Application, above. The country of origin of Whole Blood and Red Blood Cells is the country in which it is collected, processed, tested and distributed. The indications for Whole Blood and Red Blood Cells are described in section 15 of the Application, above.

6. For the purposes of listing, the application must clarify if the inclusion of the medicine is an individual medicine or an individual medicine with a square box symbol.

The applications for Whole Blood and Red Blood Cells are being submitted as an individual medicine with a square box symbol.