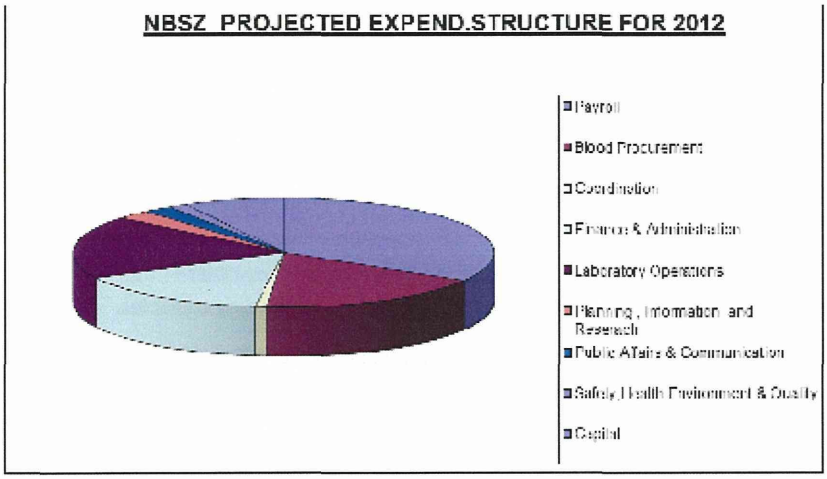

12.2 Comparative Cost effectiveness

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.

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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-preservative solution. Whole Blood units are prepared in an aseptic manner in a ratio of 14 mL of anticoagulant-preservative 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 hematinic 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 ≥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 IgAdeficient patients who develop IgA antibodies. Such patients may not have been previously transfused and may develop symptoms after infusion of very small amounts of IgAcontaining

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 CMVseronegative or leukocyte-reduced components.

Trypanosma 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 mayreach 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 containa 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 characteristiscs 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 effectivenss 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.